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Structurally dependent behavior of the nitromethyl group of aliphatic γ-nitrothioamides under nitrile oxide generation reaction conditions

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Abstract—Treatment of (3-allyl)-4-nitromethylthiolactams with phenyl isocyanate and triethylamine has been found to lead to (3-allyl)-4-isothiocyanatolactams. In the case of 3-unsubstituted 4-nitromethylthiolactams, the retro-Michael addition reaction of the nitromethyl group, affording α,β-unsaturated thiolactams and 4-nitromethyllactams, is also observed. Under the same reaction conditions acyclic (α-allyl)-γ-nitrothioamides have been unexpectedly found to lead to α,β-unsaturated nitriles. Mechanisms for these reactions are proposed.

A combination of nitro and thiocarbamoyl groups in the form of aliphatic nitrothioamides gives access to new synthons due to the versatile reactivity of nitro and thioamide groups. To the best of our knowledge, aliphatic nitrothioamides have not been extensively explored in the literature. So far only a few synthetic approaches to α-nitrothioamides[1] and one paper on their application in the synthesis of thiophene[2] have been published. Regarding the synthesis and the reactivity of aliphatic nitrothioamides, we have previously reported the syntheses of γ-nitrothioamides and 4-nitromethylthiolactams, which have been subsequently applied to the synthesis of chiral pyrrolidin-2-ylidene carboxylates.[3]

In this paper we report preliminary results of the investigation of the behavior of (3-allyl)-4-nitromethylthiolactams and (α-allyl)-γ-nitrothioamides upon treatment with phenyl isocyanate in the presence of triethylamine.

It is well known that aromatic isocyanates in the presence of the triethylamine are used as mild dehydrating agents to generate 1,3-dipoles—nitrile oxides from the nitromethyl moieties, the Mukaiyama method.[4] Moreover, thiocarbonyl as well as alkene groups are recognized as being good dipolarophiles, which in the reaction with nitrile oxides lead to [2+3] cycloadducts; 1,4,2-oxathiazoline derivatives[5,6] formed from the $-C^{+}=N-O^{-}$ and C=S moieties in an intermolecular manner; isoxazoline derivatives[6,7] formed by addition of $-C^{+}=N-O^{-}$ to C=C bonds in an inter- and intramolecular manner, also in the presence of thiocarbonyl groups.[8] It is also described that the 1,4,2-oxathiazoline ring is often unstable and, even at low temperatures, decomposes to form isothiocyanates.[9] In this context we could expect that the use of γ-nitrothioamides in the nitrile oxide generation reaction (PhNCO, Et_3N) could lead to 1,4,2-oxathiazoline, isoxazoline (allylic derivatives) or to isothiocyanates. In our investigation, 4-nitromethylthiolactams **1**–**3**, in the presence of phenyl isocyanate and triethylamine in benzene, afforded the corresponding 4-isothiocyanatolactams **1a**–**3a** in low to moderate yields (Scheme 1). Surprisingly, apart from lactams **1**, **2**, α,β-unsaturated thiolactams **1b**, **2b** and 4-nitromethyllactams **1c**, **2c** were isolated. Again unexpectedly, under the same reactions conditions, the acyclic (α-allyl)-γ-nitrothioamides (**4**, **5**), provided α,β-unsaturated nitriles, in good yields (Scheme 2). Neither oxathiazoline nor isoxazoline derivatives, typical [2+3] cycloadducts, were detected in the crude reaction mixtures.[10]

The characteristic absorption bands found in the IR spectra supported the presence of the isothiocyanato group together with amido groups in **1a**–**3a** and cyano groups in **6**, **7**. The configuration of **2a** and **3a** was determined on the basis of $^{1}H,^{1}H$ COSY, $^{1}H,^{1}H$ NOESY $^{13}C,^{1}H$ COSY and conformational analysis

Keywords: nitrothioamides; thiolactams; 4-isothiocyanatolactams; 1,3-dipolar cycloaddition; nitrile oxides.

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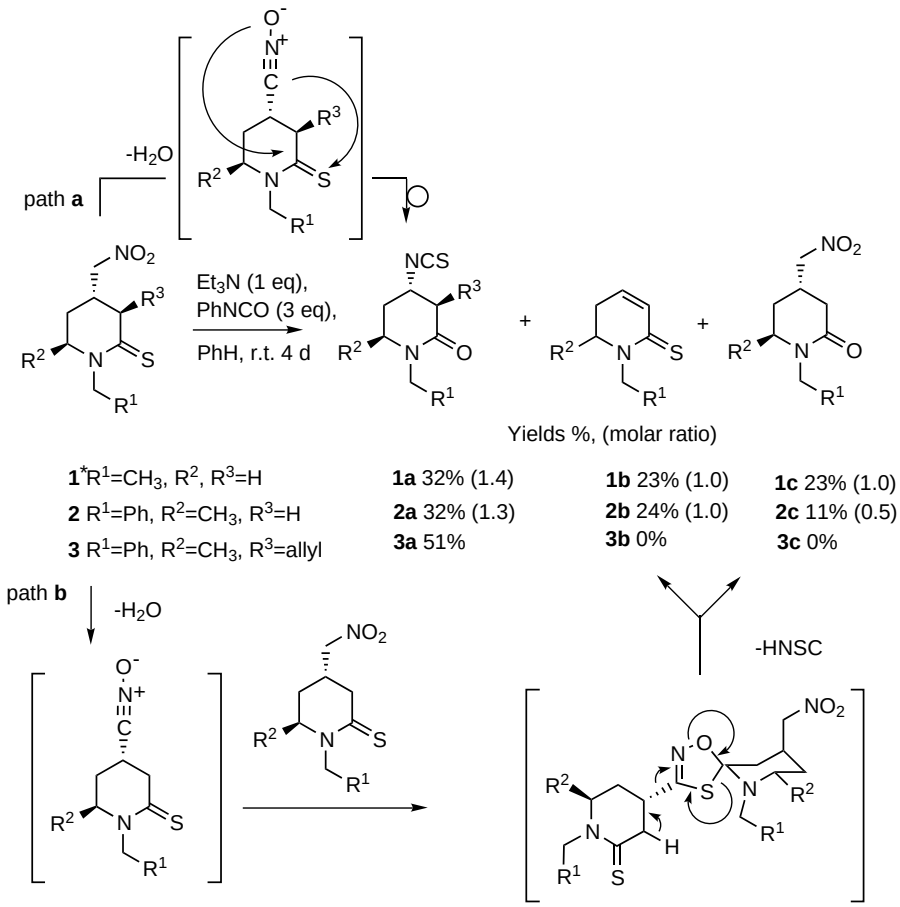
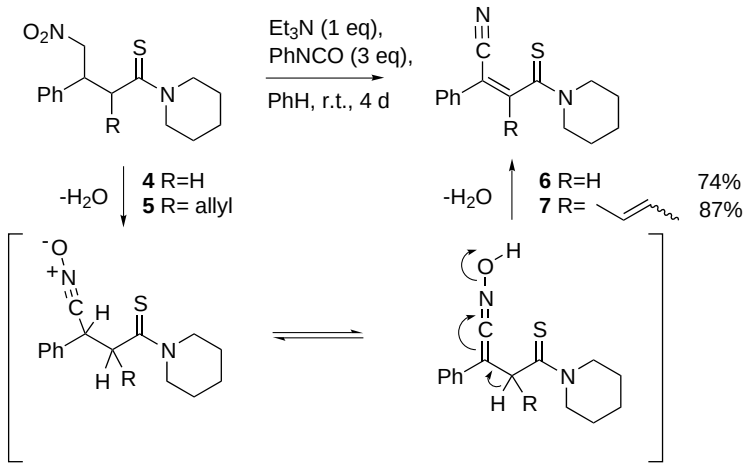


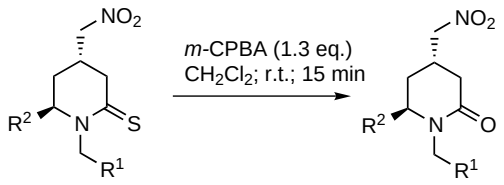
Scheme 1. *Rt, 8 days, after 4 days an additional portion of reagents was added; substrate was recovered.



Scheme 2.

using coupling constants. The structures of compounds **1b** and **2b** were identified by comparison of their spectroscopic data with those obtained for the reference samples,[11,12] whereas the structures of compounds **1c** and **2c** were supported by independent synthesis consisting of treatment of thiolactams **1**, **2** with *m*-CPBA in CH_2Cl_2 (Scheme 3). Compound **6** was obtained as a single isomer while in the case of **7** the NMR analysis showed partial (50%) isomerisation of the allylic double bond to the β,γ-position. For both compounds, the *Z* geometry around C2–C3 was determined by $^1H,^1H$ NOESY spectra.

These interesting results are not very well understood yet and a further study on their mechanistic aspects is under way. On the basis of the above results, especially



Scheme 3.

the structures and the ratios of isolated products,[13] we can conclude that the formation of 4-isothiocyanatolactams **1a**–**3a** can be interpreted as the result of an intramolecular reaction of the nitrile oxide moiety with the C=S bond leading to a 1,4,2-oxathiazoline ring, which subsequently undergoes rearrangement (Scheme 1, path a). Since isothiocyanates have been prepared recently from thiourea and primary nitrile oxides, generated from nitroalkanes,[9c] formation of 4-isothiocyanatolactams **1a**–**3a** could be regarded as a new, intramolecular version of this reaction. It is noteworthy to point out that the transfer of the sulfur atom from the thiocarbonyl to the isothiocyanate group took place with retention of substituent positions in the piperidinone rings. Almost equimolar ratios of α,β-unsaturated thiolactams and 4-nitromethyllactams (**1b**:**1c** = 1:1; **2b**:**2c** = 1:0.5, Scheme 1, path b) suggest that these compounds are formed in an intermolecular manner. The lower amount of **2c** could be the effect of subsequent dehydration of this compound. The formation of the retro-Michael products **1b**, **2b**, formed by C–C bond cleavage, should be emphasized. Although the elimination of nitrous acid in the synthesis of α,β-unsaturated carbonyl compounds is known from the literature, e.g.[14] to the best of our knowledge the formation of compounds **1b**, **2b** from **1**, **2**, respectively, is the first example of an elimination of the nitromethyl group.

In comparison with the thiolactams **1**–**3**, open chain nitrothioamides **4**, **5** are more dehydrated. They afforded derivatives **6**, **7** by elimination of two molecules of water. A probable mechanism would involve formation of a nitrile oxide, proton shift from the benzyl position to the oxygen atom and subsequent dehydration (Scheme 2). Participation of the second molecule of isocyanate in the elimination of the second molecule of water could not be excluded.

Compounds **1**, **2** and **4** were synthesized according to the procedure described earlier.[3,12] The α-allylated substrates **3** and **5** were obtained via a [3,3] sigmatropic thia-Claisen rearrangement.[15] All compounds (except **2**[3] and **2b**[11]) are new. Their composition has been confirmed by spectroscopic data and elemental analyses.

The general procedure for dehydration of the γ-nitrothioamides **1**–**5** was as follows. γ-Nitrothioamides (**1**–**5**) (1 mmol), 3 mmol of phenyl isocyanate and 1 mmol of triethylamine in anhydrous benzene was stirred at rt under an Ar atmosphere for 4–8 days. After removing diphenylurea by filtration and evaporation of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane:ethyl acetate = 7:3) to yield **6**, **7** and (*n*-hexane:ethyl acetate = 7:3 then 1:1, then 3:7) to give **1a**–**c**, **2a**–**c**, **3a**.

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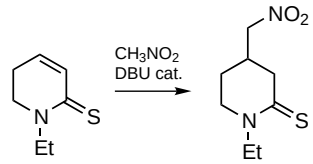
10. Selected data (**3a**): Colorless oil. [Found: C, 67.87; H, 6.59; N, 9.22; S, 10.49. $C_{17}H_{20}N_2OS$ requires C, 67.97; H, 6.71; N, 9.32; S, 10.67%]; ν_{max} (KBr pellet) 2080, 1644, 1448, 756, 700 cm^{-1}; δ_H (400.1 MHz $CDCl_3$) 1.21 (3H, d, J = 6.6 Hz, CH_3), 2.02–2.08 (2H, m, CH_2-5), 2.51–2.60 (1H, m, C<u>H</u>H), 2.71 (1H, ddd, J = 8.6, 6.0, 4.2 Hz,

H-3ax), 2.83–2.96 (1H, m, CHH), 3.49–3.59 (1H, m, H-6eq), 3.98 (1H, d, $J=15.0$ Hz, CHHPh), 4.15 (1H, td, $J=8.7$, 5.9 Hz, H-4ax), 5.15–5.23 (2H, m, $=CH_2$), 5.30 (1H, d, $J=15.0$ Hz, CHHPh), 5.68–5.79 (1H, =CH), 7.21 (2H, $J=7.1$ Hz, C_6H_5), 7.26–7.35 (3H, m, C_6H_5); δ_C (100.6 MHz $CDCl_3$) 19.98 (q, CH_3), 33.58 (t, CH_2), 35.30 (t, CH_2-5), 47.71 (t, CH_2-Ph), 48.18 (d, CH-3), 48.48 (d, CH-6), 51.28 (d, CH-4), 119.2 (d, $=CH_2$), 127.6, 127.79, 129.07, 136.94 (C_6H_5), 133.84 (d, =CH), 168.36 (s, C=O);* m/z (EI, 70 eV) 300 (51, M^+), 242 (40), 200 (11), 106 (14), 91 (100), 65 (11%). (**6**): Yellow oil. [Found: C, 70.35; H, 6.22; N, 11.03; S, 12.49. $C_{15}H_{16}N_2S$ requires C, 70.27; H, 6.29; N, 10.93; S, 12.51%]; ν_{max} (KBr pellet) 2948, 2216, 1512, 1446, 1252, 1132, 1016, 764, 688 cm^{-1}; δ_H (400.1 MHz $CDCl_3$) 1.73–1.80 (6H, m, $3CH_2$), 3.82 (2H, br s, CH_2N), 4.27–4.30 (2H, m, CH_2N), 7.28 (1H, br s, H-2), 7.38–7.45 (3H, m, C_6H_5), 7.60–7.62 (2H, m, C_6H_5); δ_C (100.6 MHz $CDCl_3$) 24.08, 25.11, 26.65 (each t, $3CH_2$), 49.52, 52.97 (each t, $2CH_2N$), 112.09, 115.57 (each s, C-3, CN), 125.98, 128.00, 128.33, 131.70 (C_6H_5), 138.06 (d, C-2), 189.97 (s, C=S); m/z (EI, 70 eV) 256 (100, M^+), 223 (23), 179 (13), 172 (22), 146 (26), 140 (24), 128 (14), 84 (51%).

*Note: The NCS signal is not observed in a routine ^{13}C NMR spectrum, recorded with short relaxation time (1 s). When a longer relaxation time (5 s) is applied this signal appears as a broad singlet at 134.0 ppm.

11. (**2b**): Sośnicki, J. G.; Jagodziński, T. S.; Liebscher, J. *J. Heterocycl. Chem.* **1997**, *34*, 643–648.
12. Compound **1** was obtained according to the procedure described earlier.[3]



1b **1**

13. Due to the overlapping of the ^1H NMR signals, the accurate determination of the ratio of the products of the crude reaction mixture was not possible.
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