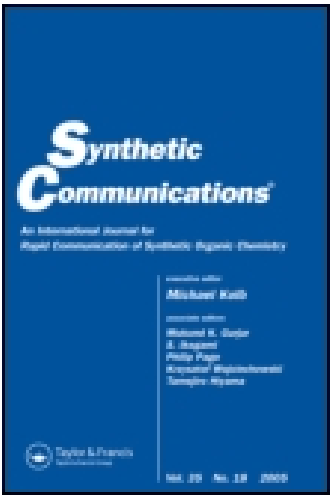

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 16 Aug 2006.

To cite this article: Weijiang Zhang , Anthony R. Haight , Kelley L. Ford & Shyamal I. Parekh (2001) A REGIOSELECTIVE SYNTHESIS OF METHYL 7-AMINO-3-PHENYLTHIENO-[2,3-b]PYRAZINE-6-CARBOXYLATE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:5, 725-730, DOI: 10.1081/SCC-100103262

To link to this article: http://dx.doi.org/10.1081/SCC-100103262

SYNTHETIC COMMUNICATIONS, 31(5), 725–730 (2001)

A REGIOSELECTIVE SYNTHESIS OF METHYL 7-AMINO-3-PHENYLTHIENO-[2,3-*b*]PYRAZINE-6-CARBOXYLATE

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ABSTRACT

A practical synthesis of methyl 7-amino-3-phenylthieno[2,3-*b*]pyrazine-6-carboxylate (**1**) has been achieved *via* a regioselective synthesis of 3-cyano-5-phenyl-3-phenylthiopyrazine (**5a**), by condensing 1,1-diethoxyacetophenone with 2,3-diamino-3-phenylthioacrylonitrile.

Thieno[2,3-*b*]pyrazines and pyrazines have found wide uses in pharmaceuticals and agrochemistry.[1–5] To support the development of a potential pharmaceutical candidate, a practical synthesis of the thieno[2,3-*b*]pyrazine (**1**) was needed. The most general method of synthesizing thieno[2,3-*b*]pyrazines has been to treat 3-cyano-2-halopyrazines with thioglycolates, and base cyclization of the resulting 3-cyano-2-*S*-acyl-mercaptopyrazines to yield the desired thieno[2,3-*b*]pyrazines.[6–10] Retrosynthetically, this approach required the preparation of pyrazine **2** where X was either a halogen or a pseudohalogen (Scheme 1).

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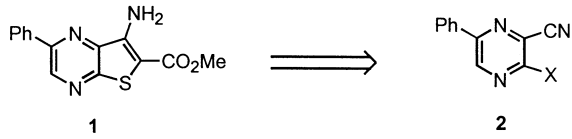
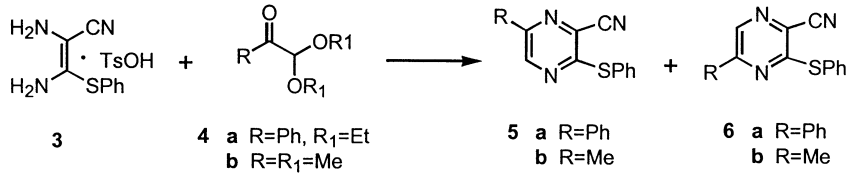


Scheme 1.

The earlier work of the synthesis of pyrazine **2** was carried out by using aminomalononitrile and an α-ketoaldoxime to make 2-amino-5-phenyl-3-cyano-pyrazine[11] followed by Sandmeyer reaction to give **2** (X = Cl or Br). While this route appeared efficient, we had concerns about the safe handling of aminomalononitrile after several episodes of allergic reactions and skin rashes related to this reagent. We believed it would be problematic to handle aminomalononitrile on a large scale. Herein we would like to report an alternative synthesis of **2** by use of 2,3-diamino-3-phenylthioacrylonitrile[13,14] (**3**) for the synthesis of pyrazine **5a** and followed by conversion of sulfide to sulfone (leaving group), which is also practical for large scale preparation.

Sato reported the synthesis of 3-phenylthiopyrazinecarbonitrile by condensing **3** with glyoxal.[15] When phenylglyoxal was employed under Sato's conditions, it gave regioisomers **5a** and **6a** in 30–60% yield without selectivity. No regioselectivity was achieved upon carrying the acids or the solvents for the condensation. To overcome this, a protected α-ketoaldehyde derivative, 2,2-diethoxyacetophenone **4a**, was employed in condensation (Scheme 2).



Scheme 2.

It was found that high selectivity for **5a** could be obtained by using **4a** stirred with **3** in the presence of excess trifluoroacetic acid (TFA) in 2-propanol. The selectivity was lower in methanol or ethanol. Mineral acids, such as hydrochloric or sulfuric acid, gave inferior selectivities and/or yields. With a weaker acid, such as acetic acid, the reaction was slow and the yield was poor due to the decomposition of the substrates. Increasing the equivalents of TFA from 2 to 8.8 improved the selectivity of the condensation from 3.6:1, (**5a**:**6a**, Table entry 1) to 13.1:1 (entry 5) respectively. With

Table. The Selectivity of Pyrazine **5a/6a** from the Condensation of **3** and **4a**[a]

Entry	CF_3CO_2H (eq.)	Ratio (**5a/6a**)[b]	Yield (%) (**5a**)[c]
1	2	3.6	41
2	2.6	5.3	45
3	4	4	55
4	6.5	11.8	73
5	8.8	13.1	67
6	17	15.5	86

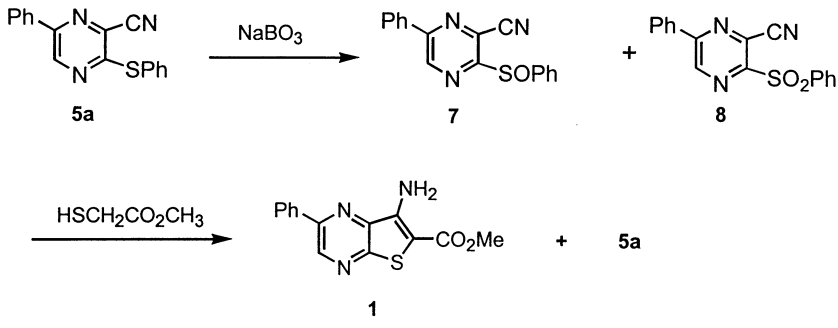
[a]Standard conditions: **1** eq. **4a**, 1.1 eq. 3, in 2-propanol(**4a**/2-propanol, 1/10, w/v) at ambient temperature for 22–24 h.
[b]Ratios of **5a**:**6a** were of crude reaction mixtures. Reactions were monitored by HPLC (Zorbax, SB-phenyl column, solvent: acetonitrile (50%) and 0.2% $HClO_4$ (50%), 1.5 mL/min, λ=210 nm.
[c]Yields are of isolated **5a**.

17 eq. of TFA (entry 6), the condensation of **3** with **4a** resulted in a 15.5:1 ratio with an 86% isolated yield of **5a**.

Presumably, an imine is first formed between 2-amino group of compound **3** and the ketone carbonyl group of **4**, subsequent cyclization then gives pyrazine **5a**. The formation of minor isomer **6a** is due to the hydrolysis of the acetal group of **4** under reaction conditions. Isolation of the product was obtained by dilution of the reaction mixture with water to give the desired product **5a** as a filterable solid. If less TFA was used (entries 1–3), **5a** could be further purified by recrystallization from methanol to remove the undesired isomer **6a**.

We extended the cyclization to pyruvic aldehyde dimethyl acetal **4b** with **3** to yield **5b** and **6b** in an unexpected 1:6.8 mixture and 60% isolated yield of **6b**.[14] This result might be due to rapid hydrolysis of dimethyl acetal under the reaction conditions.

Activation of the phenylthio group in **5a** as the sulfoxide **7** was accomplished by the oxidation with sodium perborate in acetic acid at room temperature (Scheme 3).[16,17] Unfortunately, condensation of sulfoxide **7** with 1.1 eq. of methyl thioglycolate gave a low yield of thienopyrazine **1**. A competitive reduction of **7** to the sulfide **5a** was a major side reaction.[18] Conversion of sulfide **5a** to sulfone **8** is necessary. Oxidation of **5a** by sodium perborate in acetic acid at 50°C provided a 1:3 mixture of sulfoxide **7** to sulfone **8**. With a catalytic amount of trifluoroacetic acid, significant hydrolysis of the nitrile was observed.[19] Oxidation of 3 eq. of *m*CPBA in methylene chloride provided 82% sulfone **8**,[13] however,



Scheme 3.

purification from the resulting *meta*-chlorobenzoic acid and methylene chloride proved troublesome for large scale synthesis.

We found a 3:1 mixture of acetic acid and chloroacetic acid with 3.1 eq. sodium perborate to give an 1:7.3 ratio of sulfoxide **7** to sulfone **8** in a 95% overall yield after 16 hours at 50°C. Presumably, the chloroacetic acid creates a stronger peracid[20] without causing the hydrolysis problems. Treatment of the 1:7.3 mixture of **7**:**8** with 1.1 eq. of methyl thioglycolate in ethanol with Hunig's base yielded the title compound **1** in 93% yield.

In summary, an efficient synthesis of 2-phenylthio-3-cyano-5-phenylpyrazine regioselectively has been developed. A convenient and inexpensive oxidation method is described to convert sulfides to sulfones where the substrate or product is sensitive to strongly acidic conditions. This new synthesis of methyl 7-amino-3-phenylthieno[2,3-*b*]pyrazine-6-carboxylate **1** is suitable for large scale process. Further applications of this chemistry are being studied.

SPECTRAL DATA FOR SOME SELECTED COMPOUNDS

Methyl 7-Amino-3-phenylthieno[2,3-b]pyrazine-6-carboxylate (1): mp: 198–199°C($CHCl_3$); ^{1}HNMR($CDCl_3$) δ(ppm) 9.40(s, 1H), 8.06–8.03 (m, 2H), 7.60–7.48(m, 3H), 6.27(brs, 2H), 3.95(s, 3h); ^{13}CNMR($CDCl_3$) δ(ppm) 201.1, 165.3, 149.2, 145.5, 142.3, 140.3, 136.1, 129.9, 129.1, 127.0, 51.9. MS(CI) m/z 286(M+1); Anal. Calc. for $C_{14}H_{11}N_3O_2S$: C, 58.94; H, 3.89; N, 14.73; Found: C, 58.47; H, 3.67; N, 14.66.

5-Phenyl-2-phenylthiopyrazine-3-carbonitrile (5a): mp: 133–135°C (EtOAc/Heptane); ^{1}HNMR($CDCl_3$) δ(ppm) 8.90(s, 1H), 8.00–7.90 (m, 2H), 7.70–7.60(m, 2H), 7.59–7.45(m, 6H). ^{13}CNMR($CDCl_3$) δ(ppm) 158.4, 149.1, 143.5, 135.4, 134.0, 130.6, 130.0, 129.6, 129.2, 127.1, 126.7, 126.6,

114.6; Anal. Calc. for $C_{17}H_{11}N_3S$: C, 70.57; H, 3.83; N, 14.73; Found: C, 70.35; H, 3.77; N, 14.60.

5-Methyl-2-phenylthiopyrazine-3-carbonitrile (5b): mp: 97–98°C (MeOH, lit.[13] 97–98.5°C). ^{1}HNMR($CDCl_3$) δ(ppm) 8.31(s, 1H), 7.59–7.52 (m, 2H), 7.48–7.40(m, 2H), 2.53(s, 3H). ^{13}CNMR($CDCl_3$) δ(ppm) 159.7, 157.0, 140.7, 135.2, 129.7, 129.3, 127.1, 124.5, 114.7, 22.1.

6-Phenyl-2-phenylthipyrazine-3-carbonitrile (6a): mp: 133–134°C (EtOAc/heptane); ^{1}HNMR($CDCl_3$) δ(ppm) 8.80(s, 1H), 7.75–7.70(m, 2H), 7.65–7.60(m, 2H), 7.55–7.35(m, 6H); HRMS(FAB) Calc. m/z for (M+H) $C_{17}H_{12}N_3S$: 290.0752, Found: 290.0763; IR(KBr) 3060, 2210, 1520, 1509, 860(cm^{-1}). Anal. Calc. for $C_{17}H_{11}N_3S$: C, 70.57; H, 3.83; N, 14.73; S, 11.08; Found: C, 70.46; H, 3.68; N, 14.64; S, 11.09.

6-Methyl-2-phenylthiopyrazine-3-carbonitrile (6b): mp: 81–82°C (EtOAc/heptane, lit.[13] 82–82.5°C). ^{1}HNMR($CDCl_3$) δ(ppm) 8.21(s, 1H), 7.59–7.52(m, 2H), 7.49–7.40(m, 2H), 2.44(s, 3H); ^{13}CNMR($CDCl_3$) δ(ppm) 159.7, 157.0, 140.7, 135.3, 129.7, 129.3, 114.8, 90.4, 22.1; MS(CI) m/z 228(M+1); IR(KBr) 3070, 3020, 2220, 1415, 1080, 750(cm^{-1}).

5-Phenyl-2-phenylsulfinylpyrazine-3-carbonitrile (7): mp: 173–174°C (toluene); ^{1}HNMR (DMSO-d_6) δ(ppm) 9.67(s, 1H), 8.30–8.22(m, 2H), 7.99–7.93(m, 2H), 7.76–7.62(m, 6H); ^{13}CNMR($CDCl_3$) δ(ppm) 160.7, 152.9, 145.1, 142.1, 133.2, 132.2, 131.7, 129.8, 129.3, 127.6, 126.0, 125.3, 113.9; HRMS(FAB) Calc. m/z for (M+H) $C_{17}H_{12}N_3OS$: 306.0701; Found: m/z 306.0695. Anal. Calc. for $C_{17}H_{11}N_3OS$: C, 66.87; H, 3.63; N, 13.76; S, 10.50; Found: C, 66.16; H, 3.50; N, 13.57; S, 10.75.

5-Phenyl-2-phenylsulfonylpyrazine-3-carbonitrile (8): mp: 222–224°C; ^{1}HNMR($CDCl_3$) δ(ppm) 9.19(s, 1H), 8.21(dd, 2H, $J_1 = 8$ Hz, $J_2 = 2.5$ Hz), 8.08(dd, 2H, $J_1 = 8$ Hz, $J_2 = 3$ Hz), 7.73(dt, 2H, $J_1 = 8$, $J_2 = 2.5$Hz), 7.60, (m, 5H); IR(KBr) 3125, 3070, 2250, 1555, 1325, 1160, 730(cm^{-1}); HRMS(FAB) Calc. m/z for (M+H) $C_{17}H_{12}N_3O_2S$: 322.0650, Found: m/z 322.0652. Anal. Calc. for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08; S, 9.98; Found: C, 63.49; H, 3.37; N, 13.21; S, 9.98.

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Received in the U.S.A. June 1, 2000