Monatshefte für Chemie 117, 105—110 (1986)

Monatshefte für Chemie
Chemical Monthly

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

Soad Abdel Meguid Osman[a], **Galal Eldin Hamza Elgemeie**[b,*], **Galal Abdel Moein Nawar**[a], and **Mohamed Hilmy Elnagdi**[c]

[a] National Research Centre, Dokki, A. R. Egypt
[b] Chemistry Department, Faculty of Science, Minia University, Minia, A. R. Egypt
[c] Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt

(Received 24 July 1984. Revised 31 October 1984. Accepted 28 November 1984)

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.

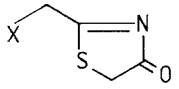
(Keywords: Michael addition; Methyl-2-thiazolin-4-one, 2-functionally substituted; Ylidenethiazolo[2,3-a]pyridine)

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 Cyanomethylenthiphen-2-yl bzw. Cyanomethylenfuran-2-yl-Derivaten hergestellt werden. Die Struktur der Reaktionsprodukte wurde mit spektroskopischen Methoden ermittelt.

Introduction

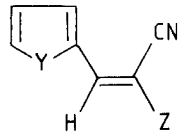
In spite of the interesting biological activities of thiazolo[2,3—*a*]-pyridines as antiinflammatory and antibacterial agents[1,2], very little attention was paid for development of efficient procedures for their synthesis. As a part of our program directed for exploring the synthetic



1

a, X = CN

b, X = $COOC_2H_5$



2

a, Y = S; Z = CN

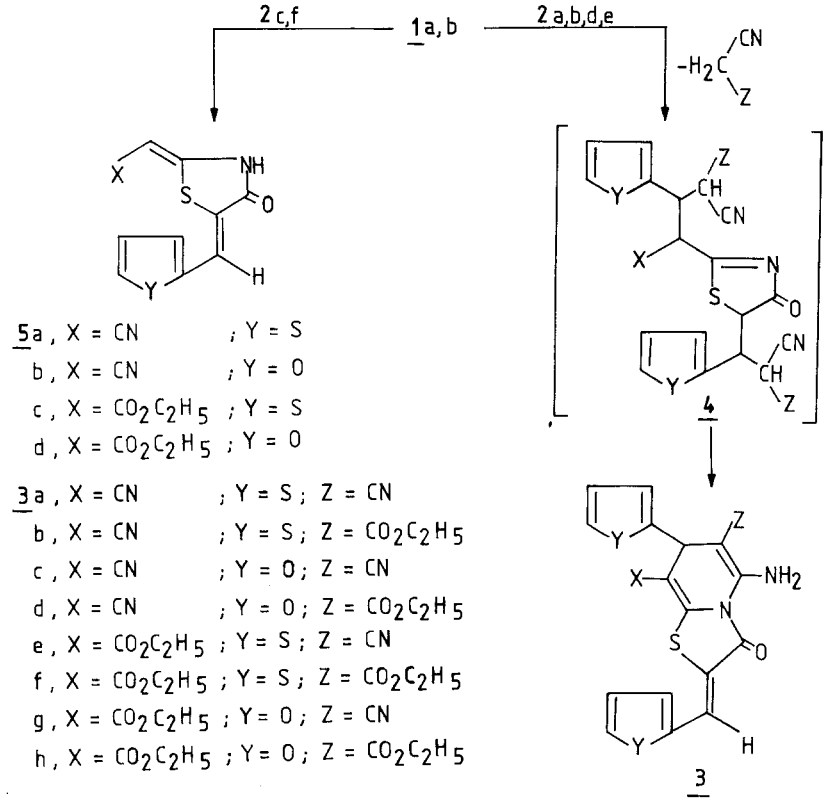
b, Y = S; Z = $COOC_2H_5$

c, Y = S; Z = COPh

d, Y = O; Z = CN

e, Y = O; Z = $COOC_2H_5$

f, Y = O; Z = COPh



5a, X = CN ; Y = S

b, X = CN ; Y = O

c, X = $CO_2C_2H_5$; Y = S

d, X = $CO_2C_2H_5$; Y = O

3a, X = CN ; Y = S; Z = CN

b, X = CN ; Y = S; Z = $CO_2C_2H_5$

c, X = CN ; Y = O; Z = CN

d, X = CN ; Y = O; Z = $CO_2C_2H_5$

e, X = $CO_2C_2H_5$; Y = S; Z = CN

f, X = $CO_2C_2H_5$; Y = S; Z = $CO_2C_2H_5$

g, X = $CO_2C_2H_5$; Y = O; Z = CN

h, X = $CO_2C_2H_5$; Y = O; Z = $CO_2C_2H_5$

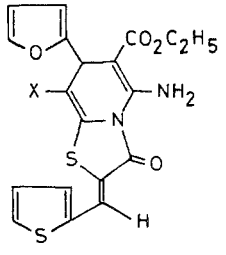
potential, scope and limitations of α,β-unsaturated nitriles in heterocyclic synthesis we have recently reported that cinnamonitrile derivatives reacts with 2-functionally substituted methyl-2-thiazolin-4-ones **1 a–c** to yield thiazolo[2,3—*a*]pyridine derivatives in excellent yields[3]. We have been 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 ^{1}H-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. ^{1}H-nmr



6 a, X = CN
b, X = $CO_2C_2H_5$

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 **5a, c** was treated with the furanylidene derivative **2e** to yield a 1 : 1 adduct for which structure **6a, 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. ^{1}H-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 **2c, f**, **3a–h**, **5a–d**, and **6a, b**.

Compounds **2a, b, d, e** were prepared following literature procedures[8–11].

Furan-2-ylidenebenzoylacetonitrile and thiophen-2-ylidenebenzoylacetonitrile (**2c, 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 (**3a–h, 6a, b**)

A solution of **1a, b** (0.01 mol) in ethanol (100 ml) is treated with **2a, 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 **6a, b** could be obtained from the reaction of **5a, c** with **2e** following the above procedure.

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

A solution of **1a** or **1b** (0.01 mol) in ethanol (100 ml) is treated with reagent **2c, 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 **5a–d** could be also obtained from the reaction of **1a, b** with furan-2-al or thiophen-2-al following the above procedure.

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

2c: 75% yield, yellow crystals from cyclohexanone, m.p. 100–101°, $C_{14}H_9NOS$ (239.22); IR: 2210 (CN), 1680 (CO), 1600 (C=C); NMR: 7.33 (q, 1H, thiophen 4-H), 7.66–7.75 (m, 5H, aromatic protons), 7.90 (q, 1H, thiophen 3-H), 8.10–8.30 (dd, 1H, thiophen 5-H), 8.42 (s, 1H, CH).

2f: 70% yield, yellow crystals from cyclohexanone, m. p. 108–109°, $C_{14}H_9NO_2$ (223.22); IR: 2210 (CN), 1660 (CO), 1610 (C=C); NMR: 6.78 (q, 1H, furan 4-H), 7.54–7.60 (dd, 1H, furan 3-H), 7.66–7.75 (m, 5H, aromatic protons), 7.80–7.90 (q, 1H, furan 5-H), 8.27 (s, 1H, CH).

3a: 80% yield, yellow crystals from *Et*OH-*DMF*, m. p. 216–217°, $C_{18}H_{10}N_4OS_3$ (441.34); MS: *m/e* 394; IR: 3400/3280/3200 (NH_2), 2220 (CN), 1700 (ring CO), 1600 (δ NH_2); NMR: 5.0 (s, 1H, pyridine CH), 7.00–7.30 (m, 2H, thiophen 5,5′-H), 7.52–7.73 (s, 2H, thiophen 4,4′-H), 7.84–8.02 (d, 2H, thiophen 3,3′-H), 8.02–8.12 (d, 1H, CH), 8.32 (s, 2H, NH_2).

3b: 82% yield, red crystals from *Et*OH-*DMF*, m. p. 235°, $C_{20}H_{15}N_3O_3S_3$ (441.34); MS: *m/e* 441; IR: 3400 ~ 3300 (NH_2), 2220 (CN), 1720 (ester CO), 1700 (ring CO), 1620–1600 (δ NH_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: 3400/3300/3220 (NH_2), 2210 (CN), 1710 (ring CO), 1620 (δ NH_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: 3480/3400/3250 (NH_2), 2210 (CN), 1725 (ester CO), 1700 (ring CO), 1620 ~ 1600 (δ NH_2 and C=C).

3e: 65% yield, yellow crystals from *Et*OH, m. p. 221–222°, $C_{20}H_{15}N_3O_3S_3$ (441.34); IR: 3380/3300/3200 (NH_2), 2210 (CN), 1720 ~ 1700 (ester CO and ring CO), 1630 (δ NH_2 and C=C); NMR: 1.25 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 4.85 (s, 1H, pyridine CH), 7.00 (m, 2H, thiophen 5,5′-H), 7.33–7.70 (m, 5H, thiophen 4,4′, 3,3′-H and ylidenic CH), 8.15 (s, 2H, NH_2).

3f: 68% yield, yellow crystals from dioxan, m. p. 191–193°, $C_{22}H_{20}N_2O_5S_3$ (488.4); IR: 3420/3400/3280 (NH_2), 1720 (two ester CO), 1700 (ring CO), 1620 (δ NH_2 and C=C). NMR: 1.33 (t, 6H, 2 CH_3), 4.22 (q, 4H, 2 CH_2), 5.18 (s, 1H, pyridine CH), 6.95 (q, 2H, thiophen 5,5′-H), 7.33 (q, 2H, thiophen 4,4′-H), 7.66 (q, 2H, thiophen 3,3′-H), 8.00 (s, 1H, CH), 8.65 (br, s, 2H, NH_2).

3g: 60% yield, orange crystals from *Et*OH-*DMF*, m. p. 249–251, $C_{20}H_{15}N_3O_5S$ (409.34); MS: *m/e* 409; IR: 3400/3350/3290 (NH_2); 2210 (CN), 1725 (ester CO), 1690 (ring CO), 1610 (NH_2); NMR: 1.11 (t, 3H, CH_3), 2.68 (d, 2H, NH_2), 4.15 (q, 2H, CH_2), 4.66 (s, 1H, pyridine CH), 6.18 (q, 1H, furan 4′-H), 6.33 (q, 1H, furan 4-H), 6.88 (q, 1H, furan 3-H), 7.18 (dd, 1H, furan 3′-H), 7.66 (m, 2H, furan 5,5′-H), 8.15 (s, 1H, 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: 3400/3280 (NH_2), 1730/1700 (two ester CO), 1690 (ring CO), 1620 (δ NH_2 and C=C); NMR: 1.15 (t, 6H, 2 CH_3), 4.18 (q, 4H, 2 CH_2), 5.00 (s, 1H, pyridine CH), 6.00 (dd, 1H, furan 4-H), 6.35 (q, 1H, furan 4′-H), 6.68 (q, 1H, furan 3-H), 7.10 (dd, 1H, furan 3′-H), 7.45 (dd, 1H, furan 5-H), 7.65 (d, 1H, furan 5′-H), 8.09 (s, 1H, CH), 8.30 (br, s, 2H, NH_2).

5a: 90% yield, brown crystals from dioxan, m. p. 245–246°, $C_{10}H_6N_2OS_2$ (234.17); IR: 3300 (NH), 2220 (CN), 1690 (ring CO), 1595 (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: 3320 (NH), 2210 (CN), 1710 (ring CO), 1600 (δ NH); NMR: 5.29 (s, 1H, CH), 6.68 (q, 1H, furan 5-H), 7.00 (q, 1H, furan 4-H), 7.52 (s, 1H, CH), 8.09 (q, 1H, furan 3-H).

5c: 88% yield, orange crystals from dioxan, m. p. 200–202°, $C_{12}H_{11}NO_3S_2$ (281.22); IR: 3400 (NH), 1720/1690 (ester CO and ring CO), 1600 (δ NH); NMR: 1.33 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 5.66 (s, 1H, CH), 7.33 (q, 1H, thiophen 5-H), 7.66 (dd, 1H, thiophen 4-H), 7.95 (s, 1H, CH), 8.00 (dd, 1H, 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: 3150 (NH), 1695 ~ 1660 (ester and ring CO), 1600

(δ NH); NMR: 1.33 (t, 3 H, CH_3), 4.15 (q, 2 H, CH_2), 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°, $C_{20}H_{15}N_3O_4S_2$ (425.34); IR: 3300 (NH_2), 2210 (CN), 1695 (ester CO), 1660 (ring CO), 1595 (δ NH_2).

6b: 92% yield, yellow crystals from dioxan, m.p. 248–250, $C_{22}H_{20}N_2O_6S_2$ (472.40); IR: 3420/3400/3280 (NH_2, 1720 (two ester CO), 1700 (ring CO), 1620 (δ NH_2 and C=C); NMR: 1.29 (t, 6 H, 2 CH_3), 4.09 (q, 4 H, 2 CH_2), 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).

References

[1] *Shen T. Y., Clark R. L., Pessolano A. A., Witzel B. E., Bruce E., Lanza T. J.*, U.S. Patent, 4, 0.38, 396 (1975); Chem. Abstr. **87**, 152185y (1977).

[2] *Hayakawa I., Tanaka Y., Nagata Y.*, Japan Patent, 77, 83, 588 (1976); Chem. Abstr. **88**, 37785c (1978).

[3] *Elmoghayar M. R. H., Ibrahim M. K. A., Elghandour A. H. H., Elnagdi M. H.*, Synthesis **1981**, 635.

[4] *Elnagdi M. H., Khalifa M. A. E., Ibrahim M. K. A., Elmoghayar M. R. H.*, J. Heterocyclic Chem. **18**, 877 (1981).

[5] *Elnagdi M. H., Elmoghayar M. R. H., Hammam A. G., Khallaf S. A.*, J. Heterocyclic Chem. **16**, 1541 (1979).

[6] *Elgemeie G. E. H., Nawar G. A., Elnagdi M. H.*, Sadtler Standard NMR Spectra (in press, 1985).

[7] *Hiroshi K., Satoshi K.*, Shitsuryo Bunseki **27**, 47 (1979).

[8] *Emerson W. S., Jr.*, J. Org. Chem. **14**, 790 (1949).

[9] *Boehm T., Grohnwald M.*, Arch. Pharm. **274**, 318 (1936).

[10] *Thiele J., Henle F.*, Liebigs Ann. Chem. **347**, 290 (1906).

[11] *Popp F. D., Catala A.*, J. Org. Chem. **26**, 2738 (1961).