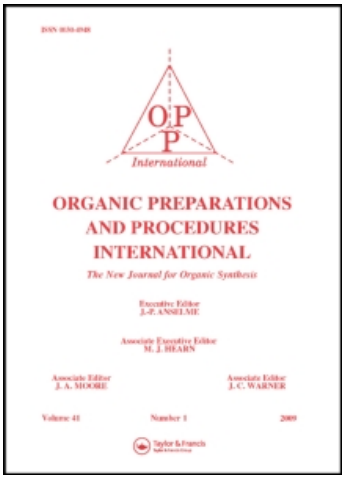

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PREPARATION OF 3-BROMO-2-(NITROMETHYLENE)PYRROLIDINE AND 3-BROMO-*N*-METHYL-l-NITRO-l-BUTEN-2-AMINE

J. Geno Samaritoni[a]
[a] Discovery Research, Dow AgroSciences LLC, Indianapolis, IN

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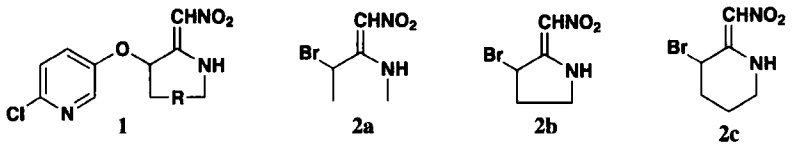
PREPARATION OF 3-BROMO-2-(NITROMETHYLENE)PYRROLIDINE AND 3-BROMO-*N*-METHYL-1-NITRO-1-BUTEN-2-AMINE

Submitted by J. Geno Samaritoni
(03/16/04)

Discovery Research, Dow AgroSciences LLC
9330 Zionsville Road, Indianapolis, IN 46268

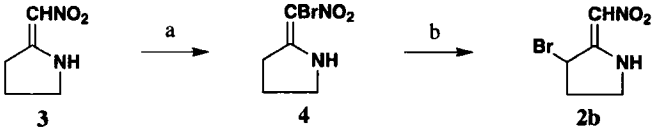
Since its discovery in the early 1970s, the nitromethylene class of insect control agents has received considerable attention within the agrochemical industry.[1] Recently we had occasion to investigate a series of compounds (**1**)[2] featuring the nitromethylene group in three slightly varied environments (*Fig. 1*). Our approach required the syntheses of the allylic bromides **2a-c**. Since the preparation of **2c** is described in the literature,[3] the same strategy was applied to the



R = no bond or atom **1a**
single bond **1b**
CH_2 **1c**

Fig. 1

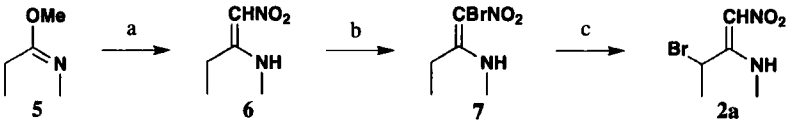
synthesis of **2b** from nitromethylenepyrrolidine **3**[4,5] (*Eq. 1*). Electrophilic bromination of **3** using *N*-bromosuccinimide (NBS)[6] gave the vinyl bromide **4**,[7] which, upon reflux in carbon tetrachloride, did not rearrange as expected to the required allylic bromide **2b**. Surprisingly, this rearrangement required a much higher temperature as **2b** was formed in boiling xylenes over a seven-hour period in moderate yield (55%).



(1)

a) NBS/CCl_4 (82%), b) refluxing xylenes (55%)

Rearrangement conditions also needed to be significantly modified to prepare the acyclic allylic bromide **2a**. The methyl imidate **5**[5] was condensed with nitromethane to give the nitrobutenamine **6** in low yield (*Eq. 2*). Treatment of **6** with NBS then gave the vinyl bromide **7** whose stability is questionable as, in one instance, a crude sample underwent a violent decomposition (see Experimental Section). Heating **7** in boiling carbon tetrachloride, however, lead to the



(2)

a) refluxing CH_3NO_2 (38%), b) NBS/CCl_4 (35%), c) 50°/CCl_4 (44%)

isolation of an intractable tar. Lower temperatures were investigated and it was found that the desired rearrangement took place at 42°C along with the formation of unwanted products which increased with reaction time. Fortunately it was possible to obtain highly pure **2a** as a precipitate from the cooled (10°C) reaction mixture after 20-25 minutes at 48-52°C.

In summary it has been shown that the key rearrangement of the vinyl bromides to the allylic bromides requires dramatically different thermal conditions even though the substrates are structurally similar. This discovery has allowed the previously undescribed preparations of allylic bromides **2a** and **2b** to be documented.

EXPERIMENTAL SECTION

Melting points are uncorrected. All reagents were purchased from Aldrich Chemical Company and were used without further purification. Solvents were dried using 3Å molecular sieves.

Chromatography was performed using 230-400 mesh ASTM silica gel 60 from EM Science, Darmstadt, Germany. Proton NMR spectra were obtained on a Varian Gemini 300 spectrometer using deuteriochloroform as solvent unless otherwise indicated and are reported in parts per million (δ) downfield from tetramethylsilane as internal reference. Infrared spectra were obtained on a Bio-Rad spectrophotometer using potassium bromide pellets or as neat oils and are reported in wavenumbers (cm^{-1}). Mass spectra were obtained on a Hewlett-Packard Model 5989A mass spectrometer using the electron impact-direct insertion probe (EI-DIP), or chemical ionization (CI) and are reported as *m/z*. Microanalyses were performed by Midwest Microlab of Indianapolis, Indiana.

2-[Bromo(nitro)methylene]pyrrolidine (4).- To a vigorously stirred mixture of 328 mg (2.56 mmol) of **3**[4] in 15 mL of carbon tetrachloride at room temperature was added in one portion 478 mg (2.68 mmol) of *N*-bromosuccinimide. The mixture was stirred overnight and was then filtered to remove most of the formed succinimide. The filtrate was concentrated to a residue which was chromatographed on silica gel using dichloromethane as eluant to afford 420 mg (79%) of **4** as a light yellow solid, mp 143-145°C (dec.) (*lit.*[4] 158-159°C [ethanol]); ^{1}H NMR: δ 2.22 (m, 2 H), 3.01 (m, 2 H), 3.90 (m, 2 H), 9.59 (br s, 1 H); IR (KBr) 1197, 1303, 1350, 1398, 1596, 3290; MS (EI-DIP) 208 ([M+2]$^+$, 59), 206 (M$^+$, 59), 132 (100).

Anal. Calcd. for $C_5H_7BrN_2O_2$: C, 29.00; H, 3.40; N, 13.53. Found: C, 29.26; H, 3.42; N, 13.37

3-Bromo-2-(nitromethylene)pyrrolidine (2b).- To 130 mL of refluxing xylenes was added in portions over a 5-10 minute period 2.0 g (9.7 mmol) of **4**. Reflux was continued for 8 h and the black mixture was allowed to cool. Volatiles were removed *in vacuo* and the residue was placed on a column of silica gel and eluted with dichloromethane followed by 96/4 dichloromethane/ethyl acetate to afford 1.10 g (55%) of **2b**, mp 140-143°C (dec.); ^{1}H NMR: δ 2.45 (m, 1 H), 2.61 (m, 1 H), 3.75 (m, 1 H), 3.87 (m, 1 H), 4.83 (dd, 1 H, J = 6.6 Hz and J = 2.1 Hz), 6.79 (s, 1 H); MS (EI-DIP) 208 ([M+2]$^+$, 80), 206 (M$^+$, 81), 160 (100).

Anal. Calcd. for $C_5H_7BrN_2O_2$: C, 29.00; H, 3.40; N, 13.53. Found: C, 29.34; H, 3.42; N, 13.22

***N*-Methyl-1-nitro-1-buten-2-amine (6).**- A solution of 1.97 g (19.5 mmol) of the imidate **5**[5] and 2.38 g of nitromethane was heated at 95°C for 17 h and was concentrated *in vacuo* giving a residue which was chromatographed on silica gel using ethyl acetate as the eluant to afford 885 mg (35%) of **6** as a light yellow solid, mp 50-53°C; ^{1}H NMR: δ 1.21 (t, 3 H, J = 7.7 Hz), 2.32 (q, 2 H, J = 7.6 Hz), 3.11 (d, 3 H, J = 5.6 Hz), 6.60 (s, 1 H), 10.2 (br s, 1 H); IR (KBr) 1218, 1330, 1360, 1377, 1616, 3167, 3223; MS (CI) 131 ([M+H]$^+$, 100).

Anal. Calcd. for $C_5H_{10}N_2O_2$: C, 46.14; H, 7.75; N, 21.53. Found: C, 46.27; H, 7.61; N, 21.26

1-Bromo-*N*-methyl-1-nitro-1-buten-2-amine (7).- To a mixture of 1.76 g (13.5 mmol) of **6** in 85 mL of carbon tetrachloride was added in portions 2.59 g (14.6 mmol) of *N*-bromosuccinimide over a 5 min period. The contents were stirred at room temperature for 18h and were filtered to remove succinimide and the filtrate was concentrated to give 2.6 g of a yellow solid consisting of **7** as the major component as evidenced by proton nmr. Chromatography of this mixture on silica gel using dichloromethane as the eluant afforded 1.0 g (35%) of **7**, mp 79-81°C;

^{1}H NMR 1.26 (t, 3 H, J = 7.6 Hz), 2.78 (q, 2 H, J = 7.6 Hz), 3.22 (d, 3 H, J = 5.5 Hz); MS (EI-DIP) 210 ([M+2]$^+$, 98), 208 (M$^+$, 100).

Anal. Calcd. for $C_5H_9BrN_2O_2$: C, 28.72; H, 4.34; N, 13.40. Found: C, 28.79; H, 4.27; N, 13.24

CAUTION: Following the preparation of a 20 g batch of compound 7, the crude material was stored in a glass round-bottomed flask at room temperature. Sometime during the next 60 h, a violent decomposition occurred and resulted in a black sooty material being deposited on the ceiling and benchtop of the hood. The flask remained unbroken. No effort was made to identify the black material and no studies were initiated to establish the thermal profile of 7. Previously, smaller batches of 7 (10 g or less) were prepared under identical conditions; however, no such violent incident had occurred with those lots.

3-Bromo-*N*-methyl-1-nitro-1-buten-2-amine (2a).- To vigorously stirred carbon tetra-chloride (200 mL) at 48-52°C was added in portions over a 2-3 minute period 3.07 g (14.7 mmol) of **7**. The contents were stirred for 25 minutes and were then cooled to 10°C. The precipitate was collected affording 1.35 g (44%) of **2a**, mp 84-87°C (dec.); ^{1}H NMR: δ 1.90 (d, 3 H, J = 7.0 Hz), 3.18 (d, 3 H, J = 5.5 Hz), 4.68 (q, 1 H, J = 7.0 Hz), 6.82 (s, 1 H), 10.1 (br s, 1 H); MS (EI-DIP) 210 ([M+2]$^+$, 31), 208 (M$^+$, 32), 101 (100).

Anal. Calcd. for $C_5H_9BrN_2O_2$: C, 28.72; H, 4.34; N, 13.40. Found: C, 28.06; H, 4.67; N, 13.35

This compound was found to have a very limited shelf-life at room temperature and its instability has resulted in the erroneous analytical data reported above. However, when stored at 0°C the material retained its properties as a workable solid and was successfully used in subsequent alkylations performed weeks later.

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6. *N*-Bromosuccinimide was substituted for molecular bromine which was used in the reported synthesis of **2c** (see ref. 3).

7. In contrast the *N*-methyl analog of **3** undergoes electrophilic bromination at the allylic position when using *N*-bromosuccinimide (see ref. 4).

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A FACILE ONE-POT PREPARATION OF ISOTHIOCYANATES FROM *N*-FORMAMIDES AND SULFUR POWDER WITH *bis*(TRICHLOROMETHYL) CARBONATE

Submitted by W. G. Shan, G. F. Bian, W. K. Su* and X. R. Liang
(04/16/04)

College of Pharmaceutical Sciences
Zhejiang University of Technology
Hangzhou, 310014, P. R. CHINA

Isothiocyanates are one of the most important synthetic intermediates for the preparation of both sulfur and nitrogen containing organic compounds and especially heterocycles.[1] The synthesis of isothiocyanates has been extensively studied over the past decades, because they play an important role as anti-proliferatives[2] and in the therapy of blood cancer, as enzyme inhibitors for the HIV virus.[3] Numerous methods for the synthesis of isothiocyanates have been reported from amines,[4] organic halides,[5] olefins,[6] and aldoximes.[7] Most of them suffer from low yields and the use of environmentally unattractive reagents such as thiophosgene and its derivatives.[4,8] The direct conversion from isocyanides with elemental sulfur have been reported previously.[9] However, it is difficult to prepare and purify isocyanides because almost all of them are volatile and have a repulsive odor.[10]

Herein, we report a facile one-pot method for the preparation of isothiocyanates from formamides and sulfur powder, which use the environmentally friendly reagent *bis*(trichloromethyl) carbonate (BTC) in the presence of selenium powder and triethylamine (*Scheme 1*). The intermediate isocyanide is not isolated from reaction because it reacts with