# SIMPLE SYNTHESIS OF POLYFUNCTIONAL NITRO-PYRIDINES

Maria Teresa Cocco*, Cenzo Congiu, and Valentina Onnis

Dipartimento Farmaco Chimico Tecnologico,
Università di Cagliari - Via Ospedale 72,
I - 09124 Cagliari, Italy

Abstract - Upon treatment with nitroketene dithioacetal (**2**) in *refluxing acetonitrile*, enaminonitriles (**1**) afforded nitrodienamines (**3**). Polysubstituted *nitropyridines* (**4** and **5**) were obtained by cyclization of intermediates (**3**) with *orthoformate* and acetic anhydride respectively.

During the last decade a great emphasis has been placed on the utility of appropriately functionalized ketene dithioacetals in the synthesis of heterocycles.[1-3] One of these, 1-nitro-2,2-bis(methylthio)ethylene is an extremely interesting synthon and is used as a two-carbon fragment for the synthesis of heterocyclic compounds which have nitro or amino groups. In general terms, nitroketene dithioacetal reacts with various nucleophilic reagents to afford the corresponding mono- or bis-addition products.[4] However, only a

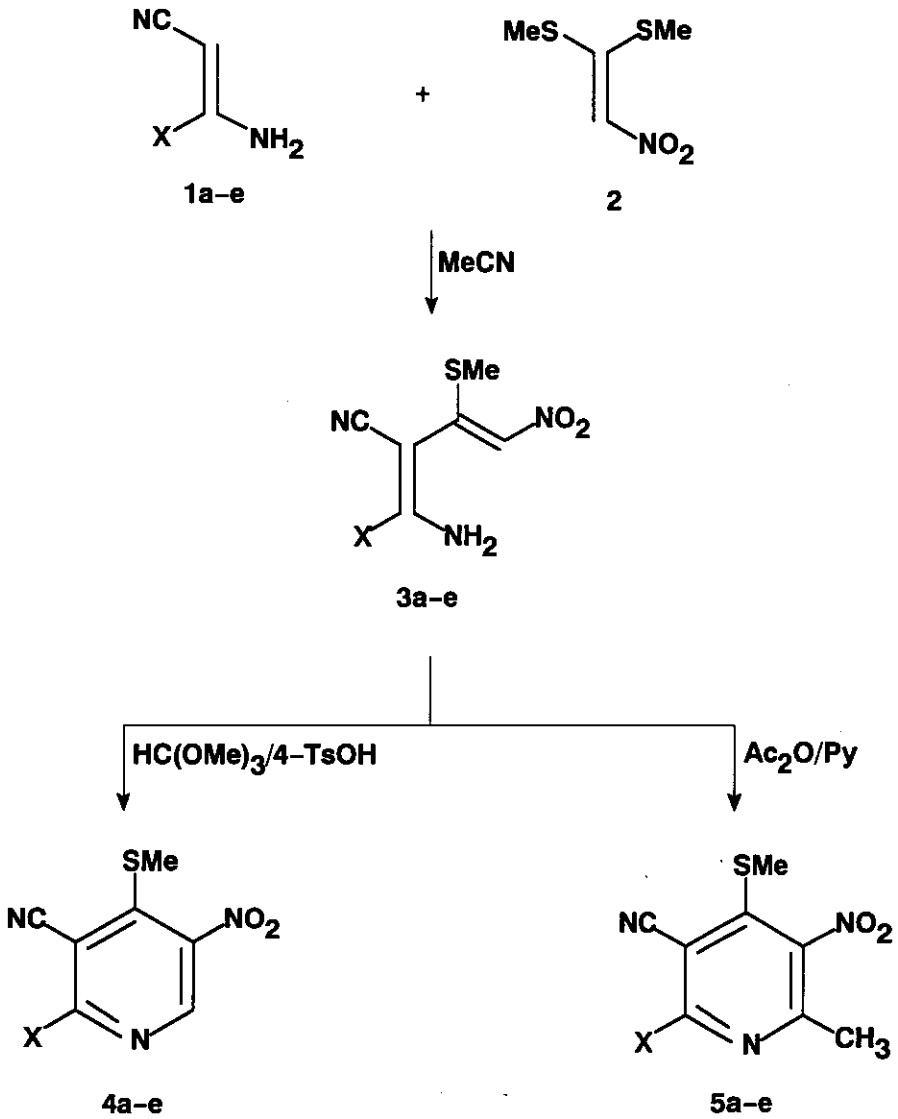
few examples of the nitroketene dithioacetal reaction with enamines[4,5] have been reported. In the last few years we have been involved in a program aiming at developing new efficient procedures for the synthesis of polyfunctionally substituted heterocycles utilizing simple laboratory enaminonitriles as starting materials.[6-11]

The 3-amino-3-dialkylaminopropenenitriles (**1**) considered by us in this paper have two nucleophilic sites (C-2 and $NH_2$) which could react with electrophilic reagents to give C- or N- adducts.

We now report the reaction of **1** with nitroketene dithioacetal (**2**). Enaminonitriles (**1**) therefore were treated with equimolecular amounts of **2** in refluxing acetonitrile for 4 h to afford only C-adducts (**3**). Spectroscopic data provide testimony that compounds (**3**) exist only in the enamino form.

The assignment of the enamino structure was straightforward on the basis of the following evidence: in the $^1H$-nmr spectra no resonance is present for the imino form, the olefinic proton resonates as a singlet at 6.56-6.59 ppm and finally two signals are observed downfield for the $NH_2$ group. These two signals collapse in a singlet by heating the solution up to 30°C. The ir spectra of **3** confirm the assigned structures by showing two stretching vibrations at 1690-1675 and 1605-1570 $cm^{-1}$, which are characteristic of conjugated enamines,[12] as well as the absorbance of the $NH_2$, CN and $NO_2$ groups.

Nitrodienamines (**3**) together with their functional substituents are versatile intermediates which can be converted into functionalized 5-nitropyridines.




| 1,3–5 | X |
|---|---|
| a | pyrrolidino |
| b | piperidino |
| c | 4–methylpiperazino |
| d | 4–phenylpiperazino |
| e | 4–ethoxycarbonylpiperazino |

**Table 1.** Physical and analytical data of compounds (**4** and **5**).

| Compd No. | Yield (%) | mp (°C) (Recryst. Solv.) | Molecular Formula | Analysis (%) Calcd/Found | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| **4a** | 91 | 155 (i-PrOH) | $C_{11}H_{12}N_4O_2S$ | 49.98/49.93 | 4.57/4.55 | 21.31/21.27 |
| **4b** | 93 | 90* | $C_{12}H_{14}N_4O_2S$ | 51.78/51.72 | 5.07/5.09 | 19.50/19.47 |
| **4c** | 80 | 140 (MeCN) | $C_{12}H_{15}N_5O_2S$ | 49.13/49.22 | 5.15/5.17 | 23.88/23.86 |
| **4d** | 95 | 135 (MeCOOEt) | $C_{17}H_{17}N_5O_2S$ | 57.44/57.37 | 4.82/4.84 | 19.70/19.66 |
| **4e** | 88 | 129 (i-PrOH) | $C_{14}H_{17}N_5O_4S$ | 52.64/52.59 | 5.36/5.34 | 21.93/21.98 |
| **5a** | 66 | 210 (MeCN) | $C_{12}H_{14}N_4O_2S$ | 51.78/51.83 | 5.07/5.05 | 19.50/19.54 |
| **5b** | 72 | 175 (i-PrOH) | $C_{13}H_{16}N_4O_2S$ | 53.40/53.46 | 5.51/5.49 | 19.16/19.10 |
| **5c** | 70 | 175 (i-PrOH) | $C_{13}H_{17}N_5O_2S$ | 50.80/50.89 | 5.57/5.55 | 22.79/22.75 |
| **5d** | 87 | 200 (MeCN) | $C_{18}H_{19}N_5O_2S$ | 58.52/58.47 | 5.18/5.21 | 18.96/19.00 |
| **5e** | 72 | 195 (i-PrOH) | $C_{15}H_{19}N_5O_4S$ | 54.03/53.97 | 5.74/5.72 | 21.01/21.06 |

* Purified by column chromatography (silica gel, petroleum ether/ ether 6:1).

**Table 2**. Ir and $^1$H-nmr spectral data of compounds (**4** and **5**)

| Compd. No. | Ir (nujol) ($cm^{-1}$) | $^1$H-nmr ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|
| **4a** | 2200, 1555, 1525, 1320 | 1.98, 3.76 (m, 8H pyrrolidinyl), 2.64 (s, 3H, $SCH_3$), 8.75 (s, 1H, H-6). |
| **4b** | 2200, 1550, 1530, 1340 | 1.68, 3.79 (m, 10H, piperidinyl), 2.66 (s, 3H, $SCH_3$), 8.75 (s, 1H, H-6). |
| **4c** | 2200, 1550, 1540, 1340 | 2.27 (s, 3H, $NCH_3$), 2.46, 3.86 (m, 8H piperazinyl), 2.64 (s, 3H, $SCH_3$), 8.75 (s, 1H, H-6). |
| **4d** | 2220, 1600, 1550, 1530, 1310 | 2.68 (s, 3H, $SCH_3$), 3.30, 4.03 (m, 8H piperazinyl), 6.89, 7.25 (m, 5H arom), 8.79 (s, 1H, H-6). |
| **4e** | 2220, 1715, 1550, 1345 | 1.23 (t, J=7.1 Hz, 3H, $CH_3$), 2.68 (s, 3H, $SCH_3$), 3.60, 3.83 (m, 8H piperazinyl), 4.13 (q, J=7.1 Hz, 2H, $CH_2$), 8.77 (s, 1H, H-6). |
| **5a** | 2220, 1765, 1640, 1575, 1375 | 1.93, 2.03, 3.78, 3.93 (m, 8H pyrrolidinyl), 2.20 (s, 3H, $CH_3$), 2.86 (s, 3H, $SCH_3$). |
| **5b** | 2220, 1770, 1635, 1565, 1360 | 1.69, 3.88, 3.94 (m, 10H piperidinyl), 2.21 (s, 3H, $CH_3$), 2.88 (s, 3H, $SCH_3$). |
| **5c** | 2210, 1765, 1635, 1560, 1365 | 2.22 (s, 3H, $CH_3$), 2.29 (s, 3H, $NCH_3$), 2.89 (s, 3H, $SCH_3$), 2.51, 3.97, 4.04 (m, 8H piperazinyl). |
| **5d** | 2210, 1770, 1635, 1600, 1555, 1360 | 2.24 (s, 3H, $CH_3$), 2.92 (s, 3H, $SCH_3$), 3.30, 4.12, 4.20 (m, 8H piperazinyl), 6.91, 7.26 (m, 5H arom). |
| **5e** | 2220, 1790, 1710, 1690, 1630, 1560, 1365 | 1.22 (t, J=7.1 Hz, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 2.88 (s, 3H, $SCH_3$), 3.59, 3.92, 3.99 (m, 8H piperazinyl), 4.12 (q, J=7.1 Hz, 2H, $CH_2$). |

Treatment of **3** with methyl orthoformate at reflux in presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH) afforded 5-nitropyridines (**4**) in good yields. However, the cyclization of **3e** was unsucessful under these conditions. Conversion of **3e** into the corresponding pyridine (**4e**) was performed without the catalyst.

Subsequently the cyclization of **3** by an acylating agent was explored using acetic anhydride ($Ac_2O$). Although no reaction was observed when **3** was treated with $Ac_2O$ at reflux, the reaction smoothly occurred on adding a small amount of pyridine and stirring the mixture at room temperature to afford 6-methyl-5-nitropyridines (**5**).

The structures of 5-nitropyridines (**4** and **5**) were determined from the analysis of their $^1$H-nmr spectra and further confirmed by their ir spectra and analytical data (Tables 1 and 2). These results show that the reaction of **1** with nitroketene dithioacetal can be utilized as a simple route to the synthesis of polyfunctional nitropyridines not easily accessible otherwise.

## EXPERIMENTAL

Melting points were determined on a Köfler hot stage and are uncorrected. Ir spectra were obtained in nujol with a Perkin-Elmer 398 spectrophotometer. $^1$H-Nmr spectra were recorded on a Varian Unity 300 spectrometer, the chemical shifts are given in $\delta$ downfield from the internal standard hexamethyldisiloxane (HMDSO). Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer. All reagents and solvents were of commercial quality from freshly opened containers. Compounds (**1a-e**) were prepared according to the literature procedure.[9]

**1-Amino-2-cyano-1-dialkylamino-3-methylthio-4-nitro-1,3-butadienes** (**3**); **General procedure**:

Compound (**2**) (4.9 g, 30 mmol) was added to a solution of enaminonitrile (**1a-e**) (30 mmol) in anhydr. MeCN (20 ml). The solution was heated at reflux for 4 h. The formed precipitate was collected by filtration and then recrystallized as indicated. Analytical and spectroscopic data are reported as follows:

(**3a**) (64% yield); mp 193-194 °C (from 2-propanol). *Anal.* Calcd for $C_{10}H_{14}N_4O_2S$: C, 47.23; H, 5.55; N, 22.03. Found: C, 47.30; H, 5.53; N, 21.98. Ir: νmax 3300, 3100, 2190, 1665, 1605, 1480, 1325 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): δ 1.88, 3.39, (m, 8H pyrrolidinyl), 2.39 (s, 3H, $SCH_3$), 6.57 (s, 1H, H-4), 7.77, 8.18 (br s, 2H, $NH_2$).

(**3b**) (36% yield); mp 184 - 185 °C (from 2-propanol). *Anal.* Calcd for $C_{11}H_{16}N_4O_2S$: C, 49.23; H, 6.01; N, 20.88. Found: C, 49.31; H, 5.99; N, 20.92. Ir: νmax 3420, 3240, 3060, 2200, 1675, 1600, 1480, 1340 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): δ 1.56, 3.40 (m, 10H piperidinyl), 2.38 (s, 3H, $SCH_3$), 6.56 (s, 1H, H-4), 7.92, 8.21 (br s, 2H, $NH_2$).

(**3c**) (56% yield); mp 185 - 186 °C (from acetonitrile). *Anal.* Calcd for $C_{11}H_{17}N_5O_2S$: C, 46.62; H, 6.05; N, 24.72. Found: C, 46.70; H, 6.03; N, 24.68. Ir: νmax 3430, 3340, 3240, 3120, 2160, 1650, 1570, 1540, 1520, 1290 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): δ 2.14 (s, 3H, $CH_3$), 2.33 (s, 3H, $SCH_3$), 2.37, 3.39 (m, 8H piperazinyl), 6.55 (s, 1H, H-4), 8.02, 8.34 (br s, 2H, $NH_2$).

(**3d**) (51% yield); mp 179 - 180 °C (from acetonitrile). *Anal.* Calcd for $C_{16}H_{19}N_5O_2S$: C,

55.63; H, 5.54; N, 20.28. Found: C, 55.58; H, 5.56; N, 20.25. Ir: νmax 3280, 3060, 2190, 1665, 1585, 1495, 1305 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): δ 2.40 (s, 3H, $SCH_3$), 3.22, 3.59 (m, 8H piperazinyl), 6.59 (s, 1H, H-4), 6.77, 6.93, 7.20 (m, 5H arom), 8.15, 8.43 (br s, 2H, $NH_2$).

(**3e**) (51% yield); mp 180 - 181 °C (from acetonitrile). *Anal.* Calcd for $C_{13}H_{19}N_5O_4S$: C, 45.73; H, 5.61; N, 20.52. Found: C, 45.80; H, 5.59; N, 20.49. Ir: νmax 3310, 3140, 2180, 1690, 1670, 1575, 1480, 1340 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): δ 1.15 (t, J=7.1 Hz, 3H, $CH_3$), 2.39 (s, 3H, $SCH_3$), 3.45 (m, 8H piperazinyl), 4.03 (q, J=7.1 Hz, 2H, $CH_2$),6.59 (s, 1H, H-4), 8.12, 8.45 (br s, 2H, $NH_2$).

**2-Dialkylamino-4-methylthio-5-nitro-3-pyridinecarbonitriles (4);**

**General Procedure:**

A catalytic amount of *p*-TsOH was added to a suspension of **3a-d** (25 mmol) in $HC(OMe)_3$ (5 ml). The mixture was heated for 30 min at 100 °C and then stirred at room temperature overnight. The mixture was dissolved in $CHCl_3$ (40 ml) and washed with $H_2O$ (2 x 10 ml), dried ($Na_2SO_4$) and evaporated at reduced pressure. The residue was purified as shown in Table 1 to give pyridines (**4**). In the case of **3e** the reaction was performed without the catalyst.

**2-Dialkylamino-6-methyl-4-methylthio-5-nitro-3-pyridinecarbonitriles(5); General Procedure:**

$Ac_2O$ (2 ml, 20 mmol) was added to a solution of **3a-e** (10 mmol) in pyridine (0.5 ml) and the resulting solution was stirred for 3 h at room temperature. The mixture was diluted with

ice – $H_2O$ and the formed precipitate filtered off, dried and repeatedly recrystallized from a suitable solvent to give pyridines (**5**) (Table 1).

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