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Furan ring opening − pyridine ring closure: an efficient approach towards 6*H*-isochromeno[4,3-*b*]pyridin-6-ones from readily available furans and phthalaldehydic acid methyl esters

Pavel M. Shpuntov,[a] Alexandra A. Kolodina,[b] Maxim G. Uchuskin[c] and Vladimir T. Abaev*[d]

Abstract: An efficient iodine-catalyzed three-component Mannich-type reaction of various 2-alkylfurans, methyl 2-formylbenzoates and carbamates under mild reaction conditions was realized. Synthetic utility of the resulting *N*-Boc-1-[2-(carbomethoxy)aryl]furfuryl amines was demonstrated by their facile two-step transformation into 2-methyl-6*H*-isochromeno[4,3-*b*]pyridin-6-ones employed in high-performance cyclometalated OLEDs.

Introduction

In the last decades multicomponent reactions (MCRs) have gained ever increasing attention from the synthetic community, due to serving as an exceptionally efficient and powerful tool for *one-pot* transformation of simple and readily available starting materials into relatively complex molecules representing valuable intermediates in the synthesis of various natural products and pharmaceuticals.[1] In particular, the Mannich-type three-component condensation reaction of diverse electron-rich arenes and heteroarenes with aldehydes and various nitrogen nucleophiles has emerged as a versatile and therewith straightforward approach to C-C bond formation which is of current importance in modern organic synthesis. Thus far, transformations of this type featuring aromatic aldehydes as electrophilic components have been extensively applied to functionalization of phenols,[2] α-naphthols,[3] β-naphthols (Betti reaction),[4] hydroxyquinolines[3a],[5] and other heteroannelated phenols,[6] some electron-rich benzenes,[7] naphthylamines,[8] indoles,[9] 7-azaindoles[10] and indolizines[11] while examples of employing other heterocycles, particularly, pyrrole, thiophene and furan derivatives, are scarcely encountered in literature. J. Jaratjaroonphong and co-workers reported a versatile iodine-catalyzed carbamoalkylation procedure utilizing benzyl- and *tert*-butyl carbamates with a variety of aldehydes which was successfully applied to 2-alkylfurans and 2-methylthiophene.[7d] Later on their group and the group of Manolikakes virtually simultaneously introduced $Bi(OTf)_3$ to promote carbamo- and amidoalkylation of various (hetero)aromatic substrates including furan and thiophene derivatives.[7b],[7c] Eventually this transformation was shown to proceed in the presence of $FeCl_3 \cdot 6H_2O$ as a cheap and green alternative.[7a]

However, despite the broad substrate scope and overall utility of the existing methods, the potential of exploiting this remarkable reaction for amidoalkylation of furans with *ortho*-functionalized benzaldehydes and carbamates yet remains completely unexplored. Meanwhile, the target products of such transformation, namely, *N*-substituted α-arylfurfuryl amines have been solidly established as promising objects for a variety of subsequent structural modifications, thereby opening up new opportunities in the synthesis of complex natural products and drug molecules. Furfuryl amines of this type are well recognized to undergo a number of furan ring transforming processes such as aza-Achmatowicz,[12] aza-Piancatelli[13] rearrangements, intra-[14] and intermolecular Diels-Alder reactions[15] and protolytic furan recyclizations[16] leading to an array of diverse carbo- and heterocycles. Moreover, the presence of an *ortho*-substituent in the aryl ring renders the target *ortho*-functionalized *N*-alkoxycarbonyl α-(α-furyl)benzylamines appropriate substrates for the Butin reaction[17] providing access to a variety of benzannelated polyheterocyclic compounds.

Hence, herein we report an efficient iodine-catalyzed three-component Mannich-type condensation of 2-alkylfurans, various phthalaldehydic acid methyl esters and carbamates as well as the novel transformation of the resulting *N*-Boc-arylfurfuryl amines into 2-methyl-6*H*-isochromeno[4,3-*b*]pyridin-6-ones *via* a straightforward two-step procedure.

Results and Discussion

In order to avoid potential complications that could arise from the intrinsic ring-chain tautomerism of phthalaldehydic acid and its active proton or from its relatively poor solubility in common weak polar organic solvents the corresponding methyl 2-formylbenzoate (**1a**), 2-methylfuran (**2a**) and ethyl carbamate (**3a**) were chosen as model substrates for initial optimization of the reaction conditions (Table 1). Molecular iodine was chosen as an inexpensive and eco-friendly catalyst to start with in a series of solvent screening experiments. Employing toluene as the reaction medium gave only moderate yield of the target product **4a** (entry 1). Bis(furyl)arylmethane **5a** resulting from the competing 2-methylfuran double addition reaction was also isolated from the reaction mixture.[18] It should be noted that bis(furyl)arylmethane **5a** was observed as the minor product in each case the reaction took place. Lowering temperature of the reaction to 0 °C resulted in a slightly increased yield of the desired product (entry 2). Switching the reaction solvent to DCM

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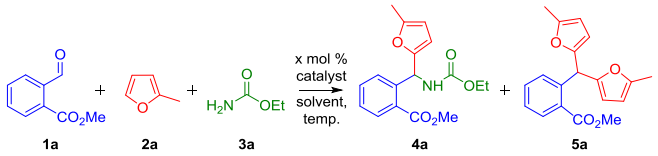
Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Catalyst (mol %)	Time (h)	t (°C)	Yield (%)[b]	
					4a	**5a**
1	toluene	I_2 (10)	2	rt	53	14
2	toluene	I_2 (10)	2	0	67	9
3	DCM	I_2 (10)	0.25	rt	53	24
4	DCM	I_2 (10)	0.5	0	75	12
5	DCM	I_2 (5)	1	0	68	9
6	DCM	I_2 (10)	1.17	0	77[c]	14
7	THF	I_2 (10)	24	0	61[d]	19
8	CH_3CN	I_2 (10)	1	rt	45	19
9	**CH_3CN**	**I_2 (10)**	**2**	**0**	**81**	**7**
10	CH_3CN	$Bi(OTf)_3$ (5)	0.75	0	78	5
11	CH_3CN	$CuBr_2$ (10)	1	0	80	7
12	CH_3CN	$BF_3{\cdot}Et_2O$ (10)	2	0	78	7
13	CH_3CN	$Cu(OTf)_2$ (5)	24	0	72	12
14	CH_3CN	$ZnCl_2$ (10)	3.5	rt	traces	–
15	CH_3CN	$TiCl_4$ (10)	1.5	-15	76	16
16	CH_3CN	I_2 (10)	4	-15	74	5

[a] Reaction conditions: methyl 2-formylbenzoate **1a** (2.4 mmol), 2-methylfuran **2a** (2.66 mmol), ethyl carbamate **3a** (2.7 mmol) and solvent (3 ml), stirring. [b] Isolated yield. [c] To a cooled solution of **1a**, **3a** and I_2 in 2 ml of DCM a solution of **2a** in 1 ml of DCM was added dropwise over a period of 30 min with stirring and then stirred for another 40 min. [d] The reaction mixture was stirred at 0 °C for 7 h and left overnight at rt for another 17 h.

accelerated the transformation significantly without any relevant improvement in the reaction outcome (entry 3). However, in this case cooling of the reaction mixture also proved beneficial (entry 4). Decreasing the catalyst loading to 5% mol led to a somewhat lower yield of the carbamoalkylation product (entry 5) while slow dropwise addition of a 2-methylfuran **2a** solution in DCM to the reaction mixture over 30 minutes did not significantly improve the yield (entry 6). Finally, CH_3CN was found to be the most suitable solvent for this *one-pot* three-component coupling reaction (entry 9). Despite the fact that cooling of the reaction mixture to 0 °C appeared crucial for obtaining high yields of the target product, further lowering of temperature to -15 °C was not advantageous due to a considerable decrease in the reaction rate (entry 16). After identifying the optimal solvent and temperature we focused on establishing the most efficient catalyst. Among a series of Lewis acids tested (entries 9-15) I_2, $Bi(OTf)_3$, $CuBr_2$ and $BF_3{\cdot}Et_2O$ proved almost equally potent at promoting this transformation (entries 9-12). However, iodine appeared to be the catalyst of choice in terms of cost, ease of handling, non-hydrophobicity and relative non-toxicity.

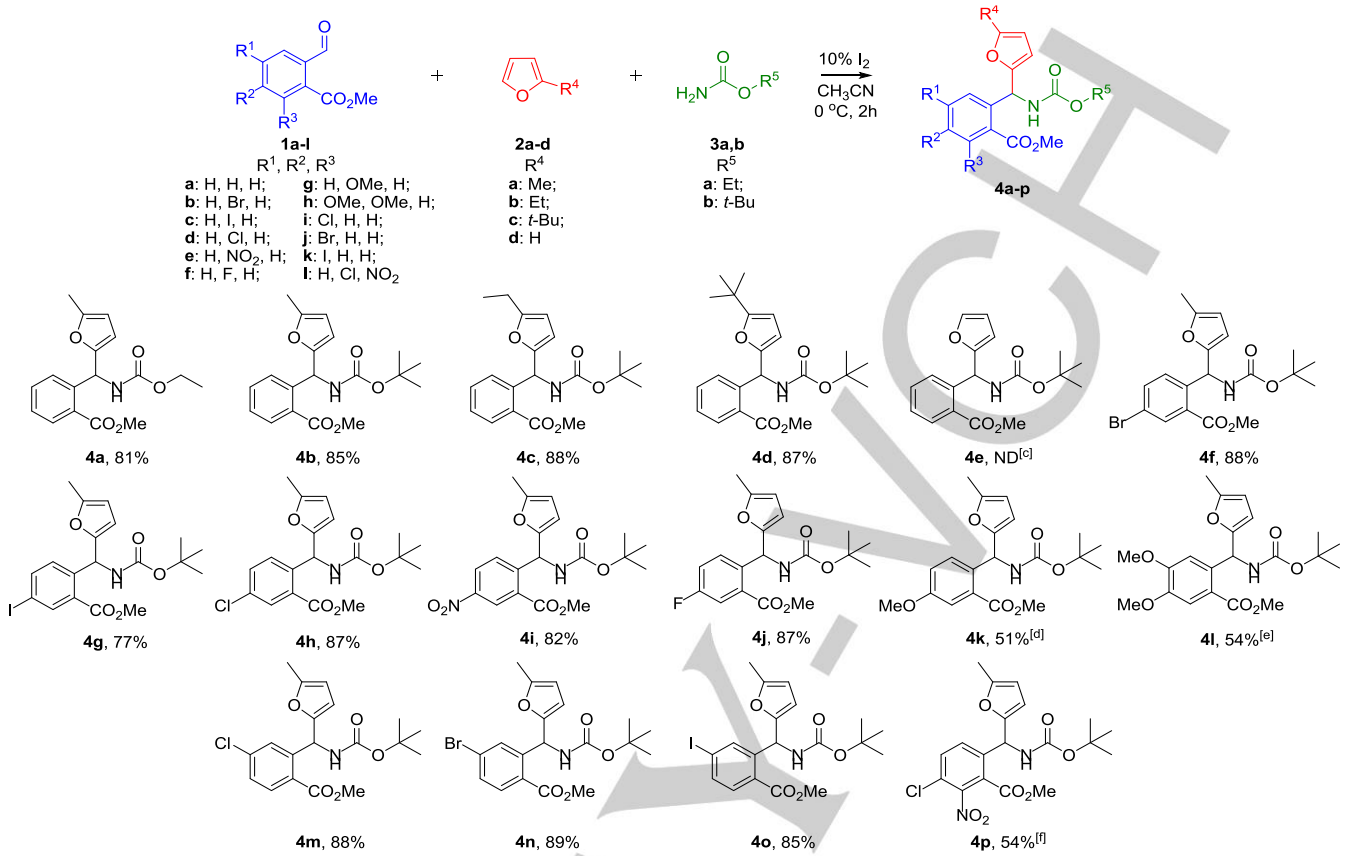
With the optimized reaction conditions in hand (CH_3CN, 10% I_2, 0 °C, 2h, stirring) the scope of the reaction was investigated by testing an array of substituted methyl 2-formylbenzoates, 2-alkylfurans and carbamates. The experimental results are summarized in Table 2. When urethane **3a** was replaced by *tert*-butyl carbamate **3b**, a slightly better yield of carbamoalkylation product **4b** was obtained. This fact along with the more feasible cleavage of the *N*-Boc protecting group encouraged us to employ *tert*-butyl carbamate as the amine component in further examinations. The reaction proceeded smoothly with 2-methyl-, 2-ethyl- and 2-*tert*-butylfurans **2a-c** furnishing the corresponding *N*-Boc-arylfurfuryl amines **4b**, **4c**, **4d** in high yields. Unfortunately, no carbamoalkylation product was detected in the reaction with unsubstituted furan **2d** under the optimized conditions, probably, due to its substantially lower nucleophilicity.

At the same time, when a series of phthalaldehydic acid methyl esters were subjected to this transformation, the outcome appeared to be dependent upon the nature of substituents. Methyl 2-formylbenzoates **1b-d**, **1f**, **1i-k** bearing halogen substituents at C4 and C5 positions of the ring generally afforded high yields of the desired products albeit 5-iodo derivative **4g** was isolated with a somewhat lower yield. Methyl 2-formylbenzoate **1e** containing strongly electron-withdrawing nitro group gave equally good results whereas the trisubstituted benzaldehyde **1l** displayed low conversion, probably, because of the undesirable steric and electronic effects interplay, and only moderate product yield was obtained in this case even after a prolonged period of time. The reaction proved less efficient with methyl 2-formylbenzoates **1g** and **1h** possessing electron-donating (OMe) substituents. In these cases the desired *N*-Boc-1-[2-(carbomethoxy)aryl]furfuryl amines **4k** and **4l** were obtained in lower yields along with sufficient amounts of the corresponding bis(furyl)arylmethanes **5b** and **5c** (25% and 23%, respectively).

It is also worth mentioning that accordingly to our initial assumption, free phthalaldehydic acid **6** appeared not suitable for this transformation as after 2 hours diminished conversion was observed by TLC, and after 12 hours at room temperature the corresponding 3-(2-furyl)phthalide **7** and bis(furyl)arylmethane **8** were isolated from the reaction mixture in 23% and 38% yield, respectively, along with 30% of recovered phthalaldehydic acid (Scheme 1). Formation of the same products was reported earlier in the acid-catalyzed condensation of phthalaldehydic acids with furans.[19]

Next, aiming to get a deeper insight into the pathway of this three-component coupling reaction, we turned our attention to a series of mechanistic experiments (for details, see ESI). When the reaction was performed in the absence of carbamate with excess of 2-methylfuran **2a**, bis(furyl)arylmethane **5a** was formed in 69% yield. Interestingly, the carbamoalkylation product **4b** could barely be converted to the corresponding bis(furyl)arylmethane **5a** *via* a Friedel-Crafts-type reaction with 2-methylfuran **2a** under the optimized conditions even after increasing the reaction temperature to 60 °C providing only 21% yield of the product along with 63% of recovered starting material. The latter observation allows us to assume that the

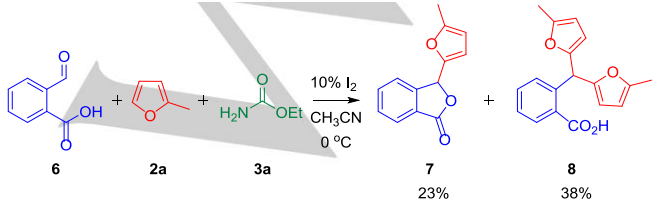
Table 2 Substrate scope of phthalaldehydic acid methyl esters, furans and carbamates[a],[b]



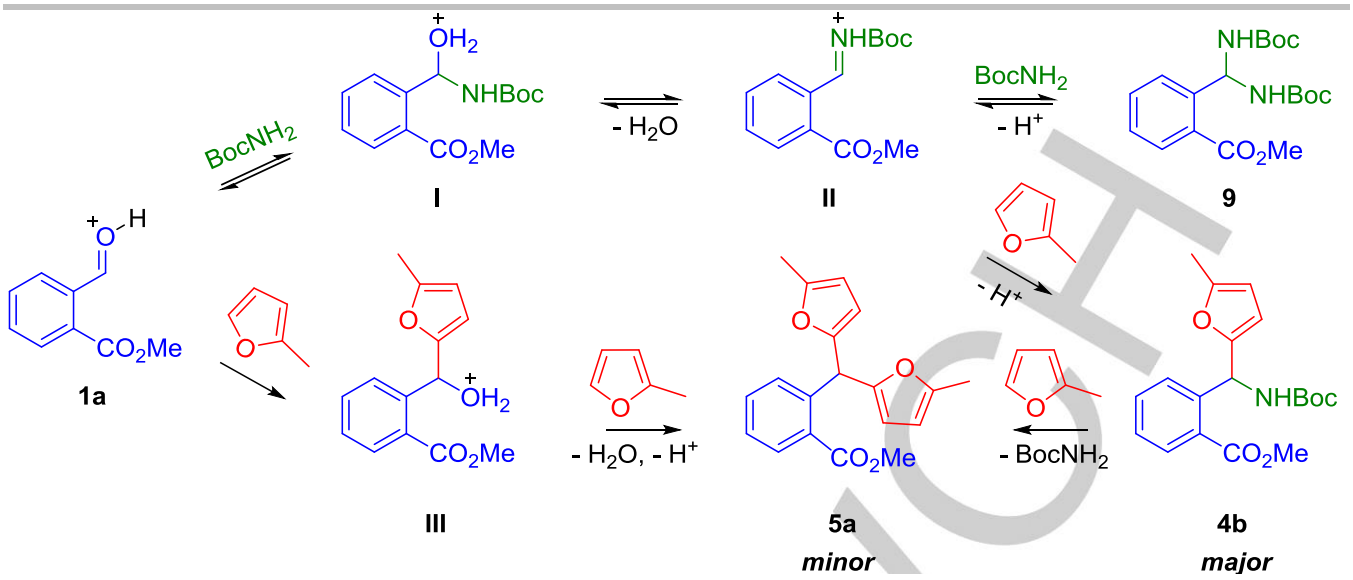
[a] Reaction conditions: methyl 2-formylbenzoate (2.4 mmol), furan (2.66 mmol), carbamate (2.7 mmol), I_2 (0.24 mmol), CH_3CN (3 ml for **1a**; 5 ml for **1b-1l**), 0 °C, stirring. [b] Isolated yields. [c] Target product not detected by TLC. [d] 25% of the corresponding bis(furyl)arylmethane **5b** and 13% of unreacted methyl 2-formylbenzoate **1g** were also isolated from the reaction mixture. [e] 23% of the corresponding bis(furyl)arylmethane **5c** and 9% of unreacted methyl 2-formylbenzoate **1h** were also isolated from the reaction mixture. [f] Time of the reaction was increased to 24 h.

desired carbamoalkylation reaction and inevitable formation of minor quantities of bis(furyl)arylmethanes proceed in parallel rather than in sequential fashion. However, in the case of substrates with electron-donating substituents such as **1g** and **1h** which can form stabilized carbocations it can not be ruled out that the formation of bis(furyl)arylmethanes by interaction of the generated N-Boc-arylfurfuryl amines with the second molecule of furan becomes more significant and is responsible for the decreased yields of the desired products **4k** and **4l**. Expectedly, subjecting bis(furyl)arylmethane **5a** to the reaction with *tert*-butyl carbamate **3b** proved unsuccessful. Condensation of methyl 2-formylbenzoate **1a** and *tert*-butyl carbamate **3b** without addition of furan component furnished the corresponding *N*-Boc-aminal **9** (Scheme 2) in only 37% yield, probably, due to unfavorable equilibrium constant. However, under the optimized reaction conditions the latter rapidly interacted with 2-methylfuran **2a** providing 84% yield of *N*-Boc-arylfurfuryl amine **4b** as well as 4% of bis(furyl)arylmethane **5a** as by-product. Hence, *N*-Boc-aminal **9** might well act as an alternative source of the intermediate protonated *N*-Boc-imine **II** in this three-component transformation despite we were never able to observe it in the reaction mixture by TLC. Examples of employing such aminals as precursors to the corresponding *N*-Boc-imines are precedented earlier.[20]

Scheme 1 Reaction with phthalaldehydic acid under the optimized reaction conditions



Based on these results, the plausible mechanism for this three-component coupling reaction is shown in Scheme 2. It should be noted that the nature of the actual catalytic species under molecular iodine catalysis is still under debate. One possible mechanism includes protic catalysis with HI that can be reversibly generated in minor quantities in the reaction of iodine with water or protic solvents. An alternative point of view was disclosed in the recent work by Breugst and colleagues[21] providing evidence for halogen-bond based activation of the Michael acceptors in reactions catalyzed by molecular iodine rather than Brønsted-acidity mode. In particular, they showed that the conjugate addition of indole to α,β-unsaturated ketones is efficiently promoted by iodine whereas the same reaction under HI catalysis leads to significantly lower yields of the corresponding product. To shed light on the mode of action of iodine we performed a control experiment with methyl 2-



Scheme 3 Plausible mechanism

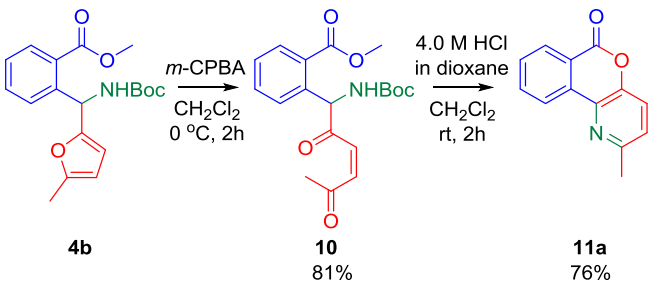
formylbenzoate **1a**, 2-methylfuran **2a** and *tert*-butyl carbamate **3b** in the presence of 5% mol HI (57% aq.) under the optimized reaction conditions. To our surprise in this case the reaction proceeded smoothly providing the target carbamoalkylation product **4b** in 88% yield. Moreover, the reaction with 5% mol HCl (37% aq.) proceeded equally well leading to the formation of product **4b** in 89% isolated yield. In contrast, the same reaction with iodine (10% mol) was completely retarded when performed in the presence of proton scavenger 2,6-lutidine (10% mol). Keeping in mind that this lack of reactivity could be caused by the formation of iodine-pyridine complex another portion of iodine (10% mol) was added to the reaction mixture but only trace amounts of the desired carbamoalkylation product **4b** were observed by TLC after 4 hours of the reaction providing an argument in favour of proton catalysis.

In order to demonstrate the synthetic utility of the resulting *N*-Boc-1-[2-(carbomethoxy)aryl]furfuryl amines **4** we envisaged an oxidative furan ring opening / recyclization sequence providing access to the corresponding 6*H*-isochromeno[4,3-*b*]pyridin-6-ones **11**. Both isocoumarin[22] and pyridine[23] frameworks are well recognized as privileged scaffolds widely represented in a great number of natural products possessing versatile biological activities. Considering this fact, 6*H*-isochromeno[4,3-*b*]pyridin-6-ones **11** containing both of these moieties fused together emerge as perspective polyheterocycles with potentially attractive biological properties.

At the same time, 2-arylpyridine skeleton is present in organoplatinum (II) complexes exhibiting potent antitumor activities,[24] in luminescent iridium (III) complexes suitable for living cells imaging[25] and in a number of compounds with fluorescence properties capable of acting as metal ion binding chemosensors with readily tunable emission wavelengths.[26] Similarly, some [4,3-*b*]-annelated isocoumarins are also reported to be potentially useful fluorophores for development of new photochromic systems owing to their inherent fluorescence "turn-off" sensing of Cu^{2+} and Fe^{3+} ions under visible and UV light.[27] Eventually it should be noted that 6*H*-isochromeno[4,3-*b*]pyridin-6-ones comprised of these two substructures were successfully applied as cyclometalating ligands for Ir(III) complexes acting as highly efficient and stable emitters in organic light-emitting diodes (OLEDs).[28]

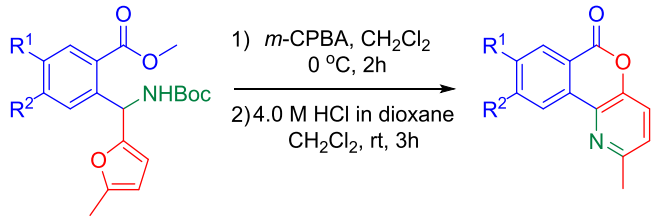
However, despite the apparent potential, the number of reported methods providing access to this pyridine-fused isocoumarin ring system is thus far rather limited.[29] The classical Hantzsch pyridine synthesis was found to be inapplicable for the preparation of compounds incorporating this structural moiety.[30] Synthesis of various annelated 6*H*-isochromeno[4,3-*b*]pyridin-6-ones was accomplished *via* an unusual rearrangement of indolizinediones under acidic conditions.[29e] However, this method appears to be of limited use due to poor availability of substrates needed. Likewise, most of other reported procedures build upon the preformed functionalized pyridine synthons which are obviously much less accessible than the benzene-based substrates, and furthermore, suffer from some other substantial drawbacks such as unsatisfactory product yields, use of expensive reagents and harsh reaction conditions operating at temperatures up to 300 °C. Hence, new synthetic approaches towards 6*H*-isochromeno[4,3-*b*]pyridin-6-ones employing readily available substrates and reagents are highly desirable.

To prove the concept *N*-Boc-arylfurfuryl amine **4b** was subjected to oxidative furan ring cleavage[31] in DCM in the presence of *m*-CPBA providing the expected ene-dione **10** in



Scheme 2 Two-step synthesis of 6*H*-isochromeno[4,3-*b*]pyridin-6-one **11a**

Table 3 Substrate scope for the two-step preparation of 6*H*-isochromeno-[4,3-*b*]pyridin-6-ones[a]



4b,f,i,l,n **11a-e**

Entry	**4**	R^1	R^2	**11**, (Yield, %)[b]
1	**4b**	H	H	**11a** (65)
2	**4f**	Br	H	**11b** (61)
3	**4i**	NO_2	H	**11c** (61)
4	**4l**	OMe	OMe	**11d** (62)
5	**4n**	H	Br	**11e** (68)

[a] Reaction conditions: 1) *N*-Boc-1-[2-(carbomethoxy)aryl]furfuryl amine **4** (1.0 mmol), *m*-CPBA (1.56 mmol), CH_2Cl_2 (3 ml), 0 °C, stirring; 2) 4.0 M HCl in 1,4-dioxane (1 ml), CH_2Cl_2 (2 ml), rt, stirring. [b] Isolated yield.

81% yield (Scheme 3). The latter under the action of 4 N HCl in dioxane smoothly underwent *N*-Boc deprotection with subsequent pyridine ring formation / lactonization furnishing the desired isochromenopyridinone **11a** in 76% yield.

Then a number of substituted *N*-Boc-arylfurfuryl amines were tested in this transformation to examine the scope of the reaction (Table 3). Gratifyingly, the procedure proved successful with both electron-withdrawing (Br, NO_2) and electron-donating (OMe) substituents leading to 61-68% overall yields of the corresponding isochromenopyridinones **11a-e** after two steps with no need for isolation of the intermediate ene-diones.

Conclusions

In conclusion, we have demonstrated a facile and efficient *one-pot* three-component procedure for α-carbamoalkylation of furans with various phthalaldehydic acid methyl esters and carbamates. The reaction proceeds under mild conditions employing I_2 as an inexpensive, non-hydrophobic and operationally simple catalyst. Scope and limitations of the devised method as well as mechanistic aspects were investigated. Moreover, a powerful and straightforward two-step reaction sequence for transformation of the resulting *N*-Boc-1-[2-(carbomethoxy)aryl]furfuryl amines into 6*H*-isochromeno[4,3-*b*]pyridin-6-ones was developed. Further investigation of the iodine catalyzed amidoalkylation of furans employing other *ortho*-functionalized benzaldehydes is currently underway.

Experimental Section

General procedure for the preparation of 4a-p: Molecular iodine (0.06 g, 0.24 mmol) was added to a stirred solution of methyl 2-formylbenzoate (2.4 mmol) and carbamate (2.7 mmol) in acetonitrile (3 ml for **1a**; 5 ml for **1b-l**) at 0 ºC (ice/water bath). The mixture was allowed to stir for 5 minutes. Then furan (2.66 mmol) was slowly added and the reaction mixture was stirred for 2 h at 0 ºC. After completion of the reaction monitored by TLC (in some cases traces of unreacted methyl 2-formylbenzoate could be observed) the reaction mixture was poured into saturated aqueous $Na_2S_2O_3$ (15 ml), extracted with CH_2Cl_2 (3 × 10 ml), washed with water (4 ml) and brine (4 ml), dried with anhydrous Na_2SO_4, filtered and organic solvents were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc as eluent) to afford the desired products **4a-p**. Analytical samples of solid compounds were obtained by recrystallization from CH_2Cl_2/petroleum ether mixture.

Methyl 2-{[(ethoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-benzoate (4a): pale yellow oil (0.61 g, 81%). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 8.18 (d, ^3J = 8.9 Hz, 1H, NH), 7.79 (d, ^3J = 7.7 Hz, 1H, H_{Ar}), 7.65-7.56 (m, 2H, H_{Ar}), 7.46-7.37 (m, 1H, H_{Ar}), 6.72 (d, ^3J = 8.9 Hz, 1H, CH), 5.92 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.69 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.98 (q, ^3J = 7.1 Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3), 1.15 (t, ^3J = 7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 167.1, 155.6, 152.7, 151.0, 141.0, 132.2, 129.8, 129.1, 127.9, 127.5, 107.9, 106.3, 60.0, 52.1, 49.0, 14.6, 13.3 ppm; IR (neat) ν_{max} = 3341, 2982, 2953, 1713, 1503, 1433, 1271, 1125, 1038, 964, 785, 750, 719 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{17}H_{20}NO_5$ $[M+H]^+$ = 318.1336, found = 318.1326.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-benzoate (4b): pale yellow oil (0.70 g, 85%). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.87 (d, ^3J = 9.0 Hz, 1H, NH), 7.78 (d, ^3J = 7.7 Hz, 1H, H_{Ar}), 7.64-7.56 (m, 2H, H_{Ar}), 7.45-7.36 (m, 1H, H_{Ar}), 6.66 (d, ^3J = 9.0 Hz, 1H, CH), 5.91 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.68 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.77 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 167.2, 154.8, 152.9, 150.8, 141.2, 132.1, 129.7, 129.1, 127.9, 127.4, 107.8, 106.2, 78.2, 52.1, 48.7, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3386, 2977, 2925, 1715, 1487, 1366, 1248, 1163, 1076, 1020, 784, 755, 719 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{24}NO_5$ $[M+H]^+$ = 346.1649, found = 346.1653.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-ethylfuran-2-yl)methyl}-benzoate (4c): colorless solid (0.75 g, 88%), mp 74−75 ºC (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.89 (d, ^3J = 9.0 Hz, 1H, NH), 7.78 (d, ^3J = 7.7 Hz, 1H, H_{Ar}), 7.66-7.55 (m, 2H, H_{Ar}), 7.45-7.35 (m, 1H, H_{Ar}), 6.67 (d, ^3J = 9.0 Hz, 1H, CH), 5.91 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.70 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.77 (s, 3H, OCH_3), 2.54 (q, ^3J = 7.5 Hz, 2H, CH_2), 1.37 (s, 9H, *t*-Bu), 1.12 (t, ^3J = 7.5 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 167.2, 156.4, 154.9, 152.8, 141.2, 132.2, 129.8, 129.2, 127.9, 127.4, 107.6, 104.7, 78.3, 52.1, 48.7, 28.2 (3C), 20.8, 12.0 ppm; IR (neat) ν_{max} = 3358, 2970, 2934, 1732, 1721, 1677, 1520, 1249, 1167, 1014, 877, 757, 720 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{26}NO_5$ $[M+H]^+$ = 360.1805, found = 360.1803.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-(*tert*-butyl)furan-2-yl)methyl}benzoate (4d): pale yellow oil (0.80 g, 87%). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.90 (d, ^3J = 9.1 Hz, 1H, NH), 7.77 (d, ^3J = 7.8 Hz, 1H, H_{Ar}), 7.63-7.53 (m, 2H, H_{Ar}), 7.44-7.35 (m, 1H, H_{Ar}), 6.70 (d, ^3J = 9.1 Hz, 1H, CH), 5.87 (d, ^3J = 3.2 Hz, 1H, H_{Fur}), 5.72 (d, ^3J = 3.2 Hz, 1H, H_{Fur}), 3.77 (s, 3H, OCH_3), 1.38 (s, 9H, *t*-Bu), 1.17 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 167.3, 162.6, 154.9, 152.6, 141.2, 132.0, 129.7, 129.2, 127.7, 127.3, 106.9, 102.5, 78.3, 52.1, 48.8, 32.1, 28.8 (3C), 28.2 (3C) ppm; IR (neat) ν_{max} = 3384, 2967, 2870, 1717, 1487, 1365, 1248, 1165, 1124, 1077, 1014, 785, 720 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{30}NO_5$ $[M+H]^+$ = 388.2118, found = 388.2130.

Methyl 5-bromo-2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}benzoate (4f): colorless crystals (0.89 g, 88%), mp 101−102 ºC (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.93 (d, ^3J = 8.8 Hz, 1H, NH), 7.91 (d, ^4J = 2.3 Hz, 1H, H_{Ar}), 7.84 (dd, ^3J = 8.5 Hz,

^4J = 2.3 Hz, 1H, H_{Ar}), 7.54 (d, ^3J = 8.5 Hz, 1H, H_{Ar}), 6.59 (d, ^3J = 8.8 Hz, 1H, CH), 5.92 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.72 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.78 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 165.8, 154.8, 152.1, 151.0, 140.6, 134.9, 132.1, 131.1, 130.2, 120.3, 108.0, 106.3, 78.4, 52.5, 48.4, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3277, 2969, 1723, 1696, 1370, 1352, 1291, 1252, 1163, 1023, 784 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}BrNO_5$ $[M+H]^+$ = 424.0754, found = 424.0770.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-5-iodobenzoate (4g): colorless solid (0.86 g, 77%), mp 78−79 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 8.07 (d, ^4J = 1.9 Hz, 1H, H_{Ar}), 7.98 (dd, ^3J = 8.3 Hz, ^4J = 1.9 Hz, 1H, H_{Ar}), 7.90 (d, ^3J = 8.8 Hz, 1H, NH), 7.38 (d, ^3J = 8.3 Hz, 1H, H_{Ar}), 6.57 (d, ^3J = 8.8 Hz, 1H, CH), 5.91 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.72 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.77 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.36 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 165.7, 154.8, 152.1, 151.0, 141.0, 140.7, 137.8, 131.0, 130.1, 108.0, 106.3, 93.0, 78.4, 52.4, 48.4, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3343, 2943, 1737, 1670, 1519, 1241, 1154, 1079, 1023, 849, 784 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}INO_5$ $[M+H]^+$ = 472.0615, found = 472.0600.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-5-chlorobenzoate (4h): colorless solid (0.78 g, 87%), mp 93.5−94.5 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.93 (d, ^3J = 8.9 Hz, 1H, NH), 7.78 (d, ^4J = 2.3 Hz, 1H, H_{Ar}), 7.71 (dd, ^3J = 8.5 Hz, ^4J = 2.3 Hz, 1H, H_{Ar}), 7.61 (d, ^3J = 8.5 Hz, 1H, H_{Ar}), 6.61 (d, ^3J = 8.9 Hz, 1H, CH), 5.92 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.72 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.79 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 165.9, 154.8, 152.2, 151.0, 140.2, 132.0 (2C), 130.9, 129.9, 129.2, 108.0, 106.3, 78.4, 52.5, 48.3, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3279, 2970, 1724, 1696, 1370, 1351, 1294, 1253, 1166, 1023, 965, 784 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}ClNO_5$ $[M+H]^+$ = 380.1259, found = 380.1266.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-5-nitrobenzoate (4i): colorless solid (0.77 g, 82%), mp 112−113 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 8.54 (d, ^4J = 2.5 Hz, 1H, H_{Ar}), 8.49 (dd, ^3J = 8.7 Hz, ^4J = 2.5 Hz, 1H, H_{Ar}), 8.11 (d, ^3J = 8.6 Hz, 1H, NH), 7.89 (d, ^3J = 8.7 Hz, 1H, H_{Ar}), 6.75 (d, ^3J = 8.6 Hz, 1H, CH), 5.94 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.78 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.85 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 165.3, 154.8, 151.4, 151.2, 148.3, 146.5, 130.2, 129.5, 126.8, 124.7, 108.5, 106.4, 78.6, 52.8, 48.7, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3276, 3132, 2971, 1731, 1699, 1526, 1343, 1311, 1260, 1168, 787, 739 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}N_2O_7$ $[M+H]^+$ = 391.1500, found = 391.1508.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-5-fluorobenzoate (4j): colorless solid (0.75 g, 87%), mp 70−71 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.91 (d, ^3J = 9.0 Hz, 1H, NH), 7.70-7.59 (m, 1H, H_{Ar}), 7.59-7.52 (m, 1H, H_{Ar}), 7.52-7.43 (m, 1H, H_{Ar}), 6.62 (d, ^3J = 9.0 Hz, 1H, CH), 5.91 (br s, 1H, H_{Fur}), 5.70 (br s, 1H, H_{Fur}), 3.79 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 166.0, 160.6 (d, $^1J_{CF}$ = 244.8 Hz), 154.8, 152.6, 151.0, 137.5, 131.0 (d, $^3J_{CF}$ = 7.0 Hz), 130.3 (d, $^3J_{CF}$ = 8.1 Hz), 119.1 (d, $^2J_{CF}$ = 20.9 Hz), 116.3 (d, $^2J_{CF}$ = 23.0 Hz), 107.9, 106.3, 78.3, 52.4, 48.2, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3354, 2985, 1735, 1674, 1520, 1496, 1299, 1252, 1204, 1164, 1021, 781 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}FNO_5$ $[M+H]^+$ = 364.1555, found = 364.1545.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-5-methoxybenzoate (4k): colorless crystals (0.45 g, 51%), mp 124−125 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.78 (d, ^3J = 9.1 Hz, 1H, NH), 7.49 (d, ^3J = 8.7 Hz, 1H, H_{Ar}), 7.27 (d, ^4J = 2.8 Hz, 1H, H_{Ar}), 7.18 (dd, ^3J = 8.7 Hz, ^4J = 2.8 Hz, 1H, H_{Ar}), 6.55 (d, ^3J = 9.1 Hz, 1H, CH), 5.90 (d, ^3J = 3.0 Hz, 1H, H_{Fur}), 5.68 (d, ^3J = 3.0 Hz, 1H, H_{Fur}), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 167.0, 158.0, 154.8, 153.3, 150.7, 133.2, 130.2, 129.5, 117.8, 114.5, 107.6, 106.2, 78.2, 55.4, 52.2, 48.3, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3357, 2983, 2950, 1725, 1708, 1511, 1258, 1210, 1164, 1070, 1044, 1021, 792 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{26}NO_6$ $[M+H]^+$ = 376.1755, found = 376.1769.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-4,5-dimethoxybenzoate (4l): colorless prisms (0.52 g, 54%), mp 98−99 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.81 (d, ^3J = 9.3 Hz, 1H, NH), 7.35 (s, 1H, H_{Ar}), 7.27 (s, 1H, H_{Ar}), 6.78 (d, ^3J = 9.3 Hz, 1H, CH), 5.89 (d, ^3J = 3.0 Hz, 1H, H_{Fur}), 5.67 (d, ^3J = 3.0 Hz, 1H, H_{Fur}), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 166.4, 154.9, 153.5, 151.9, 150.6, 147.1, 135.9, 120.2, 112.7, 111.5, 107.4, 106.2, 78.2, 55.8, 55.6, 51.9, 48.3, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3272, 3002, 2946, 1715, 1697, 1523, 1351, 1253, 1211, 1157, 1018, 1003, 784 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{28}NO_7$ $[M+H]^+$ = 406.1860, found = 406.1852.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-4-chlorobenzoate (4m): colorless crystals (0.79 g, 88%), mp 92−93 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.97 (d, ^3J = 9.0 Hz, 1H, NH), 7.82 (d, ^3J = 8.4 Hz, 1H, H_{Ar}), 7.68 (d, ^4J = 2.2 Hz, 1H, H_{Ar}), 7.50 (dd, ^3J = 8.4 Hz, ^4J = 2.2 Hz, 1H, H_{Ar}), 6.70 (d, ^3J = 9.0 Hz, 1H, CH), 5.92 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.72 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.78 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 166.2, 154.8, 152.1, 151.1, 143.8, 137.2, 131.9, 127.8, 127.7, 127.6, 108.1, 106.3, 78.5, 52.3, 48.4, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3239, 3127, 2951, 1719, 1703, 1362, 1261, 1238, 1170, 1102, 1071, 1020, 789 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}ClNO_5$ $[M+H]^+$ = 380.1259, found = 380.1256.

Methyl 4-bromo-2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}benzoate (4n): colorless solid (0.90 g, 89%), mp 109−110 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.98 (d, ^3J = 9.0 Hz, 1H, NH), 7.82 (br s, 1H, H_{Ar}), 7.73 (d, ^3J = 8.4 Hz, 1H, H_{Ar}), 7.63 (dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz, 1H, H_{Ar}), 6.69 (d, ^3J = 9.0 Hz, 1H, CH), 5.92 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.71 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.77 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 166.4, 154.8, 152.2, 151.1, 143.8, 132.0, 130.7, 130.6, 128.1, 126.2, 108.1, 106.4, 78.6, 52.4, 48.4, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3239, 3125, 2980, 1720, 1702, 1361, 1260, 1237, 1171, 1091, 1070, 1021, 790 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}BrNO_5$ $[M+H]^+$ = 424.0754, found = 424.0746.

Methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-4-iodobenzoate (4o): colorless crystals (0.95 g, 85%), mp 117−118 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 7.99 (br s, 1H, H_{Ar}), 7.94 (d, ^3J = 9.0 Hz, 1H, NH), 7.80 (dd, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1H, H_{Ar}), 7.54 (d, ^3J = 8.2 Hz, 1H, H_{Ar}), 6.65 (d, ^3J = 9.0 Hz, 1H, CH), 5.91 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 5.70 (d, ^3J = 3.1 Hz, 1H, H_{Fur}), 3.76 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 166.6, 154.8, 152.3, 151.1, 143.1, 136.5, 136.4, 131.5, 128.5, 108.0, 106.3, 100.3, 78.5, 52.3, 48.3, 28.2 (3C), 13.3 ppm; IR (neat) ν_{max} = 3242, 3123, 2980, 1721, 1699, 1360, 1262, 1237, 1170, 1084, 1070, 1021, 791 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{23}INO_5$ $[M+H]^+$ = 472.0615, found = 472.0626.

Methyl 6-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-3-chloro-2-nitrobenzoate (4p): colorless solid (0.55 g, 54%), mp 145−146 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ = 8.13 (d, ^3J = 8.6 Hz, 1H, NH), 8.01 (d, ^3J = 8.5 Hz, 1H, H_{Ar}), 7.69 (d, ^3J = 8.5 Hz, 1H, H_{Ar}), 6.20 (d, ^3J = 8.6 Hz, 1H, CH), 5.99 (br s, 2H, H_{Fur}), 3.77 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3), 1.37 (s, 9H, *t*-Bu) ppm; ^{13}C NMR (100 MHz, DMSO-*d*^{6}) δ = 163.5, 154.8, 151.8, 150.5, 147.0, 140.2, 133.4, 131.6, 126.6, 123.9, 109.0, 106.6, 78.9, 53.7, 48.7, 28.1 (3C), 13.3 ppm;

IR (neat) ν_{max} = 3321, 2982, 1746, 1685, 1545, 1523, 1367, 1298, 1242, 1217, 1160, 790 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{22}ClN_2O_7$ $[M+H]^+$ = 425.1110, found = 425.1121.

General two-step procedure for the preparation of 11a-e: *m*-CPBA (77% w/w, 0.35 g, 1.56 mmol) was added to a stirred and cooled solution of methyl 2-{[(*tert*-butoxycarbonyl)amino](5-methylfuran-2-yl)methyl}-benzoate **4** (1.0 mmol) in CH_2Cl_2 (3 ml) at 0 ºC (ice/water bath). The reaction mixture was stirred at the same temperature for 2 h until disappearance of the starting material (TLC control). Then the reaction mixture was filtered from the precipitated *m*-chlorobenzoic acid and filter pad was washed with cooled CH_2Cl_2 (2 × 1 ml). The combined filtrates were diluted with more CH_2Cl_2 (5 ml), cooled to 0 ºC, washed with saturated aqueous $NaHCO_3$ (2 × 3 ml), water (2 ml) and brine (2 ml), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (2 ml) and 4.0 M HCl in 1,4-dioxane (1 ml) was added at room temperature. The reaction mixture was allowed to stir for 3 h. After completion of the reaction (TLC control) the volatiles were removed by evaporation *in vacuo*. The residue was suspended in CH_2Cl_2 (15 ml) and the resulting pyridine hydrochloride was neutralized by washing with saturated aqueous $NaHCO_3$ (2 × 5 ml), water (3 ml) and brine (3 ml). The organic extract was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc as eluent) to afford the corresponding 2-methyl-6*H*-isochromeno[4,3-*b*]pyridin-6-ones **11a-e** (compound **11c** was purified by passing through a thin layer of silica gel with petroleum ether/EtOAc and subsequent recrystallization from CH_2Cl_2/petroleum ether mixture). Analytical samples were obtained by recrystallization from CH_2Cl_2/petroleum ether mixture.

2-Methyl-6*H*-isochromeno[4,3-*b*]pyridin-6-one (11a): colorless needles (0.14 g, 65%), mp 139−140 ºC (CH_2Cl_2/petroleum ether) (lit.: 139−140 ºC).[29a] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70-8.62 (m, 1H, H_{Ar}), 8.38-8.30 (m, 1H, H_{Ar}), 7.90-7.83 (m, 1H, H_{Ar}), 7.69-7.61 (m, 1H, H_{Ar}), 7.51 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 7.24 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 2.65 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6, 155.1, 146.0, 135.9, 135.6, 135.1, 130.3, 130.1, 125.1, 124.8, 123.5, 122.5, 24.3 ppm; IR (neat) ν_{max} = 3080, 2924, 1728, 1574, 1481, 1436, 1270, 1244, 1226, 1049, 825, 734 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_{10}NO_2$ $[M+H]^+$ = 212.0706, found = 212.0712.

8-Bromo-2-methyl-6*H*-isochromeno[4,3-*b*]pyridin-6-one (11b): colorless needles (0.18 g, 61%), mp 191−192 ºC (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (d, ^3J = 8.5 Hz, 1H, H_{Ar}), 8.43 (d, ^4J = 2.1 Hz, 1H, H_{Ar}), 7.93 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1H, H_{Ar}), 7.50 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 7.26 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 2.64 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 155.5, 145.9, 138.2, 134.9, 134.6, 132.6, 125.3, 125.22, 125.17, 124.6, 123.8, 24.3 ppm; IR (neat) ν_{max} = 3086, 2921, 1728, 1585, 1466, 1308, 1254, 1219, 1196, 841, 830, 772, 750 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_9BrNO_2$ $[M+H]^+$ = 289.9811, found = 289.9815.

2-Methyl-8-nitro-6*H*-isochromeno[4,3-*b*]pyridin-6-one (11c): yellow crystals (0.16 g, 61%), mp 223−224 ºC (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.15 (dd, ^4J = 2.4 Hz, ^5J = 0.6 Hz, 1H, H_{Ar}), 8.86 (dd, ^3J = 8.8 Hz, ^5J = 0.6 Hz, 1H, H_{Ar}), 8.64 (dd, ^3J = 8.8 Hz, ^4J = 2.4 Hz, 1H, H_{Ar}), 7.60 (d, ^3J = 8.5 Hz, 1H, H_{Pyr}), 7.39 (d, ^3J = 8.5 Hz, 1H, H_{Pyr}), 2.69 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8, 156.3, 148.7, 147.3, 140.6, 133.7, 129.1, 126.9, 125.9, 125.6, 125.5, 123.2, 24.3 ppm; IR (neat) ν_{max} = 3092, 2928, 1748, 1732, 1583, 1525, 1469, 1342, 1255, 1216, 1097, 876, 837, 762, 736 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_9N_2O_4$ $[M+H]^+$ = 257.0557, found = 257.0564.

8,9-Dimethoxy-2-methyl-6*H*-isochromeno[4,3-*b*]pyridin-6-one (11d): colorless solid (0.17 g, 62%), mp 217−219 ºC (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (s, 1H, H_{Ar}), 7.62 (s, 1H, H_{Ar}), 7,44 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 7.15 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 4.09 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3, 155.3, 154.7, 151.2, 145.5, 135.5, 131.1, 124.8, 123.9, 115.7, 110.0, 104.0, 56.6, 56.4, 24.2 ppm; IR (neat) ν_{max} = 3087, 2972, 1714, 1595, 1504, 1463, 1447, 1398, 1304, 1257, 1242, 1222, 1153, 1044, 1029, 876, 821, 787, 751 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{14}NO_4$ $[M+H]^+$ = 272.0917, found = 272.0926.

9-Bromo-2-methyl-6*H*-isochromeno[4,3-*b*]pyridin-6-one (11e): colorless solid (0.20 g, 68%), mp 238−239 ºC (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.80 (d, ^4J = 2.0 Hz, 1H, H_{Ar}), 8.18 (d, ^3J = 8.5 Hz, 1H, H_{Ar}), 7.76 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H, H_{Ar}), 7.53 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 7.28 (d, ^3J = 8.4 Hz, 1H, H_{Pyr}), 2.66 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0, 155.5, 146.5, 137.2, 134.3, 133.7, 131.7, 131.1, 126.5, 125.6, 125.3, 121.1, 24.3 ppm; IR (neat) ν_{max} = 3080, 2922, 1750, 1584, 1560, 1479, 1264, 1224, 1076, 1040, 871, 831, 749 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_9BrNO_2$ $[M+H]^+$ = 289.9811, found = 289.9814.

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Keywords: Sustainable chemistry • Iodine • Multicomponent reactions • Fused-ring systems • 6*H*-Isochromeno[4,3-*b*]pyridine-6-ones

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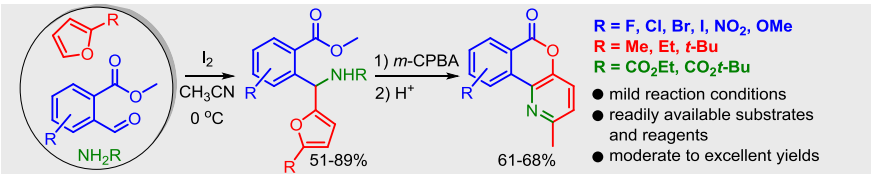

Straightforward functionalization of furans *via* a three-component Mannich-type condensation reaction with methyl 2-formylbenzoates and carbamates was accomplished. The synthetic utility of the resulting N-Boc arylfurfuryl amines was demonstrated by a practically useful two-step strategy leading to 6*H*-isochromeno[4,3-*b*]pyridin-6-ones finding application as perspective cyclometalating ligands for OLEDs.

Furan Recyclizations

*Pavel M. Shpuntov, Alexandra A. Kolodina, Maxim G. Uchuskin and Vladimir T. Abaev**

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Furan ring opening − pyridine ring closure: an efficient approach towards 6*H*-isochromeno[4,3-*b*]pyridin-6-ones from readily available furans and phthalaldehydic acid methyl esters