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A novel one-pot synthesis of 7-methoxy-2-arylthieno-[3,2-*b*]pyridine-3-ols in domino fashion

Srinu Puvvala [a,b], Vinod D. Jadhav [a,*], Sheikh M. Farooq [a], Balaram Patro [a], Ch. Venkata Ramana Reddy [b]

[a] GVK Biosciences Private Limited, Medicinal Chemistry Division, 28A, IDA Nacharam, Hyderabad 500076, India
[b] Department of Chemistry, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500085, India

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ABSTRACT

A simple and efficient synthesis of 7-methoxy-2-arylthieno[3,2-*b*]pyridine-3-ols was achieved using a novel one-pot LDA-promoted domino reaction. Although this class of compounds are not very well represented in the literature, similar skeletons are of immense biological importance. A few closely related compounds are reported with multi-step syntheses using harsh conditions and longer reaction time.

Pyridine derivatives have attracted considerable interest among medicinal and organic chemists due to their various biological activities. More particularly, thienopyridines, being bioisosters of indoles or isoquinolines, have attracted much attention for their potential biological activity. Some representative bioactive molecules containing thienopyridine core are depicted in Figure 1. Baker et al. have reported 3-hydroxyazabenzothiophene (**1**), as 5-lipoxygenase and/or cyclooxygenase inhibitors useful in the treatment of prostaglandin and/or leukotriene mediated diseases.[1] Sugano and co-workers reported (3-amino-6-thiophen-2-yl-thieno[2,3-*b*]pyridin-2-yl)phenyl methanone (**2**) as a new type of cytotoxic agent selective against a tumorigenic cell line.[2] Thienopyridine derivative (**3**) was reported as potent Luteinizing hormone receptor (LHR) agonist, useful for the treatment of infertility.[3] Boschelli et al. reported the thieno[3,2-*b*]pyridine (**4**) as Src kinase inhibitor, responsible for many cell signaling pathways. Therefore, it functions as a potential agent for the treatment of a variety of diseases like cancer, osteoporosis, and stroke.[4] New et al. have reported thienopyridine derivatives (**5**) and (**6**) showing significant CNS activity. These target molecules indicate atypical antipsychotic-like activity, coupled with potent affinity for serotonin 5-HT1 and 5-HT2 receptors.[5] Thienopyridines are also of general interest for the chemistry of ligands and theoretical organic chemistry due to the presence of a π-electron rich thiophene ring and a π-electron deficient pyridine ring.[6]

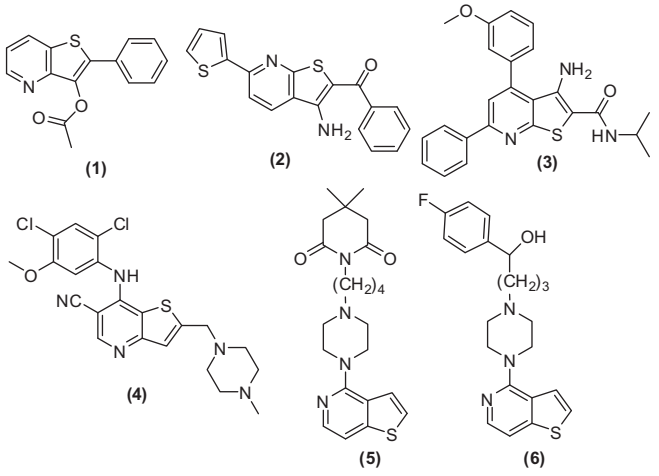

Figure 1. Bioactive thienopyridine derivatives.

Herein we report a one pot synthesis of 2-aryl-7-methoxy-3-hydroxythieno[3,2-*b*]pyridines in a domino fashion. Literature methods for the synthesis of thieno[3,2-*b*]pyridines are based on the use of either readily accessible 3-aminothiophenes[7] and their *N*-derivatives[8] with stepwise construction of the pyridine ring or by using thio-pyridines and stepwise construction of the thiophene ring.[9] Berkaoui et al. used the former approach, starting with 3-aminothiophene, in multistep synthesis to get thienopyridines.[8a] Fort and co-workers have applied a three-step process for the

* Corresponding author.
E-mail address: vinod.jadhav@gvkbio.com (V.D. Jadhav).

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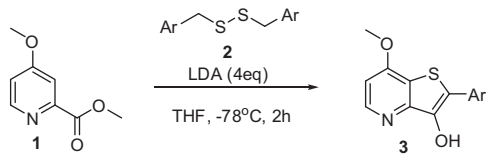


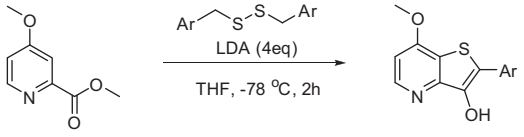
Scheme 1. Synthesis of 7-methoxy-2-arylthieno[3,2-*b*]pyridin-3-ols.

construction of the thiophene ring. The key step was regioselective lithiation–bromination of the 3-methylthiopyridine induced by the BuLi-LiDMAE superbase (DMAE: 2-(dimethylaminoethanol)). The successive steps include the Sonogashira coupling and halogenocyclization to give the corresponding 2-substituted (Ph or TMS) 3-halothieno[3,2-*b*]pyridines.[9d] However, the overall conversion was low yielding (17–34%). Recently, Queiroz et al. reported a two-step method for the synthesis of 2-(hetero)arylthieno[3,2-*b*]pyridines. The first step is a Sonogashira coupling of 2-bromo-3-chloropyridine with several (hetero)arylalkynes to obtain the corresponding 3-chloro(hetero)arylethynylpyridines. These 3-chloro(hetero)arylethynylpyridines were further cyclized by treatment with Na_2S at 130 °C affording the expected 2-(hetero)arylthienopyridines. In addition, these two reaction sequences were also performed in one-pot, without isolation of the Sonogashira product.[9e] Generally, these methods suffer from severe disadvantage of limited access to starting materials, low functional compatibility and/or long-multistep reaction sequences and low yields.

There is only one multi-step synthesis reported for the synthesis of biologically significant 3-hydroxy-2-arylthieno[3,2-*b*]pyridines.[1] This significant class of compounds is not well explored probably due to the lack of convenient synthetic methods. The diversity of biological activities and the lack of a mild method of synthesis gave us an impulse to the development of a convenient synthetic route for the thieno[3,2-*b*]pyridine system. In this context, we have developed a novel one pot method for the first synthesis of 2-aryl-7-methoxy-3-hydroxythieno[3,2-*b*]pyridines in a domino fashion. The intermediates generated in situ serve as the precursors for the next step, ultimately leading to the formation of the substituted thieno[3,2-*b*]pyridine derivatives (Scheme 1).

Thus methyl 4-methoxypicolinate **1** on treatment with excess of lithium diisopropylamide (LDA) (4–5 equiv) in THF at −78 °C, followed by the addition of arylmethyl disulfide **2** solution in THF afforded 7-methoxy-2-arylthieno[3,2-*b*]pyridin-3-ols **3** in good yield. The efficiency and generality of the method were validated by reacting several arylmethyl disulfides (Table 1) having electron withdrawing substituent (entries 5–8) and electron donating substituent (entries 2–4) with **1** to give corresponding

Table 1
LDA-promoted domino reactions: one-pot synthesis of 7-methoxy-2-arylthieno[3,2-*b*]pyridine-3-ols[a]



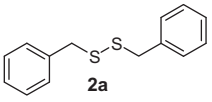
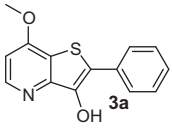
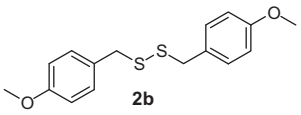
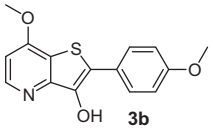
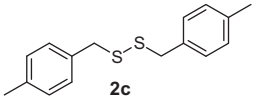
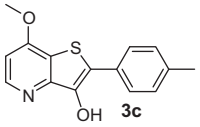
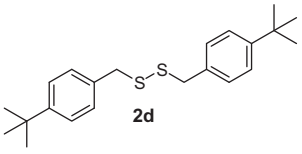
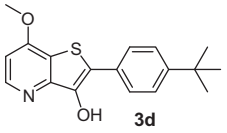
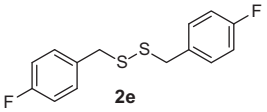
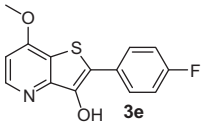
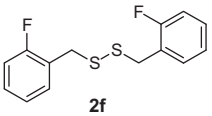
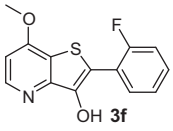
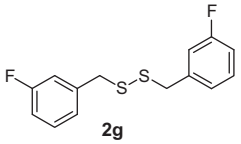
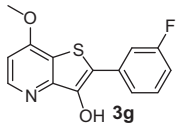
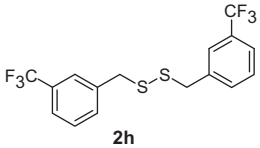
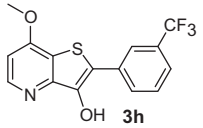
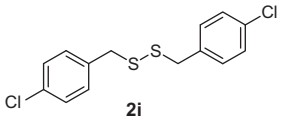
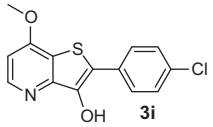
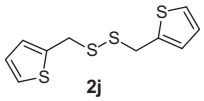
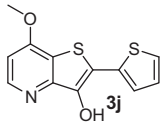
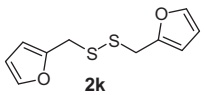
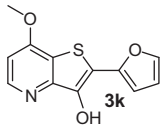
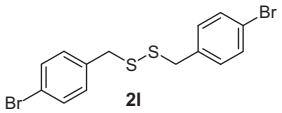
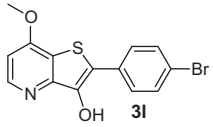
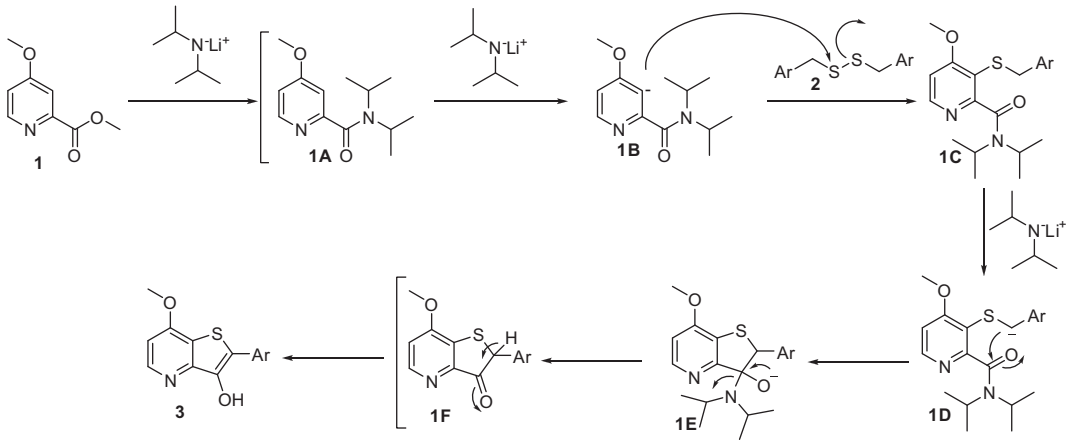
Entry	Disulfide	Product	Yield[b] (%)
1	 **2a**	 **3a**	68
2	 **2b**	 **3b**	59
3	 **2c**	 **3c**	62
4	 **2d**	 **3d**	55
5	 **2e**	 **3e**	71
6	 **2f**	 **3f**	50

Table 1 (*continued*)

Entry	Disulfide	Product	Yield[b] (%)
7	 **2g**	 **3g**	49
8	 **2h**	 **3h**	45
9	 **2i**	 **3i**	62
10	 **2j**	 **3j**	45
11	 **2k**	 **3k**	47
12	 **2l**	 **3l**	40

[a] All the compounds were characterized ^{1}H NMR ^{13}C NMR, IR, and HRMS.
[b] Isolated yields after column chromatography.



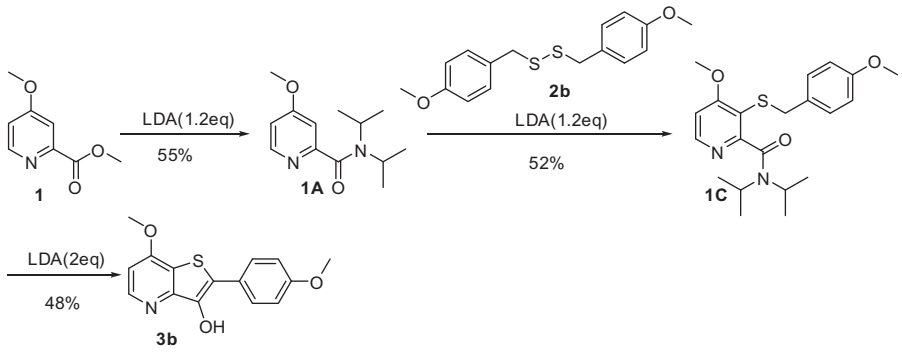
Scheme 3

Figure 2. Mechanism of synthesis of 2-arylthieno[3,2-*b*]pyridin-3-ols.

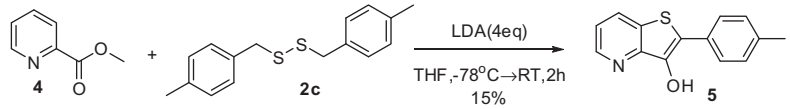
derivatives in good to acceptable yields. Even five-membered heterocyclic disulfides (entries 10 and 11) reacted to give corresponding 3-hydroxythieno[3,2-*b*]pyridine derivatives in good yields.[10]

The synthesis includes the use of readily accessible starting materials. The starting materials methyl 4-methoxypicolinate **1** and disulfides **2** required were prepared using literature methods.[11,12] The diverse availability of mercaptans allows introduction of a variety of aryl or substituted aryl functionalities at 2-position. It is pertinent to mention here that the current method allows for further functionalization at 3 and 7 positions which can open an access to further elaboration.

The plausible mechanism of the transformation proposed is shown in Figure 2. The picolinate ester **1** reacts with LDA to give amide intermediate **1A**.[13] The amide intermediate **1A** after anion generation at 3-position undergoes thioalkylation with disulfide **2** giving 3-thioalkypyridine-2-amide intermediate **1C**. The



Scheme 2. Step-wise synthesis of 2-*p*-methoxyphenyl thieno[3,2-*b*]pyridin-3-ol.



Scheme 3. Synthesis of 2-*p*-tolylthieno[3,2-*b*]pyridin-3-ol.

intermediate **1C** undergoes lithiation at methylene carbon adjacent to sulfur, followed by intramolecular nucleophilic substitution with amide carbonyl to give the corresponding thieno[3,2-*b*]pyridine system **3** (Fig. 2). The mechanism of the reaction was confirmed by the step-wise conversion of methyl 4-methoxypicolinate into 2-*p*-methoxyphenylthieno[3,2-*b*]pyridin-3-ol **3b** (Scheme 2). Thus the picolinate ester **1** was treated with LDA (1.2 equiv) at −78 °C for 30 min and after normal work-up and purification by column chromatography, intermediate **1A** was isolated in 55% yield.[14] The intermediate **1A** was treated with 1,2-bis(4-methoxybenzyl)disulfide **2b** in the presence of 1.2 equiv of LDA at −78 °C for 1 h to give intermediate **1C** in 52% yield.[15] This intermediate **1C** was treated with LDA (2.5 equiv) at −78 °C for 1 h to afford title compound **3b** in 48% yield. Thus the isolation of the intermediates **1A**, **1C** and **3b** clearly establishes the mechanism of the reaction as proposed in Figure 2.

In order to probe the role of different substituents we turned our attention to methyl 4-methoxypicolinate **1**. The methoxy group at 4-position of methyl 4-methoxypicolinate seems to facilitate the transformation. Removing the methoxy group from picolinate and carrying out the reaction with methyl picolinate **4** resulted in a considerable loss of yield of the corresponding 2-(*p*-tolyl)thieno[3,2-*b*]pyridin-3-ol **5**, clearly stating the role of the electron donating group at 4-position of the picolinate (Scheme 3).

In conclusion, we have developed an efficient, general, and useful one-pot strategy for the synthesis of 7-methoxy-2-arylthieno[3,2-*b*]pyridine-3-ols from methyl 4-methoxypicolinate in good yields. The mechanism of reaction was also confirmed by the synthesis and characterization of the intermediates. We believe that this novel one-pot synthesis of substituted aryl 4-aza-benzothiophenes will serve as a useful alternative to classical methods and open an access to this medicinally significant class of compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.024.

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10. *Representative experimental procedure for the synthesis of* ***3a***: To a stirred solution of diisopropylamine (1.01 mL, 7.18 mmol) in dry THF (4 mL) was added *n*-butyllithium in hexane (1.6 M in hexanes, (4.48 mL, 7.18 mmol) at −78 °C and stirred for 30 min at the same temperature. Methyl 4-methoxypicolinate (0.3 g, 1.794 mmol) in THF (3 mL) was added to the above solution and stirred for further 30 min at the same temperature. Disulfide **2a** (0.53 g, 2.15 mmol) in THF (3 mL) was added at −78 °C and the mixture was stirred at the same temperature with continuous monitoring by TLC for 2 h. Saturated NH_4Cl solution (10 mL) was added to the reaction mixture and slowly warmed to room temperature and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under reduced pressure. The resulting crude

material was purified by column chromatography, eluting with 40% ethyl acetate in hexanes to afford compound **3a** as a pale yellow solid; Yield: 68%; mp: 206–209 °C; IR (KBr): ν 3433.03, 2978.89, 1769.04, 1576.34, 1550.88, 1421.84, 1368.75, 1296.84, 1267.41, 1140.03, 1052.09, 695.24 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1 H), 8.57 (d, J = 5.4 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.07 (d, J = 5.4 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 160.2, 150.0, 148.8, 145.1, 133.2, 128.7, 127.1, 126.4, 117.5, 117.2, 102.4, 56.1; ES-MS: 258.0 $(M+H)^+$; HRMS (ESI^+): m/z Calcd for $C_{14}H_{12}NO_2S$: 258.0583 $(M+H)^+$. Found: 258.0580.

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14. *Analytical data of* ***1A***: mp: 116–119 °C; IR (KBr): ν 2967.62, 2931.08, 1632.89, 1595.12, 1563.55, 1464.70, 1438.85, 1340.89, 1033.32 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, J = 5.6 Hz, 1H), 6.98 (dd, J = 6.0, 2.4 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H); 3.70–3.50 (m, 2H), 1.44 (d, J = 7.0 Hz, 6H), 1.10 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 165.8, 157.9, 149.9, 110.1, 107.0, 55.5, 50.1, 44.7, 20.2, 20.1; ES-MS: 237.2 $(M+H)^+$; HRMS (ESI^+): m/z Calcd for $C_{13}H_{21}N_2O_2$: 237.1603 $(M+H)^+$. Found: 237.1615.
15. *Analytical data of* ***1C***: mp: 101–105 °C; IR (KBr): ν 2972.77, 2935.70, 1634.18, 1565.58, 151.98, 1462.45, 1430.20, 1370.09, 1335.45, 1293.80, 1248.90, 1035.06 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.36 (d, J = 5.6 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 5.6 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H); 3.99 (s, 2H), 3.89 (s, 3H), 3.71 (s, 3H), 3.60–3.50 (m, 1H), 3.38–3.28 (m, 1H), 1.46 (br s, 6H), 1.03 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.7, 166.2, 160.4, 158.3, 150.6, 130.0, 129.2, 114.7, 113.6, 106.9, 56.1, 55.0, 50.2, 44.6, 37.7, 20.0; ES-MS: 389.2 $(M+H)^+$; HRMS (ESI^+): m/z Calcd for $C_{21}H_{29}N_2O_3S$: 389.1899 $(M+H)^+$. Found: 389.1867; mp: 101–105 °C.