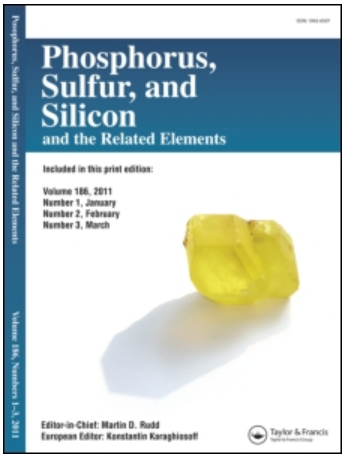


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF PYRROLO[1,2-c]IMIDAZOLE AND PYRANO[2,3-d]IMIDAZOLE DERIVATIVES

Mahfouz A. Abdelaziz[a]; H. H. Moharram[b]; Samy A. Essawy[c]; A. A. Mohamed[a]
[a] Department of Chemistry, Faculty of Science, Cairo University, [b] National Organisation for Drug Control and Research, Egypt [c] Department of Chemistry, Faculty of Science, Banha University,

To cite this Article Abdelaziz, Mahfouz A. , Moharram, H. H. , Essawy, Samy A. and Mohamed, A. A.(1990) 'ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF PYRROLO[1,2-c]IMIDAZOLE AND PYRANO[2,3-d]IMIDAZOLE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 48: 1, 269 — 273
To link to this Article: DOI: 10.1080/10426509008045908
URL: http://dx.doi.org/10.1080/10426509008045908

Phosphorus, Sulfur, and Silicon, 1990, Vol. 48, pp. 269–273
Reprints available directly from the publisher
Photocopying permitted by license only Printed in the United Kingdom

ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF PYRROLO[1,2-c]IMIDAZOLE AND PYRANO[2,3-d]IMIDAZOLE DERIVATIVES

MAHFOUZ A. ABDELAZIZ,* H. H. MOHARRAM;** SAMY A. ESSAWY*** and A. A. MOHAMED*

** Department of Chemistry, Faculty of Science, Cairo University*
*** National Organisation for Drug Control and Research, Egypt*
**** Department of Chemistry, Faculty of Science, Banha University*

(Received September 9, 1989; in final form October 23, 1989)

Several new pyrrolo[1,2-c]imidazole derivatives (**4a, b**), (**8a, b**), (**10a, b**) and pyrano[2,3-d]imidazole derivatives (**12a, b**), (**14a, b**) were synthesised via the reaction of each 2-thiohydantoin derivatives (**2**) and (**11**) with 3-(2-furanyl) or 3-(2-thienyl)-acrylonitrile derivatives (**1a, b, e, f**). On the treatment of 2-ylidene ethyl cyanoacetate (**1c, d**) with each of (**2**) and (**11**) afforded the 5-ylidene-2-thiohydantoins (**5a, b**), (**13a, b**) respectively. Compounds **5a, b** react with each of malononitrile and ethyl cyanoacetate to give the corresponding pyrroloimidazole derivatives (**4a, b**) and (**8a, b**) respectively. The structure of the isolated products were established by elemental analyse and spectral data studies.

INTRODUCTION

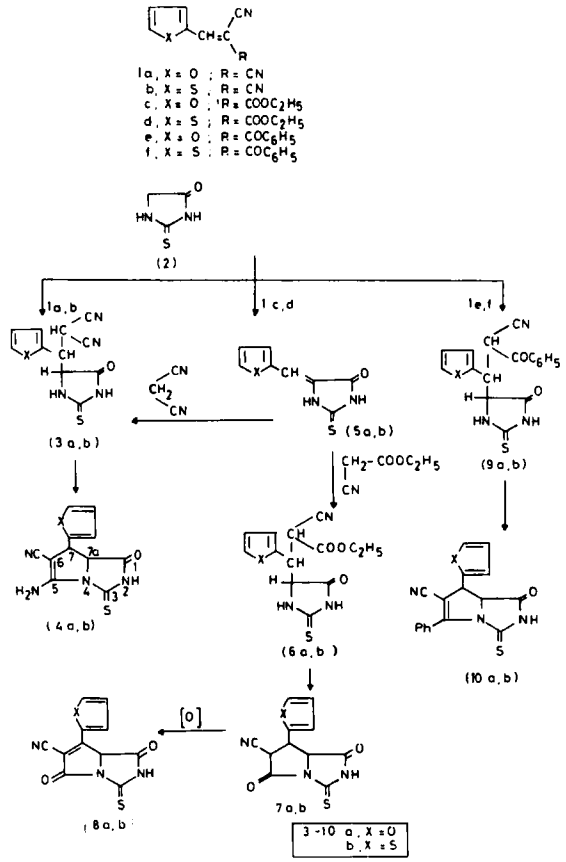
As a part of our programme directed towards the development of new simple procedures for the synthesis of fused azoles,[1–5] we have investigated the reaction of 2-thiohydantoin derivatives with 3-(2-furanyl)- or 3-(2-thienyl)acrylonitrile derivatives. The work resulted in the synthesis of several, otherwise difficult obtainable, new pyrrolo[1,2-*c*]imidazole and pyrano[2,3-d]imidazole derivatives. The newly synthesised compounds contain both a cyano group and the furanyl or the thienyl group which make them excellent candidates for both biological activity studies as well as for further chemical transformations.

RESULTS AND DISCUSSION

We have now found that 2-furfurylidene malononitrile **1a** and 2-thienylidene malonoitrile **1b** react with 2-thiohydantoin (**2**) in ethanolic solution and in presence of triethylamine as a catalyst to yield 1:1 adducts **4a, b**. The IR spectra of the adducts revealed a strong (C=O) absorption at $\sim\nu$ 1710 cm^{-1} indicating that the ring C=O group was not involved in the reaction. The ^{1}H-NMR spectra showed a pattern different from that anticipated for the acyclic structure (**3a, b**). Thus the cyclic structure **4a, b** was established for the reaction products. The formation of **4a, b** is assumed to proceed via Michael adduct by initial addition of hydrogen atom of active methylene group of compound (**2**) to the activated

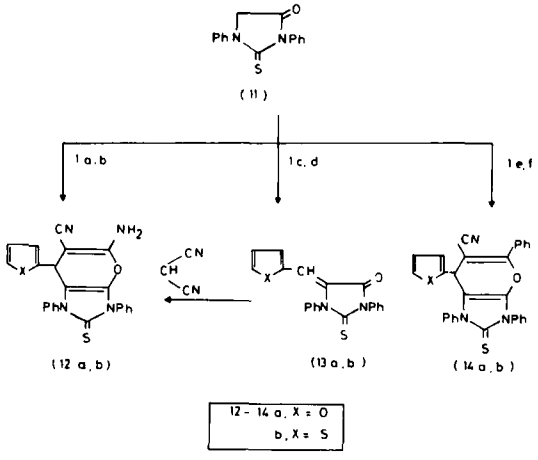
double bond of **1a, b** to yield the acyclic intermediate **3a, b** which could then be cyclized to **4a, b**. In contrast to the behaviour of (**2**) towards **1a, b**, the 2-thiohydantoin reacted with 2-furfarylidene ethylcyano-acetate **1c** or 2-thienylidene ethyl-cyanoacetate **1d** to yield 5-ylidene-2-thiohydantoins (**5a, b**),[6,7] which inturn react with malononitrile under the same experimental conditions to give the above products **4a, b** (m.p. and mixed m.p. determinations). **5a, b** react also with ethyl cyanoacetate afforded the 6-cyano-1,5-dioxo-3-thioxo-7-ylidene pyrrolo[1,2-*c*]imidazole **8a, b**. The reaction was assumed to proceed via Michael adduct by initial addition of hydrogen atom of active methylene group of ethyl cyanoacetate to the double bond of (**5a, b**) to yield the acyclic intermediate (**6a, b**) which could then be cyclized to (**7a, b**) with loss of ethanol which are consequently autoxidized under the applied reaction conditions to furnish the final isolable products **8a, b** (autoxidation of similar ring systems has been previously reported[8,9]).

Similarly 2-thiohydantoin reacted with 2-benzoyl-3-(2-furanyl)acrylonitrile **1e** or 2-benzoyl-3-(2-thienyl)acrylonitrile **1f** to yield the pyrrolo[1,2-*c*]imidazole derivatives **10a, b**. The formation of **10a, b** is assumed to proceed via initial addition to the double bond in **1e, f** to yield the acyclic intermdiate **9a, b** which could then be cyclized to **10a, b** via elimination of water (cf. Chart 1).



On the other hand 1,3-diphenyl-2-thiohydantoin (**11**) reacts with **1a, b** under the same experimental conditions afforded the pyrano[2,3-d]-imidazole derivatives (**12a, b**). The same products (**12a, b**) can be obtained when 5-ylidene-1,3-diphenyl-2-thiohydantoin(**13a, b**) were treated with malononitrile under the same experimental conditions (m.p. and mixed m.p. determinations). Treatment of (**11**) with **1c, d** afforded the products which proved to be identical with authentic specimen of the corresponding ylidene derivatives of the type (**13a, b**) (cf. experimental part).

Also, it has been found that 1,3-diphenyl-2-thioxo-5-amino-6-cyano-1,2,3,7-tetrahydropyrano[2,3-*d*]imidazole derivatives (**14a, b**) was formed from reaction of 1,3-diphenyl-2-thiohydantoin (**11**) with **1e, f**, via Michael addition, followed by cyclization with elimination of water (cf. Chart 2).



EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer using KBr discs. The ^{1}H-NMR spectra were recorded on a Varian EM-390-90 MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. The microanalyses were performed by the microanalytical center at Cairo University.

Reaction of compounds **1a–f** *with 2-thiohydantoin derivatives (***2** *or* **11***): General procedure:* A solution of each of **1a–f** (0.01 mole) in ethanol (50 ml) was treated with each of 2-thiohydantoin derivatives (**2** or **11**) (0.01 mole) in presence of 3 drops of triethylamine. The reaction mixture was refluxed for 5 hours, then evaporated to one half of its volume and triturated with water, the resulting solid product was filtered off and crystallized from ethanol to give yellow crystals of pyrrolo[1,2-*c*]imidazole derivatives **4a, b**, **10a, b**, 5-ylidene-2-thiohydantoin derivatives (**5a, b**) and (**13a, b**) [identified by comparison with authentic samples] and pyrano[2,3-d]-imidazole derivatives (**12a, b**), (**14a, b**) respectively (cf. Tables I and II).

*Reaction of 5-ylidene-2-thiohydantoins (***5a, b, 13a, b***) with malononitrile or ethyl cyanoacetate.* A solution of malononitrile or ethyl cyanoacetate (0.01 mole) and each of **5a, b** or **13a, b** (0.01 mole) in absolute ethanol (50 ml) and triethyl-amine (3 drops) was heated for 5 hours, and the reaction mixture was worked up as above to yield the products **4a, b** & **8a, b** and **12a, b**. The products **4a, b** and **12a, b** give no depression when admixed with authentic sample prepared as above. The products **8a, b** were crystallised from ethanol as pale yellow crystals (cf. Tables I and II).

TABLE I

1-Oxo-3-thioxopyrrolo[1,2-*c*]imidazoles (**4a, b**; **8a, b** and **10a, b**) and 2-thioxo-1,2,3,7-tetrahydropyrano[2,3-*d*]imidazoles (**12a, b** and **14a, b**)

Compound	M.P. [°C]	Yield [%]	Mol. Formula	% Analysis Calcd./Found C	H	N	S
4a	242	70	$C_{11}H_8N_4O_2S$	50.76	3.07	21.53	12.30
				50.5	3.2	21.8	12.5
4b	225	68	$C_{11}H_8N_4OS_2$	47.82	2.89	20.28	23.18
				48.1	3.2	20.0	23.5
8a	250	69	$C_{11}H_5N_3O_3S$	50.96	1.93	16.21	12.35
				51.2	2.1	16.0	12.1
8b	237	70	$C_{11}H_5N_3O_2S_2$	48.0	1.81	15.27	23.27
				47.7	2.0	15.0	23.5
10a	220	73	$C_{17}H_{11}N_3O_2S$	63.55	3.42	13.08	9.96
				63.3	3.6	13.2	9.6
10b	238	75	$C_{17}H_{11}N_3OS_2$	60.53	3.26	12.46	18.99
				60.3	3.5	12.2	19.2
12a	170	72	$C_{23}H_{16}N_4O_2S$	66.99	3.88	13.59	7.76
				66.8	4.1	13.7	7.5
12b	210	75	$C_{23}H_{16}N_4OS_2$	64.48	3.73	13.03	14.95
				64.6	3.9	12.8	14.7
14a	132	66	$C_{29}H_{19}N_3O_2S$	73.57	4.01	8.87	6.76
				73.4	3.8	9.1	6.5
14b	185	70	$C_{29}H_{19}N_3OS_2$	71.16	3.88	8.58	13.08
				71.4	4.1	8.4	12.7

TABLE II

Spectral data of the newly synthesised compounds

Compound	IR [cm^{-1}]	^{1}H-NMR [δppm]
4a	3410, 3330, 3280, (NH_2 and NH), 2220 (CN) and 1720 (C=O).	4.5 (d, 1H, 7a-H, J = 4.5 Hz); 4.8 (d, 1H, 7-H, J = 4.5 Hz); 6.7–7.0 (m, 3H, furan H-3, H-4, H-5) and [8.2(s, 2H, NH_2); 11.5(s, 1H, NH) exchangable with D_2O]
4b	3400, 3300, 3290 (NH_2 and NH); 2210 (CN) and 1720 (C=O).	4.3 (d, 1H, 7a-H, J = 5.0 Hz); 4.5 (d, 1H, 7-H, J = 5.0 Hz); 6.5–6.9 (m, 3H, thiophene H-3, H-4, H-5); 7.6 (s, 2H, NH_2) and 10.8 (s, 1H, NH).
8a	3370 (NH); 2225 (CN); 1710, 1700 (2C=O) and 1620 (C=C).	5.2 (s, 1H, 7a-H); 6.6–7.1 (m, 3H, furan H-3, H-4, H-5) and 11.8 (s, 1H, NH exchangable with D_2O).
8b	3340 (NH); 2220 (CN); 1710, 1700 (2C=O) and 1620 (C=C).	
10a	3320 (NH); 2220 (CN) and 1710 (C=O)	4.7 (d, 1H, 7a-H, J = 5.5 Hz); 5.0 (d, 1H, 7-H, J = 5.5 Hz); 6.6–7.0 (m, 3H, furan H-3, H-4, H-5) and 7.2–7.4 (m, 5H, aromatic protons) and 11.2 (s, 1H, NH exchangeable with D_2O).
10b	3380 (NH); 2210 (CN) and 1720 (C=O).	
12a	3400, 3380 (NH_2); 2220 (CN) and 1620 (C=C).	6.1 (s, 1H, pyran H-4); 6.8–7.1 (m, 3H, furan H-3, H-4, H-5); 7.3–7.6 (m, 10H, aromatic protons) and 8.5 (s, 2H, NH_2 exchangable with D_2O).
12b	3400, 3320 (NH_2); 2200 (CN) and 1630 (C=C).	
14a	2230 (CN), 1630 (C=C) and 1200 (C=S).	
14b	2220 (CN); 1630 (C=C) and 1205 (C=S)	6.0 (s, 1H, pyran H-4), 6.7–7.0 (m, 3H, thiophene H-3, H-4, H-5); 7.4–7.7 (m, 15H, aromatic protons).

*Preparation of 5-ylidene-1,3-diphenyl-2-thiohydantoin derivatives (**13a, b**):* A mixture of (0.01 mole) of **11**, fused sodium acetate (3 g) and a slight excess (0.011 mole) of each of furfural or thiophen-2-aldehyde in 25 ml glacial acetic acid was refluxed for 2 hours. The reaction mixture was cooled, poured over cold water, then the separated solid was filtered off, washed with water and recrystallised from ethanol as yellow crystals of **13a, b**. The structure assigned for **13a, b** was established on the basis of elemental analyses and spectral data studies.

13a: m.p. 240°C, yield 85%. Analysis: $C_{20}H_{14}N_2O_2S$. Calcd.: C, 69.36; H, 4.04; N, 8.09; S, 9.24. Found: C, 69.6; H, 4.2; N, 7.9; S, 9.1.

13b: m.p. 192°C; yield 83%. Analysis: $C_{20}H_{14}N_2OS_2$. Calcd.: C, 66.29; H, 3.86; N, 7.73; S, 17.67. Found: C, 66.0; H, 4.0; N, 7.9; S, 17.8.

REFERENCES

1. Mahfouz A. Abdelaziz, Bahia Y. Riad and A. M. Shalaby, *Arch. Pharm. Res.* **12**(1), 12 (1989).
2. Bahai Y. Riad and Mahfouz A. Abdelaziz, *Sulfur Letters* **9**(4), 175 (1989).
3. Sohair M. Hussain, Mahfouz A. Abdelaziz and Nadia A. Abdel Reheim, *Egypt. J. Pharm. Sci.*, **30**(1–4), 309 (1989).
4. Hamed A. Daboun and Mahfouz A. Abdelaziz, *Archiv der Pharmazie* **316**(5), 394 (1983).
5. Hamed A. Daboun, Mahfouz A. Abdelaziz and Fatma A. Abdelall, *Heterocycles*, **19**, 677 (1982).
6. F. Fujikawa and K. Hirai, *Yakugaku Zasshi* **82**, 1681 (1962) [*Chem. Abstr.* **59**, 2764 f (1963)].
7. H. L. Wheeler and C. A. Brauthecht, *Am. Chem. J.* **45**, 446 (1911).
8. S. Kamba, K. Saito, A. Sakurai and T. Hayashi, *Synthesis* 841 (1977).
9. H. A. Daboun and A. M. El-Reedy, *Z. Naturforsch* **386**, 1686 (1983).