General Synthetic Approach to 4-Substituted 2,3-Dihydrofuro[2,3-*b*]pyridines and 5-Substituted 3,4-Dihydro-2*H*-pyrano[2,3-*b*]pyridines

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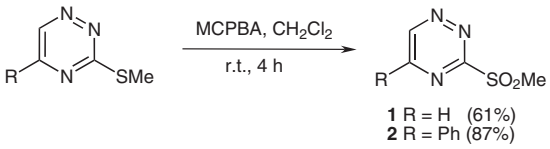
Abstract: An efficient strategy for the synthesis of functionalised 2,3-dihydrofuro[2,3-*b*]pyridines and 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines is reported. The strategy is based on an intramolecular inverse–electron-demand Diels–Alder reaction starting from 1,2,4-triazines appropriately functionalised with alkynes, followed by various cross-coupling reactions (Suzuki, Stille, and Sonogashira).

Key words: inverse-electron-demand Diels–Alder reactions, dihydrofuro[2,3-*b*]pyridines, dihydropyrano[2,3-*b*]pyridines, cycloaddition, microwave activation

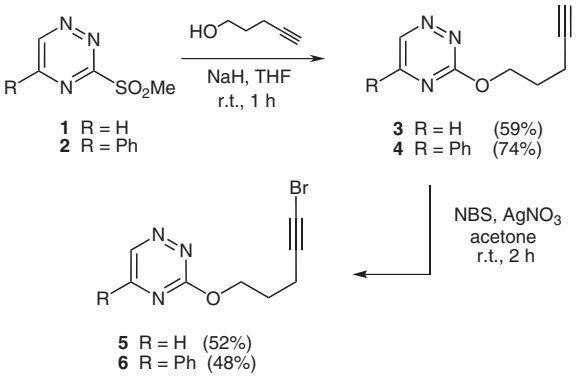
The inverse-electron-demand Diels–Alder cycloaddition between electron-deficient heteroaromatic azadienes and electron-rich dienophiles is a fundamental reaction for the construction of a wide variety of fused heterocyclic systems.[1] Among electron-deficient heteroaromatic azadienes, our group and others have been particularly interested in the use of 1,2,4-triazines because of their propensity to undergo [4+2] cycloaddition reactions across the C3/C6 diene (with subsequent elimination of molecular nitrogen) with alkynes.[2]

We recently reported that intramolecular Diels–Alder reaction of 1,2,4-triazines tethered to an alkyne by an ether linker allowed easy access to substituted 2,3-dihydrofuro[2,3-*b*]pyridines and 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines[2a] that are of interest for their structural similarities to known biologically active quinolines, substituted pyridines, and chromanes.[3] Our initial strategy involved the introduction of a substituent at the terminal position of the alkyne via Sonogashira coupling prior to the Diels–Alder cycloaddition. Nevertheless, this route showed some limitations; for example, only coupling reactions occurring on alkynes were tolerated before the cyclisation step. We sought for an alternative methodology that would not only extend the substitution pattern on the products but also allow functionalisation to be carried after the cycloaddition step.

Our strategy involves the initial functionalisation of the 1,2,4-triazine ring at C-3 with different alkoxy nucleophiles. Depending on the substituent on the starting triazine, the leaving group can either be a sulfone or a halogen, the first one being more useful due to its ready availability. Thus, 3-methylsulfanyl-1,2,4-triazines **1** and **2** were synthesized by oxidation of the corresponding thioethers with MCPBA (Scheme 1).[2m] The difficulties in isolating water-sensitive compound **1** were in part solved by precipitation of the triazine from the crude reaction mixture employing a petroleum ether–ethyl acetate (60:40) mixture.



Scheme 1 Synthesis of the starting 3-methylsulfanyl-1,2,4-triazines **1** and **2**



Scheme 2 Synthesis of bromoalkynes **5** and **6**

Nucleophilic displacement of methylsulfinate from **1** and **2** by the sodium salt of homopropargylic alcohol afforded 3-(4-pentynyloxy)-1,2,4-triazines **3** and **4** following reported procedures.[2m] The bromine was then introduced selectively at the terminal position of the alkynes following the procedure of Li and Wu,[4] allowing the formation of the corresponding bromoalkynes **5** and **6** in 52% and 48% yield, respectively (Scheme 2).

Using this strategy to prepare 3-(3-butynyloxy)-1,2,4-triazines **8** and **9** gave only low yields of the expected prod-

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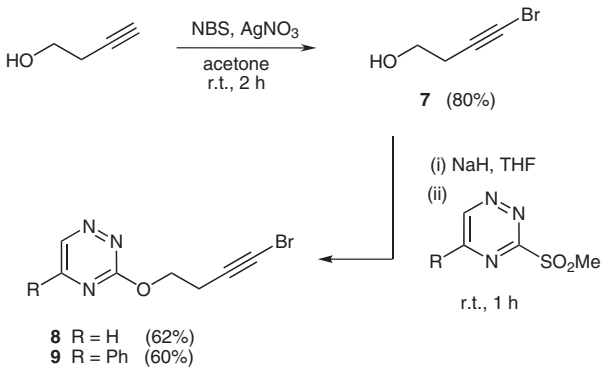


Scheme 3 Synthesis of bromoalkynes **8** and **9**

ucts. Hence, the method was adapted and the bromine introduced prior to the addition to the triazines; 4-bromobut-3-yn-1-ol (**7**) was obtained in 80% yield by treating commercially available propargylic alcohol with NBS. Subsequent deprotonation of **7** with NaH followed by the addition of 1,2,4-triazines **1** and **2** in THF produced **8** and **9** in 62% and 60% yield, respectively (Scheme 3).

Having the tethered triazines **5**, **6** and **8**, **9** in hand, we investigated the cycloaddition reaction. We have already reported the inverse-electron-demand Diels–Alder reaction with arylalkenyl triazines to be very efficient under microwave heating.[2a] As it allows easy access to high temperatures very rapidly, higher yields were achieved in short reaction times. Employing the reaction conditions already developed in our laboratory (chlorobenzene as solvent, 180 °C for five–membered-ring formation and 200 °C for six-membered-ring formation),[5] the corresponding furo- and pyranopyridines were obtained in high yields. Results are collected in Table 1.

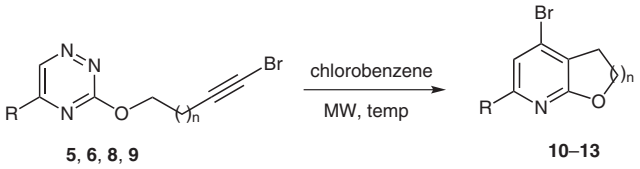
As anticipated, no dehalogenation occurred under the conditions required for the cyclisation. Notably, the introduction of a halogen at the *para* position of the pyridine ring provides a remarkable advantage by allowing further variations on these bicyclic products. Indeed, bromopyridines have been widely used for the synthesis of more complex structures employing metal-catalysed cross-coupling, and our aim was to determine whether these methodologies would be applicable with these substrates.

First, the Suzuki cross-coupling reaction with fused pyridines **10**–**13** was examined. 2-Furylboronic acid was chosen as test substrate under standard conditions [$Pd(PPh_3)_4$, Na_2CO_3 in a DME–H_2O (2:1) solvent mixture] and products **14**–**17** were isolated (Table 2).[6]

The ready coupling of **10**–**13** with arylboronic acids encouraged us to examine the Stille cross-coupling of bromofuro- and bromopyranopyridines **10**–**13** with allyltributyltin.[7] The coupled products **18**–**21** were isolated (Table 3).

Next, the Sonogashira coupling between aryl bromides **12**, **13** and terminal alkynes (trimethysilylacetylene, phenylacetylene) was studied. Thus, treating compounds

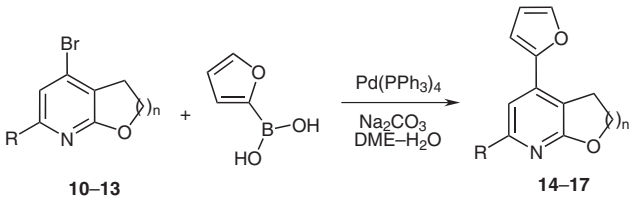
Table 1 Intramolecular Inverse-Electron-Demand Diels–Alder Reactions under Microwave Irradiation



Entry	R	Product	Temp (°C)	Time (h)	Yield (%)[a]
1	H	**10**, *n* = 1	180	0.75	82
2	H	**11**, *n* = 2	200	4	68
3	Ph	**12**, *n* = 1	180	1	75
4	Ph	**13**, *n* = 2	200	2	71

[a] Yield of pure isolated product.

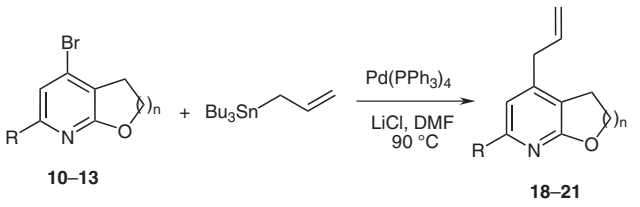
Table 2 Palladium-Catalysed Suzuki Cross-Coupling of Fused Pyridines **10**–**13** with 2-Furylboronic Acid



Entry	R	Product	Time (h)	Yield (%)[a]
1	H	**14**, *n* = 1	2	74
2	H	**15**, *n* = 2	6	71
3	Ph	**16**, *n* = 1	12	64
4	Ph	**17**, *n* = 2	48	75

[a] Yield of pure isolated product.

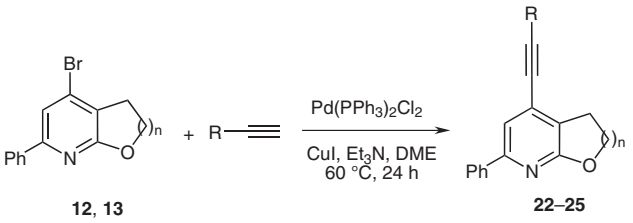
Table 3 Palladium-Catalysed Stille Cross-Coupling of Fused Pyridines **13**–**16** with Allyltributyltin



Entry	R	Product	Time (h)	Yield (%)[a]
1	H	**18**, *n* = 1	2	62
2	H	**19**, *n* = 2	2	67
3	Ph	**20**, *n* = 1	3	98
4	Ph	**21**, *n* = 2	3	79

[a] Yield of pure isolated product.

Table 4 Palladium-Catalysed Sonogashira Cross-Coupling of Fused Pyridines **12** and **13** with Terminal Alkynes



Entry	R	Product	Yield (%)[a]	RSM[b] (%)
1	C_6H_5	**22**, *n* = 1	52	30
2	C_6H_5	**23**, *n* = 2	48	19
3	TMS	**24**, *n* = 1	46	30
4	TMS	**25**, *n* = 2	44	38

[a] Yield of pure isolated product.
[b] RSM = recovered starting material.

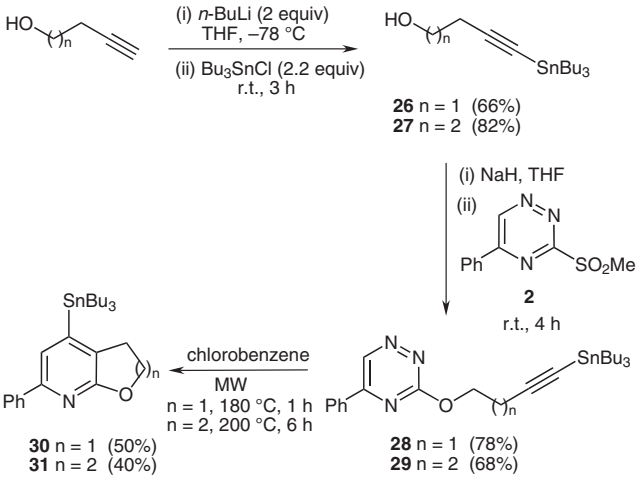
12 and **13** in nonoptimised experimental conditions, that is, DME with $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI, Et_3N, and terminal alkynes, gave cross-coupling products **22**–**25**.[8] The results are summarized in Table 4. This synthetic sequence was, however, less efficient than the Suzuki and the Stille couplings, **22**–**25** being only obtained in 19–38% yield along with remaining starting material. No degradation occurred during the reaction and the starting furo- and pyranopyridines could be recovered.

Although halopyridines are extremely useful intermediates, other potentially reactive groups on the 4-position were envisaged. We anticipated that 4-tributyltin furopyridines and 5-tributyltin pyranopyridines would give access to further diversity onto the pyridine ring as some sensitive, or difficult to obtain coupling partners could also be introduced easily.

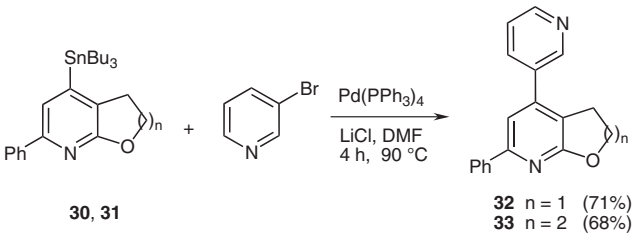
The tin-substituted triazine derivatives required for the cycloaddition were prepared by a two-step procedure. First, tri-*n*-butyltin was introduced by transmetallation of the respective terminal alkynes (*n*-BuLi, Bu_3SnCl, THF, –78 °C). Deprotonation of the hydroxyl group of **26**–**27** was performed using NaH followed by addition of 1,2,4-triazine **5** in THF at room temperature to afford the expected derivatives **28** and **29** in good yields. Subsequent cycloaddition reaction of stannyl derivatives **28** and **29** was carried out under microwave irradiation in a sealed tube under our optimal conditions to yield disubstituted heterocycles **30** and **31** in 50% and 40%, respectively (Scheme 4).

To demonstrate the utility of pyridines **30** and **31**, Stille couplings with 3-bromopyridine were carried out. In DMF at 90 °C for 4 hours, using 5% mol of $Pd(PPh_3)_4$ and LiCl, the expected products **32** and **33** were formed in 71% and 68% yield, respectively (Scheme 5).[9]

In conclusion, we have demonstrated that the intramolecular Diels–Alder reaction is a powerful methodology for



Scheme 4 Synthesis of stannyl derivatives **30** and **31**



Scheme 5 Stille cross-coupling reaction from stannane derivatives **32**, **33**, and 3-bromopyridine

the synthesis of fused pyridine heterocycles. Reactive atoms, such as bromine or tin, are compatible with the synthetic sequence and can in turn be easily replaced by various functional groups. This novel approach allows a higher diversity of substituents on the *para* position of the pyridine ring via various cross-coupling reactions. The extension of this work to the preparation of other scaffolds with potential biological properties including fused heterocyclic moieties is currently under investigation.

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References and Notes

(1) (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (c) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885.
(2) (a) Hajbi, Y.; Suzenet, F.; Khouili, M.; Lazar, S.; Guillaumet, G. *Tetrahedron* **2007**, *63*, 8286. (b) Lindsley, C. W.; Layton, M. E. In *Science of Synthesis*, Vol. 17; Weinreb, S. M., Ed.; Thieme: NewYork, **2003**, 357–447. (c) Branowska, D.; Ostrowski, S.; Rykowski, A. *Chem. Pharm. Bull.* **2002**, *50*, 463. (d) Sauer, J.; Heldmann, D. K.; Pabst, G. R. *Eur. J. Org. Chem.* **1999**, 313. (e) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807. (f) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280. (g) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**,

27, 2107. (h) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1989**, *54*, 4984. (i) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287. (j) Seitz, G.; Görge, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355. (k) Buysens, K. J.; Vandenberghe, D. M.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron* **1995**, *51*, 12463. (l) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 431. (m) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145. (n) Taylor, E. C. *Bull. Soc. Chim. Belg.* **1988**, *97*, 599. (o) Haenel, F.; John, R.; Seitz, G. *Arch. Pharm.* **1992**, *325*, 349. (p) Frissen, A. E.; Marcelis, A. T. M.; Buurman, D. G.; Pollmann, C. A. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5611. (q) Seitz, G.; Dietrich, S.; Gorge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747. (r) Seitz, G.; Dietrich, S. *Arch. Pharm.* **1985**, *318*, 1048. (s) Seitz, G.; Dietrich, S. *Arch. Pharm.* **985**, *318*, 1051. (t) Lipińska, T.; Branowska, D.; Rykowski, A. *Chem. Heterocycl. Compd.* **1999**, *35*, 334.

(3) (a) Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*, Vol. 6; Pergamon Press: Oxford, **1990**. (b) Lochead, A.; Jegham, S.; Galli, F.; Gallet, T. WO 9842713, **1998**; *Chem. Abstr.* **1998**, 672553. (c) Van Lommen, G. R. E.; Fernandez-Gadea, F. J.; Andres-Gil, J. I.; Matesanz-Ballesteros, M. E. WO 9505381, **1995**; *Chem. Abstr.* **1995**, 557282. (d) Comoy, C.; Marot, C.; Podona, T.; Baudin, M. L.; Morin-Allory, L.; Guillaumet, G.; Pfeiffer, B.; Caignard, D. H.; Renard, P.; Rettori, M. C.; Adam, G.; Guardiola-Lemaitre, B. *J. Med. Chem.* **1996**, *39*, 4285. (e) Podona, T.; Guardiola-Lemaitre, B.; Caignard, D.-H.; Adam, G.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Med. Chem.* **1994**, *37*, 1779.

(4) Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427.

(5) **General Procedure for the Intramolecular Inverse-Electron-Demand Diels–Alder Reaction for Compounds 10–13**

Bromoalkyne **5**, **6** or **8**, **9** (0.33 mmol) was dissolved in chlorobenzene (2 mL) and heated at 180–200 °C under microwave irradiation (3–6 bar of pressure can be involved). The reaction was monitored by TLC (for reaction time and temperature, see Table 1). After complete conversion of the starting material, the reaction was purified by chromatography (eluent: PE–EtOAc, 8:2) to give the desired products **10**–**13**.

4-Bromo-2,3-dihydrofuro[2,3-*b*]pyridine (10)

Yield 82%, as a colorless oil. IR (KBr): 3000, 2908, 1577, 945, 713, 698, 614 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 5.6 Hz, 1 H), 6.91 (d, *J* = 5.6 Hz, 1 H), 4.64 (t, *J* = 8.8 Hz, 2 H), 3.23 (t, *J* = 8.8 Hz, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 168.4 (C), 147.2 (CH), 129.9 (C), 121.6 (C), 119.8 (CH), 68.4 (CH_2), 29.2 (CH_2). MS: *m/z* [M + 1] = 200 (for ^{79}Br) and 202 (for ^{81}Br). HRMS: *m/z* calcd for $C_7H_7NO^{79}Br$ [M + 1]$^+$: 199.9709; found: 199.9709.

(6) **General Procedure for the Suzuki Cross-Coupling Reaction for Compounds 14–17**

A solution of compounds **10**–**13** (0.73 mmol) in ethylene glycol dimethyl ether (5 mL, freshly distilled and degassed) under argon was treated with furan-2-boronic acid. A solution of Na_2CO_3 (154 mg, 1.45 mmol) in H_2O (2.5 mL) was added before adding $Pd(PPh_3)_4$ (42 mg, 0.036 mmol), and the mixture was stirred vigorously at 75 °C and monitored by TLC (for reaction time, see Table 2). After complete conversion of the starting material, the mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine, dried over $MgSO_4$, evaporated, and purified by column chromatography (eluent: PE–EtOAc) to give the corresponding compounds **14**–**17**.

4-Fur-2-yl-2,3-dihydrofuro[2,3-*b*]pyridine (14)

Yield 74%, as a yellow solid; mp 93–95 °C. IR (KBr): 2971, 1605, 1451, 1229, 1125, 1025, 807 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 5.3 Hz, 1 H), 7.56 (t, *J* = 1.2 Hz, 1 H), 7.05 (d, *J* = 5.3 Hz, 1 H), 6.74 (d, *J* = 3.4 Hz, 1 H), 6.56 (dd, *J* = 1.2, 3.4 Hz, 1 H), 4.65 (t, *J* = 8.4 Hz, 2 H), 3.42 (t, *J* = 8.4 Hz, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.5 (C), 151.0 (C), 146.8 (CH), 143.7 (CH), 135.1 (C), 113.4 (C), 112.0 (CH), 111.5 (CH), 110.5 (CH), 68.8 (CH_2), 29.1 (CH_2). MS: *m/z* [M + 1] = 188. HRMS: *m/z* calcd for $C_{11}H_{10}NO_2$ [M + 1]$^+$: 188.0694; found: 188.0704.

(7) **General Procedure for the Stille Cross-Coupling Reaction for Compounds 18–21**

To a suspension of freshly prepared $Pd(PPh_3)_4$ (25 mg, 0018 mmol) and LiCl (42 mg, 0.99 mmol) in dry DMF was added a solution of compounds **14**–**17** (0.36 mmol) and tributyl-2-propenylstannane (169 μL, 0.54 mmol) in dry DMF under argon. After 2–3 h (see Table 3) under reflux at 90 °C, the reaction mixture was cooled to r.t. and quenched with brine (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), the organic phase were collected, dried over $MgSO_4$, and the solvents were removed under reduced pressure. Flash column chromatography (eluent: PE–EtOAc, 9:1) of the crude gave the desired products **18**–**21**.

4-Allyl-2,3-dihydrofuro[2,3-*b*]pyridine (23)

Yield 62%, as a yellow oil. IR (KBr): 2976, 2906, 1639, 1608, 1588, 1227 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 5.3 Hz, 1 H), 6.62 (d, *J* = 5.3 Hz, 1 H), 5.95–5.79 (m, 1 H), 5.16–5.03 (m, 2 H), 4.60 (t, *J* = 8.4 Hz, 2 H), 3.30 (d, *J* = 6.6 Hz, 2 H), 3.17 (t, *J* = 8.4 Hz, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 168.8 (C), 146.7 (CH), 146.3 (C), 134.0 (CH), 118.3 (C), 117.2 (CH_2), 117.1 (CH), 68.8 (CH_2), 37.3 (CH_2), 26.8 (CH_2). MS: *m/z* [M + 1] = 162. HRMS: *m/z* calcd for $C_{10}H_{12}NO$ [M + 1]$^+$: 162.0906; found: 1162.0919.

(8) **General Procedure for the Sonogashira Cross-Coupling Reaction for Compounds 22–25**

A solution of the aryl bromide **12** or **13** (1.11 mmol) in anhyd ethylene glycol dimethyl ether (2.0 mL) was treated with the appropriate alkyne (1.11 mmol) and Et_3N (3 mL). After 5 min, CuI (0.021 g, 0.11 mmol) and $Pd(PPh_3)_2Cl_2$ (0.04 mg, 0.06 mmol) were added. The mixture was then stirred vigorously at 60 °C and monitored by TLC. After 24 h, the mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine, and dried over $MgSO_4$, evaporated and purified by column chromatography (eluent: PE–EtOAc, 9:1) to give the corresponding compounds **22**–**25**.

7-Phenyl-4-[2-(trimethylsilyl)ethynyl]-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (25)

Yield 44%, as a dark oil. IR (KBr): 3049, 2248, 1580, 1428, 1352, 1233, 904, 742 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 2 H), 7.43–7.33 (m, 4 H), 4.34 (t, *J* = 5.2 Hz, 2 H), 3,30 (t, *J* = 6.5 Hz, 2 H), 2.06 (m, 2 H), 0.26 (s, 9 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 161.1 (C), 153.8 (C), 138.2 (C), 133.5 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 117.6 (C), 116.4 (CH), 103.7 (C), 100.9 (C), 67.3 (CH_2), 23.6 (CH_2), 21.8 (CH_2), –0.01 (CH_3). MS: *m/z* [M + 1] = 308. HRMS: *m/z* calcd for $C_{19}H_{22}NOSi$ [M + 1]$^+$: 308.1468; found: 308.1471.

(9) **General Procedure for the Stille Reaction with 3-Bromopyridine**

Compounds **32** and **33** were prepared in 70% yield, according to the procedure used for the synthesis of **18**–**21**. The purification was carried out by flash chromatography over SiO_2 (eluent: PE–EtOAc, 8:2 to 6:4).

7-Phenyl-5-pyrid-3-yl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (33)

Yield 68%, as a clear yellow oil. IR (KBr): 3160, 2970, 2253, 1574, 1444, 1002, 906, 740 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 8.63 (d, *J* = 1.2 Hz, 1 H), 8.00 (d, *J* = 6.5 Hz, 2 H), 7.68 (dd, *J* = 1.2 Hz, *J′* = 5.7 Hz, 1 H), 7.43–7.23 (m, 4 H), 7.23 (s, 1 H), 4.40 (t, *J* = 5.0 Hz, 2 H), 2.67 (t, *J* = 6.2 Hz, 2 H), 2.00–1.94 (m, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 161.3 (C), 154.3 (C), 149.5 (CH), 149.3 (CH), 148.8 (C), 138.3 (C), 136.0 (CH), 134.7 (C), 129.1 (CH), 128.7 (CH), 126.8 (CH), 123.4 (CH), 114.9 (C), 113.6 (CH), 67.3 (CH_2), 23.8 (CH_2), 22.0 (CH_2). MS: *m/z* [M + 1] = 289. HRMS: *m/z* calcd for $C_{19}H_{17}N_2O$ $[M + 1]^+$: 289.1350; found: 289.1341.