Tetrahedron Vol 33, pp 1057 to 1060 Pergamon Press 1977 Printed in Great Britain

NITROENAMINES—III[1]

SYNTHESIS OF 3,3-DIAMINO-2-NITROACRYLONITRILES FROM 1,1-DIAMINO-2-NITROETHYLENES†

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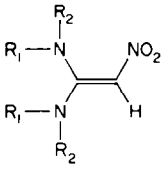
(*Received in UK 11 October 1976; Accepted for publication 26 October 1976*)

(Dedicated to Prof. R. B. WOODWARD on the occasion of his Sixtieth Birthday)

Abstract—A novel fragmentation of an isothiazoline ring is reported. Nitroketene aminals **1** react with benzoyl isothiocyanate to form the adducts **3**. These adducts can be converted to the 3,3-diamino-2-nitroacrylonitriles **2** in two discrete steps—first to an isothiazoline (**4**, **7**) by oxidation, and then to the nitriles by base-induced fragmentation; alternatively the adducts (**3c**, **11**) can be directly treated with alkaline hydrogen peroxide to provide the nitriles in one step.

The substitution of a nitrile group in place of hydrogen at the β-position of an enamine has been termed "cyanolation" by Kuehne.[2] This can be brought about by means of cyanogen chloride[3] or aryl cyanates.[4] However, yields of the nitriles are reasonable only if the enamine substrate is very reactive (e.g. pyrrolidine enamines). We now report a simple method for the conversion of the weakly enaminic nitroketene aminals **1**[5] to the 3,3-diamino-2-nitroacrylonitriles **2**.



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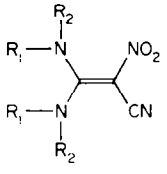

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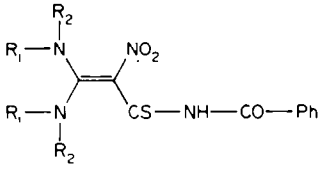
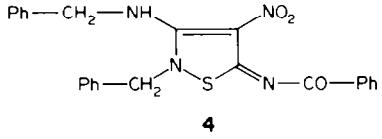


3

a: R_1 = -CH_2Ph, R_2 = H
b: R_1 = R_2 = CH_3
c: R_1 = CH_3, R_2 = H

We previously reported the results of using alkyl and aryl isothiocyanates to compare the enaminic reactivity of different types of nitroketene aminals.[5] In that study, it emerged that these reagents discriminated between the fully substituted derivatives of the type $(RRN)_2C{=}CH{-}NO_2$, the partially substituted compounds of the type $(RNH)_2C{=}CH{-}NO_2$, and the cyclic nitroketene aminals with two NH groups; the chemical reactivity seemed to decrease in the above order. In contrast to this situation, the powerfully electrophilic benzoyl isothiocyanate reacted easily with all types of nitroketene aminals to produce the corresponding adducts (e.g. **3**). Oxidation of the adduct **3a** with bromine in acetic acid gave the isothiazoline **4** in 51% yield.



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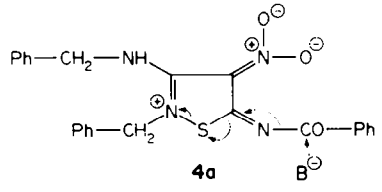


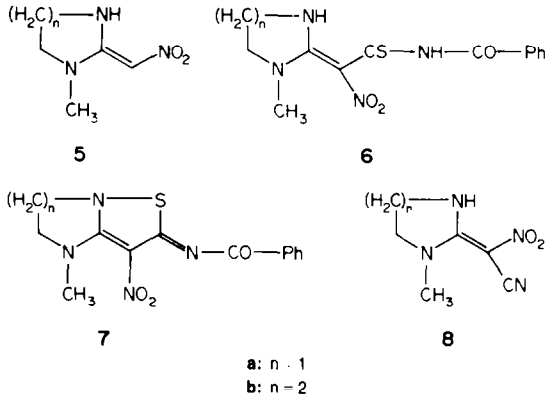
4a $B^{\ominus}$

Our aim was to subject this isothiazoline **4** to a fragmentation reaction, initiated by base and culminating in the extrusion of sulfur with concomitant formation of a nitrile (see arrows in **4a**). We argued that charged amidinium–nitronate structures such as **4a** would contribute significantly to the ground state of **4**, and these would be poised for fragmentation as depicted. Our hope was easily realised in practice by refluxing the nitroisothiazoline **4** with sodium ethoxide in ethanol. The product was the expected nitrile **2a** obtained in 75% yield. The structure was confirmed by the analytical values, molecular ion peak at 308 in the mass spectrum and IR band at 2220 cm^{-1}. The presence of free sulfur in the crude product could be seen in the mass spectrum (prominent peaks at multiples of 32 up to S_7).

The cyclic nitroketene aminals **5** could be subjected to a similar sequence of adduct formation **6** (stereochemistry uncertain), oxidation to the isothiazolines **7**, and fragmentation to produce the nitronitriles **8**. Two possibilities exist for the product stereochemistry in **8**. From a superficial perusal of the fragmentation mode, it would appear that the products should have the NH and CN *cis*. However, it should be remembered that the product exists initially as the nitronate salt and is obtained after acidification of the alkaline solution. We believe that the extra stability derived by H-bond formation between the O of the NO_2 group and the NH would result in these two groups being *cis* as depicted in **8**.

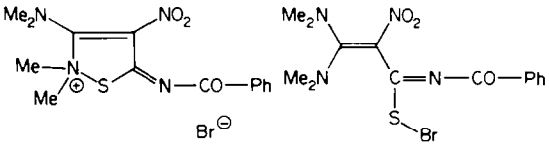
Conversion of the fully substituted aminal **1b** to the

†Contribution No. 389 from CIBA-GEIGY Research Centre.



5 6 7 8

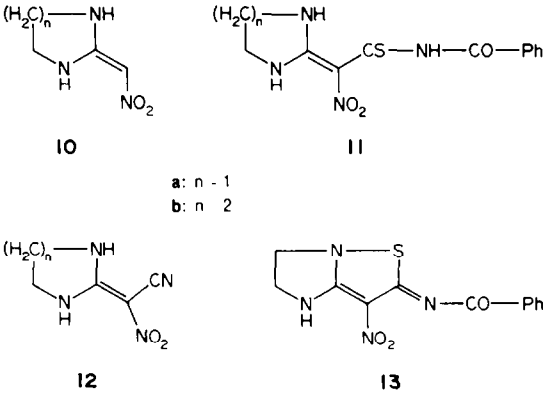
acrylonitrile **2b** could be achieved easily as follows: the adduct **3b** was oxidised with the calculated quantity of bromine in chloroform, the solvent removed, and the residue treated with excess sodium methoxide in methanol to get the nitrile **2b** in 55% yield. No attempt was made to isolate the intermediate product of oxidation; it is open to conjecture whether the intermediate is an isothiazolinium salt **9a** or the corresponding sulfenyl bromide **9b**.



9a 9b

The adduct **3c** derived from 1,1-bis-methylamino-2-nitroethylene and benzoyl isothiocyanate was too insoluble in the usual organic solvents for bromine oxidation to be successful. However, its easy solubility in aqueous alkali (without cyclising to a pyrimidine derivative) provided a simple method of combining the operations of oxidation and base-treatment in one step. Treatment of a solution of **3c** in aqueous alkali with aqueous hydrogen peroxide gave the nitrile **2c** directly in about 48% yield.

Essentially the same procedure proved effective for the conversion of the cyclic nitroketene aminals **10** to the acrylonitriles **12**. The imidazo derivative **11a** on treatment

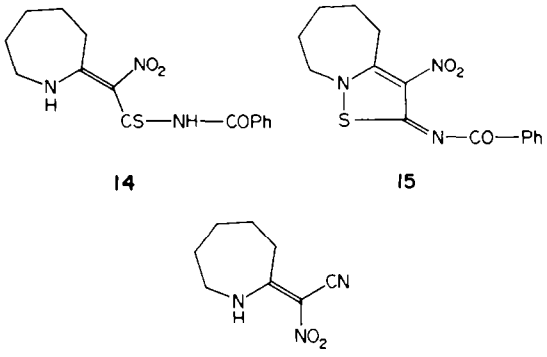


10 11 12 13

with aqueous alkaline hydrogen peroxide gave a mixture of the nitrile **12a** and the bicyclic derivative **13**; the latter could be converted to the nitrile **12a** by further treatment with sodium methoxide in methanol. The pyrimidine derivative **11b** gave only the required nitrile **12b** on alkaline peroxide treatment.

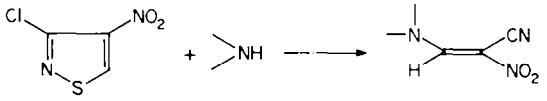
There has been only one other reaction described in the literature where such 3,3-diamino-2-nitroacrylonitriles occur as unexpected products; in a series of recent publications, Clark *et al.* have reported the formation of these in the acid or alkali-induced decomposition of 4-amino-5-nitro-6-chloropyrimidines.[7a,b,c]

In an attempt to extend our procedure to the nitrovinyl-amines, the adduct **14**[5] was oxidised to the isothiazoline **15**. Base-treatment of the latter led to the nitrile **16** in only 7.5% yield. Treatment of **14** directly with aqueous alkaline hydrogen peroxide did not lead to any product exhibiting the nitrile band in the IR.



14 15 16

In all the fragmentations we have described, the C atom of the nitrile is derived from C-5 of the isothiazole and the nitrogen from the exocyclic imine. An entirely different type of fragmentation has recently been described,[8] which gives products similar to **16**; in this mode, N-2 and C-3 of the isothiazole form the nitrile of the product:



Professor Woodward was the first to recognize the synthetic potentiality of the isothiazole ring—to mask the reactive amine and to function as a template for the construction of other features of the colchicine molecule. At the penultimate stage, the isothiazole ring was dismantled—"not to be used again until someone might see another opportunity to adopt so useful a companion on another synthetic adventure".[9] In a very small way, we have just demonstrated another example of the utility of isothiazole ring.

EXPERIMENTAL

M.ps are uncorrected. Mass spectra were determined on a Varian Mat CH 7 instrument at 70 eV utilising direct insertion. NMR spectra were taken in a Varian A-60 instrument; chemical shifts are expressed in ppm downfield from TMS.

3,3-Bis-benzylamino-2-nitroacrylonitrile (**2a**). Compound **1a**[5] (33 g) was warmed in dry acetonitrile (500 ml) and treated with benzoyl isothiocyanate (21 g). The deep red soln was set aside at room temp for 2 hr and then the solvent removed *in vacuo*. The residue was dissolved in EtOAc and set aside for crystallisation (overnight). The adduct **3a** (48 g) had m.p. 150–52°.

A soln of **3a** (48 g) in chloroform (1 l.) was stirred and cooled to 10°. Br_2 (20 g) in chloroform was added in drops until a slight excess of Br_2 remained. Stirring was continued for another 15 min at 10°, the solid hydrobromide filtered off and washed with ether.

The salt was basified with 10% NaOH aq and the base extracted with chloroform. The extract was dried (Na_2SO_4), evaporated and the residue crystallised from EtOAc–hexane to give **4** (24.5 g), m.p. 192–195°. (Found: C, 65.01; H, 4.72; N, 12.50. $C_{24}H_{20}N_4O_3S$ requires: C, 64.86; H, 4.54; N, 12.61%); MS: 444 (M^+), 398 (100%, loss of NO_2), m* 356.8 (444→398). NMR ($CDCl_3 + CD_3SOCD_3$): 4.57 (d, CH_2); 4.98 (s, CH_2); aromatic protons, and 9.43 (t, NH).

Na (1.8 g) was dissolved in abs EtOH (400 ml). To this soln was added **4** (24.5 g) and the mixture stirred and refluxed for 6 hr. A small amount of solid was filtered off and the filtrate evaporated *in vacuo*. The residue was digested with water and ether and the solid (A) filtered. The two layers in the filtrate were separated and the aqueous layer acidified with AcOH. The solid was filtered and redissolved in 2N NaOH. A small amount of alkali-insoluble material was filtered off and the filtrate re-acidified. The solid (B) was filtered off. Solids (A) and (B) were found to be the same. These were combined and crystallised from MeOH to give **2a** (10.8 g), m.p. 165–168°. Concentration of the mother liquor gave a further 2 g of the same material. (Found: C, 66.45; H, 5.56; N, 18.46. $C_{17}H_{16}N_4O_2$ requires: C, 66.22; H, 5.23; N, 18.17%); MS: 308 (M^+); 262 (M − 46). IR: ν_{max}: 2220 cm^{-1} (nujol).

1-*Methyl*-2-(*α-nitro-α-cyano*) *methylene tetrahydro imidazole* (**8a**). Compound **5a**[6] (26 g) and benzoyl isothiocyanate (30 g) in acetonitrile (300 ml) gave the adduct **6a** (32 g), m.p. 155–157°.

The adduct (3.1 g) was carefully dissolved in warm AcOH (in one expt, when the AcOH was boiling, spontaneous exothermic decomposition took place) and oxidised at 10° with Br_2 (1.6 g) in AcOH. The solvent was evaporated, the residue digested with water, filtered, washed with water and dried, to give the crude **7a** (2.7 g), m.p. 216–221°. A sample was crystallised from AcOH to give the pure **7a**, m.p. 225–227°. (Found: C, 51.18; H, 4.24; N, 18.43. $C_{13}H_{12}N_4O_3S$ requires: C, 51.31; H, 3.98; N, 18.42%); MS: 304 (M').

Na (0.4 g) was dissolved in abs MeOH (80 ml); to this soln was added the above **7a** (4.8 g) and refluxed with stirring for 2 hr. The MeOH was evaporated *in vacuo* the residue dissolved in warm water. After cooling, the methyl benzoate was removed by ether extraction. The aqueous layer was acidified, the solid filtered and recrystallised from water to give **8a** (1.4 g), m.p. 214–217° (Found: C, 42.73; H, 5.05; N, 33.66. $C_6H_8N_4O_2$ requires: C, 42.85; H, 4.80; N, 33.32%); MS: 168 (M'). IR (nujol): ν_{max} 2215 cm^{-1} (lit.[7b] reports m.p. 216–218°).

1 - *Methyl* - 2(*α* - *nitro* - *α* - *cyano*) *methylene-hexahydropyrimidine* (**8b**). Compound **5b**[5] (3.0 g) and benzoyl isothiocyanate (3.1 g) in acetonitrile (20 ml) gave the adduct **6b** (4.0 g), m.p. 163–165°.

The above adduct (9.6 g) was oxidised as before by Br_2 in AcOH and the product crystallised from AcOH to give **7b** (8.3 g) m.p. 224–226°. (Found: C, 53.05; H, 4.67; N, 17.54. $C_{14}H_{14}N_4O_3S$ requires: C, 52.83; H, 4.43; N, 17.60%); MS: 318 (M').

The above **7b** (3.2 g) was refluxed with a soln of NaOMe (from 0.25 g Na) in MeOH for 3 hr, evaporated, dissolved in water and the methyl benzoate removed by ether extraction. The aqueous soln was acidified with AcOH, filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with boiling CH_2Cl_2, filtered and the filtrate evaporated. The residual solid was crystallised from EtOAc to give **8b** (1.15 g), m.p. 128–131° (Found: C, 46.29; H, 5.87; N, 30.46. $C_7H_{10}N_4O_2$ requires: C, 46.15; H, 5.52; N, 30.76%); MS: 182 (M^+). IR (nujol): ν_{max} 2210 cm^{-1}.

3,3 - *Bis-dimethylamino* - 2 - *nitroacrylonitrile* (**2b**). Compound **1b**[5] (5 g) and benzoyl isothiocyanate (5 g) in toluene gave **3b** (5 g), m.p. 163–166° (from EtOH). (Found: C, 52.49; H, 5.79; N, 17.45. $C_{14}H_{18}N_4O_3S$ requires: C, 52.17; H, 5.63; N, 17.38%); NMR ($CDCl_3$): 3.17 (s, $4CH_3$); 7.4 to 8.2 (5Ar–H); 14.37 (NH).

The **3b** (1.6 g) in chloroform (15 ml) was cooled to 5° and treated dropwise with stirring with Br_2 (0.8 g) in $CHCl_3$ (7 ml) during a period of 5 min. The soln was stirred at 5° for a further 10 min. The $CHCl_3$ was then removed *in vacuo* (100 mm) below 40° (The residue should not be dried for too long *in vacuo*). The residual oil was quickly dissolved in a soln of NaOMe (from 0.35 g Na) in MeOH (30 ml). The soln was refluxed for 3 hr and the MeOH removed *in vacuo*. The residue was digested with a mixture of cold water (10 ml) and ether (30 ml). The solid (A) was filtered. The aqueous layer was separated from the filtrate, acidified with AcOH and evaporated to dryness. The dry residue was extracted twice with boiling EtOAc (2 × 100 ml) and the extract evaporated to give solid (B). The solids (A) and (B) were combined and crystallised first from EtOAc and then again from water to give **2b** (0.5 g), m.p. 161–163°. (Found: C, 46.04; H, 6.87; N, 30.53. $C_7H_{12}N_4O_2$ requires: C, 45.64; H, 6.57; N, 30.42%); MS: 184 (M^+). IR (nujol): ν_{max} 2220 cm^{-1}.

3,3 - *Bis-methylamino* - 2 - *nitroacrylonitrile* (**2c**). Compound **1c**[5] (15 g) was dissolved in hot acetonitrile (300 ml) and treated with benzoyl isothiocyanate (19 g) in small portions. Filtration after a few hrs gave the red adduct **3c** (27 g), m.p. 176–178°.

The above adduct (50 g) was dissolved in 10% NaOH aq (150 ml) and water (100 ml), stirred well and cooled to 0° (internal). H_2O_2 (50 ml; 30%) was added in drops, maintaining the internal temp between 0° and 5°. The addition took about 35 min. The soln was further stirred at 5° for 10 min and filtered cold. The solid was washed with water and crystallised from water (800 ml). It was dried at 80° for 16 hr to give **2c** (12.8 g), m.p. 198–201°. (Acidification of the reaction filtrate gave only benzoic acid). (Found: C, 38.65; H, 5.35; N, 36.25. $C_5H_8N_4O_2$ requires: C, 38.46; H, 5.16; N, 35.88%). MS: 156 (M^+); IR (nujol): ν_{max} 2220 cm^{-1}.

2 - (*α* - *Cyano* - *α* - *nitro*) *methylene-tetrahydro-imidazole* (**12a**). Compound **10a**[5] (18 g) and benzoyl isothiocyanate (22 g) in acetonitrile (400 ml) gave **11a** (32 g), m.p. 141–143°.

The above adduct (29 g) was dissolved in 2N NaOH (55 ml), diluted with water (150 ml), stirred, cooled to 0° and treated carefully with H_2O_2 (46 ml) in drops, maintaining the internal temp at 0° to 5°. The addition took about 45 min. During the addition, more ice-water (150 ml) was added to facilitate stirring. The mixture was stirred for a further 10 min at 0°, filtered and washed with water. The solid was digested with 2N NaOH, filtered and washed with water. The combined filtrate was acidified with 2N HCl, filtered, and the solid crystallised from water to give **12a** (4.0 g), m.p. 298–302° (d) (see below). The alkali insoluble residue was **13**; crude yield 11 g: a sample was crystallised from AcOH–water; m.p. 263–266° (d). (Found: C, 50.05; H, 3.78; N, 19.35. $C_{12}H_{10}N_4O_3S$ requires: C, 49.66; H, 3.47; N, 19.31%); MS: 290 (M').

The crude dry solid **13** (11 g) was suspended in a soln of NaOMe (from 1 g Na) in MeOH (200 ml). The mixture was stirred and refluxed for 2 hr. The solid went into soln after about 0.5 hr. The soln was cooled, the solvent evaporated *in vacuo* and the residue dissolved in water. The methyl benzoate was removed by ether extraction. The aqueous layer was acidified with 2N HCl, filtered, washed with water and recrystallised from water to give **12a** (2.3 g), m.p. 298–302 (d). Total yield—6.3 g (41%). (Found: C, 39.26; H, 4.07; N, 36.64. $C_5H_6N_4O_2$ requires: C, 38.96; H, 3.92; N, 36.35%). IR (nujol): ν_{max} 2220 cm^{-1}.

2 - (*α* - *Cyano* - *α* - *nitro*) *methylene-hexahydro-pyrimidine* (**12b**). Compound **10b**[5] (24 g) and benzoyl isothiocyanate (28 g) in warm acetonitrile (500 ml) gave the adduct **11b** (40 g), m.p. 151–153°.

It was found necessary to use two equivs of NaOH during the oxidation of the above adduct. The adduct (30.6 g) was dissolved in 2N NaOH (100 ml), diluted with water (100 ml), stirred, cooled to 0°, and oxidised as before with H_2O_2 (50 ml). The pale yellow solid was filtered, washed with water and purified by dissolving in dil NaOH, filtering off the insoluble material and recovering the product from the filtrate by acidification. In this case, the alkali-insoluble material was very little and was discarded. The nitronitrile (**12b**) was obtained pure by crystallisation from acetonitrile (9.5 g; 56.5%), m.p. 310–315° (d). (Found: C, 43.08; H, 5.08; N, 33.66. $C_6H_8N_4O_2$ requires: C, 42.85; H, 4.80; N, 33.32%); MS: 168 (M'). IR (nujol): ν_{max} 2220 cm^{-1}.

2 - (*α* - *Cyano* - *α* - *nitro*) *methylene-hexahydroazepine* (**16**). Compound **14**[5] (4.5 g) was oxidised as usual by Br_2 in $CHCl_3$ and the product crystallised from EtOH to give **15** (1.0 g), m.p. 163–167°. (Found: C, 56.80; H, 5.09; N, 12.97. $C_{15}H_{15}N_3O_3S$ requires: C, 56.78; H, 4.77; N, 13.24%); MS: 317 (M^+).

The above **15** (6.5 g) was refluxed with NaOMe (from 0.6 g Na) in MeOH (250 ml) for 3 hr. Work-up as usual gave **16** (0.28 g), m.p. 137–139° (from ethanol). (Found: C, 53.20; H, 6.27; N, 23.14. $C_8H_{11}N_3O_2$ requires: C, 53.03; H, 6.12; N, 23.19%); MS: 181 (M'). IR (nujol): ν_{max} 2220 cm^{-1}.

Acknowledgement—We thank Dr. S. Selvavinayakam and his colleagues for the analytical and spectral data.

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