SIMPLE SYNTHESIS OF POLYFUNCTIONAL NITRO-PYRIDINES

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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

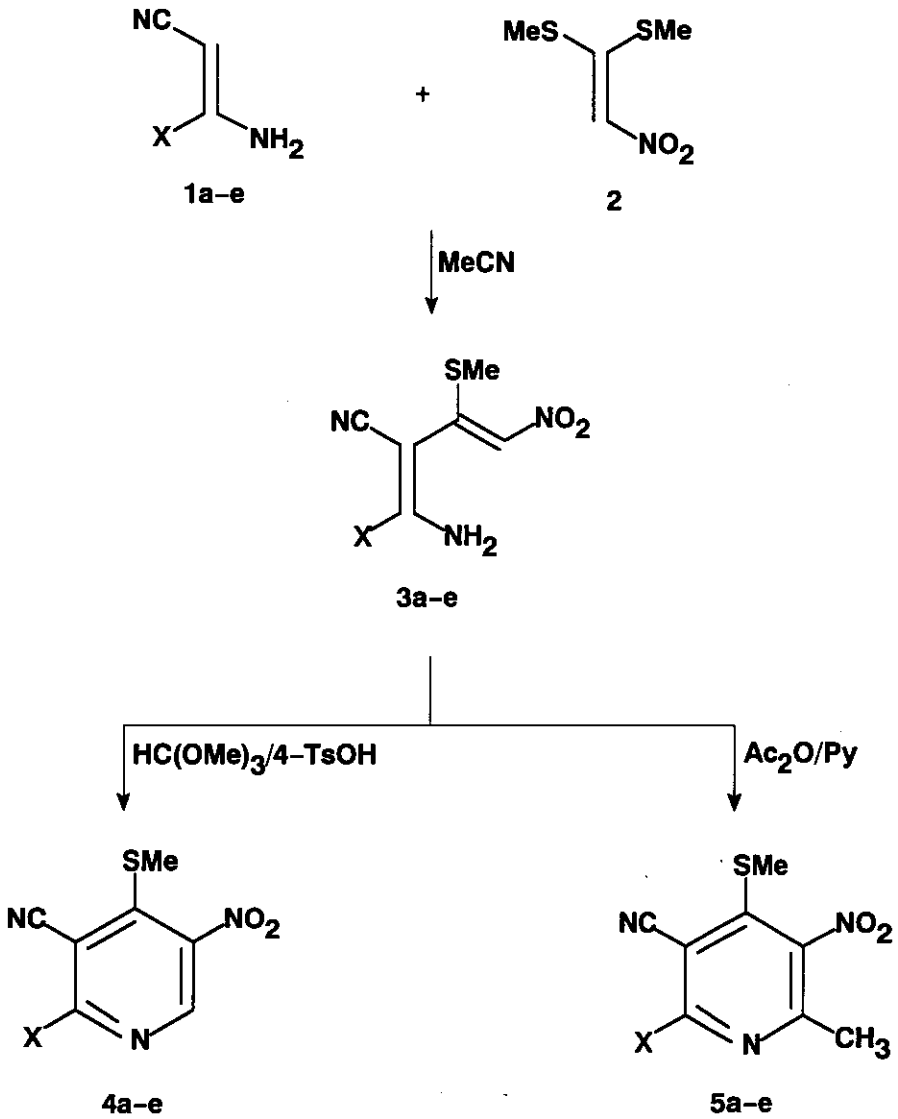
few examples of the nitroketene dithioacetal reaction with enamines[4,5] have been reported. In the last few years we have been involved in a program aiming at developing new efficient procedures for the synthesis of polyfunctionally substituted heterocycles utilizing simple laboratory enaminonitriles 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 ($CDCl_3$) δ (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 δ 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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