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Iodolactonization of 3-Alkynylthiophene-2-Carboxylic and 3-Alkynylpicolinic Acids for the Synthesis of Fused Heterocycles

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URL: https://www.unical.it/portale/strutture/dipartimenti_240/ctc/didattica/homedid/docenti/ordinari/gabriele/# (B.G.)
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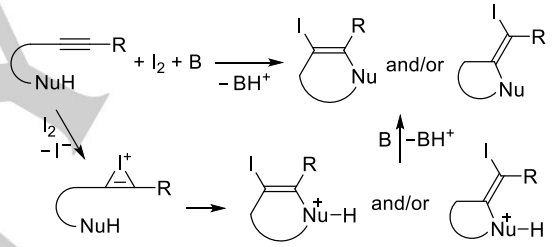
Supporting information for this article is given via a link at the end of the document.

Abstract: The iodolactonization of 3-alkynylthiophene-2-carboxylic acids and 3-alkynylpicolinic acids has been investigated. Using I_2 as the iodine source and $NaHCO_3$ as the base in MeCN, the process took place smoothly to afford thienopyranones and pyranopyridinones, respectively, from 6-*endo-dig* cyclization. The method also worked nicely for the transformation of 2-(phenylethynyl)thiophene-3-carboxylic acid and 3-(phenylethynyl)isonicotinic acid into 7-iodo-6-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one and 4-iodo-3-phenyl-1*H*-pyrano[4,3-*c*]pyridin-1-one, respectively. Although with some 3-alkynylpicolinic acids the process led to a mixture of the 6-*endo-dig* and 5-*exo-dig* products, it could be still made selective toward the pyranopyridinone compound working in 1-ethyl-3-methylimidazolium ethyl sulfate as the solvent. On the other hand, the exclusive formation of the 5-*exo-dig* product was observed in *N*-ethyl-*N*-methylmorpholinium dicyanamide starting from 3-(3,3-dimethylbut-1-yn-1-yl)picolinic acid. Some representative iodinated thienopyridinone products were successfully used as substrates for Pd-catalyzed Suzuki and Sonogashira reactions.

Introduction

Iodocyclization of acetylenic substrates bearing a suitably placed nucleophilic group is a powerful method for the direct synthesis of a variety of iodine-containing heterocyclic derivatives.[1] The process usually occurs using molecular iodine as iodinating agent in the presence of a base to buffer the hydrogen iodide that is formally eliminated in the process, as shown in Scheme 1. The intermediate formation of an iodonium species is generally accepted as the key mechanistic step, which is then followed by either *exo*- or *endo*-cyclization (Scheme 1). The resulting products bearing an iodovinyl moiety can be further conveniently decorated by cross-coupling reactions to afford more complex heterocyclic motifs.

We recently studied the iodolactonization of simple 2-alkynylbenzoic acids to give either isobenzofuranones or isochromenones, depending on reaction conditions.[2] Here, we report an extension of this kind of reactivity to the use of 3-alkynylthiophene-2-carboxylic acids **1** and 3-alkynylpicolinic acids **3** aimed at developing a simple and convenient new protocol for the direct synthesis of important iodinated fused heterocyclic derivatives.[3]



Scheme 1. Iodocyclization of acetylenic substrates leading to iodine-containing heterocycles, carried out with molecular iodine as the iodinating agent and a base (B). Both *endo*- and *exo-dig* cyclization modes are possible.

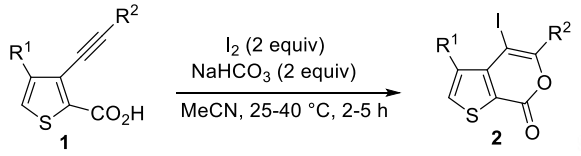
Results and Discussion

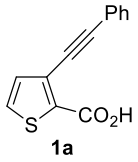
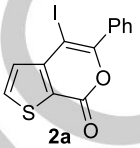
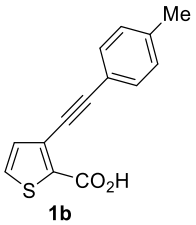
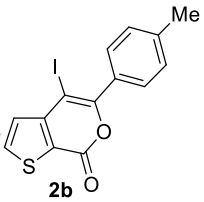
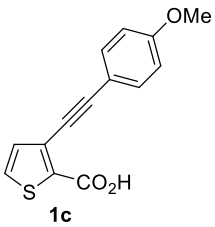
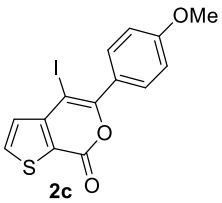
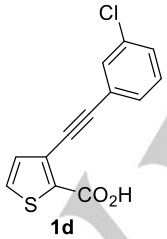
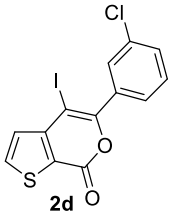
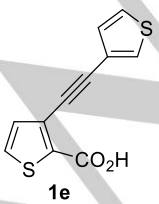
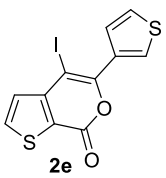
The 3-alkynylthiophene-2-carboxylic acids **1** and 3-alkynylpicolinic acids **3** used as substrates in this work were prepared by Sonogashira coupling of the corresponding methyl 3-halothiophene-2-carboxylates and methyl 3-bromopicolinate (commercially available) with terminal alkynes followed by hydrolysis, as depicted in Schemes S1 and S2 (Supporting Information) and detailed in the Experimental Section.

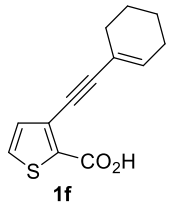
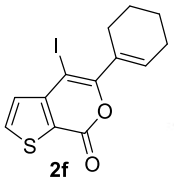
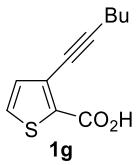
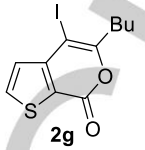
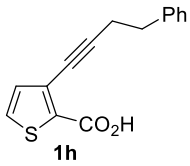
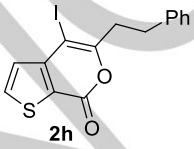
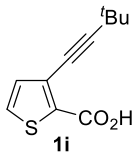
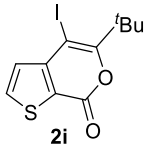
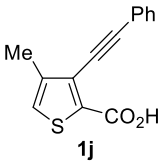
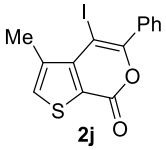
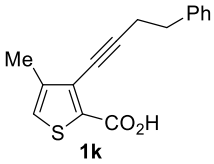
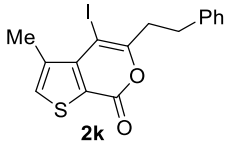
To assess the reactivity 3-alkynylthiophene-2-carboxylic acids under iodocyclization conditions, we used 3-(phenylethynyl)thiophene-2-carboxylic acid **1a** as initial substrate. The first experiment was carried out with 1.5 equiv of I_2 and $NaHCO_3$ in MeCN at room temperature. After 8 h, analysis of the reaction mixture evidenced a substrate conversion of 75% and the formation of a single product, which was isolated and identified as 4-Iodo-5-phenyl-7*H*-thieno[2,3-*c*]pyran-7-one **2a** (yield: 56%, Table 1, entry 1). Substrate conversion was quantitative using 2 equiv of iodine and the base, either after 8 h at rt or after 3 h at 40 °C, with a **2a** yield of 65% (Table 1, entry 2) and 75% (Table 1, entry 3) respectively.

The reaction could also be performed

Table 1. Synthesis of 4-Iodo-7*H*-thieno[2,3-*c*]pyran-7-ones **2** by Regioselective Iodolactonization of 3-Alkynylthiophene-2-Carboxylic Acids **1**.[a]



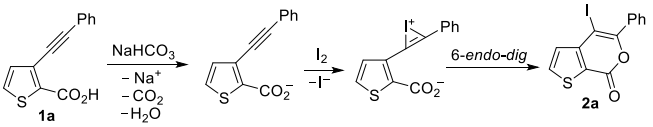
Entry	1	*T* [°C]	Time [h]	2	Yield of **2** [%][b]
1[c]	 **1a**	25	8	 **2a**	56[d]
2	**1a**	25	8	**2a**	65
3	**1a**	40	3	**2a**	75
4[e]	**1a**	60	15	**2a**	80
5[f]	**1a**	60	15	**2a**	70
6	 **1b**	40	2	 **2b**	70
7	 **1c**	40	2	 **2c**	73
8	 **1d**	40	3	 **2d**	70
9	 **1e**	40	3	 **2e**	74

10	 **1f**	40	3	 **2f**	91
11	 **1g**	40	2	 **2g**	61[g]
12	**1g**	25	3	**2g**	68[h]
13	 **1h**	25	5	 **2h**	73
14	 **1i**	25	5	 **2i**	65
15	 **1j**	40	5	 **2j**	75
16	 **1k**	40	5	 **2k**	96

[a] Unless otherwise noted, all reactions were carried using 2 equiv of I_2 and 2 equiv of $NaHCO_3$ in MeCN as the solvent (0.05 mmol of **1** per mL of MeCN) with a substrate scale of 0.25 mmol. Products yields were even higher when representative experiments were carried out in a larger scale (2.2 mol of **1**; see the Experimental Section for details). [b] Isolated yield, based on starting material **1**. [c] The reaction was carried out with 1.5 equiv of I_2 and 1.5 equiv of $NaHCO_3$. [d] Substrate conversion was 75% (determined by isolation of unreacted **1a**). [e] The reaction was carried out in 1-ethyl-3-methylimidazolium ethyl sulfate ($EmimEtSO_4$) as the solvent (0.2 mmol of **1a** per mL of solvent) in the absence of $NaHCO_3$. [f] The reaction was carried out in *N*-ethyl-*N*-methylmorpholinium dicyanamide [$Mor_{1,2}N(CN)_2$] as the solvent (0.2 mmol of **1a** per mL of solvent) in the absence of $NaHCO_3$. [g] The reaction also led to the formation of 5-butyl-7*H*-thieno[2,3-*c*]pyran-7-one **5** in 17% yield. [h] The reaction also led to the formation of **5** in 10% yield.

in the absence of $NaHCO_3$ in a basic ionic liquid (IL) as the solvent (such as 1-ethyl-3-methylimidazolium ethyl sulfate ($EmimEtSO_4$) or *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$), even though the substrate conversion rate was slower, so the process was carried out at 60 °C for 15 h (Table 1, entries 4 and 5). The regiochemical output of the process, however, did not change, as **2a** was still formed exclusively.

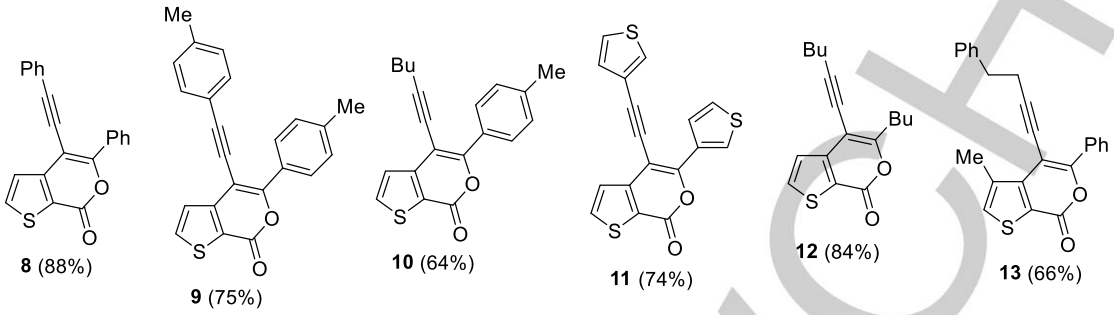
Considering the presence of the carboxylic group in the substrate, it is most likely that the cyclization takes place after substrate deprotonation by the base, as shown in Scheme 2.



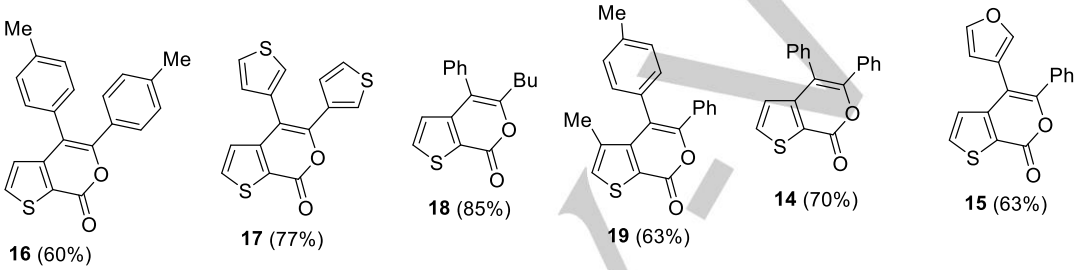
Scheme 2. Proposed Mechanism for the Regioselective 6-*endo-dig* Iodolactonization of 3-(Phenylethynyl)thiophene-2-carboxylic acid **1a** to 4-Iodo-5-phenyl-7*H*-thieno[2,3-c]pyran-7-one **2a**.

Table 2. Decoration of the Thienopyridinone core of **2** by the Sonogashira[a] and Suzuki[b] Cross-couplings Reactions.

Sonogashira products



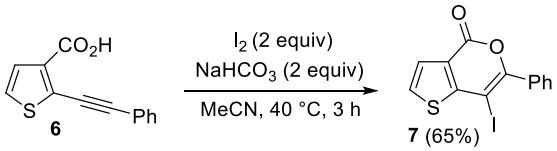
Suzuki products



[a] Sonogashira reactions were carried out with an alkyne:**2** molar ratio = 2.2 in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ (10 mol%) and CuI (6 mol%) in $^iPr_2NH$ as the solvent (0.1 mmol of **2** per mL of solvent) at 70 °C for 24 h. [b] Suzuki reactions were carried out with a boronic acid:**2** molar ratio = 1.2 in the presence of catalytic amounts of $Pd(PPh_3)_4$ (1 mol%) and Cs_2CO_3 (1.4 equiv) in DMF as the solvent (0.035 mmol of **2** per mL of DMF) at 80 °C for 24 h.

The method was then extended to other 3-alkynylthiophene-2-carboxylic acids, bearing different aryl and alkyl groups on the triple bond (Table 1, entries 6-16). Substrates bearing a *p*-tolyl (**1b**), *p*-methoxyphenyl (**1c**), or *m*-chlorophenyl group on the triple bond behaved similarly to **1a** and, under the same conditions as those of entry 3, led to the corresponding iodothienopyranones **2b-d** in good yields (70-73%, respectively) after 2-3 h reaction time (Table 1, entries 6-8). A heteroaryl grup, such as 3-thienyl (**1e**), as well as an alkenyl group, like 1-cyclohexenyl (**1f**), were also well tolerated, and the corresponding iodothienopyranone products **2e** and **2f** were formed in 74% and 91% yields, respectively (Table 1, entries 9 and 10). The reaction of 3-(hex-1-yn-1-yl)thiophene-2-carboxylic acid **1g**, substituted with a butyl group, was less chemoselective, and led to a mixture of iodothienopyranone **2g** and thienopyranone **5** (from a simple cycloisomerization process) in 61% and 17% yields, respectively (Table 1, entry 11). A more selective reaction toward **2g**, however, could be achieved by carrying out the process a room temperature for 3 h (yields of **2g** and **5** were 68% and 10%, respectively, Table 1, entry 12). 3-(4-Phenylbut-1-yn-1-yl)thiophene-2-carboxylic acid **1h** was slightly less reactive, as its conversion reached 100% after 5 h at rt, but the corresponding iodothienopyranone **2h** was formed exclusively in 73% yield (Table 1, entry 13). The method worked nicely even with sterically hindered 3-(3,3-dimethylbut-1-yn-1-yl)thiophene-2-carboxylic acid **1i**, bering a *tert*-butyl group on the triple bond, which was converted after 5 h into 5-(*tert*-butyl)-4-iodo-7*H*-thieno[2,3-*c*]pyran-7-one **2i** with a reasonable yield of 65% (Table 1, entry 14). The presence of a methyl group close to the triple bond did not hinder the iodocyclization process, as demonstrated by the results obtained with substrates **1j** and **1k**, which were converted into the corresponding iodothienopyranones in good to excellent yields (75% and 96%, respectively, Table 1, entries 15 and 16).[4]

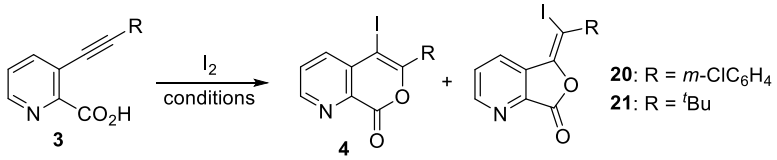
We also tested the reactivity of 2-(phenylethynyl)thiophene-3-carboxylic acid **6**, with the positions of the alkynyl and the carboxylic groups inverted with respect to substrates **1**. As can be seen from Scheme 3, the idocyclization of this substrate was also regioselective, and led to the 6-*endo-dig* product (7-iodo-6-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one **7**) in 65% yield.

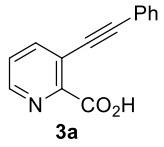
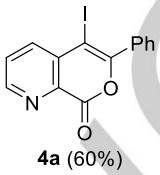
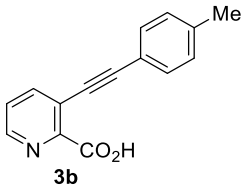
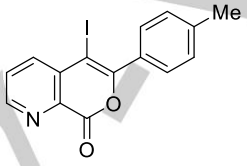
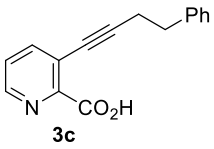
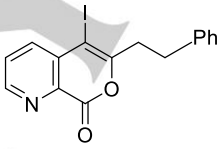
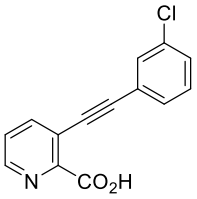
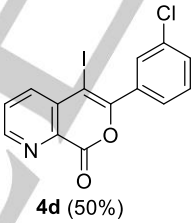
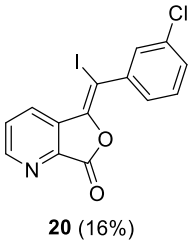
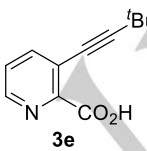
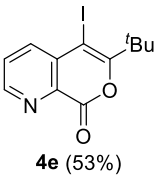
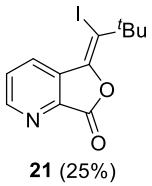


Scheme 3. Iodolactonization of 2-(Phenylethynyl)thiophene-3-carboxylic Acid **6** Leading to 7-Iodo-6-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one **7.**

To expand the synthetic potentiality of the newly prepared iodothienopyranones **2**, we carried out some paradigmatic cross-coupling reactions, such as the Sonogashira and the Suzuki reactions. The results obtained are summarized in Table 2. As can be seen from Table 2, fair to good yields of the corresponding products were obtained with all iodothienopyranones tested, using different terminal alkynes or arylboronic acids as the coupling partners.

Table 3. Iodolactonization of 3-Alkynylpicolinic Acids **3** under Different Conditions[a]

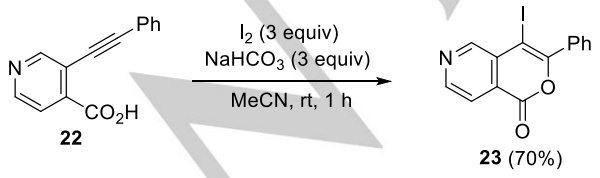


Entry	3	Conditions[a]	Products (Yield %)[b]
1	 **3a**	A	 **4a** (60%)
2	**3a**	B	**4a** (59%)
3	**3a**	C	**4a** (70%)
4	 **3b**	C	 **4b** (66%)
5	 **3c**	C	 **4c** (65%)
6	 **3d**	C	 **4d** (50%)  **20** (16%)
7	**3d**	D	**4d** (63%)
8	 **3e**	C	 **4e** (53%)  **21** (25%)
9	**3e**	D	**4e** (40%) **21** (16%)
10	**3e**	E	**21** (58%)

[a] Conditions: A: The reaction was carried using 2 equiv of I_2 and 2 equiv of $NaHCO_3$ at 25 °C in MeCN as the solvent (0.05 mmol of **3** per mL of MeCN) for 1 h with a substrate scale of 0.35 mmol. Products yields were even higher when representative experiments were carried out in a larger scale (2.2 mol of **3**; see the Experimental Section for details).; B: Same conditions as A, but at 40 °C; C: Same conditions as A, but using 3 equiv of I_2 and 3 equiv of $NaHCO_3$; D: The reaction was carried out with 1.5 equiv of I_2 in $EmimEtSO_4$ as the solvent (0.2 mmol of **3** per mL of solvent) at 50 °C 3 h in the absence of $NaHCO_3$; E: Same conditions as D, but with $Mor_{1,2}N(CN)_2$ as the solvent. [b] Isolated yield, based on starting **3**.

The iodolactonization of 3-alkynylpicolinic acids **3** was also studied (Table 3).[5] 3-(Phenylethynyl)picolinic acid **3a** was initially allowed to react with 2 equiv of I_2 and 2 equiv of $NaHCO_3$ at 25 °C in MeCN. Substrate conversion was quantitative already after 1 h, with selective formation of 5-iodo-6-phenyl-8*H*-pyrano[3,4-*b*]pyridin-8-one **4a** (from 6-*endo*-*dig* cyclization) in 60% yield (formation of heavy products, that are, chromatographically immobile materials, accounted for the difference between **1a** conversion and **4a** yield) This relatively low selectivity was probably due to the basic nature of the pyridinic ring, which may interact with iodine.[6] This result did not improve by rising the temperature at 40 °C (Table 3, entry 2). However, the use of 3 equiv of both I_2 and the base raised the yield to 70% (Table 3, entry 3). Under these latter conditions, other 3-alkynylpicolinic acids **3b** and **3c** (bearing a *p*-tolyl or a phenethyl group on the triple bond) behaved similarly, and gave the corresponding iodopyranopyrimidinones **4b** and **4c** in 66% and 65% yields, respectively (Table 3, entries 4 and 5). On the other hand, the reaction of 3-[(3-chlorophenyl)ethynyl]picolinic acid **3d** led to a mixture of the 6-*endo*-*dig* product [6-(3-chlorophenyl)-5-iodo-8*H*-pyrano[3,4-*b*]pyridin-8-one, **4d**] and the 5-*exo*-*dig* product [(*E*)-5-[(3-chlorophenyl)iodomethylene]furo[3,4-*b*]pyridin-7(5*H*)-one, **20**] in 50% and 16% yields, respectively (Table 3, entry 6) This is probably due to the steric effect exerted by the *meta*-chlorophenyl group, which tends to make the 5-*exo*-*dig* process leading to **20** competitive with the 6-*endo*-*dig* route leading to **4d**. However, the process could be made regioselective toward **4d** using $EmimEtSO_4$ as the solvent at 50 °C for 3 h in the absence of $NaHCO_3$, as shown in Table 3, entry 7. A similar effect of this IL on the regiochemical output of the iodolactonization reaction was observed with simple 2-alkynybenzoic acids, and was confirmed by DFT calculations.[2] A mixture of regioisomeric **4e** and **21** was also obtained in MeCN starting from 3-(3,3-dimethylbut-1-yn-1-yl)picolinic acid **3e**, bearing a bulky *tert*-butyl group on the triple bond (Table 3, entry 8), thus confirming the steric effect exerted by the substituent on the triple bond on the regiochemical output of the process. Interestingly, while a mixture was still obtained in $EmimEtSO_4$ (Table 3, entry 9), the exclusive formation of the 5-*exo*-*dig* product **21** was observed in $Mor_{1,2}N(CN)_2$ (58% yield, Table 3, entry 10), which is in line with the effect of this IL on iodocyclization regioselectivity previously observed with 2-alkynylbenzoic acids.[2]

The synthetic versatility of the process was further demonstrated by the reaction of 3-(phenylethynyl)isonicotinic acid **22** (isomeric with respect to **3a**) which, under the usual conditions, was smoothly converted into 4-iodo-3-phenyl-1*H*-pyrano[4,3-*c*]pyridin-1-one **23** in 70% yield (Scheme 4).



Scheme 4. Iodolactonization of 3-(Phenylethynyl)isonicotinic acid **22** Leading to 4-Iodo-3-phenyl-1*H*-pyrano[4,3-*c*]pyridin-1-one **23**.

Conclusion

In conclusion, we have reported that iodocyclization of 3-alkynylthiophene-2-carboxylic acids **1** and 3-alkynylpicolinic acids **3** takes place under mild reaction conditions (25-40 °C) in MeCN as the solvent using 2-3 equiv of I_2 as the iodine source and $NaHCO_3$ as the base. With 3-alkynylthiophene-2-carboxylic acids, the process is completely regioselective, and affords the 6-*endo*-*dig* cyclization products (4-iodo-7*H*-thieno[2,3-*c*]pyran-7-ones **2**) in fair to excellent yields (65-96%). In a similar manner, 3-alkynylpicolinic acids **3** are selectively converted into and 5-iodo-8*H*-pyrano[3,4-*b*]pyridin-8-ones **4** in 50-70% yields. With some picolinic substrates, however, the reaction also leads to not negligible amounts of the 5-*exo*-*dig* product [iodomethylene]furo[3,4-*b*]pyridin-7(5*H*)-one derivative], but the process can still be made selective toward either the pyranopyridinone or the furopyridinone product working in an appropriate basic ionic liquid [$EmimEtSO_4$ or $Mor_{1,2}N(CN)_2$] as the solvent in the absence of $NaHCO_3$. Some representative iodinated thienopyridinone products were successfully used as substrates for Pd-catalyzed cross-coupling reactions.

Experimental Section

General Experimental Methods. Solvent and chemicals were reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh) or neutral alumina (90-170). Evaporation refers to the removal of solvent under reduced pressure. Melting points are uncorrected. ^{1}H NMR and ^{13}CNMR spectra were recorded at 25 °C on a 300 Spectrometer in $CDCl_3$ and DMSO-d_6 with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage (normal resolution) and by electrospray ionization mass spectrometry (ESI-MS) (high resolution) with a UHD accurate-mass Q-TOF spectrometer equipped with a Dual AJS ESI source working in positive mode, and were recorded in the 150–1000 *m/z* range. The LC-MS experimental conditions were as follows: N_2 was employed as desolvation gas at 300°C and a flow rate of 9 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 350°C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V.

Preparation of Substrates. 3-Alkynylthiophene-2-carboxylic acids **1a-k**, 2-(phenylethynyl)thiophene-3-carboxylic acid **6**, 3-alkynylpicolinic acids **3a**-**e** and 3-(phenylethynyl)isonicotinic acid **22** were prepared by Sonogashira coupling of the corresponding methyl 3-halothiophene-2-carboxylate, methyl 2-bromothiophene-3-carboxylate, methyl 3-bromopicolinate, and methyl 3-bromoisonicotinate with terminal alkynes to give methyl alkynylthiophene carboxylates, followed by hydrolysis (Schemes S1 and S2, Supporting Information), as described below.

1st Step: Sonogashira Coupling of Methyl Halothiophene Carboxylates with Terminal Alkynes to Give Methyl Alkynylthiophene Carboxylates. Methyl 3-bromothiophene-2-carboxylate, methyl 3-iodo-4-methylthiophene-2-carboxylate, and methyl 2-bromothiophene-3-carboxylate were commercially available. A solution of the methyl halothiophene carboxylate (4.5 mmol; 3-bromothiophene-2-carboxylate, 1.00 g; methyl 3-iodo-4-methylthiophene-2-carboxylate, 1.27 g; 2-bromothiophene-3-carboxylate, 1.00 g), $PdCl_2(PPh_3)_2$ (325.0 mg, 0.46 mmol), CuI (54.0 mg, 0.28 mmol), and the terminal alkyne

(phenylacetylene, 1.01 g; 1-ethynyl-4-methylbenzene, 1.15 g; 1-ethynyl-4-methoxybenzene, 1.31 g; 1-chloro-3-ethynylbenzene, 1.35 g; 3-ethynylthiophene, 1.07 g; 1-ethynylcyclohexene, 1.05 g; 1-hexyne, 0.81 g; but-3-yn-1-ylbenzene, 1.29 g; 3,3-dimethyl-1-butyne, 0.81 g) (9.91 mmol) in anhydrous diisopropylamine (45 mL) was allowed to stir under nitrogen at 70 °C (oil bath) for 15 h. After cooling to room temperature, AcOEt (100 mL) was added, and the mixture was washed with water (3 × 100 mL). The organic layer was washed with a saturated solution of NH_4Cl (1x100 mL) and then water until neutral pH. After drying over Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane-AcOEt (9:1) as eluent.

Methyl 3-(phenylethynyl)thiophene-2-carboxylate. Yield: 827.5 mg, 76% based on methyl 3-bromothiophene-2-carboxylate. Brown solid, mp = 70-72 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63-7.54 (m, 2 H), 7.48-7.43 (m, 1 H), 7.39-7.31 (m, 3 H), 7.22-7.17 (m, 1 H), 3.93 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 161.8, 133.4, 132.1, 131.8, 130.5, 128.8, 128.4, 127.4, 122.9, 95.3, 84.0, 52.2; IR (KBr): v = 2210 (w), 1717 (s), 1697 (s), 1439 (m), 1238 (s), 1099 (m), 1076 (m), 772 (m), 756 (m), 691 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 242 (M^+, 100), 227 (73), 211 (35), 199 (27), 171 (18), 139 (99); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{11}O_2S^+$: 243.0463; found: 243.0467. The spectroscopic data agreed with those reported.[7]

Methyl 3-(p-tolylethynyl)thiophene-2-carboxylate. Yield: 875.5 mg, 76% based on methyl 3-bromothiophene-2-carboxylate. Yellow solid, mp = 72-73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.51-7.43 (m, 3 H), 7.21-7.13 (m, 3 H), 3.93 (s, 3 H), 2.37 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 161.9, 139.0, 133.0, 132.1, 131.7, 130.5, 129.2, 127.6, 119.8, 95.6, 83.4, 52.2, 21.6; IR (KBr): v = 2210 (w), 1717 (s), 1697 (s), 1531 (m), 1435 (m), 1238 (s), 1099 (m), 1076 (m), 818 (m), 775 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 256 (M^+, 100), 241 (78), 225 (27), 213 (28), 197 (6), 185 (11), 169 (8), 139 (7), 112 (10), 98 (8); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{13}O_2S^+$: 257.0631; found: 257.0623. The spectroscopic data agreed with those reported.[8]

Methyl 3-((4-methoxyphenyl)ethynyl)thiophene-2-carboxylate. Yield: 1.14 g, 94% based on methyl 3-bromothiophene-2-carboxylate. Light yellow solid, mp = 96-98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.52 (d, *J* = 8.7, 2 H), 7.45 (d, *J* = 5.1, 1 H), 7.18 (d, *J* = 5.1, 1 H), 6.89 (d, *J* = 8.7, 2H), 3.93 (s, 3 H), 3.82 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 162.0, 160.0, 133.4, 132.6, 132.0, 130.4, 127.9, 115.0, 114.0, 95.6, 82.9, 55.3, 52.2; IR (KBr): v= 2207 (w), 1713 (s), 1697 (s), 1605 (m), 1531 (s), 1439 (m), 1298 (m), 1238 (s), 1076 (m), 1030 (m), 833 (m), 775 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 272 (M^+, 100), 257 (70), 241 (12), 229 (16), 201 (11), 169 (18); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{13}O_3S^+$: 273.0571; found: 273.0571. The spectroscopic data agreed with those reported.[8]

Methyl 3-((3-chlorophenyl)ethynyl)thiophene-2-carboxylate. Yield: 1.20 g, 97% based on methyl 3-bromothiophene-2-carboxylate. Yellow solid, mp = 93-94 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.59-7.55 (m, 1H), 7.50-7.44 (m, 2 H), 7.36-7.25 (m, 2 H), 7.23-7.18 (m, 1 H), 3.93 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 161.7, 134.2, 133.8, 132.0, 131.6, 130.6, 130.0, 129.6, 129.0, 126.9, 124.6, 93.6, 85.0, 52.3; IR (KBr): v = 1709 (s), 1593 (w), 1435 (m), 1304 (w), 1234 (m), 1076 (m), 941 (m), 772 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 278 [(M+2)$^+$, 41), 276 (M^+, 100), 263 (24), 261 (62), 247 (16), 245 (40), 226 (28), 175 (15), 173 (46); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{10}ClO_2S^+$: 277.0084; found: 277.0083.

Methyl 3-(thiophen-3-ylethynyl)thiophene-2-carboxylate. Yield: 0.94 g, 84% based on methyl 3-bromothiophene-2-carboxylate). Yellow solid, mp = 102-103 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63-7.59 (m, 1 H), 7.56 (d, *J* = 5.1, 1 H), 7.33-7.29 (m, 1 H), 7.27-7.22 (m, 1 H), 7.19 (d, *J* = 5.1, 1 H), 3.92 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 161.8, 133.1, 132.1, 130.5, 130.0, 129.6, 127.4, 125.5, 121.9, 90.5, 83.5, 52.2; IR (KBr): v = 2210 (vw), 1701 (s), 1539 (w), 1435 (m), 1281 (m), 1238 (m), 1076 (w), 787 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 248 (M^+, 100), 233 (71), 217 (30), 205 (43), 177 (16), 145 (85); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{12}H_9O_2S_2^+$: 249.0038; found: 249.0039.

Methyl 3-(cyclohex-1-en-1-ylethynyl)thiophene-2-carboxylate. Yield: 0.84 g, 76% based on methyl 3-bromothiophene-2-carboxylate. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.41 (d, *J* = 5.1, 1 H), 7.09 (d, *J* = 5.1, 1 H), 6.35-6.26 (m, 1 H), 3.89 (s, 3 H), 2.30-2.21 (m 4 H), 2.31-2.11 (m, 2 H), 1,74-1.55 (m, 4 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 161.9, 136.7, 132.5, 132.1, 130.3, 128.1, 120.6, 97.5, 81.5, 52.1, 28.9, 25.9, 22.3, 21.5; IR (film): v = 2203 (w), 1724 (s), 1697 (s), 1524 (m), 1435 (m), 1384 (m), 1231 (s), 1099 (m), 1076 (m), 922 (w), 775 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 246 (M^+, 100), 231 (30), 203 (28), 187 (32), 171 (23), 147 (25), 115 (43); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{15}O_2S^+$: 247.0787; found: 247.0785.

Methyl 3-(hex-1-yn-1-yl)thiophene-2-carboxylate. Yield: 0.91 g, 91% based on methyl 3-bromothiophene-2-carboxylate). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40 (d, *J* = 6.9, 1 H), 7.08 (d, *J* = 5.1, 1 H), 3.89 (s, 3 H), 2.49 (t, *J* = 6.9, 2 H), 1.70-1.42 (m, 4 H), 0.95 (t, *J* = 7.2, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 162.0, 132.54, 132.50, 130.2, 128.4, 97.3, 75.2, 52.0, 30.6, 22.0, 19.5, 13.7; IR (film): v = 2234 (w), 1724 (s), 1701 (s), 1524 (m), 1439 (m), 1377 (m), 1273 (m), 1227 (m), 1080 (m), 775 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 222 (M^+, 10), 180 (100), 165 (30), 137 (35); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{12}H_{15}O_2S^+$: 223.0787; found: 223.0785. The spectroscopic data agreed with those reported.[8]

Methyl 3-(4-phenylbut-1-yn-1-yl)thiophene-2-carboxylate. Yield: 1.17 g, 96% based on methyl 3-bromothiophene-2-carboxylate. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.39 (d, *J* = 5.1, 1 H), 7.33-7.25 (m, 5 H), 7.04 (d, *J* = 5.1, 1 H), 3.87 (s, 3 H), 2.97 (t, *J* = 7.5, 2 H), 2.81-2.73 (m, 2 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 161.9, 140.6, 132.5, 130.3, 128.5, 128.4, 128.2, 126.3, 96.3, 75.8, 52.1, 34.9, 22.0; IR (film): v = 2234 (w), 1717 (s), 1697 (s), 1524 (m), 1435 (m), 1269 (m), 1223 (s), 1080 (m), 775 (m), 698 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 270 (M^+, 5), 269 (15), 238 (38), 149 (13), 91 (100)); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{16}H_{15}O_2S^+$: 271.0787; found: 271.0788. Spectroscopic data were in good agreement with those reported.[9]

Methyl 3-(3,3-dimethylbut-1-yn-1-yl)thiophene-2-carboxylate. Yield: 0.76 g, 76% based on methyl 3-bromothiophene-2-carboxylate. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.39 (d, *J* = 5.1, 1 H), 7.06 (d, *J* = 5.1, 1 H), 3.89 (s, 3 H), 1.35 (s, 9 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 162.0, 132.8, 132.3, 130.2, 128.2, 105.0, 73.8, 51.9, 30.8, 28.3; IR (film): v = 2222 (m), 1724 (s), 1701 (s), 1524 (m), 1439 (m), 1377 (m), 1242 (s), 1076 (m), 871 (w), 775 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 222 (M^+, 30), 207 (100), 175 (68), 163 (94), 148 (55), 147 (60); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{12}H_{15}O_2S^+$: 223.0787; found: 223.0787.

Methyl 4-methyl-3-(phenylethynyl)thiophene-2-carboxylate. Yield: 0.82 g, 71% based on methyl 3-Iodo-4-methylthiophene-2-carboxylate. Yellow solid, mp = 62.2-63.5 °C.^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64-7.56 (m, 2 H), 7.39-7.32 (m, 3 H), 7.16-7.12 (m, 1 H), 3.92 (s, 3 H), 2.36 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 162.0, 141.3, 133.0, 131.8, 128.7, 128.44, 128.38, 126.4, 123.1, 97.9, 83.6, 52.1, 15.2; IR (KBr): v = 2210 (w), 1717 (s), 1701 (s), 1454 (m), 1373 (m), 1296 (m), 1227 (s), 1123 (m), 756 (m), 691 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 256 (M^+, 100), 241 (78), 225 (39), 213 (22), 197 (13), 152 (25); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{13}O_2S^+$: 257.0631; found: 257.0633.

Methyl 4-methyl-3-(4-phenylbut-1-yn-1-yl)thiophene-2-carboxylate. Yield: 1.16 g, 91% based on methyl 3-Iodo-4-methylthiophene-2-carboxylate. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.33-7.19 (m, 5 H), 7.07-7.03 (m, 1 H), 3.85 (s, 3 H), 2.98 (distorted t, *J* =7.2, 2 H), 2.84 (distorted t, *J* =7.2, 2 H), 2.15 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 162.1, 141.6, 140.5, 132.3, 129.2, 128.5, 128.4, 126.3, 126.1, 98.8, 75.4, 52.0, 35.0, 22.0, 15.1; IR (film): v = 2230 (w), 1717 (s), 1694 (m), 1454 (m), 1369 (m), 1273 (s), 1200 (s), 1146 (m), 1080 (m), 1018 (w), 779 (m), 698 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 284 (M^+, 6), 283 (12), 252 (78), 237 (17), 225

(17), 193 (31), 169 (30), 163 (22), 91 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{17}H_{17}O_2S^+$: 285.0943; found: 285.0946.

Methyl 2-(phenylethynyl)thiophene-3-carboxylate. Yield: 0.93 g, 85% based on methyl 2-bromothiophene-3-carboxylate. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.61-7.54 (m, 2 H), 7.44 (d, *J* = 5.4, 1 H), 7.40-7.32 (m, 3 H), 7.19 (d, *J* = 5.4, 1 H), 3.91 (s, 3 H, OMe); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 162.8, 134.1, 131.7, 129.6, 129.0, 128.9, 128.4, 125.8, 122.6, 99.1, 81.8, 51.8; IR (film): v = 2207 (w), 1713 (s), 1524 (w), 1435 (m), 1300 (m), 1242 (s), 1153 (m), 999 (w), 756 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 242 (M$^+$, 93), 227 (57), 211 (30), 199 (21), 171 (13), 139 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{11}O_2S^+$: 243.0474; found: 243.0472.

1st Step: Sonogashira Coupling of Methyl 3-bromopicolinate and Methyl 3-bromoisonicotinate with Terminal Alkynes to Give Methyl 3-Alkynylpicolinate and Methyl 3-(Phenylethynyl)isonicotinate. Methyl 3-bromopicolinate and methyl 3-bromoisonicotinate were commercially available. A solution of methyl 3-bromopicolinate (4.65 mmol; 1.00 g), or methyl 3-bromoisonicotinate (4.65 mmol; 1.00 g), $PdCl_2(PPh_3)_2$ (327.0 mg, 0.46 mmol), CuI (53.0 mg, 0.28 mmol), the terminal alkyne (phenylacetylene, 1.05 g; 1-ethynyl-4-methylbenzene, 1.20 g; 1-hexyne, 0.84 g; but-3-yn-1-ylbenzene, 1.34 g; 1-chloro-3-ethynylbenzene, 1.40 g; 3,3-dimethyl-1-butyne, 0.85 g) (10.3 mmol) in anhydrous diisopropylamine (23 mL) was allowed to stir under nitrogen for at 70 °C (oil bath) for 15 h. After cooling, AcOEt (50mL) was added, and the mixture was washed with water (3 × 60 mL). The organic layer was washed with a saturated solution of NH_4Cl (1x80 mL) and then with water until neutral pH. After drying over Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane-AcOEt (9:1) as eluent.

Methyl 3-(phenylethynyl)picolinate. Yield: 0.97 g, 88% based on methyl 3-bromopicolinate. Brown solid, mp = 66-68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.63 (d, *J* = 3.7, 1 H), 7.96 (dd, *J* = 7.9, 1.1, 1 H), 7.64-7.55 (m, 2 H), 7.43 (dd, J = 7.9, 4.7, 1 H), 7.41-7.31 (m, 3 H), 4.04 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 165.0, 149.1, 148.0, 141.5, 31.8, 129.1, 128.5, 125.4, 122.5, 120.9, 97.3, 85.2, 52.9; IR (KBr): v = 2218 (w), 1732 (s), 1493 (m), 1443 (m), 1296 (s), 1207 (m), 1134 (m), 1088 (m), 760 (m), 691 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 237 (M$^+$, 87), 222 (20), 179 (100), 178 (67), 177 (29), 166 (35), 151 (55); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{12}NO_2^+$: 238.0862; found: 238.0872. The spectroscopic data agreed with those reported.[10]

Methyl 3-(p-tolylethynyl)picolinate. Yield: 1.05 g, 90% based on methyl 3-bromopicolinate. Brown solid, mp= 79-81 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.63 (d, *J* = 3.4, 1 H), 7.96 (dd, *J* = 7.9, 1.5, 1 H), 7.52-7.38 (m, 3 H), 7.17 (d, *J* = 7.9, 2 H), 4.04 (s, 3 H), 2.38 (s, 3 H, Me); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 165.1, 149.0, 147.8, 141.4, 139.4, 131.8, 129.2, 125.4, 121.1, 119.5, 97.7, 84.7, 52.9, 21.6; IR (KBr): v = 2218 (m), 1732 (s), 1512 (w), 1447 (m), 1296 (m), 1207 (w), 1134 (w), 1084 (m), 964 (w), 818 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 251 (M$^+$, 100), 236 (30), 208 (19), 194 (15), 193 (54), 180 (22); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{16}H_{14}NO_2^+$: 252.1019; found: 252.1025.

Methyl 3-(4-phenylbut-1-yn-yl)picolinate. Yield: 1.07 g, 87% based on methyl 3-bromopicolinate. Brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.58 (dd, *J* = 4.5, 1.1, 1 H), 7.78 (dd, *J* = 7.9, 1.1, 1 H), 7.40-7.19 (m, 6 H), 3.98 (s, 3 H), 2.97 (m, 2 H), 2.79 (m, 2 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 165.3, 149.3, 147.5, 141.9, 140.4, 128.5, 128.4, 126.4, 125.3, 121.3, 98.4, 76.7, 52.8, 34.7, 22.0; IR (film): v = 2234 (w), 1732 (s), 1454 (m), 1420 (w), 1300 (s), 1204 (m), 1134 (m), 1099 (m), 702 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 265 (M$^+$, 14), 264 (41), 250 (17), 232 (29), 206 (31), 204 (34), 116 (15), 91 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{17}H_{16}NO_2^+$: 266.1176; found: 266.1174.

Methyl 3-((3-chlorophenyl)ethynyl)picolinate. Yield: 1.07 g, 85% based on methyl 3-bromopicolinate. Brown solid, mp= 70.2-71.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.66 (dd, *J* = 4.6, 1.6, 1 H), 7.97 (dd, *J* = 7.9, 1.6, 1 H), 7.61-7.51 (m, 1 H), 7.51-7.40 (m, 2 H), 7.40-7.28 (m, 2 H), 4.05 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 164.9, 149.1, 148.3, 141.6, 134.3, 131.6, 130.0, 129.7, 129.3, 125.5, 124.2, 120.5, 95.7, 86.3, 53.0; IR (KBr): v = 2222 (vw), 1721 (s), 1474 (m), 1420 (m), 1304 (s), 1088 (s), 887 (m), 810 (w), 787 (w), 702 (m), 679 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 273 [(M+2)$^+$, 35), 271 (M$^+$, 94), 213 (100), 177 (46), 150 (30); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{11}NO_2^+$: 272.0473; found: 272.0474.

Methyl 3-(3,3-dimethylbut-1-yn-yl)picolinate. Yield: 0.90 g, 89% based on methyl 3-bromopicolinate. Brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.57 (dd, *J* = 4.7, 1.7, 1 H), 7.82 (dd, *J* = 7.9, 1.7, 1 H), 7.37 (dd, *J* = 7.9, 4.7, 1 H), 4.00 (s, 3 H), 1.35 (s, 9 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 165.5, 149.8, 147.4, 141.4, 125.1, 121.2, 106.9, 75.1, 52.6, 30.6, 28.3; IR (film): v = 2241 (w), 1740 (s), 1450 (m), 1420 (w), 1308 (m), 1292 (m), 1196 (m), 1134 (m), 1096 (m), 810 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 217 (M$^+$, 34), 202 (87), 187 (37), 186 (21), 158 (100), 142 (47), 130 (23), 115 (31); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_{16}NO_2^+$: 218.1176; found: 218.1169.

Methyl 3-(phenylethynyl)isonicotinate. Yield: 1.07 g, 97% based on methyl 3-bromoisonicotinate. Brown solid, mp= 50-51 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.91 (s, br, 1 H), 8.70-8.75 (m, 1 H), 7.78 (d, *J* = 4.8, 1 H), 7.65-7.51 (m, 2 H), 7.45-7.30 (m, 3 H), 4.00 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 165.2, 154.5, 148.5, 138.3, 131.9, 129.1, 128.5, 123.1, 122.5, 119.4, 97.4, 85.0, 52.8; IR (KBr): v= 2218 (w), 1740 (s), 1493 (m), 1435 (m), 1396 (w), 1276 (m), 1099 (m), 964 (w), 756 (m), 671 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 237 (M$^+$, 100), 222 (41), 206 (11), 194 (23), 178 (15), 166 (21), 151 (29); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{12}NO_2^+$: 238.0862; found: 238.0867.

2nd Step: Hydrolysis of Methyl Alkynylthiophene Carboxylates to Give Alkynylthiophene carboxylic acids 1a-1k and 6. A stirred solution of the methyl alkynylthiophene carboxylate [2.5 mmol; methyl 3-(phenylethynyl)thiophene-2-carboxylate, 610 mg; methyl 3-(*p*-tolylethynyl)thiophene-2-carboxylate, 645 mg; methyl 3-((4-methoxyphenyl)ethynyl)thiophene-2-carboxylate, 680 mg; methyl 3-((3-chlorophenyl)ethynyl)thiophene-2-carboxylate, 693 mg; methyl 3-(thiophen-3-ylethynyl)thiophene-2-carboxylate, 626 mg; methyl 3-(cyclohex-1-en-1-ylethynyl)thiophene-2-carboxylate, 621 mg; methyl 3-(hex-1-yn-1-yl)thiophene-2-carboxylate, 558 mg; methyl 3-(4-phenylbut-1-yn-1-yl)thiophene-2-carboxylate, 670 mg; methyl 3-(3,3-dimethylbut-1-yn-1-yl)thiophene-2-carboxylate, 555 mg; methyl 4-methyl-3-(phenylethynyl)thiophene-2-carboxylate, 643 mg; methyl 4-methyl-3-(4-phenylbut-1-yn-1-yl)thiophene-2-carboxylate, 705 mg; methyl 2-(phenylethynyl)thiophene-3-carboxylate, 608 mg] and 1 N NaOH (14.0 mL) in THF (3.0 mL) was heated at 50 °C for 15 h. After cooling to room temperature, the mixture was washed with Et_2O (3 × 15 mL), further cooled with the aid of an ice bath, and neutralized with 1 N HCl. The resulting mixture was extracted at room temperature with CH_2Cl_2 (3 × 50 mL), and the collected organic layers were dried over Na_2SO_4. Filtration and evaporation of the solvent (at 20 °C, under vacuum) afforded the crude alkynylthiophene carboxylic acids, which were further purified by crystallization with Et_2O/hexane.

3-(Phenylethynyl)thiophene-2-carboxylic acid (**1a**). Yield: 515 mg, 90% based on methyl 3-(phenylethynyl)thiophene-2-carboxylate. Light yellow solid, mp = 146-147 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.92 (d, *J* = 5.1, 1 H), 7.61-7.51 (m, 2 H), 7.51-7.41 (m, 3 H), 7.36 (d, *J* = 5.1, 1 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ= 161.8, 135.0, 132.0, 131.9, 131.3, 129.0, 128.7, 125.7, 122.3, 94.1, 84.4; IR (KBr): v = 2210 (vw), 1744 (s), 1678 (m), 1423 (m), 1258 (w), 918 (m), 775 (m), 752 (s), 691 (m) cm^{-1}; HRMS-ESI (*m/z*): [(M-H)$^-$] cald for $C_{13}H_7O_2S^-$: 227.0172; found: 227.0172. The spectroscopic data agreed with those reported.[7]

3-(p-Tolylethynyl)thiophene-2-carboxylic acid (**1b**). Yield: 502 mg, 83% based on methyl 3-(*p*-tolylethynyl)thiophene-2-carboxylate. White solid,

mp = 162-164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.93 (s, br, 1 H), 7.55 (d, *J* = 5.1, 1 H), 7.48 (d, *J* = 8.0, 2 H), 7.23 (d, *J* = 5.1, 1 H), 7.13 (d, *J* = 7.8, 2 H), 2.36 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 167.0, 139.1, 132.5, 132.4, 132.0, 131.8, 129.2, 128.9, 119.7, 96.8, 83.3, 21.6; IR (KBr): v= 2210 (vw), 1682 (s), 1659 (s), 1447 (m), 1423 (m), 1300 (m), 1261 (m), 1103 (w), 914 (m), 818 (m), 775 (w) cm^{-1}; HRMS-ESI (*m/z*): [(M-H)$^-$] cald for $C_{14}H_9O_2S^-$: 241.0328; found: 241.0330.

3-((4-Methoxyphenyl)ethynyl)thiophene-2-carboxylic acid (**1c**). Yield: 475 mg, 74% based on methyl 3-((4-methoxyphenyl)ethynyl)thiophene-2-carboxylate. White solid, mp = 175-177 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.90 (d, *J* = 5.1, 1 H), 7.49 (d, *J* = 8.6, 2 H), 7.31 (d, *J* = 5.1, 1 H), 7.00 (d, *J* = 8.6, 2 H), 3.81 (s, 3 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ= 162.0, 159.7, 134.3, 132.9, 131.9, 131.8, 126.1, 114.4, 114.2, 94.6, 83.3, 55.2; IR (KBr): v= 2207 (vw), 1674 (s), 1647 (s), 1450 (s), 1288 (m), 1146 (w), 1226 (m), 833 (s) cm^{-1}; HRMS-ESI (*m/z*): [(M-H)$^-$] cald for $C_{14}H_9O_3S^-$: 257.0277; found: 257.0278.

3-((3-Chlorophenyl)ethynyl)thiophene-2-carboxylic acid (**1d**). Yield: 363 mg, 55% based on methyl 3-((3-chlorophenyl)ethynyl)thiophene-2-carboxylate. Yellow solid, mp = 150-151 °C.^{1}H NMR (DMSO-d_6, 300 MHz): 7.93 (d, *J* = 5.1, 1 H), 7.63-7.57 (m, 1 H), 7.57-7.45 (m, 3 H), 7.36 (d, *J* = 5.1, 1 H), 3.86 (s, br, 1 H); ^{13}CNMR (DMSO-d_6, 300 MHz): δ= 162.4, 136.2, 133.8, 132.54, 132.45, 131.1, 130.4, 129.6, 125.5, 124.7, 92.9, 86.1; IR (KBr): v= 2214 (vw), 1682 (s), 1667 (s), 1520 (w), 1435 (s), 1304 (s), 1273 (s), 995 (w), 880 (w), 772 (s) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_8ClO_2S^+$: 262.9928; found: 262.9929.

3-(Thiophen-3-ylethynyl)thiophene-2-carboxylic acid (**1e**). Yield: 563 mg, 96% based on methyl 3-(thiophen-3-ylethynyl)thiophene-2-carboxylate. Yellow solid, mp = 133-136 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.94-7.84 (m, 2 H), 7.71-7.63 (m, 1 H), 7.32 (d, *J* = 5.0, 1 H), 7.26 (d, *J* = 4.4, 1 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ= 161.9, 134.6, 132.0, 131.9, 130.2, 129.4, 127.0, 125.7, 121.1, 89.8, 83.7; IR (KBr): v= 2210 (w), 1667 (s), 1504 (m), 1427 (m), 1296 (m), 999 (m), 845 (w), 779 (s) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{11}H_7O_2S_2^+$: 234.9882; found: 234.9889.

3-(Cyclohex-1-en-1-ylethynyl)thiophene-2-carboxylic acid (**1f**). Yield: 520 mg, 90% based on methyl 3-(cyclohex-1-en-1-ylethynyl)thiophene-2-carboxylate. Yellow solid, mp = 110-113°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.38 (s, br, 1 H), 7.51 (d, *J* = 5.1, 1 H), 7.13 (d, *J* = 5.1, 1 H), 6.35-6.25 (m, 1 H), 2.31-2.09 (m, 4 H), 1.75-1.55 (m, 4 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 166.9, 137.1, 132.4, 132.0, 131.8, 129.2, 120.6, 98.6, 81.3, 28.8, 25.9, 22.3, 21.4; IR (KBr): v= 2203 (w), 1678 (s), 1524 (m), 1431 (m), 1288 (m), 1246 (w), 1107 (w), 981 (w), 779 (w) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_{11}O_2S^+$: 231.0485; found: 231.0484.

3-(Hex-1-yn-1-yl)thiophene-2-carboxylic acid (**1g**). Yield: 260 mg, 50% based on methyl 3-(hex-1-yn-1-yl)thiophene-2-carboxylate. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.72 (s, br, 1 H), 7.53-7.46 (m, 1 H), 7.14-7.07 (m, 2 H), 2.49 (t, *J* = 6.8, 2 H), 1.73-1.44 (m, 4 H), 0.96 (t, *J* = 7.2, 3 H); ^{13}CMR ($CDCl_3$, 75 MHz): δ= 167.0, 132.8, 132.0, 131.8, 129.7, 98.6, 75.1, 30.5, 22.0, 19.5, 13.6; IR (film): v= 2230 (vw), 1717 (s), 1624 (m), 1524 (w), 1427 (m), 1211 (w), 1099 (w), 999 (w) cm^{-1}; HRMS-ESI (*m/z*): [(M-H)$^-$] cald for $C_{11}H_{11}O_2S^-$: 207.0485; found: 207.0482.

3-(4-Phenylbut-1-yn-1-yl)thiophene-2-carboxylic acid (**1h**). Yield: 560 mg, 87% based on methyl 3-(4-phenylbut-1-yn-1-yl)thiophene-2-carboxylate. White solid, mp = 84-86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.26 (s, br, 1 H), 7.47 (d, *J* = 5.1, 1 H), 7.35-7.18 (m, 5 H), 7.06 (d, *J* = 5.1, 1 H), 2.94 (t, *J* = 7.3, 2 H), 2.75 (t, *J* = 7.3, 2 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 166.8, 140.4, 132.9, 131.8, 129.4, 129.3, 128.5, 128.4, 126.4, 97.6, 75.7, 34.7, 22.0; IR (KBr): v= 2230 (w), 1678 (s), 1524 (m), 1427 (m), 1281 (s), 1234 (w), 779 (w), 667 (w) cm^{-1}; HRMS-ESI (*m/z*): [(M-H)$^-$] cald for $C_{15}H_{11}O_2S^-$: 255.0485; found: 255.0490.

3-(3,3-Dimethylbut-1-yn-1-yl)thiophene-2-carboxylic acid (**1i**). Yield: 421 mg, 81% based on methyl 3-(3,3-dimethylbut-1-yn-1-yl)thiophene-2-carboxylate. White solid, mp = 120-123 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.50 (s, br, 1 H), 7.49 (d, *J* = 5.1, 1 H), 7.09 (d, *J* = 5.1, 1 H), 1.35 (s, 9 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 166.9, 132.5, 132.4, 131.7, 129.4, 106.5, 73.7, 30.6, 28.4; IR (KBr): v= 2222 (w), 1678 (s), 1524 (w), 1427 (m), 1292 (m), 1258 (m), 872 (w), 779 (w) cm^{-1}; HRMS-ESI (*m/z*): [(M-H)$^-$] cald for $C_{11}H_{11}O_2S^-$: 207.0485; found: 207.0486.

4-Methyl-3-(phenylethynyl)thiophene-2-carboxylic acid (**1j**). Yield: 523 mg, 86% based on methyl 4-methyl-3-(phenylethynyl)thiophene-2-carboxylate. Yellow solid, mp = 168-170 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 13.26 (s br, 1H, OH), 7.63-7.51 (m, 3 H), 7.51-7.41 (m, 3 H), 2.31 (s, 3 H); ^{13}CNMR (DMSO-d_6, 300 MHz): δ= 162.0, 140.4, 134.9, 131.2, 128.9, 128.7, 127.2, 126.5, 122.3, 96.7, 83.9, 14.8; IR (KBr): v= 2214 (vw), 1651 (s), 1458 (m), 1304 (m), 1242 (w), 1034 (w), 918 (m), 756 (m) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{10}$ O_2S^+: 243.0474; found: 243.0480.

4-Methyl-3-(4-phenylbut-1-yn-1-yl)thiophene-2-carboxylic acid (**1k**). Yield: 585 mg, 87% based on methyl 4-methyl-3-(4-phenylbut-1-yn-1-yl)thiophene-2-carboxylate. Yellow solid, mp = 108-110 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.52-7.45 (m, 1 H), 7.37-7.25 (m, 4 H), 7.25-7.15 (m, 1 H), 2.95-2.74 (m, 4 H), 2.06 (s, 3 H); ^{13}CNMR (DMSO-d_6, 300 MHz): δ= 162.1, 141.3, 140.3, 133.6, 128.5, 128.1, 127.7, 126.9, 126.1, 98.5, 75.5, 34.1, 21.1, 14.7; IR (KBr): v= 2230 (w), 1682 (s), 1651 (s), 1543 (w), 1458 (m), 1288 (m), 1211 (w), 1072 (w), 926 (w), 864 (w), 787 (m), 733 (m), cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{16}H_{15}O_2S^+$: 271.0787; found: 271.0792.

2-(Phenylethynyl)thiophene-3-carboxylic acid (**6**). Yield: 560 mg, 98% based on Methyl 2-(phenylethynyl)thiophene-3-carboxylate. Yellow solid, mp = 122.5-125.2 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.30 (s, 1 H), 7.66 (d, *J* = 5.3, 1 H), 7.61-7.51 (m, 2 H), 7.51-7.40 (m, 4 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ= 162.9, 135.6, ,131.2, 129.3, 129.0, 128.8, 127.8, 127.4, 121.8, 98.0, 82.0; IR (KBr): v= 2199 (vw), 1667 (s), 1528 (m), 1443 (m), 1304 (s), 1258 (m), 1165 (w), 1072 (w), 926 (s), 756 (s), 733 (s) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_9O_2S^+$: 229.0318; found: 229.0318.

2nd Step: Hydrolysis of Methyl 3-Alkynylpicolinate and Methyl 3-Phenylisonicotinate to Give 3-Alkynylpicolinic Acids 3a-f and of 3-(Phenylethynyl)isonicotinic Acid 22. To a stirred solution of the methyl 3-alkynylpicolinate [4.0 mmol; methyl 3-(phenylethynyl)picolinate, 958 mg; methyl 3-(*p*-tolylethynyl)picolinate, 1.00 g; methyl 3-(4-phenylbut-1-yn-yl)picolinate, 1.05 g; methyl 3-((3-chlorophenyl)ethynyl)picolinate, 1.08 g; methyl 3-(3,3-dimethylbut-1-ynyl)picolinate, 875 mg] or methyl 3-(phenylethynyl)isonicotinate (4.0 mmol, 960 mg) in MeOH (26.5 mL) was added a solution of KOH (3.3 N in H_2O, 6 mL) at 0°C with stirring. After stirring at 0 °C for 15 min, the mixture was allowed to warm up to room temperature and then stirred for additional 2 h. The solution was then cooled with the aid of an ice bath, and neutralized with 1 N HCl until pH=3. The resulting mixture was extracted with AcOEt (3 × 50 mL), and the collected organic layers were dried over Na_2SO_4. Filtration and evaporation of the solvent (at 20 °C, under vacuum) afforded the crude products, which were further purified by crystallization with Et_2O/hexane.

3-(Phenylethynyl)picolinic acid (**3a**). Yield: 850 mg, 95% based on methyl 3-(phenylethynyl)picolinate. Yellow solid, mp = 110-112 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.65 (dd, *J* = 6.0, 1.4, 1 H), 8.13 (dd, *J* = 7.9, 1.4, 1 H), 7.66-7.53 (m, 3 H), 7.53-7.43 (m, 3 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ = 166.4, 151.8, 148.2, 140.7, 131.3, 129.3, 128.8, 125.2, 121.8, 117.6, 95.5, 85.2; IR (KBr): v = 2218 (w), 1748 (s), 1639 (m), 1493 (m), 1431 (m), 1072 (m), 930 (w), 841 (w), 760 (s), 691 (m) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{10}NO_2^+$: 224.0706; found: 224.0703. The spectroscopic data agreed with those reported.[10]

3-(p-Tolylethynyl)picolinic acid (**3b**). Yield: 856 mg, 90% based on Methyl 3-(*p*-tolylethynyl)picolinate. Brown solid, mp = 108-110 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.64 (s, br, 1 H), 8.16-8.04 (m, 1 H), 7.67-7.55

(m, 1 H), 7.52-7.39 (m, 2 H), 7.35-7.20 (m, 2 H), 2.36 (s, 3 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ = 167.0, 152.2, 148.5, 141.1, 139.7, 131.8, 129.9, 125.7, 119.3, 118.3, 96.3, 85.2, 21.5; IR (KBr): ν = 2222 (w), 1744 (s), 1636 (m), 1512 (m), 1335 (m), 1312 (s), 1204 (w), 810 (s), 687 (m) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{11}NO_2^+$: 238.0862; found: 238.0870.

3-(4-Phenylbut-1-yn-1-yl)picolinic acid (**3c**). Yield: 954 mg, 95% based on methyl 3-(4-phenylbut-1-yn-yl)picolinate. Brown solid, mp = 83-84 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.52 (m, 1 H), 7.85 (m, 1 H), 7.48 (s, br, 1 H), 7.40-7.11 (m, 6 H), 2.95-2.62 (m, 4 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ = 166.9, 152.9, 147.4, 140.6, 140.3, 128.5, 128.2, 126.2, 124.7, 117.7, 96.9, 77.1, 34.0, 21.2; IR (KBr): ν = 2222 (w), 1736 (s), 1497 (m), 1450 (m), 1427 (m), 1327 (s), 1242 (w), 1103 (w), 810 (s), 748 (m), 694 (m) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_{14}NO_2^+$: 252.1019; found: 252.1020.

3-((3-Chlorophenyl)ethynyl)picolinic acid (**3d**). Yield: 966 mg, 94% based on methyl 3-((3-chlorophenyl)ethynyl)picolinate. Brown solid, mp = 120-121 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.71-8.62 (m, 1 H), 8.14 (d, *J* = 7.33, 1 H), 7.70-7.42 (m, 5 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ =166.3, 151.8, 148.5, 140.9, 133.4, 130.8, 130.7, 130.0, 129.4, 125.3, 123.8, 117.3, 93.9, 86.7; IR (KBr): ν= 2222 (vw), 1736 (s), 1474 (m), 1335 (s), 1108 (s), 810 (m), 779 (m), 679 (s) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_9ClNO_2^+$: 258.0363; found: 258.0368.

3-(3,3-Dimethylbut-1-yn-1-yl)picolinic acid (**3e**). Yield: 750 mg, 92% based on methyl 3-(3,3-dimethylbut-1-yn-yl)picolinate. Yellow solid, mp = 97-99 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.53 (d, *J* = 3.4, 1 H), 7.88 (d, *J* = 6.9, 1 H), 7.56-7.42 (m, 1 H), 1.29 (s, 9 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ = 166.7, 152.6, 147.4, 140.2, 124.8, 117.8, 105.1, 74.9, 30.2, 27.8; IR (KBr): ν = 2253 (w), 1697 (s), 1450 (m), 1381 (w), 1273 (m), 1196 (m), 1142 (m), 926 (m), 810 (s) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{12}H_{14}NO_2^+$: 204.1019; found: 204.1015.

3-(Phenylethynyl)isonicotinic acid (**22**). Yield: 848 mg, 95% based on methyl 3-(phenylethynyl)isonicotinate. Brown solid, mp = 120-123 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.93 (s, br, 1 H), 8.79-8.65 (m, 1 H), 7.90-7.78 (m, 1 H), 7.71-7.35 (m, 5 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ = 165.9, 153.6, 149.2, 140.1, 131.4, 129.3, 128.8, 122.8, 121.9, 117.6, 96.0, 85.4; IR (KBr): ν= 2222 (w), 1736 (s), 1489 (w), 1281 (s), 1219 (s), 1065 (m), 795 (m), 718 (m) cm^{-1}; HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{10}NO_2^+$: 224.0706; found: 224.0710.

Preparation of Ionic Liquids. 1-Ethyl-3-methylimidazolium ethyl sulfate (EmimEtSO$_4$), and *N*-ethyl-*N*-methylmorpholinium dicyanamide [Mor$_{1,2}$N(CN)$_2$] were prepared according to literature procedures.[2]

General Procedure for the Iodolactonization of 3-Alkynylthiophene-2-Carboxylic Acids 1a-k and 2-(Phenylethynyl)thiophene-3-carboxylic Acid 6 in MeCN for the Synthesis of 4-Iodo-7*H*-thieno[2,3-*c*]pyran-7-ones 2a-k and 7-Iodo-6-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one 7, Respectively (Table 1 and Scheme 3). To a solution of **1** (0.25 mmol) (**1a**, 57 mg; **1b**, 61 mg; **1c**, 65 mg; **1d**, 66 mg; **1e**, 59 mg; **1f**, 58.0 mg; **1g**, 52 mg; **1h**, 64 mg; **1i**, 52 mg; **1j**, 61 mg; **1k**, 68 mg) or **6** (0.25 mmol, 56 mg) in MeCN (5 mL) were added NaHCO$_3$ (42 mg, 0.5 mmol) and I$_2$ (127 mg, 0.5 mmol) in this order under nitrogen. The mixture was allowed to stir at 40 °C for 2 h (**1b,c**) or 3h (**1a**, **1d-f**, **6**) or at 25°C for 3h (**1g**) or 5 h(**1h-k**). Saturated aqueous Na$_2$S$_2$O$_3$ (7 mL) was then added, and the mixture was allowed to stir for 10 min. The phases were separated, and the aqueous phase was extracted with Et$_2$O (3 × 10 mL). The collected organic layers were dried over Na$_2$SO$_4$. After filtration and evaporation of the solvent, products **2a−k** and **7** were purified by column chromatography on silica gel using 99:1 hexane−AcOEt as the eluent.

4-Iodo-5-phenyl-7H-thieno[2,3-c]pyran-7-one (**2a**). Yield: 66 mg, starting from 57 mg of **1a** (75%) (Table 1, entry 3). White solid, mp = 149-150 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.87 (d, *J* = 5.2, 1 H), 7.76-7.68 (m, 2 H), 7.51-7.43 (m, 3 H), 7.40 (d, *J* = 5.2, 1 H); ^{13}CNMR (CDCl$_3$, 75 MHz): δ = 157.6, 156.3, 150.1, 135.7, 133.9, 130.3, 130.1, 129.9, 128.1, 121.5, 67.4; IR (KBr): ν = 1717 (s), 1493 (w), 999 (w), 899 (w), 764 (m), 691 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 354 (M$^+$, 100), 326 (32), 227 (10), 199 (49), 171 (46), 77 (56); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_8IO_2S^+$: 354.9284; found: 354.9276. The spectroscopic data agreed with those reported.[11]

4-Iodo-5-(p-tolyl)-7H-thieno[2,3-c]pyran-7-one (**2b**). Yield: 64 mg, starting from 61 mg of **1b** (70%) (Table 1, entry 6). White solid, mp = 153-155 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.85 (d, *J* = 5.2, 1 H), 7.64 (d, *J* = 7.9, 2 H), 7.40 (d, *J* = 5.1, 1 H), 7.27 (d, *J* = 7.9, 2 H), 2.43 (s, 3 H, Me); ^{13}CNMR (CDCl$_3$, 75 MHz): δ = 157.7, 156.6, 150.2, 140.7, 135.5, 131.0, 130.1, 129.8, 128.8, 121.4, 67.0, 21.5; IR (KBr): ν = 1724 (s), 1578 (w), 1504 (m), 1427 (w), 1007 (m), 903 (w), 768 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 368 (M$^+$, 100), 340 (39), 241 (12), 213 (48), 185 (24); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{10}IO_2S^+$: 368.9441; found: 368.9438.

4-Iodo-5-(4-methoxyphenyl)-7H-thieno[2,3-c]pyran-7-one (**2c**). Yield: 70 mg, starting from 65 mg of **1c** (73%) (Table 1, entry 7). White solid, mp = 166-167 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.85 (d, *J* = 5.2, 1 H), 7.71 (d, *J* = 8.8, 2 H), 7.39 (d, *J* = 5.2, 1 H), 6.97 (d, *J* = 8.8, 2 H), 3.87 (s, 3 H); ^{13}CNMR (CDCl$_3$, 75 MHz): δ = 161.0, 157.8, 156.3, 150.4, 135.5, 131.5, 130.1, 126.2, 121.2, 113.5, 66.6, 55.4; IR (KBr): ν = 1717 (s), 1504 (m), 1258 (m), 1177 (w), 829 (m), 764 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 384 (M$^+$, 100), 356 (38), 341 (10), 313 (18), 257 (10), 229 (32); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{10}IO_3S^+$: 384.9317; found: 384.9385.

5-(3-Chlorophenyl)-4-Iodo-7H-thieno[2,3-c]pyran-7-one (**2d**). Yield: 68 mg, starting from 66 mg of **1d** (70%) (Table 1, entry 8). White solid, mp = 181-182 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): *δ* = 8.41-8.35 (m, 1 H), 7.82-7.76 (m, 1 H), 7.72-7.65 (m, 1 H), 7.65-7.54 (m, 2 H), 7.49-7.43 (m, 1 H); ^{13}CNMR (DMSO-d_6, 75 MHz): *δ* = 156.7, 154.0, 150.0, 138.1, 135.9, 132.7, 130.2, 130.0, 129.8, 129.4, 128.5, 121.0, 69.9; IR (KBr): ν = 1713 (s), 1574 (m), 1080 (w), 1011 (m), 918 (m), 764 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 390 [(M+2)$^+$, 38], 388 (M$^+$, 100), 360 (25), 325 (47), 261 (13), 233 (31), 205 (36); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_7ClIO_2S^+$: 388.8894; found: 388.8910.

4-Iodo-5-(thiophen-3-yl)-7H-thieno[2,3-c]pyran-7-one (**2e**). Yield: 67 mg, starting from 59 mg of **1e** (74%) (Table 1, entry 9). White solid, mp =127-128 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 8.08 (dd, *J* = 3.0, 1.3, 1 H), 7.84 (d, *J* = 5.2, 1 H), 7.68 (distorted dd, *J* = 5.0, 1.3, 1 H), 7.43-7.33 (m, 2 H); ^{13}CNMR (CDCl$_3$, 75 MHz): δ = 157.2, 151.9, 150.3, 135.5, 134.1, 130.3, 129.2, 128.3, 125.4, 121.2, 66.2; IR (KBr): ν = 1721 (s), 1574 (m), 1501 (w), 1076 (w), 999 (m), 768 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 360 (M$^+$, 100), 332 (29), 233 (12), 205 (57), 177 (43); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{11}H_6IO_2S_2^+$: 360.8848; found: 360.8841.

5-(Cyclohex-1-en-1-yl)-4-Iodo-7H-thieno[2,3-c]pyran-7-one (**2f**). Yield: 81 mg, starting from 58 mg of **1f** (91%) (Table 1, entry 10). Yellow solid, mp = 103-104 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.83 (d, *J* = 5.2, 1 H), 7.32 (d, *J* = 5.2, 1 H), 6.27-6.19 (m, 1 H), 2.38-2.28 (m, 2 H), 2.28-2.17 (m, 2 H), 1.83-1.64 (m, 4 H); ^{13}CNMR (CDCl$_3$, 75 MHz): δ = 158.8, 157.9, 150.1, 135.5, 135.4, 132.5, 130.0, 121.0, 66.0, 26.5, 25.1, 22.2, 21.5; IR (KBr): ν = 1728 (s), 1574 (m), 1427 (m), 1034 (m), 995 (w), 772 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 358 (M$^+$, 100), 329 (16), 304 (32), 277 (6), 231 (32), 203 (36); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_{12}IO_2S^+$: 358.9597; found: 358.9583.

5-Butyl-4-Iodo-7H-thieno[2,3-c]pyran-7-one (**2g**). Yield: 57 mg, starting from 52 mg of **1g** (68%) (Table 1, entry 12). Yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.82 (d, *J* = 5.2, 1 H), 7.26 (d, *J* = 5.2, 1 H), 2.87 (t, *J* = 7.7, 2 H), 1.78-1.64 (m, 2 H), 1.51-1.38 (m, 2 H), 0.96 (t, *J* = 7.3, 3 H);

^{13}CNMR ($CDCl_3$, 75 MHz): δ = 160.1, 158.2, 149.7, 135.7, 129.1, 120.7, 67.6, 35.7, 29.5, 22.2, 13.8; IR (film): ν = 1724 (s), 1585 (m), 1427 (m), 1099 (w), 999 (m), 772 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 334 (M^+, 74), 291 (12), 263 (18), 165 (100), 137 (97); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{11}H_{12}IO_2S^+$: 339.9597; found: 334.9627. The spectroscopic data agreed with those reported.[11]

4-Iodo-5-phenethyl-7H-thieno[2,3-c]pyran-7-one (**2h**). Yield: 70 mg, starting from 64 mg of **1h** (73%) (Table 1, entry 13). Yellow solid, mp = 82-84 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.82 (d, *J* = 5.2, 1 H), 7.33-7.17 (m, 6 H), 3.19-3.10 (m, 2 H), 3.07-2.98 (m, 2 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.6, 157.9, 149.5, 139.8, 135.7, 129.1, 128.6, 128.4, 126.5, 120.9, 68.2, 38.0, 33.5; IR (KBr): ν = 1726 (s), 1589 (m), 1426 (m), 1099 (w), 769 (m), 699 (w) cm^{-1}; GC-MS (EI, 70 eV): m/z = 382 (M^+, 13), 291 (3), 255 (10), 227 (3), 136 (5), 91 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{12}IO_2S^+$: 382.9597; found: 382.9577.

5-(tert-Butyl)-4-Iodo-7H-thieno[2,3-c]pyran-7-one (**2i**). Yield: 54 mg, starting from 52 mg of **1i** (65%) (Table 1, entry 14). Yellow solid, mp = 50-51 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.80 (d, *J* = 5.2, 1 H), 7.43 (d, *J* = 5.2, 1 H), 1.58 (s, 9 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 163.8, 157.4, 151.5, 134.7, 130.4, 120.5, 64.6, 38.7, 29.0; IR (KBr): ν = 1728 (s), 1551 (m), 1504 (w), 1427 (m), 1092 (m), 1042 (m), 1003 (m), 937 (w), 845 (w), 768 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 334 (M^+, 100), 319 (25), 291 (18), 277 (38), 249 (19), 207 (58), 192 (16), 165 (56), 164 (57); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{11}H_{12}IO_2S^+$: 334.9597; found: 334.9589.

4-Iodo-3-methyl-5-phenyl-7H-thieno[2,3-c]pyran-7-one (**2j**). Yield: 69 mg, starting from 61 mg of **1j** (75%) (Table 1, entry 15). White solid, mp = 163-164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64-7.57 (m, 2 H), 7.56-7.52 (m, 1 H), 7.50-7.44 (m, 3 H), 2.67 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 158.0, 156.4, 144.5, 137.2, 135.3, 134.7, 130.1, 130.0, 128.2, 124.9, 66.3, 19.4; IR (KBr): ν = 1713 (s), 1443 (w), 1381 (w), 1072 (m), 1003 (w), 764 (m), 694 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 368 (M^+, 100), 340 (39), 241 (12), 213 (41), 185 (25), 184 (21); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_{10}IO_2S^+$: 368.9441; found: 368.9436.

4-Iodo-3-methyl-5-phenethyl-7H-thieno[2,3-c]pyran-7-one (**2k**). Yield: 95 mg, starting from 68 mg of **1k** (96%) (Table 1, entry 16). Yellow solid, mp = 84-86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50-7.45 (m, 1 H), 7.36-7.19 (m, 5 H), 3.30-3.17 (m, 2 H), 3.08-2.97 (m, 2 H), 2.62 (s, 3 H, Me); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.4, 157.9, 144.2, 140.0, 136.6, 134.7, 128.6, 128.4, 126.5, 124.1, 66.8, 39.0, 33.4, 19.2; IR (KBr): ν = 1728 (s), 1574 (m), 1450 (m), 1389 (w), 1026 (m), 748 (m), 702 (w) cm^{-1}; GC-MS (EI, 70 eV): m/z = 396 (M^+, 36), 305 (14), 277 (12), 269 (6), 241 (5), 150 (8), 91 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{16}H_{14}IO_2S^+$: 396.9754; found: 396.9751.

7-Iodo-6-phenyl-4H-thieno[3,2-c]pyran-4-one (**7**). Yield: 58 mg, starting from 56 mg of **6** (65%) (Scheme 3). White solid, mp = 124-126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.88 (d, *J* = 5.4, 1 H), 7.79-7.72 (m, 2 H), 7.51-7.44 (m, 3 H), 7.43 (d, *J* = 5.4, 1 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 157.8, 155.6, 133.4, 130.5, 129.8, 128.2, 127.2, 126.0, 122.6, 63.9; IR (KBr): ν = 1728 (s), 1562 (w), 1489 (w), 1053 (m), 976 (m), 895 (w), 772 (m), 698 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 354 (M^+, 100), 326 (24), 227 (7), 199 (42), 171 (33), 77 (49); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{13}H_8IO_2S^+$: 354.9284; found: 354.9283. The spectroscopic data agreed with those reported.[12]

5-Butyl-7H-thieno[2,3-c]pyran-7-one (**5**). Yield: 5 mg, starting from 52 mg of **1g** (10%) (Table 1, entry 12). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.80 (d, *J* = 5.1, 1 H), 7.12 (d, *J* = 5.1, 1 H), 6.45 (s, 1 H), 2.56 (t, *J* = 7.6, 2 H), 1.69 (quint, *J* = 7.5, 2 H), 1.39 (hexuplet, *J* = 7.5, 2 H), 0.94 (t, *J* = 7.3, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 161.0, 159.2, 147.6, 136.5, 124.2, 122.1, 100.5, 33.2, 29.2, 22.1, 13.8; IR (film): ν = 1717 (s), 1628 (m), 1524 (w), 1439 (m), 1099 (w), 999 (m), 837 (w), 772 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 208 (M^+, 27), 166 (24), 151 (13), 137 (19), 124 (100), 95 (28); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{11}H_{13}O_2S^+$: 209.0631; found: 209.0624. The spectroscopic data agreed with those reported.[11]

Typical Procedure for the Iodolactonization of 3-Alkynylthiophene-2-Carboxylic Acids 1 in MeCN in larger scale. To a solution of **1** (2.2 mmol; **1a**, 502 mg; **1b**, 533 mg; **1e**, 515 mg) in MeCN (44 mL) were added $NaHCO_3$ (370 mg, 4.4 mmol) and I_2 (1.12 g, 4.4 mmol) in this order under nitrogen. The mixture was allowed to stir at 40 °C for 2 h (**1b**) or 3 h (**1a** and **1e**). Saturated aqueous $Na_2S_2O_3$ (50 mL) was then added, and the mixture was allowed to stir for 10 min. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 80 mL). The collected organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, products **2** were purified by column chromatography on silica gel using 99:1 hexane−AcOEt as the eluent to give 4-iodo-5-phenyl-7*H*-thieno[2,3-*c*]pyran-7-one (**2a**; 723 mg, 93%); 4-iodo-5-(*p*-tolyl)-7*H*-thieno[2,3-*c*]pyran-7-one (**2b**; 730 mg, 90%); 4-iodo-5-(thiophen-3-yl)-7*H*-thieno[2,3-*c*]pyran-7-one (**2e**; 704 mg, 89%).

General Procedure for the Iodolactonization of 3-Alkynylpicolinic Acids 3a-e and of 3-(Phenylethynyl)isonicotinic acid 22 in MeCN for the Synthesis of 5-iodo-8*H*-pyrano[3,4-*b*]pyridin-8-ones 4a-e and of 4-Iodo-3-phenyl-1*H*-pyrano[4,3-*c*]pyridin-1-one 23, Respectively (Table 3 and Scheme 4). To a solution of **3** (0.35 mmol) (**3a**, 78 mg; **3b**, 83 mg; **3c**, 88 mg; **3d**, 90 mg; **3e**, 72 mg) or **22** (0.35 mmol, 79 mg) in MeCN (7 mL) were added $NaHCO_3$ (88 mg, 1.05 mmol) and I_2 (267 mg, 1.05 mmol) in this order under nitrogen. The mixture was allowed to stir at 25 °C for 1 h. Saturated aqueous $Na_2S_2O_3$ (10 mL) was then added, and the mixture was allowed to stir for 10 min. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 15 mL). The collected organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, products **4a−e** and **23** were purified by column chromatography on silica gel using 99:1 hexane−AcOEt as the eluent.

5-Iodo-6-phenyl-8H-pyrano[3,4-b]pyridin-8-one (**4a**). Yield: 86 mg, starting from 78 mg of **3a** (70%) (Table 3, entry 3). Yellow solid, mp = 204-206 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.57 (d, *J* = 3.1, 1 H), 8.26 (d, *J* = 6.0, 1 H), 7.81-7.66 (m, 3 H), 7.56-7.41 (m, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 159.2, 155.7, 151.5, 139.8, 136.9, 135.9, 134.2, 130.6, 129.9, 129.6, 128.2, 73.8; IR (KBr): ν = 1740 (s), 1269 (w), 1180 (w), 1072 (m), 945 (m), 806 (w), 756 (w), 702 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 349 (M^+, 100), 321 (51), 222 (10), 194 (36), 166 (76), 139 (33), 105 (31), 77 (41); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_9INO_2^+$: 349.9672; found: 349.9676. The spectroscopic data agreed with those reported.[11]

5-Iodo-6-(p-tolyl)-8H-pyrano[3,4-b]pyridin-8-one (**4b**). Yield: 84 mg, starting from 83 mg of **3b** (66%) (Table 3, entry 4). Yellow solid, mp = 204-206 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.85 (d, *J* = 4.0, 1 H), 8.25 (d, *J* = 8.2, 1 H), 7.75 (dd, *J* = 8.2, 4.0, 1 H), 7.63 (d, *J* = 7.8, 2 H), 7.28 (d, *J* = 7.8, 2 H), 2.44 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 159.4, 155.8, 151.4, 141.0, 139.8, 136.8, 136.0, 131.4, 129.9, 129.6, 128.8, 73.4, 21.6; IR (KBr): ν = 1751 (s), 1508 (m), 1454 (w), 1180 (w), 1069 (m), 945 (m), 810 (m), 756 (m) cm^{-1}; GC-MS (EI, 70 eV): m/z = 363 (M^+, 89), 335 (100), 236 (13), 208 (62), 180 (74), 179 (13), 152 (32); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_{11}INO_2^+$: 363.9829; found: 363.9828.

5-Iodo-6-phenethyl-8H-pyrano[3,4-b]pyridin-8-one (**4c**). Yield: 86 mg, starting from 88 mg of **3c** (65%) (Table 3, entry 5). Yellow solid, mp = 101-105 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.79 (d, *J* = 4.2, 1 H), 8.09 (d, *J* = 8.2, 1 H), 7.87 (dd, *J* = 8.2, 4.2, 1 H), 7.35-7.14 (m, 5 H), 3.23-3.07 (m, 2 H), 3.04-2.89 (m, 2 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ = 158.4, 157.1, 150.8, 139.8, 138.4, 136.2, 135.1, 130.0, 128.4, 128.2, 126.2, 75.3, 32.4; IR (KBr): *ν* = 1748 (s), 1582 (m), 1454 (m), 1308 (w), 1084 (m), 988 (w), 752 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 377 (M^+, 10), 250 (5), 91 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{16}H_{13}INO_2^+$: 377.9985; found: 377.9996.

6-(3-Chlorophenyl)-5-iodo-8H-pyrano[3,4-b]pyridin-8-one (**4d**). Yield: 67 mg, starting from 90 mg of **3d** (50%) (Table 3, entry 6). Grey solid, mp = 231-233 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.91-8.82 (m, 1 H), 8.26 (d, J = 9.0, 1 H), 8.00-7.91 (m, 1 H), 7.78 (s, br, 1 H), 7.72-7.55 (m, 3 H); ^{13}CNMR (DMSO-d_6, 75 MHz): δ = 158.2, 153.2, 151.4, 139.4, 136.8, 135.2, 132.7, 130.2, 130.1, 129.4, 128.5, 76.2; IR (KBr): *v* = 1744 (s), 1586 (w), 1474 (w), 1408 (w), 1180 (m), 1072 (m), 953 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 383 (M$^+$, 100), 355 (42), 320 (13), 228 (15), 200 (60), (24); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_8ClINO_2^+$: 383.9283; found: 383.9272.

6-(tert-Butyl)-5-iodo-8H-pyrano[3,4-b]pyridin-8-one (**4e**). Yield: 61 mg, starting from 72 mg of **3e** (53%) (Table 3, entry 8). Brown solid, mp = 120-122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.87 (s, br, 1 H), 8.35 (d, *J* = 6.0, 1 H), 7.70 (s, br, 1 H), 1.63 (s, 9 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 163.3, 159.2, 151.3, 139.5, 136.62, 136.59, 129.3, 71.3, 39.2, 29.0; IR (KBr): *v* = 1755 (s), 1574 (m), 1454 (w), 1265 (w), 1076 (m), 960 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 329 (M$^+$, 83), 244 (20), 202 (72), 174 (30), 160 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{12}H_{13}INO_2^+$: 329.9985; found: 329.9989.

4-Iodo-3-phenyl-1H-pyrano[4,3-c]pyridin-1-one (**23**). Yield: 85 mg, starting from 79 mg of **22** (70%) (Scheme 4). Brown solid, mp = 178.3-180.1 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.15 (s, br, 1 H), 8.95-8.85 (m, 1 H), 8.02-7.93 (m, 1 H), 7.25-7.63 (m, 2 H), 7.63-7.48 (m, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 160.3, 155.9, 153.7, 150.2, 135.1, 131.7, 130.8, 130.2, 128.7, 126.7, 120.6, 72.9; IR (KBr): *v* = 1748 (s), 1408 (w), 1238 (m), 1076 (m), 1003 (w), 853 (w), 752 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 349 (M$^+$, 100), 321 (46), 222 (36), 194 (48), 166 (68), 139 (70), 105 (50), 77 (84); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_9INO_2^+$: 349.9672; found: 349.9695.

(E)-5-((3-chlorophenyl)iodomethylene)furo[3,4-b]pyridin-7(5H)-one (**20**). Yield: 22 mg, starting from 90 mg of **3d** (16%) (Table 3, entry 6). Yellow solid, mp = 205-207 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.26 (d, *J* = 8.2, 1 H), 8.98 (d, *J* = 4.4, 1 H), 7.74 (dd, *J* = 7.7, 4.3, 1 H), 7.54 (s, br, 1 H), 7.50-7.40 (m, 1 H), 7.40-7.30 (m, 1 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 162.9, 153.6, 144.5, 142.6, 140.7, 134.1, 133.7, 132.9, 130.1, 129.5, 128.3, 127.4, 81.1; IR (KBr): *v* = 1778 (s), 1408 (w), 1107 (m), 1007 (s), 868 (w), 764 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 283 (M$^+$, 15), 256 (100), 228 (25), 200 (41), 165 (21); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{14}H_8ClINO_2^+$: 383.9283; found: 383.9298.

(E)-5-(1-Iodo-2,2-dimethylpropylidene)furo[3,4-b]pyridin-7(5H)-one (**21**). Yield: 29 mg, starting from 72 mg of **3e** (25%) (Table 3, entry 8). Yellow solid, mp = 135-136 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.41-9.26 (m, 1 H), 8.95-8.80 (m, 1 H), 7.67-7.56 (m, 1 H), 1.52 (s, 9 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 163.0, 152.6, 144.1, 141.1, 135.1, 133.8, 126.9, 106.3, 41.0, 32.4; IR (KBr): *v* = 1790 (s), 1474 (m), 1404 (w), 1099 (w), 1015 (m), 818 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 329 (M$^+$, 37), 273 (44), 202 (100), 187 (48), 159 (19), 130 (33); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{12}H_{13}INO_2^+$: 329.9985; found: 329.9995.

Typical Iodolactonization Procedure of 3-(Phenylethynyl)picolinic acid in MeCN in Larger Scale. To a solution of 3-(phenylethynyl)picolinic acid **3a** (2.2 mmol, 490 mg) in MeCN (44 mL) were added $NaHCO_3$ (6.6 mmol, 555 mg) and I_2 (1.67 g, 6.6 mmol) in this order under nitrogen. The mixture was allowed to stir at 25 °C for 1 h. Saturated aqueous $Na_2S_2O_3$ (50 mL) was then added, and the mixture was allowed to stir for 10 min. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 80 mL). The collected organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, product 5-iodo-6-phenyl-8*H*-pyrano[3,4-*b*]pyridin-8-one **4a** was purified by column chromatography on silica gel using 99:1 hexane−AcOEt as the eluent (yield: 576 mg, 75%).

Typical procedure for the Iodolactonization of 3-[(3-Chlorophenyl)ethynyl]picolinic Acid 3d in EmimEtSO$_4$ for the Synthesis of 6-(3-Chlorophenyl)-5-iodo-8*H*-pyrano[3,4-*b*]pyridin-8-one 4d (Table 3, Entry 7). In a Schlenk flask containing $EmimEtSO_4$ (2 mL) was added, under nitrogen, 3-((3-chlorophenyl)ethynyl)picolinic acid **3d** (0.40 mmol; 103 mg). To the solution of the substrate in the IL, was added, under nitrogen, I_2 (152 mg, 0.6 mmol), and the resulting mixture was heated with stirring at 50 °C (oil bath) for 3 h. After cooling, the product was extracted with diethyl ether (3 mL, followed by 6 × 4 mL). The collected ethereal phases were concentrated. After evaporation of the solvent, product 6-(3-chlorophenyl)-5-iodo-8*H*-pyrano[3,4-*b*]pyridin-8-one **4d** was purified by column chromatography on silica gel using 95:5 hexane–AcOEt as the eluent (yield: 97 mg, 63%).

Typical procedure for the Iodolactonization of 3-(3,3-Dimethylbut-1-yn-1-yl)picolinic Acid 3e in Mor$_{1,2}$N(CN)$_2$ for the Synthesis of (*E*)-5-(1-Iodo-2,2-dimethylpropylidene)furo[3,4-*b*]pyridin-7(5*H*)-one 21 (Table 3, Entry 10). In a Schlenk flask containing $Mor_{1,2}N(CN)_2$ (2 mL) was added, under nitrogen, 3-(3,3-dimethylbut-1-yn-1-yl)picolinic acid **3e** (0.40 mmol; 81 mg). To the solution of the substrate in the IL, was added, under nitrogen, I_2 (151 mg, 0.6 mmol), and the resulting mixture was heated with stirring at 50 °C (oil bath) for 3 h. After cooling, the product was extracted with diethyl ether (3 mL, followed by 6 × 4 mL). The collected ethereal phases were concentrated. After evaporation of the solvent, product (*E*)-5-(1-Iodo-2,2-dimethylpropylidene)furo[3,4-*b*]pyridin-7(5*H*)-one **21** was purified by column chromatography on silica gel using 95:5 hexane–AcOEt as the eluent (yield: 76 mg, 58%).

General Procedure for the Sonogashira Coupling Between 4-Iodo-7*H*-thieno[2,3-*c*]pyran-7-ones 2 and Terminal Alkynes (Table 2). A solution of 4-iodo-7*H*-thieno[2,3-c]pyran-7-one (0.3 mmol; **2a**, 106 mg; **2b**, 110 mg; **2e**, 108 mg; **2g**, 100 mg; **2j**, 110 mg), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (4 mg, 0.018 mmol), the terminal alkyne (0.66 mmol; phenylacetylene, 68 mg; 1-ethynyl-4-methylbenzene, 77 mg; 3-ethynylthiophene, 71 mg; 1-hexyne, 54 mg; but-3-yn-1-ylbenzene, 86 mg) in anhydrous diisopropylamine (3 mL) was allowed to stir under nitrogen at 70 °C (oil bath) for 24 h. After cooling to room temperature, AcOEt (8 mL) was added, and the mixture was washed with water (3 × 10 mL). The organic layer was washed with a saturated solution of NH_4Cl (1x10 mL) and then water until pH=7. After drying over Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane-AcOEt (9:1) as eluent.

5-Phenyl-4-(phenylethynyl)-7H-thieno[2,3-c]pyran-7-one (**8**). Yield: 87 mg, starting from 106 mg of **2a** (88%). Yellow solid, mp = 105.8-108.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.27-8.18 (m, 2 H), 7.89 (d, *J* = 5.1, 1 H), 7.57-5.43 (m, 6 H), 7.42-7.34 (m, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.5, 156.9, 148.3, 136.8, 131.8, 131.3, 130.6, 128.9, 128.6, 128.4, 128.3, 125.3, 122.5, 121.9, 98.3, 96.6, 82.8; IR (KBr): v = 2210 (vw), 1732 (s), 1489 (m), 1447 (m), 1096 (w), 999 (m), 941 (w), 756 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 328 (M$^+$, 100), 299 (13), 271 (57), 239 (14); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{21}H_{13}O_2S^+$: 329.0631; found: 329.0641. The spectroscopic data agreed with those reported.[13]

5-(p-Tolyl)-4-(p-tolylethynyl)-7H-thieno[2,3-c]pyran-7-one (**9**). Yield: 80 mg, starting from 110 mg of **2b** (75%). Yellow solid, mp = 164-166.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.13 (d, *J* = 8.2, 2 H), 7.84 (d, *J* = 5.1, 1 H), 7.49 (d, *J* = 5.1, 1 H), 7.37 (distorted d, *J* = 8.0, 2 H), 8.27 (d, *J* = 8.2, 2 H), 7.16 (distorted d, *J* = 8.0, 2 H), 2.41 (s, 3 H), 2.37 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.4, 157.0, 148.6, 140.9, 139.1, 136.6, 131.2, 129.3, 129.1, 129.0, 128.2, 125.3, 121.5, 119.6, 97.8, 96.9, 82.4, 21.6, 21.5; IR (KBr): v= 2214 (vw), 1728 (s), 1504 (m), 1096 (w), 1072 (w), 1011 (m), 945 (w), 779 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 356 (M$^+$, 100), 341 (28), 313 (19), 285 (17); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{23}H_{17}O_2S^+$: 357.0944; found: 357.0964. The spectroscopic data agreed with those reported.[13]

4-(Hex-1-yn-1-yl)-5-(p-tolyl)-7H-thieno[2,3-c]pyran-7-one (**10**). Yield: 62 mg, starting from 110 mg of **2b** (64%). Yellow solid, mp = 85-86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.09 (d, *J* = 7.3, 2 H), 7.82 (d, *J* = 4.2, 1 H), 7.10 (d, *J* = 4.2, 1 H), 7.25 (d, *J* = 7.3, 2 H), 2.49 (t, *J* = 6.3, 2 H), 2.41 (s, 3 H), 1.70-1.55 (m, 2 H), 1.55-1.40 (m, 2 H), 0.96 (t, *J* = 6.6, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ =158.1, 157.2, 149.3, 140.6, 136.4, 129.2, 128.9, 128.1, 125.4, 121.5, 98.3, 73.9, 30.5, 22.1, 21.5, 19.5, 13.6; IR (KBr): v = 2226 (vw), 1732 (s), 1504 (m), 1435 (m), 1084 (m), 999 (m), 822 (w), 772 (m). cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 322 (M^+, 100), 293 (32), 280 (65), 265 (20), 251 (40), 208 (28), 119 (44), 91 (61); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{20}H_{19}O_2S^+$: 323.1100; found: 323.1114.

5-(Thiophen-3-yl)-4-(thiophen-3-ylethynyl)-7H-thieno[2,3-c]pyran-7-one (**11**). Yield: 75 mg, starting from 108 mg of **2e** (74%). Yellow solid, mp =110-112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.39-8.31 (m, 1 H), 8.00 (dd, *J* = 5.1, 1.2, 1 H), 7.85 (d, *J* = 5.1, 1 H), 7.64-7.53 (m, 1 H), 7.46 (d, *J* = 5.1, 1 H), 7.43-7.32 (m, 2 H), 7.29-7.17 (m, 1 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 156.6, 154.4, 148.4, 136.7, 133.5, 129.5, 129.4, 127.8, 126.9, 126.0, 125.8, 125.2, 121.5, 121.3, 96.7, 93.2, 82.5; IR (KBr): v = 2214 (vw), 1721 (s), 1582 (m), 1520 (m), 1080 (m), 1003 (w), 972 (w), 778 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 340 (M^+, 100), 311 (13), 283 (54), 251 (17); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{17}H_9O_2S_3^+$: 340.9759; found: 340.9756.

5-Butyl-4-(hex-1-yn-1-yl)-7H-thieno[2,3-c]pyran-7-one (**12**). Yield: 73 mg, starting from 100 mg of **2g** (84%). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.82 (d, *J* = 5.2, 1 H), 7.30 (d, *J* = 5.2, 1 H), 2.80 (t, *J* = 7.5, 2 H), 2.49 (t, *J* = 6.9, 2 H), 1.80-1.35 (m, 8 H), 1.03-0.91 (m, 6 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 164.3, 157.9, 148.3, 136.5, 124.6, 121.2, 99.5, 97.2, 72.5, 31.8, 30.8, 29.5, 22.2, 22.0, 19.3, 13.8, 13.6; IR (film): v = 2230 (vw), 1736 (s), 1597 (m), 1520 (w), 1435 (m), 1096 (w), 995 (m), 779 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 288 (M^+, 80), 259 (53), 245 (100), 203 (43), 189 (29), 161 (16), 147 (16), 115 (14), 89 (12); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{17}H_{29}O_2S^+$: 289.1257; found: 289.1295. The spectroscopic data agreed with those reported.[13]

3-Methyl-5-phenyl-4-(4-phenylbut-1-yn-1-yl)-7H-thieno[2,3-c]pyran-7-one (**13**). Yield: 73 mg, starting from 110 mg of **2j** (66%). Yellow solid, mp = 103.2-106.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.00-7.92 (m, 2 H), 7.47-7.33 (m, 4 H), 7.33-7.13 (m, 5 H), 2.87 (dist t, *J* = 7.3, 2 H), 2.71 (t, *J* = 7.3, 2 H), 2.51 (s, 3 H, Me); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 159.0, 157.5, 144.8, 140.2, 136.3, 133.2, 132.2, 130.0, 128.9, 128.5, 128.3, 127.9, 126.5, 123.6, 100.0, 97.3, 75.0, 34.2, 21.7, 16.5; IR (KBr): v = 2220 (vw), 1728 (s), 1582 (w), 1489 (m), 1450 (m), 1396 (w), 1072 (m), 995 (m), 748 (m), 694 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 370 (M^+, 100), 279 (97), 251 (58), 234 (7), 221 (27), 208 (25), 105 (37), 91 (22); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{24}H_{19}O_2S^+$: 371.1100; found: 371.1126.

General Procedure for the Suzuki Coupling Between 4-Iodo-7*H*-thieno[2,3-*c*]pyran-7-ones 2 and Arylboronic Acids (Table 2). A solution of the 4-iodo-7*H*-thieno[2,3-*c*]pyran-7-one **2** (0.3 mmol; **2a**, 107 mg; **2b**, 110 mg; **2e**, 109 mg; **2g**, 101 mg; **2j**, 110 mg), boronic acid (0.36 mmol; phenylboronic acid, 44 mg; furan-3-ylboronic acid, 40 mg; *p*-tolylboronic acid; 49 mg; thiophen-3-ylboronic acid, 46 mg), $Pd(PPh_3)_4$ (0.03 mmol, 35 mg), and Cs_2CO_3 (0.42 mmol; 136 mg) in anhydrous DMF (8.6 mL) was allowed to stir under nitrogen at 80 °C (oil bath) for 24 h. After cooling to room temperature, AcOEt (10 mL) and a saturated solution of NH_4Cl (10 mL) were added. The organic layer was washed with a saturated solution of NH_4Cl (3x10 mL) and then with brine (1X10 mL). After drying over Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane-AcOEt (9:1) as eluent.

4,5-Diphenyl-7H-thieno[2,3-c]pyran-7-one (**14**). Yield: 64 mg, starting from 107 mg of **2a** (70%). White solid, mp = 182-184 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.76 (d, *J* = 4.7, 1 H), 7.46-7.17 (m, 10 H), 6.96 (d, *J* = 4.7, 1 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.2, 153.4, 149.5, 136.3, 134.8, 132.3, 130.3, 129.3, 129.2, 129.1, 128.2, 128.0, 125.2, 122.8, 115.9; IR (KBr): v = 1721 (s), 1489 (m), 1443 (w), 1427 (w), 1080 (m), 1026 (m), 779 (m), 694 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 304 (M^+, 100), 276 (21), 227 (50), 215 (10), 199 (15), 171 (19), 105 (66), 77 (59); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{19}H_{13}O_2S^+$: 305.0631; found: 305.0626. The spectroscopic data agreed with those reported.[14]

4-(Furan-3-yl)-5-phenyl-7H-thieno[2,3-c]pyran-7-one (**15**). Yield: 56 mg, starting from 106 mg of **2a** (63%). White solid, mp = 181.8-184.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.82 (distorted d, *J* = 5.2, 1 H), 7.55-7.41 (m, 3 H), 7.41-7.21 (m, 4 H), 7.15 (distorted d, *J* = 5.2, 1 H), 6.32 (s, br, 1 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.0, 154.1, 149.3, 143.7, 141.4, 136.5, 132.4, 129.5, 129.2, 128.1, 125.0, 122.8, 118.8, 112.0, 106.9; IR (KBr): v = 1713 (s), 1435 (w), 1157 (w), 1011 (m), 872 (w), 772 (m), 702 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 294 (M^+, 100), 266 (41), 237 (57), 208 (35), 165 (30), 105 (31), 77 (58); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{17}H_{11}O_3S^+$: 295.0423; found: 295.0426.

4,5-di-p-Tolyl-7H-thieno[2,3-c]pyran-7-one (**16**). Yield: 60 mg, starting from 110 mg of **2b** (60%). White solid, mp =152-154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.74 (d, *J* = 5.1, 1 H), 7.33-7.07 (m, 6 H), 7.02 (d, *J* = 8.0, 2 H,), 6.95 (d, *J* = 5.1, 1 H), 2.40 (s, 3 H), 2.29 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.3, 153.4, 149.9, 139.3, 137.9, 136.0, 132.0, 130.1, 129.8, 129.6, 129.2, 128.7, 125.2, 122.5, 115.3, 21.3; IR (KBr): v = 1721 (s), 1504 (m), 1427 (w), 1080 (w), 1018 (m), 826 (m), 756 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 332 (M^+, 100), 304 (36), 289 (8), 261 (11), 241 (34), 213 (11), 119 (50), 91 (37); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{21}H_{17}O_2S^+$: 333.0944; found: 333.0948.

4,5-Di(thiophen-3-yl)-7H-thieno[2,3-c]pyran-7-one (**17**). Yield: 73 mg, starting from 109 mg of **2e** (77%). White solid, mp = 195-197 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.76 (d, *J* = 5.2, 1 H), 7.51 (distorted dd, *J* = 4.9, 2.9, 1 H), 7.43 (distorted dd, *J* = 2.9, 1.2, 1 H), 7.32 (distorted dd, *J* = 2.9, 1.2, 1 H), 7.15 (distorted dd, *J* = 5.2, 2.9, 1 H), 7.04 (dd, *J* = 5.2, 1.2, 1 H), 6.91 (d, *J* = 5.2, 1 H), 7.81 (dd, *J* = 5.2, 1.2, 1 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 157.7, 149.8, 149.7, 136.4, 134.4, 133.5, 128.8, 127.2, 126.9, 125.3, 125.0, 121.9, 109.7; IR (KBr): v = 1713 (s), 1597 (w), 1504 (w), 1165 (w), 1011 (m), 772 (s), 648 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 316 (M^+, 100), 288 (70), 259 (45), 227 (37), 111 (47); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{15}H_9O_2S_3^+$: 316.9759; found: 316.9782.

5-Butyl-4-phenyl-7H-thieno[2,3-c]pyran-7-one (**18**). Yield: 72 mg, starting from 101 mg of **2g** (85%). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.72 (d, *J* = 5.2, 1 H), 7.54-7.38 (m, 3 H), 7.35-7.25 (m, 2 H), 6.78 (d, *J* = 5.2, 1 H), 2.48 (t, *J* = 7.6, 2 H), 1.67 (quintuplet, *J* = 7.6, 2 H), 1.29 (hexuplet, *J* = 7.6, 2 H), 0.83 (t, *J* = 7.3, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.8, 157.7, 149.2, 136.1, 134.6, 129.9, 128.9, 128.2, 124.7, 121.8, 115.6, 30.5, 30.0, 22.2, 13.7 ; IR (film): v = 1728 (s), 1620 (w), 1520 (m), 1427 (m), 1096 (w), 1011 (m), 779 (m), 702 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 284 (M^+, 100), 241 (20), 227 (81), 213 (37), 200 (42), 171 (28); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{17}H_{16}O_2S^+$: 285.0944; found: 285.0995.

3-Methyl-5-phenyl-4-(p-tolyl)-7H-thieno[2,3-c]pyran-7-one (**19**). Yield: 63 mg, starting from 111 mg of **2j** (63%). White solid, mp = 162-164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38-7.37 (m, 1 H), 7.35-7.29 (m, 2 H), 7.23-7.12 (m, 7 H), 2.38 (s, 3 H), 1.62 (s, 3 H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ = 158.8, 153.1, 146.1, 138.1, 136.2, 133.4, 132.9, 131.1, 129.29, 129.27, 128.7, 127.8, 124.1, 116.6, 21.4, 16.6; IR (KBr): v = 1728 (s), 1512 (w), 1489 (w), 1450 (m), 1072 (m), 1003 (w), 756 (m), 694 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 332 (M^+, 100), 255 (69), 227 (23), 207 (16), 105 (72), 77 (39); HRMS-ESI (*m/z*): [(M+H)$^+$] cald for $C_{21}H_{17}O_2S^+$: 333.0944; found: 333.0948.

Keywords: alkynylcarboxylic acids • fused heterocycles • iodolactonization • iodothienopyranones • iodothienopyrimidinones •

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[4] Reactions were typically carried out with a substrate scale of 0.25 mmol. Products yields were even higher when representative experiments were carried out in a larger scale (2.2 mol of **1**; for example, the yields of **2a**, **2b**, and **2e** were 93%, 90%, and 89%, respectively. See the Experimental Section for details).

[5] Reactions were typically carried out with a substrate scale of 0.35 mmol. Products yields were even higher when representative experiments were carried out in a larger scale (2.2 mol of **3**), for example, the yield of **4a** was 75% (see the Experimental Section for details).

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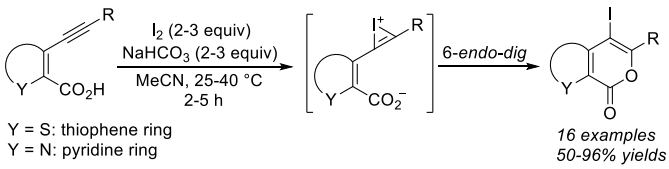
Entry for the Table of Contents



High value added iodinated fused heterocycles from simple substrates: Iodothienopyranones and iodopyranopyrimidinones are obtained under mild reaction conditions (25-40 °C, 2-3 equiv of I_2 and $NaHCO_3$ in MeCN) by iodolactonization of readily available 3-alkynylthiophene-2-carboxylic and 3-alkynylpicolinic acids, respectively.

KEY TOPIC: FUSED HETEROCYCLES