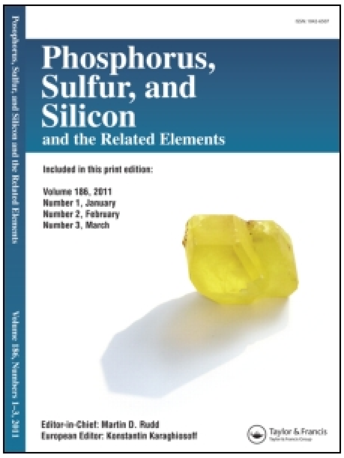


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

HETEROCYCLES FROM NITRILE OXIDES: SYNTHESIS AND REACTIONS OF 2-THIENOYLHYDROXAMOYL CHLORIDE

Abdou O. Abdelhamid[a]; Fathy A. Khalifa[a]; Sami S. Ghabrial[b]
[a] Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt [b] National Organization for Drug Control and Research, Cairo, Egypt

To cite this Article Abdelhamid, Abdou O. , Khalifa, Fathy A. and Ghabrial, Sami S.(1988) 'HETEROCYCLES FROM NITRILE OXIDES: SYNTHESIS AND REACTIONS OF 2-THIENOYLHYDROXAMOYL CHLORIDE', Phosphorus, Sulfur, and Silicon and the Related Elements, 40: 1, 41 — 46

To link to this Article: DOI: 10.1080/03086648808072891

URL: http://dx.doi.org/10.1080/03086648808072891

Phosphorus and Sulfur, 1988, Vol. 40, pp. 41–46
Reprints available directly from the publisher
Photocopying permitted by license only

HETEROCYCLES FROM NITRILE OXIDES: SYNTHESIS AND REACTIONS OF 2-THIENOYLHYDROXAMOYL CHLORIDE

ABDOU O. ABDELHAMID, FATHY A. KHALIFA
Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

and

SAMI S. GHABRIAL
National Organization for Drug Control and Research, P.O. Box 29, Cairo, Egypt

(Received March 15, 1988; in final form May 17, 1988)

Nitroso derivatives of imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrimidine and imidazo[1,2-a]pyrazine were obtained in good yields by the action of 2-thienoylhydroxamoyl chloride (**2**) on 2-aminopyridines, 2-aminopyrimidine and 2-aminopyrazine, respectively. Benzotriazine, benzothiadiazine and quinazoline were obtained from **2** via its reactions with *o*-phenylendiamine, *o*-aminothiophenol and methylanthranilate, respectively. **2** was treated with ethylenic and acetylenic dipoloraphiles to afford 3-thienoylisoxazolines and isoxazole, respectively. The structures of the products were assigned and confirmed on the basis of their elemental analyses, spectral data and alternative synthesis wherever possible.

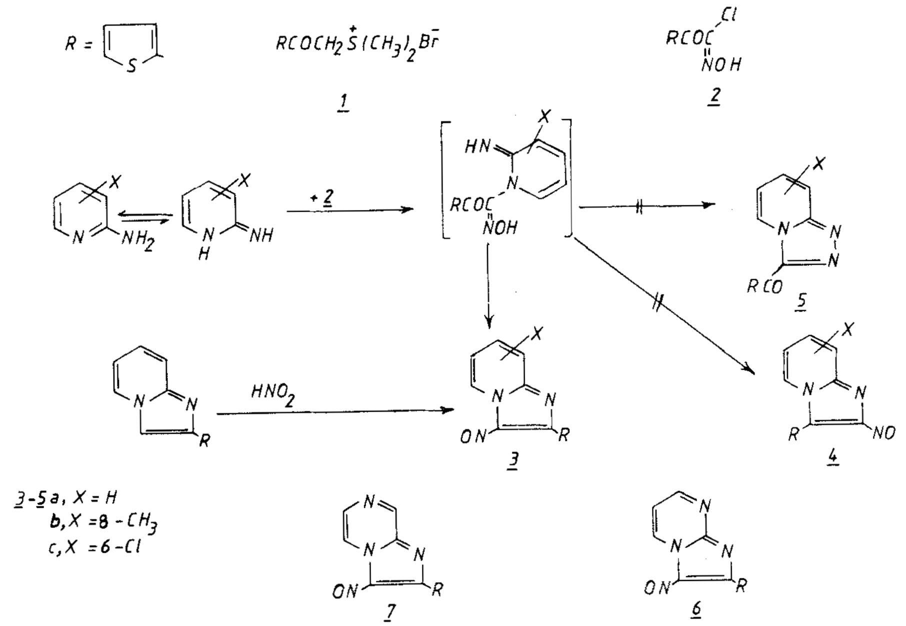
Key words: Imidazopyridines, Imidazopyrimidines, Imidazopyrazines, Benzotriazines, Benzothiadiazines, Quinazolines, 1,3-Cycloaddition.

INTRODUCTION

While 1,3-dipolar addition reactions of nitrile oxides with a variety of nucleophilic species have been extensively studied,[1–3] the use of these compounds in the preparation of fused heterocyles has been relatively little explored. In conjunction with our previous work[4–7] we report, here, on the synthesis of fused heterocyclic, derivatives required for a medicinal chemistry program. The synthesised products are expected to be biologically active. For example, some derivatives of 2-arylimidazo[1,2-a]pyrimidine have been reported to possess analgesic, antiinflammatory, antimicrobial and antiviral properties.[8–11]

RESULTS AND DISCUSSION

Treatment of a mixture of **1** and sodium nitrite in dioxane–water (1:1) with hydrochloric acid gave **2** in a 80% yield. The structure of **2** was established by elemental analysis and also by study of its spectral data. The IR spectrum (KBr) showed carbonyl absorption at 1660 cm^{-1} and (OH) group at 3470 cm^{11}. A brief



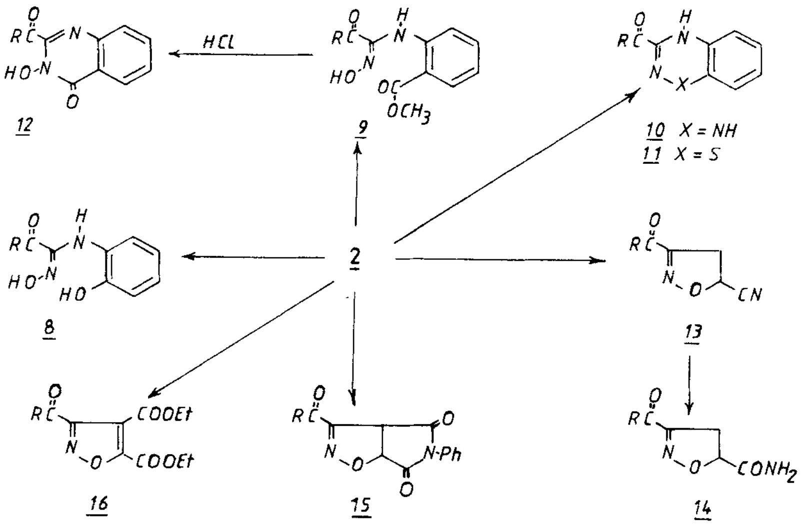
SCHEME 1

chemical study of the product **2** is shown in Scheme 1. The results show that **2** is highly reactive and reacts with nucleophiles with displacement of its halogen atom, and with a base to form the 1,3-dipolar intermediate. Treatment of **2** with two equivalents of 2-aminopyridine in ethanol gave one isolable product whose mass spectral data and elemental analysis indicated a molecular formula $C_{11}H_7N_3SO$. Structure **5** was excluded as the IR spectrum of the isolated product contains no characteristic band for the carbonyl group. The isomeric structure **4** was ruled out because the reaction of 2-aminopyridine with α-halogenated ketone was reported previously to yield 2-substituted imidazo[1,2-a]pyridines[12] (cf. Scheme 1). On the basis of these date, the product was assigned the 3-nitroso-2-thienylimidazo-[1,2-a]pyridine structure **3a**.

Similarly, the reaction of **2** with 2-amino-3-picoline and 2-amino-5-chloropyridine in ethanol at room temperature afforded the corresponding 3-nitroso-2-thienylimidazo[1,2-a]pyridines **3b,c**, in approximately 85% yields. The structure of the latter products was deduced from their spectra and elemental analyses. For example, the ^{1}H-NMR spectrum of **3b** in chloform-*d* showed a singlet at 2.5 ppm (3H, CH_3) and a multiplet at 7.0–8.8 (6H, ArH's and thiophene protons). The IR spectra of **3** revealed the absence of bands in the regions 1650–1800 and 3100–3500 cm^{-1} due to the CO and NH groups, respectively. The reaction of **2** with 2-aminopyrimidine in ethanol at room temperature produced 3-nitroso-2-thienylimidazo[1,2-a]pyrimidine **6** in a 75% yield. The proposed structure **6** in accord with elemental analysis and spectral data. The IR spectrum of **6** exhibited a moderately strong band at 1530 cm^{-1} due to the nitroso group[5,13] and no band in the carbonyl region was detected.

3-Nitroso-2-thienylimidazo[1,2-a]pyrazine **7** was obtained in 60% yield by condensation of **2** with 2-aminopyrazine in ethanol. The structure of **7** was consistent with elemental analysis and spectral data. Treatment of **2** with *o*-aminophenol and methyl anthranilate afforded the linear adducts, *N*-thienylglyoxalyl-*o*-aminophenol oxime (**8**) and methyl *N*-thienylglyoxalylanthranilate oxime (**9**), respectively. On the other hand, the reaction of **2** with *o*-phenylenediamine and *o*-aminothiophenol gave the cyclized products, 3-thienoyl-1,4-dihydro-1,2,4-benzotriazine (**10**) and 3-thienoyl-1,2,4-benzothiadiazine (**11**), respectively, instead of the expected benzoxazole or quinazoline or benzimidazole and benzothiazole[14,15] in the similar reactions of aromatic hydroxamoyl chlorides. **9** was cyclized, however, to 3-hydroxy-4-oxo-2-thienoyl-3,4-dihydroquinazoline (**12**) on treatment with hydrochloric acid.

In order to examine the 1,3-dipolar cycloaddition reactivity, **2** was treated in ether with triethylamine in the presence of a dipolarophile (acrylonitrile for example) according to the general procedure for preparing the nitrile oxides[16] to give a product which was characterized as 3-thienoyl-5-cyanoisoxazoline (**13**). **13** showed no nitrile absorption in its IR spectrum, which supports the 5-cyano structure[17,18]. Acidic hydrolysis of **13** with sulfuric acid resulted in its conversion into the corresponding 3-thienoyl-5-carboxamido-Δ^2-isoxazoline **14**. IR spectrum of **14** revealed bands at 3400, 3350 (NH_2), 1450 (CO thienoyl) and 1680 (CO amide). Similarly, **2** reacted with *N*-phenylmaleimide and acetylenedicarboxylic acid diethyl ester to afford the 3-thienoylpyrrolidino[3,4-d]-Δ^2-isoxazoline (**15**) and 4,5-diethoxycarbonyl-3-thienoylisoxazole (**16**), respectively (cf. Scheme 2). Since the products **13**, **15**, **16** could be obtained by the thermal 1,3-dipolar cycloaddition reactions of **2** in almost quantitative yields, the thermal reactions were performed using several dipolarophiles.



SCHEME 2

EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallenkamp melting point apparatus. The IR spectra were taken in KBr using Pye Unicam SP_3-300 spectrophotometer. The ^1H-NMR spectra were obtained in chloroform-*d* and dimethylsulfoxide-d_6 on a Varian EM-360 spectrometer (90 MHz), with tetramethylsilane as the internal reference. Elemental analyses were carried out by the Microanalytical Centre at Cairo University. Dimethylsufonium bromide **1** was prepared from 2-bromoacetylthiophene and dimethylsufide according to literature procedure.[19]

2-Thienoylhydroxamoyl chloride (**2**):
To a solution of 10.7 g (0.04 mol) of **1** and 3.5 g (0.05 mol) of sodium nitrite in 50 ml of water and 50 ml of dioxane, 100 ml of concentrated hydrochloric acid were added with stirring for a period of 1 h at room temperature. Stirring was continued for 2 h to produce a white solid which was separated by filtration. Crystallization of the white solid from chloroform afforded 6 g (85%) of **2** as white crystals, mp. 144°C (cf. Table I).

Synthesis of the nitroso derivatives **3a–c**, **6** *and* **7**: *General method:*
A mixture of hydroximoyl chloride **2** (0.95; 5 mmol) and each of 2-aminopyridine, 2-amino-3-picoline, 5-chloro-2-aminopyridine, 2-aminopyrimidine and 2-aminopyrazine (10 mmol) in ethanol (25 ml) was

TABLE I

Characterization data of the newly synthesized compounds

				% Analysis			Calcd. found
Comp.	Color	M.p.	Mol. formula	C	H	N	S
2	pale yellow	144	$C_6H_4ClNSO_2$	38.00	2.13	7.38	16.90
			(189.60)	37.80	2.30	7.10	16.80
3a	green	190–1	$C_11H_7N_3SO$	57.63	3.07	18.33	13.97
			(229.24)	57.80	2.90	18.10	14.20
3b*	green	143–4	$C_{12}H_9N_3SO$	59.24	3.72	17.27	13.12
			(243.27)	59.10	3.60	17.40	13.30
3c	yellowish green	210	$C_{11}H_6ClN_3SO$	50.10	2.29	15.93	12.15
			(263.69)	50.20	3.10	16.10	12.00
6	green	245–7	$C_{10}H_6N_4SO$	52.16	2.62	24.33	13.91
			(230.23)	52.30	2.70	24.10	14.10
7	brown	240–1	$C_{10}H_6N_4SO$	52.16	2.62	24.33	13.95
			(230.23)	52.00	2.80	24.50	13.80
8	buff	121–2	$C_{12}H_{10}N_2SO_3$	54.92	3.84	10.68	12.21
			(262.27)	54.80	3.90	10.80	12.40
9	colorless	211–12	$C_{14}H_{12}N_2SO_4$	55.25	3.97	9.20	10.53
			(304.31)	55.10	4.00	9.40	10.30
10	yellow	191–2	$C_{12}H_9N_3SO$	59.24	3.72	17.27	13.17
			(243.27)	59.40	3.60	17.40	13.00
11	canary yellow	195	$C_{12}H_8N_2S_2O$	55.37	3.09	10.76	24.62
			(260.30)	55.50	3.10	10.90	24.70
12	pale yellow	174–6	$C_{13}H_8N_2SO_3$	57.34	2.96	10.29	11.77
			(272.26)	57.40	2.80	10.00	11.90
13	colorless	138	$C_9H_6N_2SO_2$	52.42	2.93	13.58	15.54
			(206.20)	52.20	3.00	13.70	15.70
14	pale yellow	156	$C_9H_8N_2SO_3$	48.21	3.59	12.49	14.29
			(224.22)	48.30	3.70	12.60	14.30
15	colorless	193	$C_{14}H_{10}N_2SO_4$	58.89	3.08	98.58	9.82
			(302.29)	58.90	3.20	8.80	10.00
16	colorless	67	$C_{14}H_{13}NSO_6$	52.00	4.05	4.33	9.91
			(323.31)	51.80	4.20	4.10	9.70

* M.p. not depressed on admixture with an authentic sample [20].

TABLE II

JR- and ^{1}H-NMR-Data

Comp.	IR (cm^{-1})	^{1}H NMR δ ppm)
2	3340 (OH) and 1660 (CO)	6.9–7.5 (m, 3H, thiophene protons) and 11.1 (s, 1H, oxime).
8	3400-3340 (OH) and 1650 (CO)	7–7.8 (m, 8H, ArH's and thiophene protons), 8.4 (s, 1H, NH) and 10.8 (s, 1H, oxime).
9	3440 (OH), 1715 (CO ester) and 1660 (CO)	3.6 (s, 3H, $-COOCH_3$); 7–7.8 (m, 7H, ArH's and thiophene protons), 8.6 (s, 1H, NH) and 10.8 (s, 1H, oxime).
12	3450 (OH); 1680 (CO amide) and 1650 (CO).	6.9–8.2 (m, ArH's, thiophene and OH protons).
13	1650 (CO)	3.6 (d, 2H, H-4) and 5.1 (t, 1H, H-5) and 7–7.5 (m, 3H, thiophene protons).
15	1780-1710 and 1710–1690 (CONRCO) and 1660 (CO)	4.7 (d, 1H, pyrrole H-4); 5.5 (d, 1H, pyrrole H-5) and 7.1–8.3 (m, 8H, ArH's and thiophene protons)
16	1730 (CO ester) and 1650 (CO)	1.3 (t, 6H, $2CH_2CH_3$); 4.1 (q, 4H, $2CH_2CH_3$) and 7.1–8.2 (m, 3H, thiophene protons).

stirred at room temperature for 30 min and then left for 2 h. The green precipitate was collected and crystallized from ethanol or dioxane to give **3a-c**, **6** and **7** respectively (cf. Table I).

N-Thienoylglyoxlyl-o-aminophenol oxime (**8**):

A solution of **2** (0.95 g; 5 mmol) and 1.1 gm (10 mmol) of *o*-aminophenol in ethanol (20 ml) was allowed to react at room temperature for 24 h. The solid so formed was collected and crystallized from ethanol to give **8** (yield, ca 60%).

Methyl-N-thienoylglyoxylylanthranilate oxime (**9**):

A solution of **2** (0.95 g; 5 mmol) and 1.5 g (10 mmol) of methylanthranilate in ethanol (25 ml) was left to stand at room temperature for two days. The solid so formed was collected and crystallized from ethanol to give **9** (yield, ca 40%, cf. Table I).

Synthesis of benzotriazine and benzothiazine derivatives **10**, **11**:

A solution of **2** (0.95 g; 5 mmol) and each of *o*-phenylenediamine and *o*-aminothiophenol (10 mmol) in ethanol (25 ml) was stirred at room temperature for 3 h. The solid so formed was collected and crystallized from ethanol to give **10** and **11**, respectively in 74 and 81% yields (cf. Table I).

3-Hydroxy-4-oxo-2-thienoyl-3,4-dihydroquinazoline (**12**): *Method A*:

A solution of **9** (0.5 g) in conc. hydrochloric acid (2 ml) was warmed at 60°C for 20 min. After cooling, the resulting crystals were collected and crystallized from ethanol to afford 0.22 g (50% yield) of **12** (cf. Table I).

Method B:

A solution of (**2** 0.95 g; 5 mmol) and 1.5 g methylanthranilate in ethanol (20 ml) was left to stand at room temperature for 2 days. The solid was removed and the filtrate was left to stand at room temperature for 7 days. The solid so formed was collected and crystallized from ethanol. The product obtained was completely identical with the authentic sample of **12** obtained by method A above.

Synthesis of 13, 15 and 16: Method A:

To a stirred solution of **2** (0.95; 5 mmol) and each of acrylonitrile, N-phenylmaleimide and acetylenedicarboxylic acid diethylester (5 mmol) in ether (50 ml) was added a solution of 0.5 g of triethylamine in ether (10 ml) at 0°C. The reaction mixture was stirred at room temperature for overnight. The resulting precipitate (triethylamine hydrochloride) was removed and the filterate was concentrated.The residual oily product was triturated with methanol. The solid so formed was collected and crystallized from ethanol or acetic acid to afford **13**, **15** and **16** respectively in 60–65% yields (cf. Table I).

Method B:

A solution of the same amount of the two components as above in toluene (50 ml) was refluxed for 20 h. The solvent was removed and the solid so formed was crystallized as above to give **13**, **15** and **16** respectively. The products obtained were completely identical with the authentic sample of **13**, **15** and **16** obtained by method A above.

Synthesis of 3-thienoyl-5-carboxamido-Δ^2-isoxazoline (**14**):

A solution of 0.5 g of **13** in 4 ml of conc. sulfuric acid was stirred at room temperature for 2 h. The reaction mixture was poured onto ice-water and the resulting pale yellow product was collected and recrystallized from water to affort **14** in 75% yield (cf. Table I).

REFERENCES

1. C. Grundmann and P. Grunanger, "The Nitrile Oxides" Springer-Verlag, Berlin, 1971; R. Huisgen, *J. Org. Chem.*, **23,** 2291 (1968); K. Bast, M. Christ, R. Huisgen, W. Mach and K. Sustmann. *Chem. Ber.*, **166,** 3258 (1978).
2. K. J. Dignam, A. F. Hegarty and P. L. Quain, *J. Org. Chem.*, **43,** 388 (1978).
3. M. H. Benn., Can. J. Chem., **42,** 2392 (1964); J. Plenkiewicz, *Tetrahedron,* **34,** 2961 (1978); H. Gozlan, R. Michelot, C. Riche and R. Rips, *Tetrahedron,* **33,** 2535 (1977); G. Leroy, M. T. Nguyen, M. Sana, K. J. Dignam and A. F. Hegarty, *J. Am. Chem. Soc.*, **101,** 1988 (1979).
4. S. S. Ghabrial and A. O. Abdelhamid, *Arch. Pharm* (Weinheim), **320,** 1281 (1987).
5. C. Parkanyi, A. O. Abdelhamid, J. C. S. Cheng and A. S. Shawali, *J. Heterocylic Chem.*, **21,** 1029 (1984).
6. A. O. Abdelhamid, C. Parkanyi, M. A. Abdalla and A. S. Shawali, *J. Heterocyclic Chem.*, **20,** 1049 (1984).
7. A. O. Abdelhamid, H. M. Hassaneen and A. S. Shawali and C. Parkanyi, *J. Heterocylic Chem.*, **20,** 639 (1983).
8. L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Gamba, A. Olivi and W. Murman, *J. Med. Chem.*, **9,** 29 (1966).
9. L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba and W. Murmann, *J. Med. Chem.*, **8,** 305 (1965).
10. R. J. Collins, A. H. Tang and H. H Keasling, *J. Pharmacol. Exp. Ther.*, **159,** 428 (1967).
11. L. Pentimalli and S. Bozzini, *Boll. Sci. Fac. Chim. Ind. Bologna,* **23,** 181 (1965); *Chem. Abstr.*, **63,** 14848 e (1965).
15. W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms", Part I, Interscience, New York, NY, 1961, Chapter V, p 460.
13. R. N. Jones and C. Sandorfy "Techniques of Organic Chemistry" Vol. **9,** W. West, ed, Interscience, New York, NY, 1965, p. 247.
14. T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.*, **42,** 3335 (1969).
15. T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.*, **41,** 2206 (1968).
16. R. Huisgen and W. Mack, *Tetrahedron Lett.*, 1961, 583.
17. L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Methuen & Co., Ltd. New York (1969), p. 266.
18. T. Sasaki, T. Yoshioka and Y. Suzuki, *Bull. Chem. Soc. Jpn.*, **44,** 185 (1971).
19. A. O. Abdelhamid and F. A. Attaby, *Sulfur Lett.*, 1988 (in press).
20. S. N. Godovikova, Khim. Geterotsikly, 166, (1967); *Chem. Abstr.*, **70,** 87678 u (1969).