

**Activated Nitriles in Heterocyclic Synthesis:
Synthesis of 6-Thiophen-2-yl
and 6-Furan-2-ylthiazolo[2,3—*a*]pyridine Derivatives**

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A variety of new 6-thiophen-2-yl and 6-furan-2-ylthiazolo[2,3—*a*]pyridine derivatives could be prepared via the reaction of 2-functionally substituted methyl-2-thiazolin-4-one with cyanomethylenethiophen-2-yl and cyanomethylenefuran-2-yl derivatives. The structure of the reaction products was established based on spectral data.

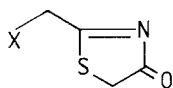
(Keywords: Michael addition; Methyl-2-thiazolin-4-one, 2-functionally substituted; Ylidenethiazolo[2,3-*a*]pyridine)

*Aktivierte Nitrile in der Heterocyclen-Synthese: Die Synthese von 6-Thiophen-2-yl- und 6-Furan-2-yl-thiazolo[2,3—*a*]pyridin-Derivaten*

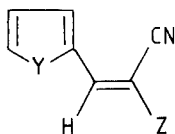
Es konnte eine Reihe neuer 6-Thiophen-2-yl- und 6-Furan-2-yl-thiazolo[2,3—*a*]pyridine über die Reaktion von 2-funktionell-substituierten Methyl-2-thiazolin-4-onen mit Cyanomethylenethiophen-2-yl bzw. Cyanomethylenfuran-2-yl-Derivaten hergestellt werden. Die Struktur der Reaktionsprodukte wurde mit spektroskopischen Methoden ermittelt.

Introduction

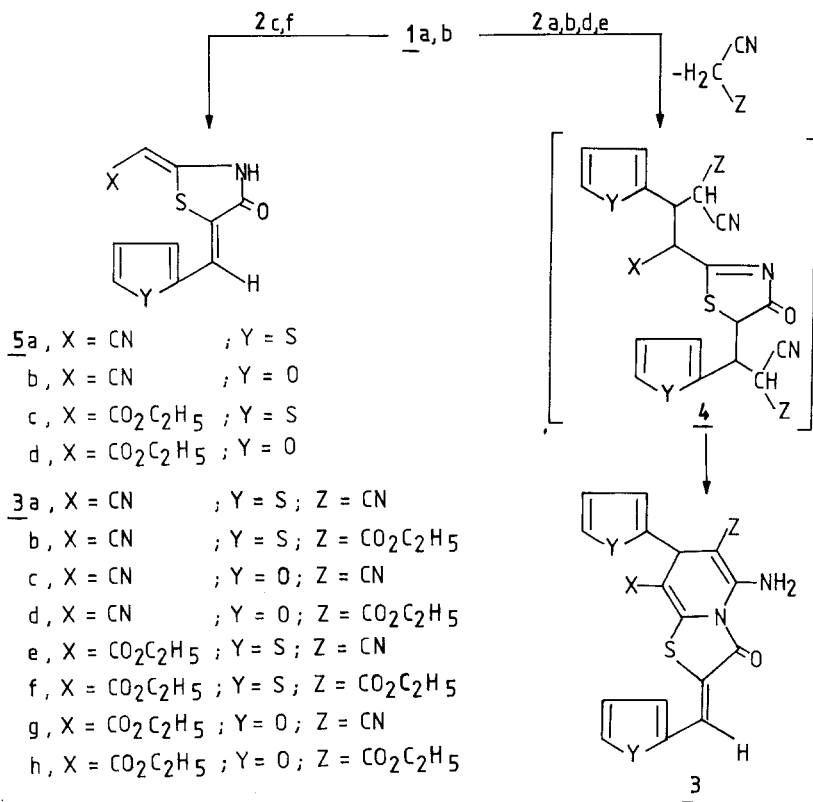
In spite of the interesting biological activities of thiazolo[2,3—*a*]pyridines as antiinflammatory and antibacterial agents^{1,2}, very little attention was paid for development of efficient procedures for their synthesis. As a part of our program directed for exploring the synthetic



1
a, X = CN
b, X = COOC₂H₅



2
a, Y = S; Z = CN
b, Y = S; Z = COOC₂H₅
c, Y = S; Z = C⁶H₅
d, Y = O; Z = CN
e, Y = O; Z = COOC₂H₅
f, Y = O; Z = C⁶H₅



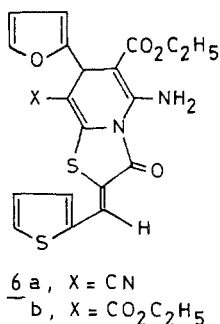
potential, scope and limitations of α,β -unsaturated nitriles in heterocyclic synthesis we have recently reported that cinnamionitrile derivatives reacts with 2-functionally substituted methyl-2-thiazolin-4-ones **1 a-c** to yield thiazolo[2,3-*a*]pyridine derivatives in excellent yields³. We have been particularly interested to see if reactions of this type can be extended to constitute a more general method for preparation of thiazolo[2,3-*a*]pyridines. In the present paper we report the results of our investigation on the reactivity of **1 a, b** toward the 2- β -cyanoethylenethiophen derivatives **2 a-c** and 2- β -cyanoethylenefuran derivatives **2 d-f**. The newly required derivatives **2 c, f** were prepared via condensation of thiophen-2-al and of furan-2-al with benzoylacetonitrile.

Results and Discussion

Compounds **1 a, b** reacted with **2 a, b, d, e** to yield products for which structures **3** could be suggested based on analytical and mass spectral data. The formation of **3** from **1** and **2** may be assumed to proceed via the 1 : 2 adduct **4** which cyclise with the loss of malononitrile or ethyl cyanoacetate to yield the final isolable **3**. Alternately loss of malononitrile and ethyl cyanoacetate may proceed the cyclization. In contrast to the behaviour of **1 a, b** toward **2 a, b, d, e**, compounds **1 a, b** reacted with **2 c, f** to yield only ylidene derivatives. Structure **5** however could be established for the reaction product based on ¹H-nmr spectra which revealed absence of either thiazolin-4-one 5-H methylene protons or thiazol 5-H proton and revealed a pattern that can only be interpreted in terms of structure **5**. Compounds **5 a-d** could be also obtained via direct condensation of **1 a, b** and thiophen-2-al or furan-2-al, the behaviour of **1 a, b** is in contrast to the reported behaviour toward aromatic aldehydes^{4,5}.

Compound **5** reacted with **2** to yield the corresponding thiazolo[2,3-*a*]pyridine derivatives **3**.

Compounds **3** can have either the *E* form or the *Z* form. ¹H-nmr



revealed that all the prepared derivatives are the *E* isomers as the ylidene proton appeared in each case at 8.1 ppm. The ylidene proton of the *Z* isomer would have been expected to resonate at much higher frequency^{6,7}.

In order to prepare thiazolopyridine derivatives containing both thiophen and furan substituents, the thiophenylidene derivative **5 a, c** was treated with the furanylidene derivative **2 e** to yield a 1 : 1 adduct for which structure **6 a, b** was established based on spectral and analytical data.

Experimental

All melting points are uncorrected. Ir spectra were recorded (KBr) on a pye Unicam sp-1100 spectrophotometer. ¹H-nmr spectra were measured in *DMSO-d*₆ on a varian EM-360-60 HMZ using *TMS* as internal standard and chemical shifts are expressed as δ /ppm. Mass spectra were recorded on a Varian MAT 112 spectrometer. Microanalytical data (C,H,N) were obtained from the Microanalytical Data Unit at Cairo University and were in excellent agreement with the required values for **2 c, f**, **3 a-h**, **5 a-d**, and **6 a, b**.

Compounds **2 a, b, d, e** were prepared following literature procedures⁸⁻¹¹.

Furan-2-ylidenebenzoylacetonitrile and thiophen-2-ylidenebenzoylacetonitrile (2 c, f)

A suspension of benzoylacetonitrile (0.1 mol) in acetic acid (100 ml) and triethylamine (1 ml) was treated with 0.1 mol of either furan-2-al or thiophen-2-al. The reaction mixture was refluxed for 5 h then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised from the proper solvent.

4-Amino-2,5,6,7-tetrasubstituted-3-oxo-2,3-dihydro-6H-thiazolo[2,3-a]-pyridines (3 a-h, 6 a, b)

A solution of **1 a, b** (0.01 mol) in ethanol (100 ml) is treated with **2 a, b, d, e** (0.02 mol) then with piperidine (1 ml). The mixture is heated under reflux for 3 h and evaporated *in vacuo*. The residue is triturated with water, the resulting solid product is collected by filtration and crystallised from the proper solvent.

Compounds **6 a, b** could be obtained from the reaction of **5 a, c** with **2 e** following the above procedure.

2-Substituted methylidene-5-substituted thiazolidene-4-one derivatives (5 a-d)

A solution of **1 a** or **1 b** (0.01 mol) in ethanol (100 ml) is treated with reagent **2 c, f** (0.01 mol) then with piperidine (1 ml). After refluxing for 3 h and evaporation, the residue was triturated with water and the resulting solid product was collected by filtration and crystallised from the proper solvent. Compounds **5 a-d** could be also obtained from the reaction of **1 a, b** with furan-2-al or thiophen-2-al following the above procedure.

List of compounds 2 c, f, 3 a-h, 5 a-d, and 6 a, b

2 c: 75% yield, yellow crystals from cyclohexanone, m.p. 100–101°, C₁₄H₉NOS (239.22); IR: 2 210 (CN), 1 680 (CO), 1 600 (C=C); NMR: 7.33 (q, 1 H, thiophen 4-H), 7.66–7.75 (m, 5 H, aromatic protons), 7.90 (q, 1 H, thiophen 3-H), 8.10–8.30 (dd, 1 H, thiophen 5-H), 8.42 (s, 1 H, CH).

2f: 70% yield, yellow crystals from cyclohexanone, m. p. 108–109°, $C_{14}H_9NO_2$ (223.22); IR: 2 210 (CN), 1 660 (CO), 1 610 (C=C); NMR: 6.78 (q, 1 H, furan 4-H), 7.54–7.60 (dd, 1 H, furan 3-H), 7.66–7.75 (m, 5 H, aromatic protons), 7.80–7.90 (q, 1 H, furan 5-H), 8.27 (s, 1 H, CH).

3a: 80% yield, yellow crystals from *EtOH-DMF*, m. p. 216–217°, $C_{18}H_{10}N_4OS_3$ (441.34); MS: *m/e* 394; IR: 3 400/3 280/3 200 (NH_2), 2 220 (CN), 1 700 (ring CO), 1 600 (δNH_2); NMR: 5.0 (s, 1 H, pyridine CH), 7.00–7.30 (m, 2 H, thiophen 5,5'-H), 7.52–7.73 (s, 2 H, thiophen 4,4'-H), 7.84–8.02 (d, 2 H, thiophen 3,3'-H), 8.02–8.12 (d, 1 H, CH), 8.32 (s, 2 H, NH_2).

3b: 82% yield, red crystals from *EtOH-DMF*, m. p. 235°, $C_{20}H_{15}N_3O_3S_3$ (441.34); MS: *m/e* 441; IR: 3 400 ~ 3 300 (NH_2), 2 220 (CN), 1 720 (ester CO), 1 700 (ring CO), 1 620–1 600 (δNH_2 and C=C).

3c: 75% yield, yellow crystals from dioxan, m. p. 232–234°, $C_{18}H_{10}N_4O_3S$ (362.29); MS: *m/e* 362; IR: 3 400/3 300/3 220 (NH_2), 2 210 (CN), 1 710 (ring CO), 1 620 (δNH_2 and C=C).

3d: 60% yield, brown crystals from *DMF*, m. p. 218°, $C_{20}H_{15}N_3O_5S$ (409.34); MS: *m/e* 409; IR: 3 480/3 400/3 250 (NH_2), 2 210 (CN), 1 725 (ester CO), 1 700 (ring CO), 1 620 ~ 1 600 (δNH_2 and C=C).

3e: 65% yield, yellow crystals from *EtOH*, m. p. 221–222°, $C_{20}H_{15}N_3O_3S_3$ (441.34); IR: 3 380/3 300/3 200 (NH_2), 2 210 (CN), 1 720 ~ 1 700 (ester CO and ring CO), 1 630 (δNH_2 and C=C); NMR: 1.25 (t, 3 H, CH_3), 4.25 (q, 2 H, CH_2), 4.85 (s, 1 H, pyridine CH), 7.00 (m, 2 H, thiophen 5,5'-H), 7.33–7.70 (m, 5 H, thiophen 4,4', 3,3'-H and ylidenic CH), 8.15 (s, 2 H, NH_2).

3f: 68% yield, yellow crystals from dioxan, m. p. 191–193°, $C_{22}H_{20}N_2O_5S_3$ (488.4); IR: 3 420/3 400/3 280 (NH_2), 1 720 (two ester CO), 1 700 (ring CO), 1 620 (δNH_2 and C=C). NMR: 1.33 (t, 6 H, 2 CH_3), 4.22 (q, 4 H, 2 CH_2), 5.18 (s, 1 H, pyridine CH), 6.95 (q, 2 H, thiophen 5,5'-H), 7.33 (q, 2 H, thiophen 4,4'-H), 7.66 (q, 2 H, thiophen 3,3'-H), 8.00 (s, 1 H, CH), 8.65 (br, s, 2 H, NH_2).

3g: 60% yield, orange crystals from *EtOH-DMF*, m. p. 249–251°, $C_{20}H_{15}N_3O_5S$ (409.34); MS: *m/e* 409; IR: 3 400/3 350/3 290 (NH_2); 2 210 (CN), 1 725 (ester CO), 1 690 (ring CO), 1 610 (NH_2); NMR: 1.11 (t, 3 H, CH_3), 2.68 (d, 2 H, NH_2), 4.15 (q, 2 H, CH_2), 4.66 (s, 1 H, pyridine CH), 6.18 (q, 1 H, furan 4'-H), 6.33 (q, 1 H, furan 4-H), 6.88 (q, 1 H, furan 3-H), 7.18 (dd, 1 H, furan 3'-H), 7.66 (m, 2 H, furan 5,5'-H), 8.15 (s, 1 H, CH).

3h: 64% yield, yellow crystals from dioxan, m. p. 180–182°, $C_{22}H_{20}N_2O_7S$ (456.40); MS: *m/e* 456; IR: 3 400/3 280 (NH_2), 1 730/1 700 (two ester CO), 1 690 (ring CO), 1 620 (δNH_2 and C=C); NMR: 1.15 (t, 6 H, 2 CH_3), 4.18 (q, 4 H, 2 CH_2), 5.00 (s, 1 H, pyridine CH), 6.00 (dd, 1 H, furan 4-H), 6.35 (q, 1 H, furan 4'-H), 6.68 (q, 1 H, furan 3-H), 7.10 (dd, 1 H, furan 3'-H), 7.45 (dd, 1 H, furan 5-H), 7.65 (d, 1 H, furan 5'-H), 8.09 (s, 1 H, CH), 8.30 (br, s, 2 H, NH_2).

5a: 90% yield, brown crystals from dioxan, m. p. 245–246°, $C_{10}H_6N_2OS_2$ (234.17); IR: 3 300 (NH), 2 220 (CN), 1 690 (ring CO), 1 595 (δNH).

5b: 92% yield, red crystals from dioxan, m. p. 228–229°, $C_{10}H_6N_2O_2S$ (218.17); MS: *m/e* 218; IR: 3 320 (NH), 2 210 (CN), 1 710 (ring CO), 1 600 (δNH); NMR: 5.29 (s, 1 H, CH), 6.68 (q, 1 H, furan 5-H), 7.00 (q, 1 H, furan 4-H), 7.52 (s, 1 H, CH), 8.09 (q, 1 H, furan 3-H).

5c: 88% yield, orange crystals from dioxan, m. p. 200–202°, $C_{12}H_{11}NO_3S_2$ (281.22); IR: 3 400 (NH), 1 720/1 690 (ester CO and ring CO), 1 600 (δNH); NMR: 1.33 (t, 3 H, CH_3), 4.25 (q, 2 H, CH_2), 5.66 (s, 1 H, CH), 7.33 (q, 1 H, thiophen 5-H), 7.66 (dd, 1 H, thiophen 4-H), 7.95 (s, 1 H, CH), 8.00 (dd, 1 H, thiophen 3-H).

5d: 90% yield, yellow crystals from dioxan, m. p. 182–184°, $C_{12}H_{11}NO_4S$ (265.22); MS: *m/e* 265; IR: 3 150 (NH), 1 695 ~ 1 660 (ester and ring CO), 1 600

(δ NH); NMR: 1.33 (t, 3 H, CH₃), 4.15 (q, 2 H, CH₂), 5.70 (s, 1 H, CH), 6.66 (q, 1 H, furan 5'-H), 6.80 (dd, 1 H, furan 4-H), 7.45 (s, 1 H, CH), 7.92 (q, 1 H, furan 3-H).

6a: 88% yield, orange crystals from benzene, m.p. 166°, C₂₀H₁₅N₃O₄S₂ (425.34); IR: 3300 (NH₂), 2210 (CN), 1695 (ester CO), 1660 (ring CO), 1595 (δ NH₂).

6b: 92% yield, yellow crystals from dioxan, m.p. 248–250, C₂₂H₂₀N₂O₆S₂ (472.40); IR: 3420/3400/3280 (NH₂, 1720 (two ester CO), 1700 (ring CO), 1620 (δ NH₂ and C=C); NMR: 1.29 (t, 6 H, 2 CH₃), 4.09 (q, 4 H, 2 CH₂), 5.05 (d, 1 H, pyridine CH), 6.00 (q, 1 H, furan 5-H), 6.33 (q, 1 H, furan 4-H), 6.95 (q, 1 H, thiophen 5'-H), 7.30 (q, 1 H, thiophen 4'H), 7.35 (s, 1 H, CH), 7.66 (dd, 1 H, furan 3-H), 8.00 (dd, 1 H, thiophen 3'-H).

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