A Novel Synthesis of Thiazolo[2,3-*a*]pyridine Derivatives

Mohamed Rifaat Hamza ELMOGHAYAR, Mohamed Kamal Ahmed IBRAHEIM, Ahmed Hafez Hussin ELGHANDOUR, Mohamed Hilmy ELNAGDI*

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

As a part of a medicinal chemistry project we became interested in the synthesis of some thiazolo[2,3-*a*]pyridines. Derivatives of this ring system are generally synthesised via alkylation of 2-mercaptopyridine derivatives with α-functionalised reagents and subsequent cyclisation of the resulting alkylated products[1,2,3]. This approach is limited by the accessibility of polyfunctionally substituted 2-mercaptopyridines. Two syntheses of thiazolo[2,3-*a*]pyridines from thiazoles have been reported[4,5]. Both are limited because of the nature of the intermediates utilised in these synthesis.

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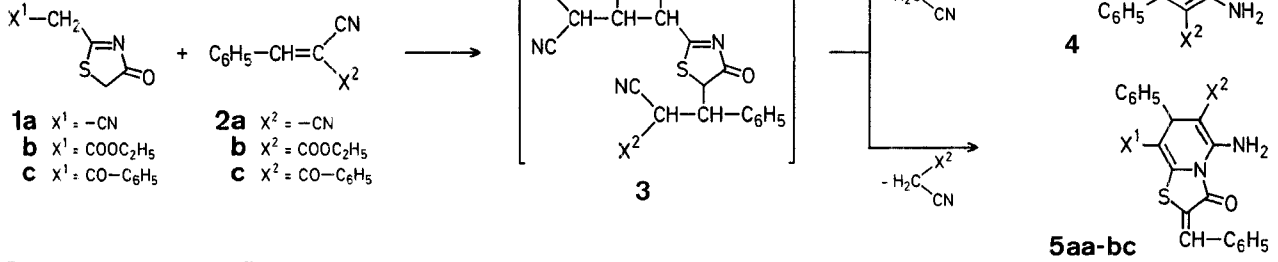
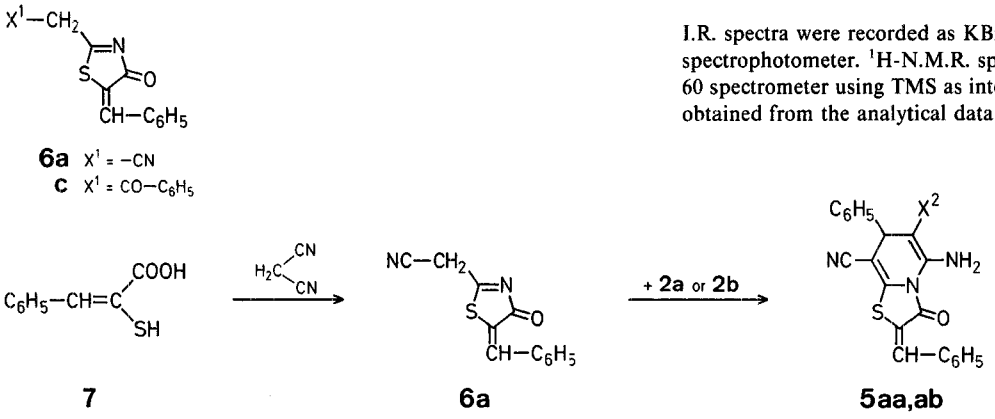
We have previously reported a simple and efficient synthesis of 2-(α-functionally substituted alkyl)-4-hydroxythiazoles **1a–c**[6,7]. We now report a novel synthesis of thiazolo[2,3-*a*]pyridines utilising **1a–c** as starting components. Thus, it has been found that **1a** reacts with 2-cyanocinnamonitrile **(2a)** to yield a product **4aa** or **5aa**. Better yields were obtained using a 2:1 molar ratio of **2a**:**1a**.



Structure **5aa** was confirmed by the presence of a C=O absorption in the I.R. spectrum at $\nu = 1720\ cm^{-1}$ and by independent synthesis from 2-cyanomethyl-5-benzylidene-2-thiazolin-4-one **(6a)** and **2a**. Compound **6a** was, in turn, prepared from mercaptocinnamic acid **(7)** and malononitrile.

Reactions of **1b** with **2a–c** proceded similarly. In contrast, **1c** reacted with **2a–c** to give the corresponding benzylidene derivatives **6**. Formation of **5** from **1** and **2** may be assumed to proceed via the 1:2 adduct **3** which cyclises with loss of malononitrile, ethyl cyanoacetate, or benzoylacetonitrile to give the product. Further work is now in progress to explore the potential utility of **2a–c** and other α,β-unsaturated nitriles for the synthesis of other heterocyclic systems.



I.R. spectra were recorded as KBr discs using a Pye-Unicam SP-1100 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a Varian A-60 spectrometer using TMS as internal standard. Analytical data were obtained from the analytical data unit at Cairo University.

Table. 7*H*-Thiazolo[2,3-*a*]pyridines **5** prepared

Product No.	X^1	X^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. δ [ppm]
5aa	—CN	—CN	70	265° (DMF/C_2H_5OH)	$C_{22}H_{14}N_4OS$ (382.4)	3420, 3320, 3230 (NH_2); 2980, 2940 (CH); 2200 (CN); 1730 (CO); 1660 (C=C); 1630 (NH_2)	4.50 (s, 1H); 6.73 (br s, 2H); 7.3–7.6 (m, 10H); 7.93 (s, 1H)
5ba	$COOC_2H_5$	—CN	70	267° (dioxan)	$C_{24}H_{19}N_3O_3S$ (429.4)	3400, 3320 (NH_2); 3000, 2950 (CH, CH_2, CH_3); 2220 (CN); 1730, 1690 (CO)	1.16 (t, 3H); 4.16 (m, 2H); 4.50 (s, 1H); 6.73 (br s, 2H); 7.3–7.9 (m, 11H)
5ab	—CN	$COOC_2H_5$	55	228° (dioxan)	$C_{24}H_{19}N_3O_3S$ (429.4)	3400, 3320 (NH_2); 3000, 2950 (CH, CH_2, CH_3); 2200 (CN); 1700, 1600 (CO); 1630 (C=C)	1.16 (t, 3H); 4.16 (m, 2H); 5.01 (s, 1H, CH); 6.66 (br s, 2H); 7.3–7.9 (m, 11H)
5ac	—CN	CO—C_6H_5	55	160° (dioxan)	$C_{28}H_{19}N_3O_2S$ (461.5)	3500–3050 (NH_2); 2200 (CN); 1730 (CO); 1670–1630 (CO, C=C)	4.73 (s, 1H); 6.83 (br s, 2H); 7.3–7.9 (m, 16H)
5bb	$COOC_2H_5$	$COOC_2H_5$	60	213° (dioxan)	$C_{26}H_{24}N_2O_5S$ (476.5)	3440, 3300 (NH); 3000, 2960, 2940 (CH, CH_2, CH_3); 1730–1700 (CO); 1670 (CO); 1630 (C=C)	1.16 (2t, 6H); 4.16 (2q, 4H); 5.00 (s, 1H); 6.33 (br s, 2H); 7.3–7.9 (m, 11H)
5bc	$COOC_2H_5$	CO—C_6H_5	75	195° (dioxan)	$C_{30}H_{24}N_2O_4S$ (508.6)	3400 (NH); 3000, 2950 (CH); 1730–1700 (CO ester); 1680 (CO-ring); 1622 (C=C)	1.16 (t, 3H); 4.16 (q, 2H); 5.01 (s, 1H); 6.73 (br s, 2H); 7.3–7.9 (m, 16H)

[a] Satisfactory microanalyses obtained: C ±0.22, H ±0.32, N ±0.34, S ±0.36.

5-Amino-2-benzylidene-6,8-disubstituted-7-phenyl-3-oxo-2,3-dihydro-7*H*-thiazolo[2,3-*a*]pyridines (5aa–bc); General Procedure:
A solution of **1a** or **1b** (0.1 mol) in ethanol (100 ml) is treated with reagent **2** (0.1 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 a suitable solvent (Table).

Compounds **5** can also be obtained from the reaction of **6a** with **2a** or **2b** following the above procedure.

2-Cyanomethyl-5-benzylidene-2-thiazolin-4-one (6a):
To a solution of malononitrile (6.6 g, 0.1 mol) in acetic acid (100 ml), α-mercaptocinnamic acid (**7**; 18.0 g, 0.1 mol) is added. The mixture is heated under reflux for 3 h and then evaporated. The residue is triturated with ethanol, the resulting solid product is collected by filtration, and crystallised from ethanol to give yellow crystals; yield: 11.5 g (50%); m.p. 202 °C.

$C_{12}H_8N_2OS$	calc.	C 63.16	H 3.53	N 12.28	S 14.00
(228.2)	found	63.34	3.75	12.30	13.88

I.R. (KBr): $\nu = 2960, 2950$ (CH, CH_2); 2230 (CN); 1720 cm^{-1} (CO).

2-Benzoylmethyl-5-benzylidene-2-thiazolin-4-one (6c):
Prepared from the reaction of **1c** with **2a–c** following the general procedure for **5** to give yellow crystal of **6c**; yield: 70–80%; m.p. 184 °C (from dioxan).

$C_{18}H_{13}NO_2S$	calc.	C 70.35	H 4.26	N 4.56	S 10.41
(307.3)	found	70.46	4.30	4.66	10.50

I.R. (KBr): $\nu = 1680$ cm^{-1} (CO).

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[2] G. A. Ulsaker, H. Breivik, K. Undheim, *J. Chem. Soc. Perkin Trans. 1* **1979**, 2420.
[3] G. Barteis, R. P. Hinz, D. Weillbrandt, *Justus Liebigs Ann. Chem.* **1980**, 168.
[4] K. T. Potts, D. R. Choudhury, T. R. Westby, *J. Org. Chem.* **41**, 187 (1976).
[5] P. J. Abbdt, R. M. Acheson, U. Eisner, D. J. Watkin, J. P. Carruthers, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1269.
[6] M. H. Elnagdi, M. R. H. Elmoghayar, A. G. Hammam, S. A. Khallaf, *J. Heterocycl. Chem.* **16**, 1591 (1979).
[7] M. H. Elnagdi, M. R. H. Elmoghayar, M. A. Khalifa, M. K. A. Ibraheim, *Bull. Chem. Soc. Jpn.*, in press.

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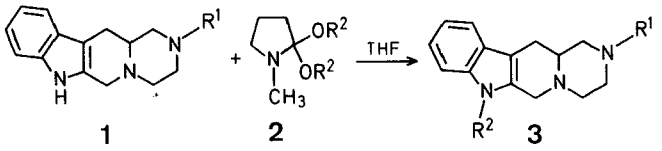
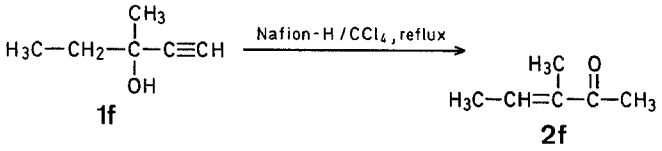
S. K. Agarwal, A. K. Saxena, N. Anand, *Synthesis* **1981** (6), 465-466:
The formula scheme (p. 465) should be:



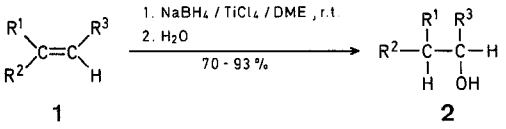
1 2 3

G. A. Olah, A. P. Fung, *Synthesis* **1981** (6), 473-474:
The reaction scheme **1f→2f** should be:



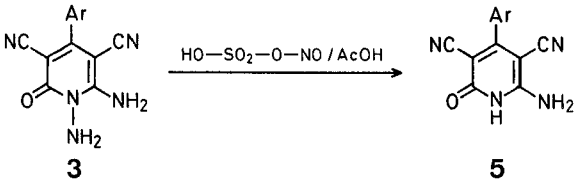
1f 2f

Abstract 6127, *Synthesis* **1981** (6), 498:
The formula scheme **1→2** should be:



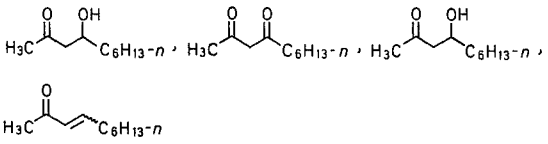
1 2

J. L. Soto, C. Seoane, P. Zamorano, F. J. Cuadrado, *Synthesis* **1981** (7), 529-530:
The reaction scheme **3→5** (p. 529) should be:

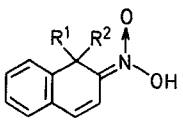


3 5

A. B. Smith, III, P. A. Levenberg, *Synthesis* **1981** (7), 567-570:
The heading for Table 1 (p. 567) should be Oxidation of 4-Hydroxy-2-decanone **(3a)** under various conditions. The structure given in the first column of Table 1 should be, respectively:

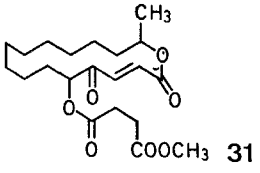


G. Bartoli, M. Bosco, A. C. Boicelli, *Synthesis* **1981** (7), 570-572:
The structure of products **4aa-cd** (p. 571) should be:



4aa-cd

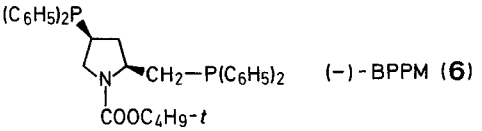
Y.-H. Lai, *Synthesis* **1981** (8), 585-604:
The structure of compound **31** (p. 588) should be:



31

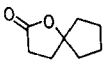
M. R. H. Elmoghayar, M. K. A. Ibraheim, A. H. H. Elghandour, M. H. Elnagdi, *Synthesis* **1981** (8), 635-637:
The title compounds **5** are thiazolo[3,2-*a*]pyridine derivatives.

A. Kleemann, J. Martens, M. Samson, W. Bergstein, *Synthesis* **1981** (9), 740-741:
The structure of compound **6** should be:



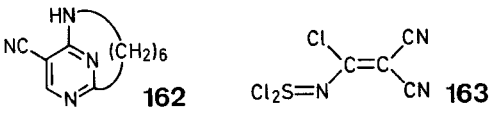
(-)-BPPM (6)

Abstract 6236, *Synthesis* **1981** (11), 922:
The structure of product **3** should be:



3

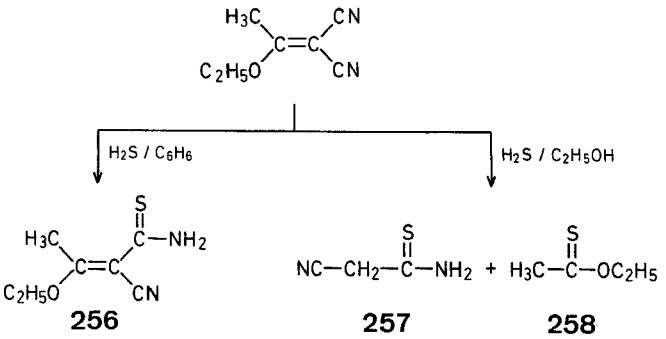
F. Freeman, *Synthesis* **1981** (12), 925-954:
The structures of compounds **162** and **163** (p. 937) should be:



162 163

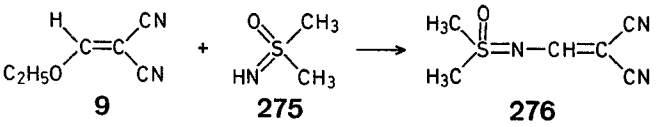
The text of the first paragraph starting on p. 943 (right-hand column) should be: Hydrogen sulfide reacts with 1-ethoxyethylidenemalononitrile, the methyl homolog of **9**, to give different products depending on the solvent used[293].

The following formula scheme should be:



256 257 258

The first formula scheme on p. 944 (right-hand column) should be:

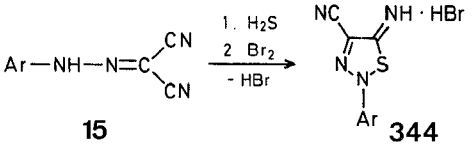


9 275 276

The last sentence on page 946 (left-hand column) should be: An analogous reaction with cyclopentadiene leads to the 2-azabicyclo[2.2.1]heptene **(299)** and with cyclohexadiene to 2-azabicyclo[2.2.2]octene **(301)** derivatives[317].

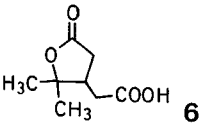
The correct names for compounds **336** and **337** (p. 949) are 5-hydroxy-2-oxo-3-phenylazo-1,2,3,7-tetrahydropyrazolo[1,5-*a*]pyrimidine **(336)** and α-(*N*-methylphenylhydrazono)-cyanoacetamidrazone **(337)**.

The formula scheme **15→344** (p. 950) should be:



15 344

A. Guzmán, S. Mendoza, E. Diaz, *Synthesis* **1981** (12), 989-991:
The structure of compound **6** (p. 990) should be:



6

Abstract 6269, *Synthesis* **1981** (12), 1015:
The legend under the formula scheme should read: n = 1, 2, 3.