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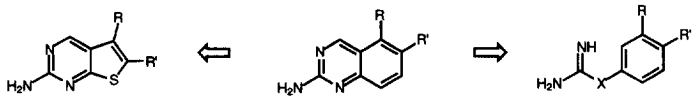
# A CONCISE SYNTHETIC ENTRY TO SUBSTITUTED 2-AMINOTHIENO[2,3-*d*]PYRIMIDINES VIA A GEWALD PRECURSOR

Minsheng Zhang* and Richard W. Harper

*Lilly Research Laboratories, A Division of Eli Lilly and Company,*
*Lilly Corporate Center, Indianapolis, Indiana 46285*

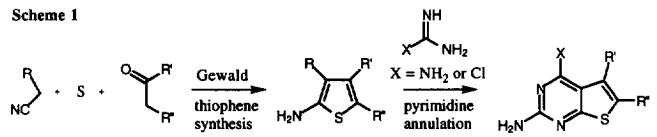
**Abstract:** A concise synthesis of substituted 2-aminothieno[2,3-*d*]pyrimidines is described based on pyrimidine annulation of tetrasubstituted thiophene precursors assembled by a Gewald thiophene ring synthesis. © 1997 Elsevier Science Ltd.

2-Aminothieno[2,3-*d*]pyrimidines (**1**) are considered to be bioisosteres of 2-aminoquinazolines (**2**),[1-2] which are, in turn, potential surrogates for substituted guanidines (**3**) or amidines (**4**), frequently encountered pharmacophoric components in medicinal chemistry. In the course of a structure-based drug design program, we have investigated the versatility of a Gewald precursor (**5**) as a synthetic entry to substituted 2-aminothieno[2,3-*d*]pyrimidines (**6a-c**; Scheme 1).[1] The versatility of this approach lies not only in the ease of controlled introduction of C4 and C5 substituents into the target thiophenes **5** through the Gewald thiophene ring synthesis,[3] but also in the ease of incorporation of different electrophilic substituents in the C3 position that allows for variation of the substitution pattern of the pyrimidine portion of **6** using a common pyrimidine annulation procedure.[4] Herein, we wish to report our initial results from this investigation.



**1** **2** **3**, X = NH; **4**, X = $CH_2$

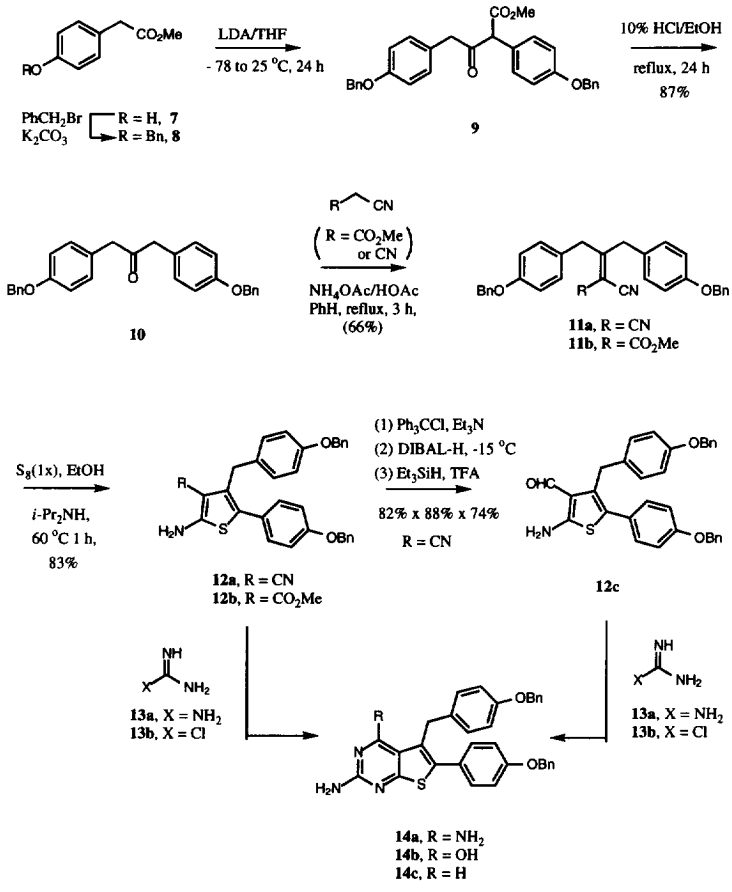
**Scheme 1**




**5a**, R = CN; **5b**, R = $CO_2Me$; **5c**, R = CHO

**6a**, X = $NH_2$; **6b**, X = OH; **6c**, X = H

**Scheme 2**




Our initial targets were compounds **14a-c** (Scheme 2). Retrosynthetic analysis based on the approach outlined in Scheme 1 quickly points to the requirement of the symmetric ketone **10**, which we envisioned constructing through a Claisen self-condensation of **8** followed by decarboxylation of the Claisen product **9**. Thus, treatment of **8** with LDA (1.0 equiv) in THF at - 78 °C followed by a slow warm up to ambient temperature over 22 h afforded the clean Claisen condensation product **9** in nearly quantitative yield after neutralization with dilute HCl and a simple extraction of the reaction mixture with ethyl acetate from brine. Treatment of **9** under base-catalyzed decarboxylation conditions (NaOH, acetone/$H_2O$, reflux) gave mainly 4-benzoxyphenylacetic acid, derived from a retro-Claisen reaction of **9**. However, treatment of **9** under acid-catalyzed decarboxylation conditions (10% HCl in EtOH, reflux, 24 h) afforded cleanly the desired symmetric ketone **10** as a white precipitate. A simple filtration followed by recrystalization from ethyl acetate afforded **10**

as a white crystalline solid in an overall yield of 87% from **8**. The Gewald thiophene synthesis of **12** from **10** was conducted in a stepwise fashion through a Knoevenagel condensation to give the intermediate **11** followed by base promoted thiophene cyclization with sulfur.[3] It was found that the Knoevenagel condensation of **10** with malononitrile or methyl cyanoacetate was best conducted at reflux in benzene with catalytic amount of ammonium acetate (0.2 equiv) and acetic acid (0.6 equiv) in a Dean–Stark apparatus with azotropic removal of water. The intermediate **11a** or **11b** was generally obtained in 66–85% yield after a simple aqueous workup and recrystalization from ethyl acetate-hexane. Cyclization of **11** with sulfur under normal Gewald conditions ($S_8$, 1.0 equiv; *i*-$Pr_2NH$, 1.0 equiv; EtOH; 60 °C; 1 h) proved to be straight forward and provided the desired **12a-b** in excellent yields.[5,6] The aldehyde derivative **12c** was obtained from a *N*-trityl protected **12a** through a DIBAL-H reduction at -15 °C in dichloromethane followed by *N*-trityl deprotection.[7]

**Table 1**. Summary of the Pyrimidine Annulation Conditions

| Entry | Thiophene | Reagent (equiv) | | Solvent | Temp (°C) | Time (h) | Product (yield%)[a] | |
|---|---|---|---|---|---|---|---|---|
| 1 | **12a** | **13a** | (3) | Diglyme | 150 | 5 | **14a** | (trace) |
| 2 | **12a** | **13a** | (3) | NMP | 190 | 2 | **14a** | (31) |
| 3 | **12a** | **13a** | (4) | HMPA | 190 | 2 | **14a** | (47) |
| 4 | **12a** | **13a** | (3) | DMSO | 190 | 2 | **14a** | (43) |
| 5 | **12a** | **13a** | (5) | DMSO | 190 | 2 | **14a** | (58) |
| 6 | **12a** | **13b** | (3) | Diglyme | 150 | 2 | **14a** | (24) |
| 7 | **12a** | **13b** | (2) | Diglyme | 130 | 17 | **14a** | (44) |
| 8 | **12b** | **13a** | (3) | Diglyme | 150 | 5 | **14b** | -- |
| 9 | **12b** | **13a** | (3) | HMPA | 190 | 2 | **14b** | -- |
| 10 | **12b** | **13a** | (3) | DMSO | 190 | 2 | **14b** | -- |
| 11 | **12b** | **13b** | (2) | Diglyme | 150 | 2 | **14b** | (31) |
| 12 | **12b** | **13b** | (6) | Diglyme | 150 | 2 | **14b** | (46) |
| 13 | **12c** | **13a** | (3) | Diglyme | 150 | 2 | **14c** | (20) |
| 14 | **12c** | **13a** | (4) | Diglyme | 150 | 8 | **14c** | (67) |
| 15 | **12c** | **13a** | (2) | Diglyme | 150 | 6 | **14c** | (54) |
| 16 | **12c** | **13a** | (2) | Diglyme | 165 | 16 | **14c** | (79) |
| 17 | **12c** | **13b** | (3) | Diglyme | 150 | 2 | **14c** | (20) |

[a] All yields are isolated yields by flash chromatography.

While the pyrimidine annulation has been employed extensively in 2-aminoquinazoline synthesis,[4] its application to 2-aminothieno[2,3-*d*]pyrimidine synthesis has been limited to 2,4-diaminothieno[2,3-*d*]pyrimidines where an unconventional "fusion" technique was employed.[1] Consequently, we have explored this reaction in a number of solvent systems with three different thiophene derivatives (**12a-c**) and two slightly different cyclizing agents: guanidine carbonate (**13a**) and chloroformamidine hydrochloride (**13b**).[4(c)] It was found that chloroformamidine hydrochloride (**13b**) reacts with all the thiophene derivatives employed (**12a-c**) in diglyme at 130 °C or above (Table 1, entries 6, 7, 11, 12, and 17). Guanidine carbonate (**13a**), however, only reacts with **12a** and **12c** (Table1, entries 1, 8, and 13–16). Higher temperature and more polar solvents seemed to help with the conversion of **12a** and **12c** to **14a** and **14c**, but they had no effect on the reaction of **12b** and **13a** (Table 1, entries 9 and 10). Apparently, cyclization with **13a** operates through a neucleophilic addition of the guanidine to the electrophiles on the thiophene followed by an intramolecular displacement. On the other hand, cyclization with **13b** operates through an intermolecular displacement of the chloride on chloroformamidine by the amino group on the thiophene followed by an intramolecular condensation. Entropic assistance plays a major role in the reaction of **12b** with **13b** (Table 1, entries 11 and 12). While heating at 130 °C appeared to be sufficient for the reaction of **12a,c** with **13b**, heating at 150 °C or above was required for the reaction of **12b** with **13b**. Although 190 °C appeared to be the optimum temperature for the reaction of **12a,b** with **13a,b**, side reactions became significant with **12c** at these elevated temperatures.[8] Polar solvents, especially DMSO, appeared to dissolve **13a,b** better, generally giving higher yields.

In a typical synthesis of **14a-c**, a solution of **10** (4.7 mmol), $NH_4OAc$ (1.3 mmol), glacial acetic acid (2.6 mmol) and malononitrile or methyl cyanoacetate (4.7 mmol) in benzene (4.0 mL) was allowed to stir at reflux in a Dean–Stark apparatus for 2 h. After cooling to room temperature the reaction mixture was diluted with brine and extracted with EtOAc. The combined organic layers were dried ($Na_2SO_4$) and concentrated. Recrystalization of the residue in EtOAc-hexane gave pure **11**. A solution of **11** (3.6 mmol), sulfur (3.6 mmol) and diisopropylamine (3.6 mmol) in ethanol (18 mL) was allowed to warm at 60 °C for 1 h while stirring. The cooled reaction mixture was diluted with an aqueous solution of HCl (0.2 N, 25 mL) and extracted with EtOAc. The combined organic layers were dried ($Na_2SO_4$) and concentrated. Recrystalization of the residue from EtOAc-hexane provided pure **12**. Compounds **12** (1.0 mmol) and **13** (2–6 equiv) were suspended in the solvent indicated in table 1 (7 mL) in a dry flask, allowed to stir at the desired temperature (Table 1) under an argon atmosphere for 2–17 h. The cooled reaction mixture was then diluted with water and extracted with EtOAc. The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. The desired products (**14a-c**) were purified by flash chromatography on silica gel (230–400 mesh) eluting with MeOH:EtOAc:hexane (0–10:50–90:50–0, gradient elusion).[9–11]

Application of this synthetic approach to the preparation of biologically relevant molecules and extension of the synthesis to related systems are currently in progress and will be reported in due course.

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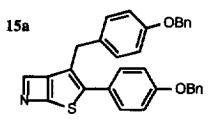
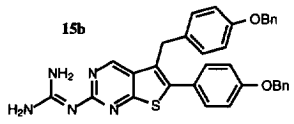
5. For **12a**: $^1$H NMR ($CDCl_3$) δ 7.44–7.32 (m, 10H, aromatic), 7.25 (d, $J$ = 8.6 Hz, 2H, aromatic), 7.04 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.97 (d, $J$ = 8.8 Hz, 2H, aromatic), 6.88 (d, $J$ = 8.8 Hz, 2H, aromatic), 5.07 (s, 2H, $PhCH_2$), 5.03 (s, 2H, $PhCH_2$), 4.24 (bs, 2H, $NH_2$), 3.88 (s, 2H, $CH_2$). Anal. Calcd for $C_{32}H_{26}N_2O_2S$: C, 76.46; H, 5.21; N, 5.57. Found: C, 76.72; H, 5.33; N, 5.29. FDMS: *m/e* 502 ($M^+$).
6. For **12b**: $^1$H NMR ($CDCl_3$) δ 7.44–7.33 (m, 10H, aromatic), 7.25 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.98 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.92 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.86 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.09 (s, 2H, $NH_2$), 5.05 (s, 2H, $PhCH_2$), 5.02 (s, 2H, $PhCH_2$), 4.05 (s, 2H, $CH_2$), 3.58 (s, 3H, $OCH_3$). Anal. Calcd for $C_{33}H_{29}NO_4S$: C, 74.99; H, 5.46; N, 2.61. Found: C, 74.80; H, 5.74; N, 2.36. mp 112-115°C.
7. For **12c**: $^1$H NMR ($CDCl_3$): δ 9.44 (s, 1H, CHO), 7.38 (m, 8H, aromatic), 7.25 (d, $J$ = 8.7 Hz, 2H, aromatic), 7.07 (d, $J$ = 8.7 Hz, 2H, aromatic), 6.91 (m, 6H, aromatic), 5.06 (s, 2H, $PhCH_2$), 5.03 (s, 2H, $PhCH_2$), 4.00 (s, 2H, $CH_2$). FDMS: *m/e* 506 ($M^+$+1). Anal. Calcd for $C_{32}H_{27}NO_3S$: C, 76.01; H, 5.38; N, 2.77. Found: C, 76.14; H, 5.26; N, 2.48.

8. Two significant side products were isolated when **12c** and **13a** were allowed to stir at 190 °C in DMSO. $^1$H NMR and FDMS appeared to indicate **15a** and **15b** shown below as the side products derived from an intramolecular condensation of **12c** and further reaction of **14c** with **13a**, respectively. For **15a**: $^1$H NMR ($CDCl_3$) δ 7.98 (s, 1H, N=CH), 7.60–7.35 (m, 12H, aromatic), 7.13 (d, $J$ = 8.6 Hz, 2H, aromatic), 7.12 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.98 (d, $J$ = 8.6 Hz, 2H, aromatic), 5.21 (s, 2H, $PhCH_2$), 5.15 (s, 2H, $PhCH_2$), 4.17 (s, 2H, $CH_2$). FDMS: *m/e* 487 ($M^+$). For **15b**: FDMS: *m/e* 571 ($M^+$).




9. For **14a**: $^1$H NMR (DMSO-$d_6$) δ 7.44-7.29 (m, 12H, aromatic), 7.07 (d, $J$ = 8.7 Hz, 2H, aromatic), 7.00 (d, $J$ = 8.7 Hz, 2H, aromatic), 6.92 (d, $J$ = 8.7 Hz, 2H, aromatic), 5.10 (s, 2H, $PhCH_2$), 5.02 (s, 2H, $PhCH_2$), 4.18 (s, 2H, $CH_2$). FDMS: *m/e* 544 ($M^+$). mp 234–236 °C.
10. For **14b**: $^1$H NMR (DMSO-$d_6$) δ 10.8 (s, 1H, OH), 7.50–7.30 (m, 10H, aromatic), 7.25 (d, $J$ = 8.6 Hz, 2H, aromatic), 7.04 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.95 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.85 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.60 (bs, 2H, $NH_2$), 5.11 (s, 2H, $PhCH_2$), 5.02 (s, 2H, $PhCH_2$), 4.18 (s, 2H, $CH_2$). FDMS: *m/e* 546 ($M^+$+1). Anal. Calcd for $C_{33}H_{27}N_3O_3S$: C, 72.64; H, 4.99; N, 7.70. Found: C, 72.47; H, 5.06; N, 7.78. mp 263-265°C.
11. For **14c**: $^1$H NMR ($CDCl_3$) δ 8.40 (s, 1H, aromatic), 7.47–7.31 (m, 12H, aromatic), 7.11 (d, $J$ = 8.7 Hz, 2H, aromatic), 7.03 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.91 (d, $J$ = 8.6 Hz, 2H, aromatic), 6.82 (bs, 2H, $NH_2$), 5.14 (s, 2H, $PhCH_2$), 5.02 (s, 2H, $PhCH_2$), 4.10 (s, 2H, $CH_2$). FDMS: *m/e* 529 ($M^+$). Anal. Calcd for $C_{33}H_{27}N_3O_2S$: C, 74.83; H, 5.14; N, 7.81. Found: C, 74.63; H, 5.27; N, 7.81. mp 198–200 °C.

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