

SYNTHESIS OF THIENO[3,2-b]PYRIDINES

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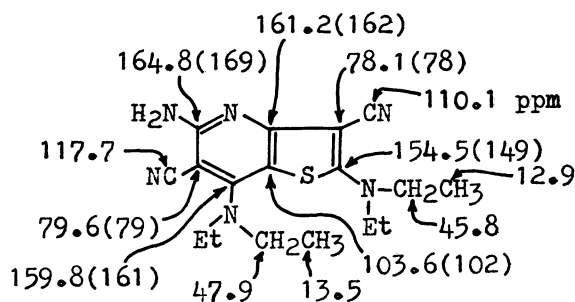
Several thieno[3,2-b]pyridines could be easily synthesized by methallation using LDA directly from 3-(disubstituted amino)-2-cyano-3-methylthioacrylonitriles.

We have recently reported the synthesis of 2,4-diaminothiazoles and 2,4-diaminothiophenes by an intramolecular cyclization of cyano group and thiomethanide ion.¹⁾ This reaction was now extended to one step synthesis of thieno[3,2-b]pyridines 6 from 3-(disubstituted amino)-2-cyano-3-methylthioacrylonitriles 2. The thieno[3,2-b]pyridines hitherto known have been synthesized from thiophene or pyridine derivatives.²⁾ In this respect, our method involving simultaneous formation of thiophene and pyridine rings provides a convenient preparative procedure for thieno[3,2-b]pyridines. This paper deals with this new synthetic method and a discussion of its reaction pathway.

The following preparation of 5-amino-3,6-dicyano-2,7-bis(diethylamino)-thieno[3,2-b]pyridine 6d is representative: A solution containing LDA (1.2 mmol) in 5 ml of THF was added dropwise with a syringe to a stirred solution of 2-cyano-3-diethylamino-3-methylthioacrylonitrile 2d (195 mg, 1 mmol) in 2 ml of THF under nitrogen atmosphere at -60 °C. After the mixture was stirred for an additional 30 min, it was quenched with water and allowed to stand for 30 min to form white precipitates. Recrystallization from pyridine gave 6d as white powder in 57 % yield.

In the case of the reaction of 2b, a small amount of 6b was separated from the reaction solution by filtration immediately after it was quenched with water. The filtrate was rotary-evaporated to afford 3-amino-4-cyano-2-(2,2-dicyano-1-piperidinovinyl)-5-piperidinothiophene 7b as yellow crystals in 31 % yield.³⁾ Table 1 shows compounds 6⁴⁾ synthesized by the present method.

The structures of 6 were determined on the basis of spectroscopic evidence together with elemental analyses. The nmr spectrum (pyridine-d₅) of 6a showed a broad amino signal at δ 7.2, and broad methylene ones at δ 3.75 (8 protons) and 3.55 (8 protons). Its ir spectrum gave two strong CN stretching bands (2200 and 2190 cm⁻¹) and a strong C=N stretching band of pyridine (1450 cm⁻¹).



In addition, the Cmr datum of 6d supports the structure of thieno[3,2-b]pyridine derivative. The figures in parentheses show approximate δ values estimated from the chemical shift values of thiophene and pyridine using incremental ones of monosubstituted benzene.⁹⁾







Next, the ir spectrum of 7b showed two strong CN stretching bands at 2200 and 2180 cm^{-1} , and no absorption of C=N stretching band of pyridine. In the nmr datum (CCl_4) a broad amino peak appeared at δ 4.9. Its uv datum (99 % EtOH) gave a strong absorption at 400 nm due to a longer conjugated π -system. On treatment with ethanol solution containing potassium hydroxide, 7b was readily converted into 6b in quantitative yield. the

structure of 7b was deduced on the basis of these results.

The formation of 6 can be explained by assuming two intermediates 4 and 5 which are derived from dimerization of 2 as shown in Scheme 1; an anion of 2 attacks another 2 to form 4 with loss of a methanethiolate ion, followed by cyclization to generate 5, which in turn, is converted into 6 by quenching with water. Isolation of 7 confirms the presence of 5 in the present reaction.

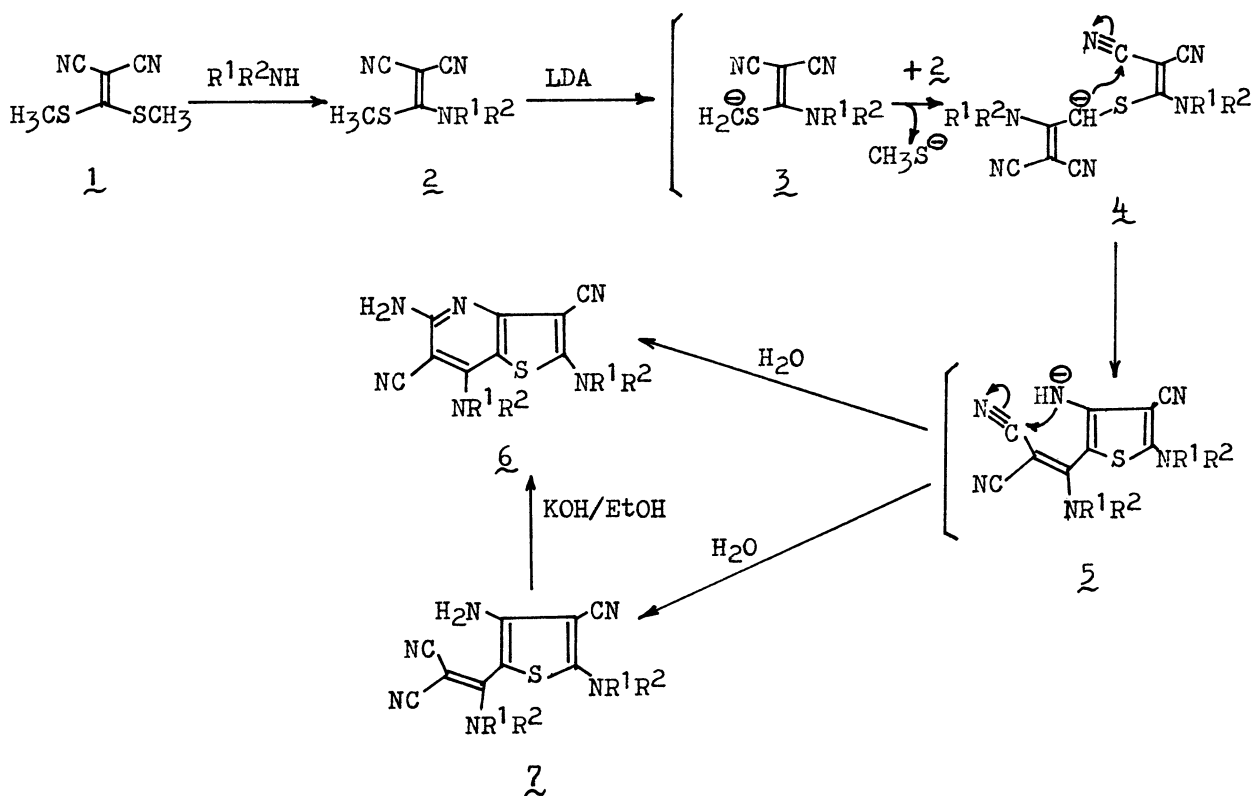
On the other hand, 3-(substituted amino)-2-cyano-3-methylthioacrylonitriles 8, which produced from 1 with primary amines, were cyclized by the present

Table 1. Compounds 2 and 6

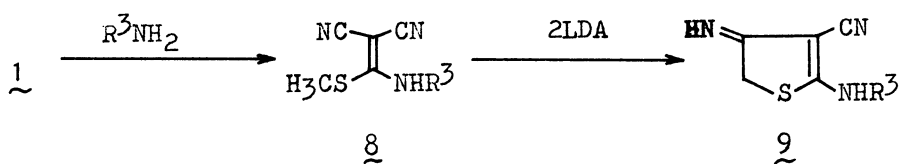
R ¹ R ² NH	Compds	Mp °C (recry. solv.)	Isolated Yield (%)
	<u>2a</u> ⁵⁾	140-141 (EtOH)	93
	<u>6a</u>	ca.315(dec) (pyridine)	49
	<u>2b</u> ⁶⁾	94-95 (EtOH)	78
	<u>6b</u>	ca.330(dec) (pyridine)	51
	<u>2c</u> ⁶⁾	89-90 (EtOH)	86
	<u>6c</u>	ca.270(dec) (pyridine)	52
	<u>2d</u> ⁷⁾	67-68 (EtOH)	87
	<u>6d</u>	240-241 (pyridine-hexane)	57
	<u>2e</u> ⁷⁾	21-22 (EtOEt)	99
	<u>6e</u>	202-203 (pyridine-hexane)	54
	<u>2f</u> ⁸⁾	97-98 (EtOH)	91
	<u>6f</u>	261-262 (pyridine-hexane)	12

reaction to form cyclized products, 5-(substituted amino)-4-cyano-3-imino-2,3-dihydrothiophenes 9¹⁰⁾ instead of dimerized products such as 6 (see Scheme 2). This is perhaps because a dianion of 8 can not attack a monoanion of 8 as a nucleophile owing to electrostatic repulsion.

Scheme 1



Scheme 2



References

- 1) M.Yokoyama, M.Kurauchi, and T.Imamoto, *Tetrahedron Lett.*, 1981, 2285.
- 2) J.M.Barker, *Adv. Heterocycl. Chem.*, 21, 65 (1977) and references cited therein; K.Hartke and G.Golz, *Liebigs Ann. Chem.*, 1973, 1644; F.Outurquin, G.Ah-Kow, and C.Paulmier, *Bull. Soc. Chim. Fr.*, 1976, 883; C.Paulmier and F.Outurquin, *J. Chem. Res. (S)*, 1977, 318; M.A.Khan and A.E.Guarconi, *J. Heterocycl. Chem.*, 1977, 807; J.M.Barker, *Heterocycles*, 9, 621 (1978); J.M.Barker, P.R.Huddleston, N.Chadwick, and G.J.Keenen, *J. Chem. Res., Synop.*, 1980, 6; O.M.Cohn, B.Narine,

and B.Tarnowski, J. Chem. Soc. Perkin I, 1981, 1531; C.L.Hickson, and H.Mcnab, Synthesis, 464 (1981).

- 3) Compounds 7c and 7f were also isolated from 2c and 2f in 43 % and 23 % yields, respectively.
- 4) 6a: mass m/e 370(M⁺), 200(characteristic fragment ion); uv $\lambda_{\max}^{99\% \text{ EtOH}}$ 234 nm (sh), 251($\epsilon = 25000$), 293(sh), 320(15000), 361(20000).
6b: nmr(DMSO-d₆) δ 6.6(br, 2H, NH₂), 3.85(m, 8H, 4CH₂), 1.7(m, 12H, 6CH₃); mass m/e 366(M⁺), 200; uv $\lambda_{\max}^{99\% \text{ EtOH}}$ 235 nm (sh), 253($\epsilon = 26000$), 292(sh), 320(15500), 360(21500); ir(KBr) 3450, 3310, 3200 cm⁻¹(NH), 2940, 2850(CH), 2200, 2190(CN), 1450(C=N).
6c: nmr(DMSO-d₆) δ 6.15(br, 2H, NH₂), 3.6(br, 8H, 2N(CH₂)₂), 2.0(br, 8H, 4CH₂); mass m/e 338(M⁺), 200; uv $\lambda_{\max}^{99\% \text{ EtOH}}$ 236 nm (sh), 253($\epsilon = 26000$), 292(sh), 321(15000), 361(22000); ir(KBr) 3420, 3300, 3190 cm⁻¹(NH), 2925, 2850(CH), 2200, 2190(CN), 1450(C=N).
6d: nmr(DMSO-d₆) δ 6.35(br, 2H, NH₂), 3.6(q, 8H, 4CH₂), 1.35(t, 6H, 2CH₃), 1.10(t, 6H, 2CH₃); mass m/e 342(M⁺), 200; uv $\lambda_{\max}^{99\% \text{ EtOH}}$ 235 nm (sh), 252($\epsilon = 31000$), 292(sh), 318(18000), 361(27000); ir(KBr) 3430, 3300, 3180 cm⁻¹(NH), 2950, 2910(CH), 2200, 2190(CN), 1450(C=N).
6e: nmr(DMSO-d₆) δ 6.55(br, 2H, NH₂), 3.7(m, 8H, 4CH₂), ca. 1.45(m, 16H, 8CH₂), 0.95(m, 12H, 4CH₃); uv $\lambda_{\max}^{99\% \text{ EtOH}}$ 236 nm (sh), 254($\epsilon = 32000$), 293(sh), 321(19000), 363(28000); ir(KBr) 3425, 3300, 3180 cm⁻¹(NH), 2940, 2910, 2850(CH), 2200, 2190(CN), 1450(C=N).
6f: nmr(DMSO-d₆) δ ca. 7.5(m, 10H, 2Ph), 6.8(br, 2H, NH₂), 3.88(s, 3H, CH₃), 3.55(s, 3H, CH₃); mass m/e 410(M⁺), 200; uv $\lambda_{\max}^{99\% \text{ EtOH}}$ 206 nm ($\epsilon = 32000$), 243(33000), 265(sh), 297(sh), 322(16000), 374(19000); ir(KBr) 3440, 3310, 3210 cm⁻¹(NH), 2910, 2850(CH), 2220, 2200(CN), 1460(C=N).
- 5) Compound 2b was prepared according to the literature; R.Gompper and W.Töpfl, Chem. Ber., 95, 2861 (1962).
- 6) Compounds 2b and 2c were prepared by Gompper's method in Ref. 5. Melting point of 2b has been reported as 93-95 °C in the following literature; H.Eilingsfeld and L.Möbius, Chem. Ber., 98, 1293 (1965).
- 7) Compounds 2d and 2e were synthesized by stirring the benzene solution containing 1 and the corresponding secondary amines overnight at room temperature.
- 8) Compound 2f was prepared by methylation of 3-anilino-2-cyano-3-methylthioacrylonitrile [an overnight stirring in benzene-acetone (1 : 1) solution containing KOH and CH₃I].
- 9) E.Breitmaier and W.Voelter, "13C-NMR Spectroscopy", Verlag Chemie, pp. 198 (1978).
- 10) 5-Anilino-4-cyano-3-imino-1,2-dihydrothiophene (mp. 197-198dec°C), 5-(p-anisidino)-cyano-3-imino-1,2-dihydrothiophene (mp. 146-147dec°C), and 2-(1-naphthylamino)-3-cyano-4-imino-4,5-dihydrothiophene (mp. 157-158dec°C) were obtained from the corresponding 2 in 56 %, 59 %, and 71 % yields, respectively. The structures of 2 have been described in Ref. 1.

(Received September 30, 1982)