Activated Nitriles in Heterocyclic Synthesis: Novel Syntheses of Pyrrolo[1,2-*c*]imidazole and Pyrano[2,3-*d*]imidazole Derivatives

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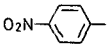
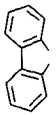
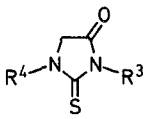
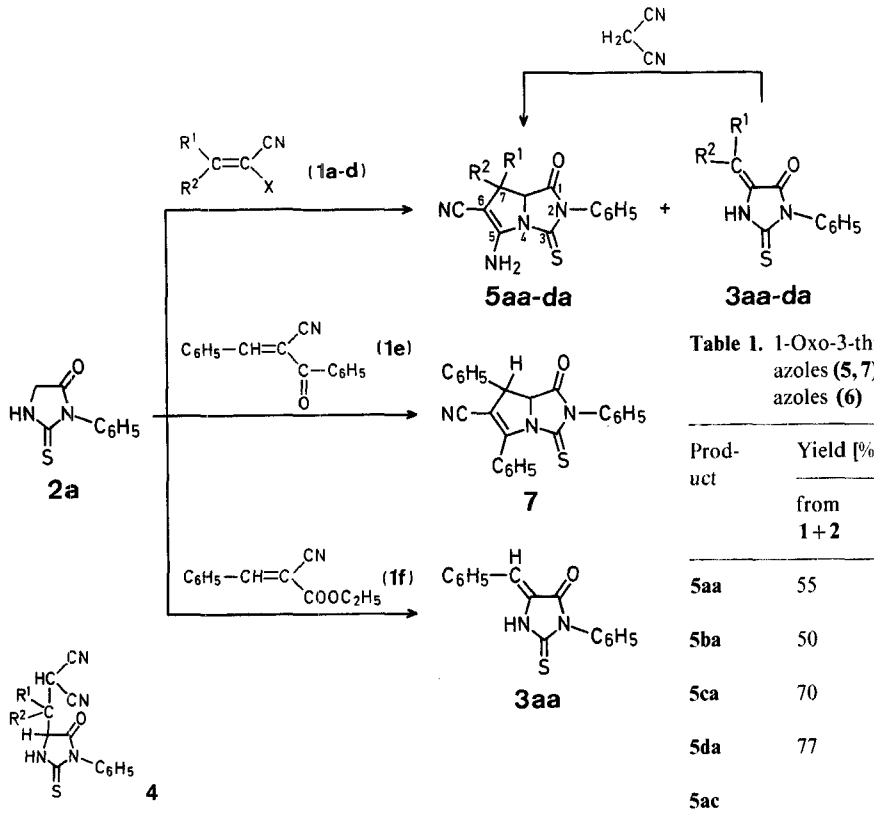
As part of our investigations on the synthesis of fused azoles of potential biological activity[1,2,3] we report here a new synthesis of pyrrolo[1,2-*c*]imidazole and pyrano[2,3-*d*]imidazole derivatives from 2-thiohydantoins and substituted cinnamonitriles such as benzylidenemalononitrile, diphenylmethylenemalononitrile, 2-benzoylcinnamonitrile, and 2-benzylidenecyanoacetic esters. Except for the recently reported additions of benzylidenemalononitrile[4,5], ethyl benzylidenecyanoacetate[4], and 2-benzoylcinnamonitrile[4] to 2-alkyl-4-oxo-4,5-dihydro-1,3-thiazoles or their tautomers, the reaction of these activated nitriles with heterocyclic compounds containing active methylene groups has hitherto not been investigated. We have now found that the activated nitriles **1a–d** react with 3-phenyl-2-thiohydantoin **(2a)** to yield 1:1 adducts together with the 5-benzylidene-2-thiohydantoin derivatives **3aa–da.** The same products were obtained when **3aa–da** were treated with malononitrile. The I.R. spectra of the adducts revealed a strong C=O absorption at $\nu = 1720\ cm^{-1}$ indicating that the ring C=O group was not involved in the reaction. The ^1H-N.M.R. spectrum showed a pattern different from that anticipated for the acyclic structure **4.** Thus, the cyclic structure **5aa–da** was established for the reaction products.

1	R^1	R^2	X
a	H		—CN
b	H		—CN
c			—CN
d			—CN
e	H		
f	H		—$COOC_2H_5$



2	R^3	R^4
a		H
b		
c	H	H

0039-7881/82/0632-0502 $ 03.00



In contrast to the behaviour of compound **2a** toward **1a–d**, the 2-thiohydantoin derivatives **2b, c** reacted with **1a, b** to yield the 5-arylidene derivatives **3ab, 3bb**, and **3ac**, respectively, as the sole isolable products and were recovered almost unaffected after treatment with **1c** under the same experimental conditions. Treatment of compounds **3ab** and **3bb** with malononitrile afforded the pyrano[2,3-*d*]imidazole derivatives **6ab** and **6bb**, respectively, whereas treatment of **3ac** with malononitrile afforded the pyrrolo[1,2-*c*]imidazole derivative **5ac**.

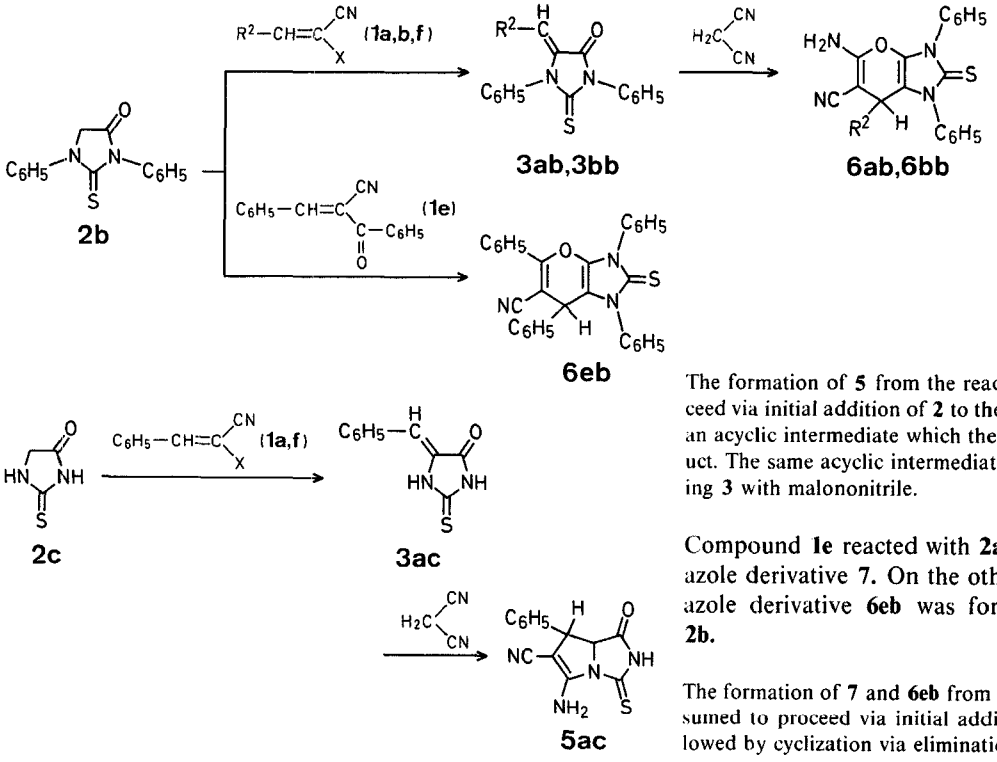


Table 1. 1-Oxo-3-thioxo-2,3,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazoles (**5, 7**) and 2-Thioxo-1,2,3,7-tetrahydropyrano[2,3-*d*]imidazoles (**6**)

Product	Yield [%] from 1+2	Yield [%] from 3	m.p. [°C] (solvent)	Molecular formula[a]
5aa	55	78	255–256° (DMF/water)	$C_{19}H_{14}N_4OS$ (346.4)
5ba	50	70	205° (ethanol)	$C_{19}H_{13}N_5O_3S$ (391.5)
5ca	70	75	245–247° (DMF/water)	$C_{25}H_{18}N_4OS$ (422.4)
5da	77	76	260–261° (ethanol)	$C_{25}H_{16}N_4OS$ (420.5)
5ac		60	242–243° (ethanol)	$C_{13}H_{10}N_4OS$ (270.2)
6ab		60	150° (ethanol)	$C_{25}H_{18}N_4OS$ (422.4)
6bb		55	118° (ethanol/water)	$C_{25}H_{17}N_5O_3S$ (467.5)
6eb	50		175° (ethanol)	$C_{31}H_{21}N_3OS$ (483.5)
7	68		175–177° (ethanol)	$C_{25}H_{17}N_3OS$ (407.4)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.30; H, ±0.31; N, ±0.24; S, ±0.28. Exception: **6bb**: S, −0.40.

The formation of **5** from the reaction of **1** and **2** is assumed to proceed via initial addition of **2** to the activated double bond in **1** to yield an acyclic intermediate which then cyclises to the final isolable product. The same acyclic intermediate is assumed to be formed on reacting **3** with malononitrile.

Compound **1e** reacted with **2a** to yield the pyrrolo[1,2-*c*]imidazole derivative **7**. On the other hand, the pyrano[2,3-*d*]imidazole derivative **6eb** was formed from reaction of **1e** and **2b**.

The formation of **7** and **6eb** from reaction of **1e** with **2a** and **2b** is assumed to proceed via initial addition to the double bond in **1e** followed by cyclization via elimination of water.

Table 2. I.R. and ^{1}H-N.M.R. Data of Compounds **5**, **6**, and **7**

Product	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$) δ [ppm]
5aa	3360, 3320 (NH_2); 2210 (conjugated CN); 1740 (ring C=O); 1630 (C=C)	4.7 (d, 1 H, 7a-H); 5.0 (d, 1 H, 7-H); 7.4–7.5 (m, 10 H_{arom}); 7.6 (s, br, 2 H, NH_2)
5ba	3400–3100 (NH); 2210 (CN); 1760 (ring C=O); 1650 (C=C)	4.5 (d, 1 H, 7a-H); 5.0 (d, 1 H, 7-H); 6.2 (s, br, 2 H, NH_2); 7.4–8.0 (m, 9 H_{arom})
5ca	3420, 3280 (NH); 2200 (CN); 1740 (ring C=O); 1650 (C=C)	4.6 (d, 1 H, 7a-H); 6.3 (s, br, 2 H, NH_2); 7.2–8.2 (m, 15 H_{arom})
5da	3420, 3360, 3300 (NH); 2210 (CN); 1770 (ring C=O); 1650 (C=C)	4.6 (d, 1 H, 7a-H); 6.2 (s, br, 2 H, NH_2); 7.2–8.0 (m, 13 H_{arom})
5ac	3380–3000 (chelated NH); 2220 (CN); 1730 (ring C=O); 1650 (C=C)	4.16 (s, br, 2 H, NH_2); 6.45 (s, br, 1 H, 7-H); 7.4 ~ 7.8 (m, 5 H_{arom}); 8.0–8.3 (m, 2 H, NH and OH)
6ab	3400, 3340, 3240 (NH_2); 2220 (CN); 1650 (C=C)	6.4 (s, br, 3 H, NH_2 and 7-H); 7.4–7.6 (m, 15 H_{arom})
6bb	3400–3100 (chelated NH); 2220 (CN); 1650 (C=C)	
6eb	2200 (CN); 1650 (C=C)	6.2 (s, 1 H, 7-H); 7.2–7.9 (m, 15 H_{arom})
7	2220 (CN); 1750 (ring C=O)	

In contrast to the behaviour of compounds **1a–e** toward **2**, ethyl benzylidenecyanoacetate **(1f)** reacted with imidazolidines **2a, b, c** to give the benzylidene derivatives **3aa, 3ab,** and **3ac,** respectively.

All melting points are uncorrected. 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. The microanalyses were performed by the microanalytical unit at Cairo University. Compounds **1**[6,7,8] and **3**[9,10] were prepared according to literature procedures.

Reaction of Compounds 1a–f with Thiohydantoins 2a, b, c; General Procedure:

Compound **1** (0.01 mol) and piperidine (1 ml) are added to a stirred suspension of the imidazolidine **2** (0.01 mol) in ethanol (50 ml). The mixture is refluxed for 5 h and then allowed to cool. The solid precipitate is isolated by suction and recrystallised (Table 1) to give the respective *5-amino-6-cyano-1-oxo-3-thioxo-2,3,7,7a-tetrahydro-1H-pyrrolo[1,2-a]imidazole* **(5)**, *5-amino-6-cyano-1,3-diphenyl-2-thioxo-1,2,3,7-tetrahydropyrano[2,3-d]imidazole* **(6)**, or *6-cyano-1-oxo-3-thioxo-2,5,7-triphenyl-2,3,7,7a-tetrahydro-1H-pyrrolo[1,2-a]imidazole* **(7)**. The mother liquor is evaporated and the residue recrystallises (Table 1) to give the respective *4-benzylidene-5-oxo-2-thioxoimidazolidine* **(3)** [identified by comparison with authentic samples].

Reaction of Compounds 3 with Malononitrile; General Procedure:

Malononitrile (0.661 g, 0.01 mol) and triethylamine (1 ml) are added to a stirred suspension of the imidazolidine **3** (0.01 mol) in ethanol (30 ml). The mixture is refluxed for 6 h and then evaporated in vacuo. The residue is triturated with water (20 ml), the solid product isolated by suction, and recrystallised (Table 1). The yields of compounds **3** thus obtained are similar to those obtained from the reaction of compounds **1** and **2**. [Products **5** thus obtained were identical with compounds **5** obtained from **1** and **2**].

Received: September 22, 1981
(Revised form: November 30, 1981)

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0039-7881/82/0632-0504 $ 03.00