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A PREPARATIVE ROUTE TO FUSED 4-HYDROXY-3-PHENYLINDENO(BENZOTHIENO)PYRIDIN-2-ONES

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Abstract- Syntheses of fused 4-hydroxy-3-phenylindeno(benzothieno)pyridin-2-one derivatives **(1a,b)** are described.

From extensive reseach over the last twenty years, it has been concluded that L-glutamate is the major fast excitatory neurotransmitter in the mammalian central nervous system (CNS). [1] Glutamate plays an essential role in many physiological CNS functions through the activation of three major types of postsynaptic ionotropic receptors designated according to the non-natural substances that selectively activate them: NMDA (*N*-methyl-D-aspartate), AMPA (2-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid) and kainate receptors. [2] In addition, glutamate activates several types of metabotropic receptors signaling through a G-protein coupled. [3] Competitive or non-competitive antagonists of these biological targets (such as AMPA receptor) acting at the *N*-methyl-D-aspartate (NMDA) receptor subtype have been proposed as potential neuroprotective agents in human. [4] In connection with our own research projects directed towards the synthesis of such potent AMPA receptor antagonists, [5] an easy and efficient method leading to fused 4-hydroxy-3-phenylbenzothienopyridin-2-one (**1a**) and 4-hydroxy-3-phenylindenopyridin-2-one (**1b**) has been developed (Figure 1).

To our knowledge, only 4-hydroxy-3-phenylpyridin-2-one (**2**), [6] 4-hydroxy-3-phenyl-5,6,7,8-tetrahydro-quinolin(1,8-naphthyridine)-2-one (**3a,b**), [7] 4-hydroxy-3-phenylquinolin-2-one (**4**), [8] 4-hydroxy-3-phenyl-1,8(1,5)-naphthyridin-2-one (**5a,b**), [9] 5-hydroxy-6-phenylpyrido[2,3-*d*]pyrimidin-7-one (**5c**), [10] pyridino-[2,3-*d*]pyrimidinone (**6**) [11] and 4-hydroxy-5-phenylthieno[2,3-*b*]pyridin-6-one derivatives (**7**) [11] were described (Figure 1).We therein report the efficient synthesis of new fused pyridin-2-one derivatives (**1a**) and (**1b**) [13] bearing original fused moieties**,** within a three steps synthesis as summarized in Schemes 1 and 3.

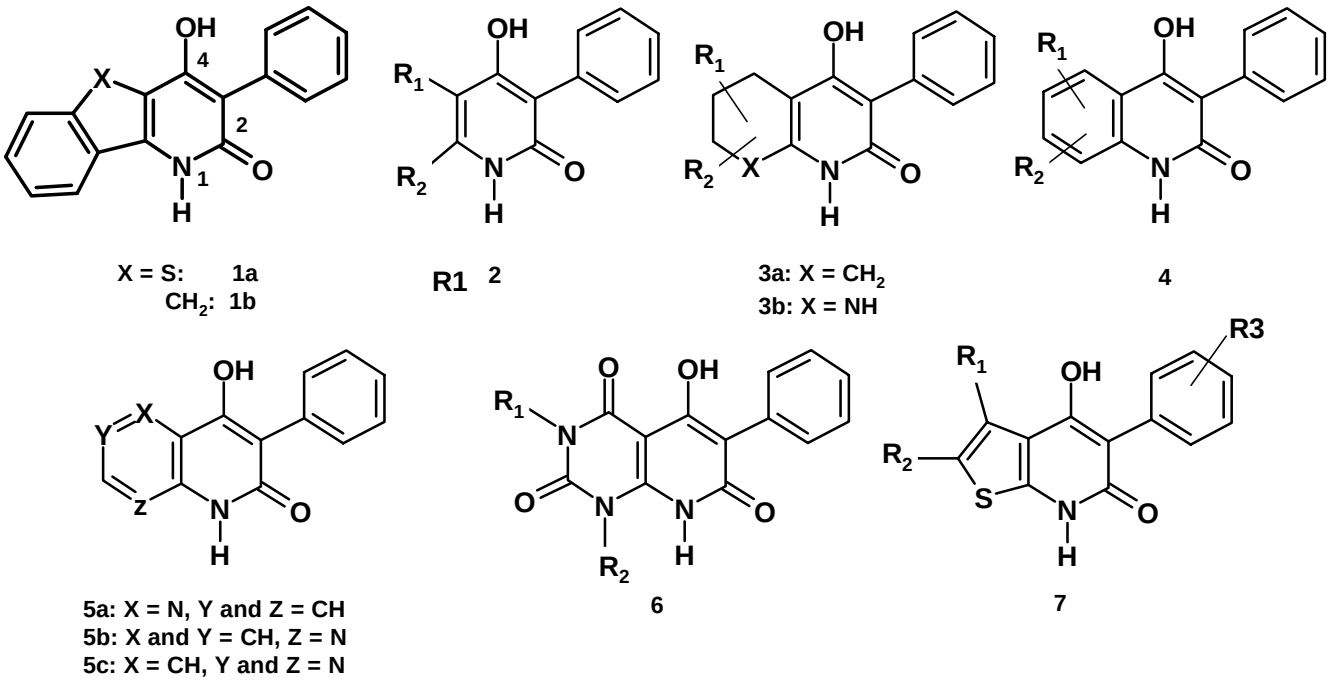
As illustrated in Scheme 1, condensation of 2-cyanothiophenol (**8**) with ethyl bromoacetate in the presence of 5% aq. NaOH afforded the ethyl acetate derivative (**9**) with 53% yield. Action of an excess of NaH (2 eq.) with **9** in THF at reflux did not lead to the expected cyclic compound (**10**) but to the 3-aminobenzo[*b*]thiophene (**11**) with 40% yield. This synthetic pathway represents an convenient procedure for the preparation of **11**. [14] Changing our mind, and according to the procedure described by K. Clarke and his co-workers, ethyl 3-amino[1]benzothiophene-2-carboxylate (**10**) [15] was easily prepared in a one-step synthesis from **8** by the action of potassium carbonate with ethyl bromoacetate in acetone at reflux with a high yield (81.5%). Then, treatment of **10** with phenylacetyl chloride in the presence of triethylamine at reflux gave **12** with 78.5% yield. Finally, the intramolecular ring closure reaction of the benzothiophene derivative (**12**) was carried out using 3 equivalents of 1M lithium bis(trimethylsilyl)amide (room temperature to reflux) in THF affording the pure 4-hydroxy-3-phenylbenzothienopyridin-2-one (**1a**) with 51% yield.

Our initial strategy to synthesize 4-hydroxy-3-phenylindenopyridin-2-one (**1b**) was to use the indene derivative (**15**) and apply the same synthetic methodology as that for the preparation of **1a**. However, the

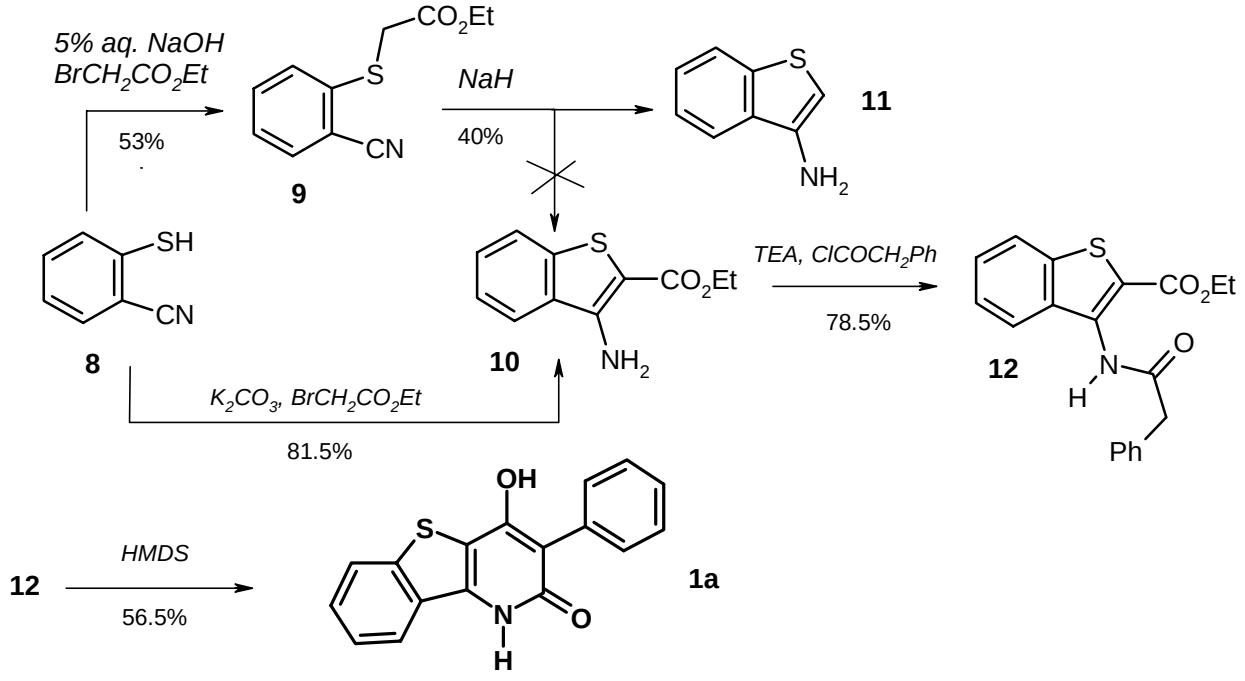
transformation of **14** [16] into **15** proved to be much more challenging than anticipated. Under the standard conditions used – such as : NH_4NO_3, THF, reflux; NH_4OAc, toluene, reflux, Dean-Stark; or gNH_3, toluene, room temperature - the condensation of ammonia could not be achieved and the starting material (**14**) or the corresponding amide was obtained.

On the other hand the starting 2-ethoxycarbonylinden-1-one (**14**) was readily prepared with 61% yield from the commercially available inden-1-one (**13**) using diethyl oxalate in presence of NaH as base in THF at reflux (Scheme 2).

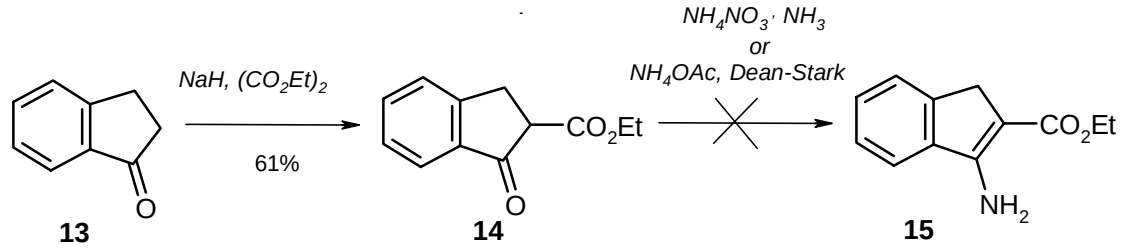
Figure 1



Scheme 1



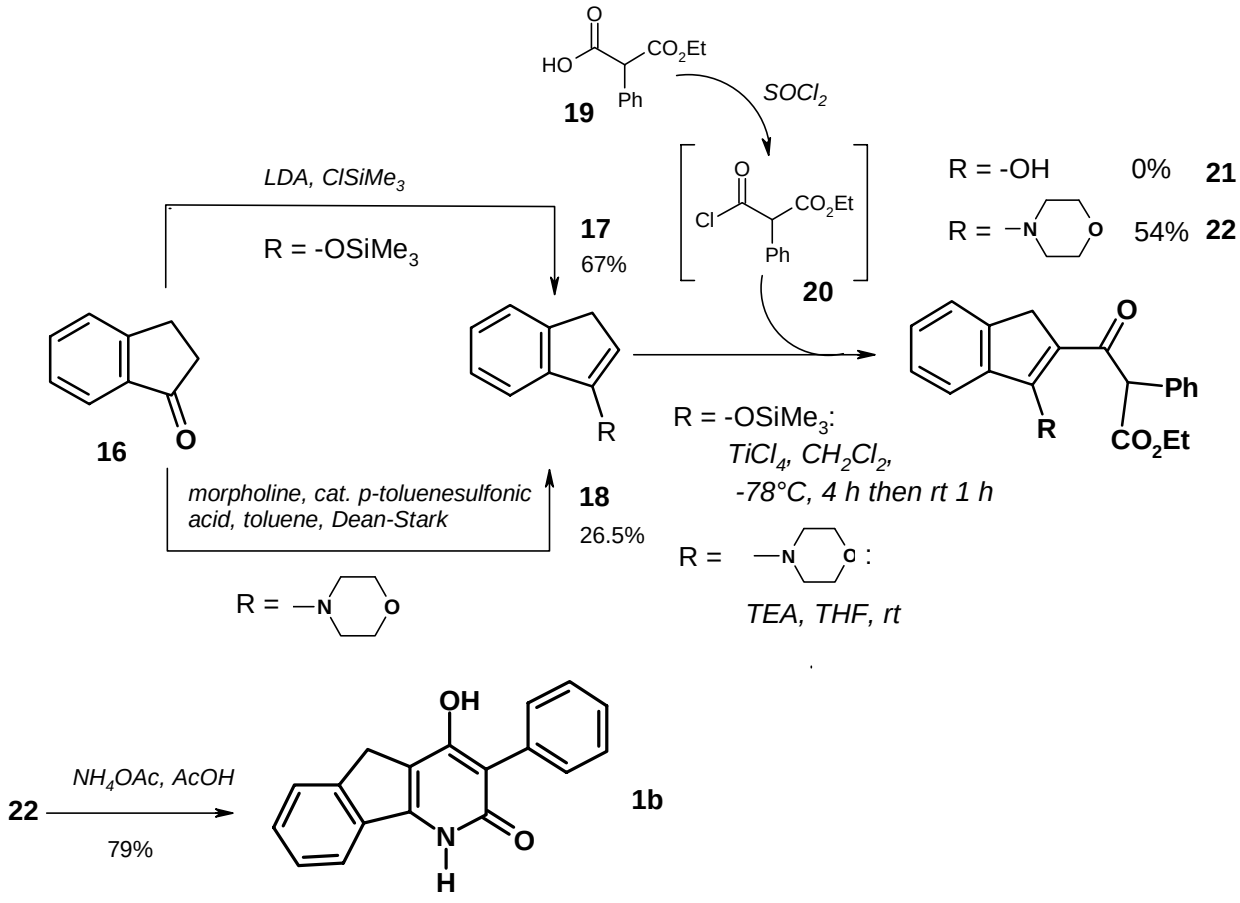
Scheme 2



At this point, we decided to modify our synthetic approach, taking into account the nucleophilic site offered by the β-carbon atom of the corresponding enol silyl ether or enamine of inden-1-one (**13**). As shown in Scheme 3, the synthesis of **1b** started with the preparation of **17** [17] and **18** [18] which were obtained from **16** with moderate to good yields by the action of either Me_3SiCl in presence of LDA in dry THF (-75°C to room temperature) or morpholine in dry toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid at reflux using a water trap separator. Then, condensation of **18** with ethyl 2-phenyl-3-chloro-3-oxopropionate (**20**) in the presence of TEA in THF at room temperature generated the expected indene derivative (**22**) with 54% yield, whereas the treatment of **17** with **20** under standard conditions [$TiCl_4$ (1 eq.), CH_2Cl_2, -78°C 4 h then room temperature 1 h] did not furnish the required adduct (**21**). Finally the targeted 4-hydroxy-3-phenylindenopyridin-2-one (**1b**) was obtained by the treatment of **22** with an excess of ammonium acetate in presence of acetic acid at reflux. Pure **1b** was isolated with 79% yield.

As a conclusion, we have developed the rapid synthetic route towards the new fused pyridine-2-one derivatives (**1a**) and (**1b**) which are readily adaptable to scale-up.

Scheme 3



EXPERIMENTAL

Commercially available reagents were used as received from suppliers, while solvents were dried in the classical way. The progresses of the reactions were monitored using TLC on silica gel plates (Merck Kieselgel $60F_{254}$). Melting points were determined on a Reicher-Kofler instrument and are uncorrected. ^1H NMR spectra were recorded using AC 200, AC 300 Bruker spectrometers. Chemical shifts are given in ppm (δ DMSO-d_6 = 2.5 or $CDCl_3$ = 7.24) while coupling constants J are expressed in Hz. IR spectra were recorded on a FT-IR 60SX-R Nicolet spectrophotometer, samples being dispersed as a KBr pellet. MS spectra were obtained on a Finnigan 4000 (EI, 70eV) mass spectrometer.

Ethyl 3-amino[1]benzothiophene-2-carboxylate (10)

To a stirred solution of 2-cyanothiophenol (16 g, 0.12 mol) and potassium carbonate (36 g, 0.13 mol) in dry acetone (250 mL) - kept under nitrogen atmosphere – ethyl bromoacetate (14.5 mL, 0.13 mol) was added dropwise at rt. The reaction mixture was heated to reflux for 7 h and then cooled to rt. The mixture was filtered through a small Celite column, and the filtrate was concentrated *in vacuo* to afford 21.4 g (81.5%) of **10** as a cream solid which was used in the next step without further purification, R_f = 0.4 in cyclohexane/ethyl acetate mixture (80/20).

Ethyl 3-phenylacethylaminobenzo[*b*]thiophene-2-carboxylate (12)

To a stirred solution of **10** (6 g, 0.027 mol) and TEA (7.5 mL, 0.054 mol) in dry THF (70 mL) - under a nitrogen atmosphere at 0°C - was added dropwise phenylacetyl chloride (4 mL, 0.030 mol). The reaction mixture was stirred overnight and allowed to reach at rt and then concentrated *in vacuo*. The resulting red oil was purified by flash chromatography on silica gel using dichloromethane/cyclohexane (80/20) as eluent to give 7.1 g (78.5%) of **12** as a pale yellow lac, R_f = 0.2 in dichloromethane/cyclohexane mixture (80/20). MS (EI) m/z: 339 ($M^{+\cdot}$, 60%), 221 (100%). NMR (200 MHz, $CDCl_3$) δ : 1.35 (3H, t, *J* = 7, CH_3), 3.84 (2H, s, CH_2), 4.32 (2H, q, *J* = 7, CH_2O), 7.30 to 7.50 (7H, m, aromatics), 7.74 (1H, dd, *J* = 9; 1.5, H7), 8.12 (1H, dd, *J* = 9; 1.5, H4), 9.50 (1H, br s, NH).

4-Hydroxy-3-phenyl[1]benzothieno[3,2-*b*]pyridin-2-one (1a)

To a stirred solution of **12** (1.32 g, 3.9 mmol) in dry THF (80 mL), kept under nitrogen atmosphere, 1M HMDS (11.7 mL, 11.7 mmol) was added dropwise at rt. After 12 h at rt, the mixture was heated at 55°C for 4.5 h and then cooled to rt. Methanol (10 mL) was added and the mixture was concentrated *in vacuo*. The residue was triturated successively in ethyl acetate (100 mL) and 5N NaOH (50 mL). The mixture was washed successively with ethyl acetate (50 mL) and methanol (50 mL) and then acidified with 1N HCl until pH = 1 at rt. The precipitate obtained was filtered off, washed with water until pH = 7 and finally recrystallized from hot DMF/water (1/1) mixture (40 mL) to afford 0.68g (51%) of **1a** as a pale yellow solid (mp 330°C). IR (KBr) : 1620, 1590, 1550, 1350, 1250 cm^{-1}. MS (EI) m/z : 293 ($M^{+\cdot}$, 95%), 176 (100%). NMR (200MHz, DMSO-d_6) δ : 7.20 to 7.70 (7H, m, aromatics), 8.08 (1H, dd, *J* =9; 1.5, H6), 8.46 (1H, dd, *J* = 9; 1.5, H9), 10.80 (1H, br s, OH), 12.60 (1H, br s, H1). Anal. Calcd for $C_{17}H_{11}NO_2S$: C, 69.61 ; H, 3.78 ; N, 4.77 ;S, 10.93. Found : C, 69.28 ; H, 3.75 ; N, 4.57 ; S, 10.56.

3-Morpholino-1*H*-indene (18)

A mixture of 1-indanone (10 g, 76 mmol), morpholine (13.2 mL, 152 mmol) and a catalytic amount of *p*-toluenesulfonic acid in dry toluene (50 mL) was refluxed until the separation of water had ceased (~20 h). Then, the reaction mixture was cooled to rt under nitrogen atmosphere and concentrated *in vacuo* to about one-third volume and then distilled off under vacuum (0.001 psi) to give 4.5 g (26.5%) of **18** as a pale

yellow oil (bp 125-135°C, 0.001 psi) which was used in the next step without further purification.

Ethyl 3-[3-morpholino-1*H*-inden-2-yl]-3-oxo-2-phenylpropionate (22)

To a stirred solution of **18** (16.1 g, 72 mmol) in dry THF (150 mL) - under nitrogen atmosphere - was added dropwise TEA (13.4 mL, 0.1 mol) at rt and then ethyl 2-phenyl-3-chloro-3-oxopropionate (**20**) [prepared from **19** (10 g, 48 mmol) and $SOCl_2$ (60 mL, 0.82 mol)] in dry THF (50 mL). The reaction mixture was maintained at rt for 24 h. The mixture was filtered through a small Celite column, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using a cyclohexane/ethyl acetate mixture (80/20) as eluent to give 10.1g (54%) of **22** as a pale yellow lac, R_f = 0.45 in ethyl acetate/cyclohexane mixture (50/50). MS (EI) m/z : 391 ($M^{+\cdot}$, 5%), 228 (100%), 115 (40%). NMR (300 MHz, DMSO-d_6) δ : 1.20 (3H, t, *J* = 7, CH_3), 3.58 (5H, m, CH_2N and H1), 3.82 (4H, m, CH_2O), 3.93 (1H, d, *J* = 22.5, H1), 4.18 (2H, q, *J* = 7, CH_2O), 5.44 (1H, s, CH side chain), 7.30 to 7.55 (8H, m, aromatics), 7.8 (1H, br d, *J* = 9, H7).

4-Hydroxy-3-phenylindeno[1,2-*b*]pyridin-2-one (1b)

To a stirred solution of **22** (2 g, 5 mmol) in acetic acid (80 mL) was added portionwise ammonium acetate (20 g, 244 mmol) at rt. The reaction mixture was then heated at reflux for 12 h, cooled to rt. The precipitate was filtered off and washed successively with water (150 mL) and acetone (100 mL) to afford a white solid (0.88 g). More water was added to the liquid phases until complete precipitation occurred. The solid (0.48 g) thus obtained was filtered and washed successively with water (50 mL) and acetone (50 mL). The two solids thus obtained were joined and recrystallized from a DMF/water mixture to give 1.16 g (79%) of **1b** as a pale yellow solid (mp 260°C). IR (KBr) :1635, 1565, 1355, 1245 cm^{-1}. MS (EI) m/z : 275 ($M^{+\cdot}$, 100%), 130 (50%). NMR (200 MHz, DMSO-d_6) δ : 3.78 (2H, s, H5), 7.20 to 7.48 (7H, m, aromatics), 7.66 (1H, dd, *J* = 9; 1.5, H6), 8.04 (1H, dd, *J* = 9; 1.5, H9), 10.2 (1H, br s, OH), 12.34 (1H, br s, H1). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53 ; H, 4.76 ; N, 5.09. Found : C, 78.42 ; H, 4.64 ; N, 5.2.

ACKNOWLEDGEMENTS

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14. a) To a stirred suspension of 80% NaH (286 mg, 9.4 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere at rt, was added dropwise a solution of **9** (1 g, 4.5 mmol) in anhydrous THF (10 mL). The mixture was then heated to reflux. After 5 h, the heterogeneous reaction mixture was cooled to rt, and water (10 mL) was added. The reaction mixture was extracted with ether (20 mL) and then with CH_2Cl_2 (20 mL). The aqueous solution was concentrated *in vacuo* and treated with 1N HCl until pH ~ 4. Finally, the solution was extracted with EtOAc (50 mL) and the organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo* to afford **11** as a yellow oil, 330 mg (40%), R_f = 0.30 in dichloromethane/methanol mixture (90/10). b) 3-Aminobenzo[*b*]thiophene was previously prepared by: 1) reduction of 3-nitrobenzo[*b*]thiophene using ethanolic ammonium sulfide with 75% yield. 3-Nitrobenzo[*b*]thiophene was obtained from benzo[*b*]thiophene through the sequence of reactions involving sulfonation, nitration and desulfonation with ~8% overall yield (D. E. Boswell, J. A. Brennan, P. S. Landis, and P. G. Rodewald, *J. Heterocycl. Chem.,* 1968, **5**, 69. 2) thermal decomposition of 3-azidobenzo[*b*]thiophene in diethyl- or dimethylamine in a sealed tube at 90°C with 6-10% yield (M. Toselli, P. Spagnolo, and P. Zanirato, *Gaz. Chim. Ital.,* 1989, **119**, 411).

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