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Nucleophilic Behaviour of DBU and DBN in Reactions with 4-Halo-3,5-dimethyl-1-nitro-1H-pyrazoles[1]

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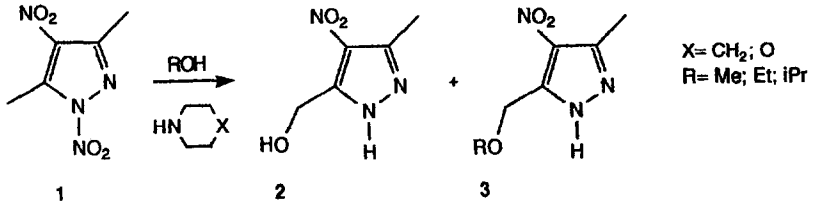
Abstract: Addition of 3 equivalents of DBU or DBN to a solution of 4-halo-3,5-dimethyl-1-nitro-1H-pyrazole (**5a-c**) in acetonitrile affords the unexpected products **6a-c** and **7a-c** in fair to good yields. A reaction mechanism is proposed involving an elimination of HNO_2 giving a diazafulvene intermediate **8** followed by the addition of a second molecule of DBU or DBN to **8**.

INTRODUCTION

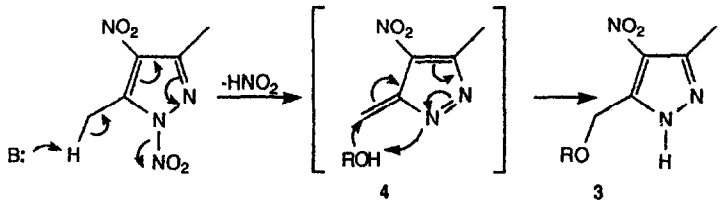
The efficiency of the bicyclic amidines DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) as non-nucleophilic strong bases in organic and inorganic chemistry has been widely demonstrated.[3] Especially their use as dehydrohalogenation reagents has been of great importance.[3,4] However, recently Reed *et al.*[5] described the remarkable strong nucleophilic behaviour of DBU and DBN in reaction with halogenated compounds of main group elements. Their results elucidate earlier observed and unexplained behaviour of DBU and DBN in several dehydrohalogenation reactions.[6-8] In this contribution we report the remarkable nucleophilic behaviour of DBU and DBN in another base-induced reaction.



1 2 3

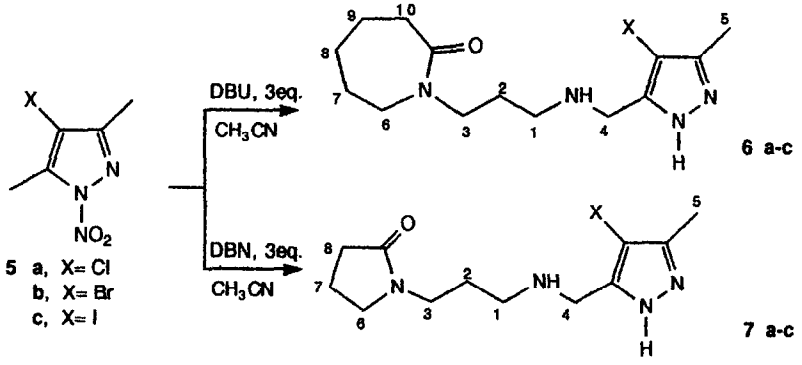
Scheme 1

In 1977 Habraken and Bonser[9] reported the reaction of 3,5-dimethyl-1,4-dinitro-1H-pyrazole (**1**) with secondary amines in alcoholic solution affording 3-hydroxymethyl-5-methyl-4-nitro-1H-pyrazole (**2**) and 3-alkoxymethyl-5-methyl-4-nitro-1H-pyrazoles (**3**) (Scheme 1). This functionalization of the 5-methyl group was assumed to proceed by an elimination-addition reaction involving the diazafulvene **4** as an intermediate (Scheme 2).



Scheme 2

To elaborate this functionalization for further synthetic means, the reaction of 4-halo-3,5-dimethyl-1-nitro-1H-pyrazoles (**5a-c**) was studied.[10] The lower electronegativity of the halo atoms, now in position 4, prompted us to use stronger bases such as DBU and DBN for the elimination of HNO_2. Surprisingly, **6a-c** and **7a-c** obtained ultimately, are derivatives of adducts of a diazafulvene and DBU and DBN (Scheme 3). We present a reaction mechanism for the formation of these unexpected compounds.



Scheme 3

RESULTS AND DISCUSSION

The reaction was initially carried out in EtOH, however higher yields of **6a-c** and **7a-c** were obtained in acetonitrile solution using 3 eq. of base. The yields are summarized in Table 1.

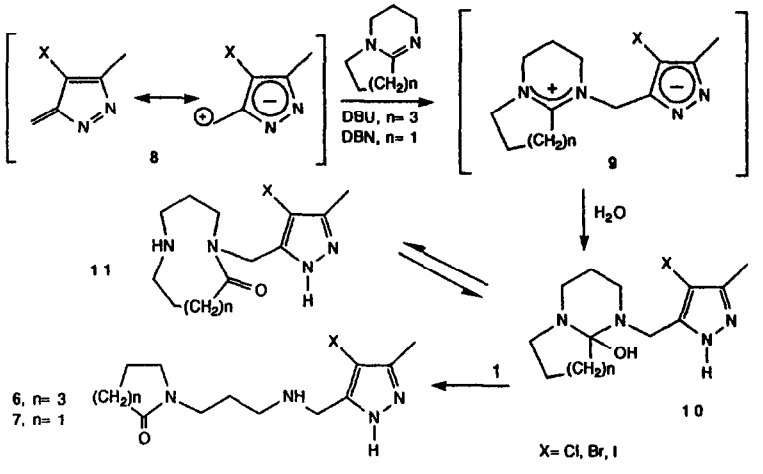
Structure assignments were carried out, mainly by IR, ^1H NMR, and MS. From the values of the amide C=O stretch vibrations of the products it can be concluded that we are dealing with γ-lactam (1650 cm^{-1}) and ε-lactam (1610 cm^{-1}) derivatives.[11]

A detailed ^1H NMR and MS study of the compounds **6b** and **7b** has been carried out. The numbering as depicted in Scheme 3 was followed. In the ^1H NMR spectra the methylene protons of the propylene unit ($A_2M_2X_2$ spin system) could be distinguished from the methylene protons of the ring. Due to the lower flexiblity of the ring protons second order effects in these spin systems are observed. Especially in **6b** the methylene protons of the ε-lactam gave unresolved multiplets. In the proton spectrum of **7b** the discrimination is less obvious but can be deduced from the incorrect peak intensities of the observed $A_2M_2X_2$ spin system corresponding to the methylene protons of the γ-lactam. The protons of the methylene group attached to the pyrazole ring are shifted downfield (δ = 3.6-3.9 ppm) due to the N-functionalization.

Table 1. Highest Yields of **6a-c** and **7a-c** (Scheme 3) obtained from the Reaction of **5** and 3 eq. DBU or DBN in Acetonitrile.

Compound	Yield (%)
6a	51
6b	74
6c	54
7a	21
7b	32
7c	34

The four bond-breakings in the acyclic part of the obtained lactams are observed in the fragmentation pattern of the MS spectra of the obtained products. For example in the MS spectrum of **6b** the bond-breaking between C4 and nitrogen gave three signals at 173, 175, and 169 m/z. Bond-breaking between C1 and nitrogen gave three signals at 188, 190 and 154 m/z. Bond-breaking between C1 and C2 gave three signals at 202, 204, and 140 m/z and bond-breaking between C2 and C3 gave three signals at 216, 218, and 126 m/z.



Scheme 4

In Scheme 4 a mechanism proposed for the formation of **6** and **7** is depicted. The first step is a HNO_2 elimination by DBU or DBN giving diazafulvene[12,13] **8** as proposed by Habraken and Bonser.[9] Presumably the electrophilicity of the exocyclic methylene of **8** is even more pronounced than in carbocyclic fulvenes. Consequently, **8** can react with the imine N-atom of a second molecule of DBU or DBN affording the intermediate **9** which is then trapped by a molecule of H_2O present in the reaction

mixture giving **10**. Being a tertiary amino alcohol, **10** may be in equilibrium with either **11** or **6/7**. Similar equilibria have been described extensively by Deslongchamps *et al.*[14] for the basic hydrolysis of bicyclic imidates. Clearly, in the present case, γ- and ϵ- lactams **6** and **7** being the ultimate products, are the thermodynamically stable compounds.

CONCLUSION

The addition of 3 eq. DBU or DBN to a solution of 4-halo-3,5-dimethyl-1-nitro-1H-pyrazole (**5**) in acetonitrile gave the unexpected products **6** and **7** in fair to good yields. The compounds **6** and **7** are formed by *nucleophilic* attack of a second molecule of DBU or DBN on an electrophilic diazafulvene **8** formed by HNO_2 elimination from the 4-halo-3,5-dimethyl-1-nitro-1H-pyrazoles **5** by DBU or DBN. Therefore DBU and DBN, under the proper conditions, do react both as nucleophiles as well as strong bases.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a JEOL FX 200 FT NMR spectrometer and Bruker WM 300 and 400 MHz (TMS as internal reference). IR spectra (KBr pellets or neat) were obtained on a Pye Unicam SP3-200 spectrometer. Mass spectra were obtained using a ITD ion-trap detetector (GC-MS), HP-5985A (MS) and a TSQ (LC-MS) specrometer with EI ionization, electron beam energy 70eV, source temperature 423 K. The compounds were purified by short column chromatography on silica H (Merck 7736, $CHCl_3$/MeOH 1/1) according to Stahl as described by Hunt and Rigby[15]. Spraying with a Rhodamine B solution (0.05% in EtOH) was used for detection of nitropyrazoles. The purple coloured spots characteristic for all nitropyrazoles turned yellow on standing in the case of N-nitropyrazoles. TLC plates were used from Schleicher & Schuell F11500/ LS 254. All solvents used for column chromatography and reactions were purified according to standard procedures. Compounds **5a-c** were synthesized as described earlier.[16-18]

To a solution of 0.5 g 4-halo-3,5-dimethyl-1-nitro-1H-pyrazole (**5a-c**) in 2 ml CH_3CN, 3 eq. of DBU or DBN (obtained from Janssen Chimica) were slowly added at room temperature. The reaction was monitored by TLC. When the reaction was finished CH_3CN was evaporated, and the resulting oil was purified by column chromatography. All products were obtained as oils. The yields of isolated pure **6** and **7** are reported in Table 1. Physical data follow:

1-[3-[(4-Chloro-3-methyl-1H-pyrazol-5-yl)methylamino]propyl]azepan-2-one (**6a**). Yellow oil ^{1}H NMR (CD_3OD, 200 MHz): δ (ppm) 1.72 (m, 8H, H2, H7, H8, H9); 2.20 (s, 3H, H5); 2.52 (m, 2H, H10); 2.84 (t, 2H, H1); 3.40 (m, 4H, H3, H6); 3.96 (s, 2H, H4). IR ν_{max} (KBr) 1610 cm^{-1}. MS m/z: 300, 298 (M^+); 263 (M^+ - Cl); 169; 154; 126; 56 (100%). HR-MS $C_{14}H_{23}{}^{35}ClN_4O$ (M^+): calcd 298.1560; obsd 298.1551
1-[3-[(4-Bromo-3-methyl-1H-pyrazol-5-yl)methylamino]propyl]azepan-2-one (**6b**). Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.58 (m, 4H, H8, H9); 1.69 (m, 2H, H7); 1.92 (q, 2H, H2); 2.26 (s, 3H, H5); 2.47 (m, 2H, H10); 2.83 (t, 2H, H1); 3.32 (m, 2H, H6); 3.44 (t, 2H, H3); 4.08 (s, 2H, H4). IR ν_{max} (KBr) 1610 cm^{-1}. MS m/z (%); 344, 342 (M^+, 25); 263 (M^+ - Br, 25); 218 (10); 216 (10); 126 (65); 204 (15); 202 (15); 140 (12); 190 (60); 188 (60; 154 (30); 175 (35); 173 (35); 169 (50); 56 (100). HR-MS $C_{14}H_{23}{}^{79}BrN_40$

(M^+): calcd 342.1055; obsd 342.1047

1-[3-[(4-Iodo-3-methyl-1H-pyrazol-5-yl)methylamino]propyl]azepan-2-one (**6c**). Yellow oil ^1H NMR (CD_3OD, 200 MHz): δ (ppm) 1.68 (m, 8H, H2, H7, H8, H9); 2.24 (s, 3H, H5); 2.52 (m, 2H, H10); 2.84 (t, 2H, H1); 3.48 (m, 4H, H3, H6); 3.96 (s, 2H, H4). IR ν_{max} (KBr) 1610 cm^{-1}. MS m/z: 390 (M^+); 263 (M^+ - I); 169; 154; 126; 56 (100%). HR-MS $C_{14}H_{23}IN_4O$ (M^+): calcd 390.0917; obsd 390.0921

1-[3-[(4-Chloro-3-methyl-1H-pyrazol-5-yl)methylamino]propyl]pyrrolidin-2-one (**7a**). Light brown oil ^1H NMR ($CDCl_3$, 200 MHz); δ (ppm) 1.84 (q, 2H, H2); 2.04 (q, 2H, H7); 2.24 (s, 3H, H5); 2.40 (t, 2H, H8); 2.76 (t, 2H, H1); 3.46 (m, 4H, H3, H6); 3.92 (s, 2H, H4). IR ν_{max} 1650 cm^{-1}. MS m/z: 272, 270 (M^+); 235 (M^+ - Cl); 144; 129; 112. HR-MS $C_{12}H_{19}{}^{35}ClN_4O$ (M+): calcd 270.1247; obsd 270.1239.

1-[3-[(4-Bromo-3-methyl-1H-pyrazol-5-yl)methylamino]propyl]pyrrolidin-2-one (**7b**). Light brown oil ^1H NMR ($CDCl_3/C_6D_6$, 400 MHz): δ (ppm) 1.57 (q, 2H, H2); 1.71 (q, 2H, H7); 2.20 (s, 3H, H5); 2.23 (t, 2H, H8); 2.44 (t, 2H, H1); 3.04 (t, 2H, H6); 3.21 (t, 2H, H3); 3.76 (s, 2H, H4). IR ν_{max} (KBr) 1650 cm^{-1}. MS m/z (%): 316, 314 (M^+, 5); 235 (M^+ - Br, 42); 218 (5); 216 (5); 204 (20); 202 (20); 112 (10); 190 (100); 126 (30); 175 (83); 173 (83); 141 (60). HR-MS $C_{12}H_{19}{}^{79}BrN_4O$ (M+): calcd 314.0742: obsd 314.0753.

1-[3-[(4-Iodo-3-methyl-1H-pyrazol-5-yl)methylamino]propyl]pyrrolidin-2-one (**7c**). Light brown oil ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.68 (q, 2H, H2); 1.92 (q, 2H, H7); 2.16 (s, 3H, H5); 2.28 (t, 2H, H8); 2.78 (t, 2H, H1); 3.32 (m, 4H, H3, H6); 3.62 (s, 2H, H4). IR ν_{max} (KBr) 1650 cm^{-1}. MS m/z: 362 (M^+); 235 (M^+ - I); 221; 141; 98. HR-MS $C_{12}H_{19}IN_4O$ (M^+): calcd 362.0604; obsd 362.0612.

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