Direct Synthesis of Nitroheterocycles: The Use of Nitroketene Aminals as Enamines[1]

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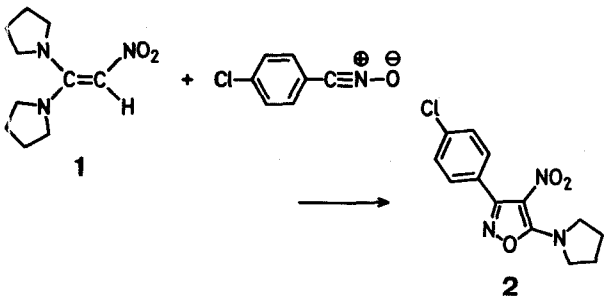
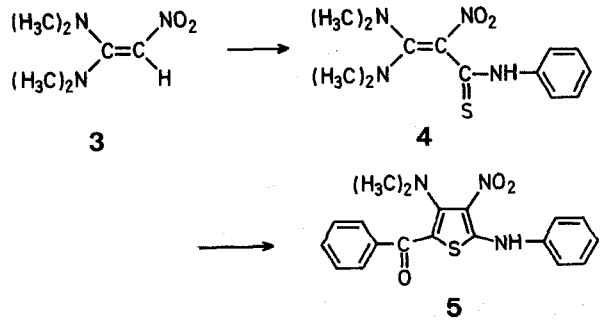
We report below the first two examples of the use of nitroketene aminals for the synthesis of heteroaromatic nitro compounds.

It is known that enamines react as dipolarophiles in cycloaddition reactions[2]. We have now found that nitroketene aminals (e. g. **1**)[3] undergo cycloaddition with nitrile oxides to give 4-nitroisoxazoles (e. g. **2**) in low to moderate yields: an example is given below. The isoxazoles that have been prepared are listed in Table 1.



1 **2**

The reactivity of nitroketene aminals (e. g. **3**) with isothiocyanates also enabled us to prepare 3-nitrothiophenes (e. g. **5**) by a route which we had discovered a few years back[4]. The adduct is reacted with an α-halo ketone as shown below.

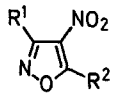


3 **4**

5

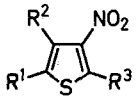
Table 2 lists some of the thiophenes that have been synthesised by this method.

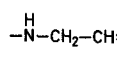
Table 1. Preparation of Isoxazoles



R^1	R^2	m.p.	Yield (%)
		172–174°	25
		192–195°	10
		156–159°	14
t-C_4H_9		98–100°	12

Table 2. Preparation of Thiophenes



R^1	R^2	R^3	m.p.	Last Step Reflux time	Yield (%)
			150–151°	1.5 h	47[a]
			159–161°	3.0 h	49[b]
			140–142°	2.5 h	48
			95–97°	15 h	20[c]
			145–147°	20 h	26

[a] We suspect that the final elimination of methylamine hydrobromide takes place during recrystallisation, when the product colour changes from pale yellow to deep reddish brown.
[b] Final cyclisation/elimination is achieved by refluxing with ammonia ($^1/_2$ h).
[c] Chromatographed in benzene over alumina

3-(4-Chlorophenyl)-4-nitro-5-pyrrolidinoisoxazole (2):
A solution of the bis-pyrrolidino compound (**1**; 8.0 g) and *p*-chlorobenzohydroxamoyl chloride (8.0 g) in toluene (200 ml) was cooled to 10–15° and treated during 45 min with stirring with triethylamine (4.0 g) in toluene (25 ml). The mixture was further stirred at room temperature for $2^1/_2$ h, and filtered. The filtrate was washed twice with water, dried (Na_2SO_4) and evaporated to dryness in vacuum. The residual solid was crystallised from ethanol to give yellow shining crystals of the isoxazole (**2**); yield: 2.8 g; m.p. 172–174°.

$C_{13}H_{12}ClN_3O_3$	calc.	C 53.15	H 4.12	N 14.31
(293.71)	found	53.48	4.50	14.55

^{1}H-N.M.R. ($CDCl_3$): 3 sets of signals of equal intensity at about 2.03, 3.78, and 7.45 ppm downfield from TMS.

Mass spectrum: $m/e = 295$ and 293 (M^+).

2-Anilino-5-benzoyl-4-dimethylamino-3-nitrothiophene (5):
1-Nitro-2,2-bis[methylmercapto]ethylene[3] (16.5 g) was refluxed for 1 h with a 33% alcoholic solution of dimethylamine (50 ml) and then evaporated in vacuo. The residual solid was digested with ether and recrystallised from isopropyl alcohol/ether to give the bis-dimethylamino compound (**3**); yield: 9.0 g; m.p. 113–116°.

$C_6H_{13}N_3O_2$	calc	C 45.27	H 8.23	N 26.40
(159.19)	found	45.48	8.48	26.76

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.98$ (s, 6H), 6.30 ppm (s, 1H).

A mixture of the nitroketene aminal (**3**; 4.8 g) and phenyl isothiocyanate (4.1 g) in toluene (50 ml) was refluxed for 15 h, cooled, and the solid filtered. It was recrystallised from ethanol to give the adduct (**4**); yield: 6.0 g; m.p. 153–156°.

$C_{13}H_{18}N_4O_2S$	calc.	C 53.05	H 6.16	N 19.04
(294.31)	found	53.21	6.53	19.03

A mixture of the above adduct (**4**; 1.5 g) and phenacyl bromide (1.0 g) in alcohol (30 ml) was refluxed for $2^1/_2$h and then the solvent removed in vacuo. The residue was partitioned between ethyl acetate and water, the organic layer dried, and concentrated to give a deep red solid. This was recrystallised from a large volume of methanol to give the thiophene (**5**); yield: 0.9 g; m.p. 140–142°.

$C_{19}H_{17}N_3O_3S$	calc.	C 62.12	H 4.66	N 11.44
(367.35)	found	62.40	4.97	11.21

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.7$ (s, 6H), about 7.5 (m, 10H), 10.7 ppm (broadened singlet, NH)

We are grateful to Professor T. R. Govindachari for his interest and encouragement and to Dr. S. Selvavinayakam and his associates for the analytical and spectral data.

Received: March 19, 1974 (Revised form: June 5, 1974)

[1] Contribution No. 351 from CIBA-GEIGY Research Centre.
[2] M. E. Kuehne in "*Enamines*", Ed. A. G. Cook, Marcel Dekker, 1969, p. 434.
G. Stork, J. E. McMurry, *J. Amer. Chem. Soc.* **89**, 5461 (1967).
[3] R. Gompper, H. Schaefer, *Chem. Ber.* **100**, 591 (1967); we have also prepared unsymmetrical nitroketene aminals by reaction of *S*-methyl pseudothioureas with nitromethane.
[4] S. Rajappa, B. G. Advani, *Tetrahedron Lett.* **1969**, 5067.