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Transformation of methyl *N*-methyl-*N*-(6-substituted-5-nitro-4-pyrimidinyl)aminoacetates into 4-methylamino-5-nitrosopyrimidines and 9-methylpurin-8-ones

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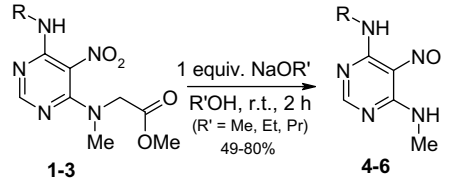
Abstract—*N*-Methyl-*N*-(6-substituted-5-nitro-4-pyrimidinyl)aminoacetic acid methyl esters under the treatment of sodium alkoxides, depending on the nature of substituents in 6 position of the pyrimidine ring, undergo ring closure and rearrangement to give 6-substituted-4-methylamino-5-nitrosopyrimidines or 9-methylpurin-8-ones.

Pyrimidines bearing formyl or cyano groups in position 5 and an active methyleneamino group in position 4 of the pyrimidine ring, on treatment with base, undergo Dieckmann-type cyclisations to give the corresponding pyrrolo[2,3-*d*]pyrimidine derivatives.[1] Some examples of cyclisations of the nitro derivatives by nucleophilic attack of a carbanion onto the nitro group are also known.[2] For example, 5-nitro-4-phenacylaminopyrimidines in aqueous sodium hydroxide solution were shown to undergo a cyclocondensation reaction with the formation of 9*H*-purine-7-oxides.[3] The latter compounds attract attention as possible antitumor, antimicrobial and antiviral agents.[4] However, to the best of our knowledge no work has been done on reactions of *N*-methyl-*N*-(5-nitro-4-pyrimidinyl)aminoacetates under basic non-reductive conditions for the synthesis of purine derivatives. In this context and in continuation of our ongoing program aimed towards the synthesis of pyrimidine-containing heterocycles of biological interest,[1c,5] we report herein our findings on the reaction of the title compounds with sodium alkoxides.

Methyl *N*-methyl-*N*-(5-nitro-4-pyrimidinyl)aminoacetates (**1**–**3** and **7**–**9**) were synthesised from 6-substituted 4-chloro-5-nitropyrimidines[6] by substitution of the chlorine group with sarcosine methyl ester[7] or from methyl *N*-methyl-*N*-(6-chloro-5-nitro-4-pyrimidinyl)aminoacetate with selected amines. However, compounds **1**–**3** and **7**–**9** on treatment with 1 equiv of a sodium alkoxide in the appropriate alcohol at room temperature underwent unexpected transformations.

Compounds **1**–**3** bearing a primary or secondary amino groups in position 6 of the pyrimidine ring, in the reaction with alkoxides, turned into intense blue (**4**) or green (**5**, **6**) products[8] (Scheme 1). It should be mentioned that neither the ^{1}H nor ^{13}C NMR spectra gave evidence about the structure of the products **4**–**6** obtained. These spectra contained two sets of all signals. For example, in the ^{1}H NMR spectrum of **4**, four broadened singlets due to the NH_2 group and two quartets due to the NH group were observed.[9] The ratio between these signals remained constant and did not depend on the sample concentration or solvent (solutions in DMSO, acetone, dichloromethane, acetonitrile have been investigated). Fortunately, slow crystallisation of **4** from DMSO



1-3 **4-6**

R = H (**1**, **4**), R = Ph (**2**, **5**), R = 3-$CF_3C_6H_4$ (**3**, **6**)

Scheme 1.

Keywords: *N*-Methyl-*N*-(6-substituted-5-nitro-4-pyrimidinyl)aminoacetates; Cyclisation; Rearrangement; Purines; Nitrosopyrimidines.
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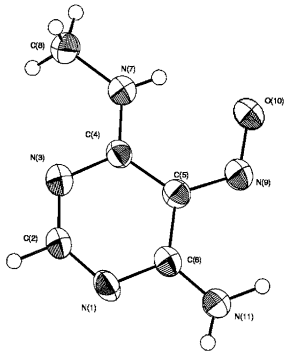


Figure 1. ORTEP drawing of compound **4**.

provided single crystals suitable for the X-ray crystallographic analysis[10] (Fig. 1), which enabled the outcome of the reaction to be elucidated. Thus, the products formed in the reaction of compounds **1**–**3** with a sodium alkoxide were the corresponding 6-substituted-4-methylamino-5-nitrosopyrimidines **4**–**6**.

Moreover, the crystallographic data of **4** showed that in the solid state the molecule adopted a conformation in which the methyl C atom is directed away from the nitroso group and the nitroso group is turned towards the methylamino substituent. The distance N(7)…O(10) and the angle N(7)–H(7)–O(10) were found to be 2.654 Å and 139°, respectively, indicating that in **4** an intramolecular hydrogen bond between the oxygen of the nitroso group and the hydrogen of the methylamino group had been formed. In solution, perhaps, two forms of the nitrosopyrimidines exist (Fig. 2) and, therefore, two sets signals were observed in the NMR spectra.[9]

Compounds **7**–**9** bearing dialkylamino groups in position 6 of the pyrimidine ring on treatment with a sodium alkoxide in an alcohol gave 9-methylpurin-8-ones **10**–**12**, respectively (Scheme 2). The spectral data of **10**–**12** were in accordance with the proposed structures. For example, the IR spectrum of **10** was characterised by the

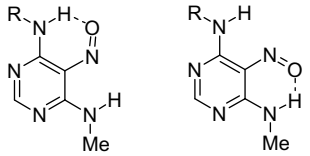
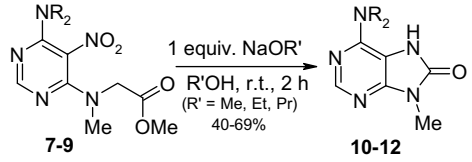


Figure 2. Conformers of 5-nitrosopyrimidines **4**–**6**.



R_2N = $MeNCH_2CO_2Me$ (**7**,**10**), R_2N = $N(CH_2)_6$ (**8**,**11**), R_2N = PhNMe (**9**, **12**)

Scheme 2.

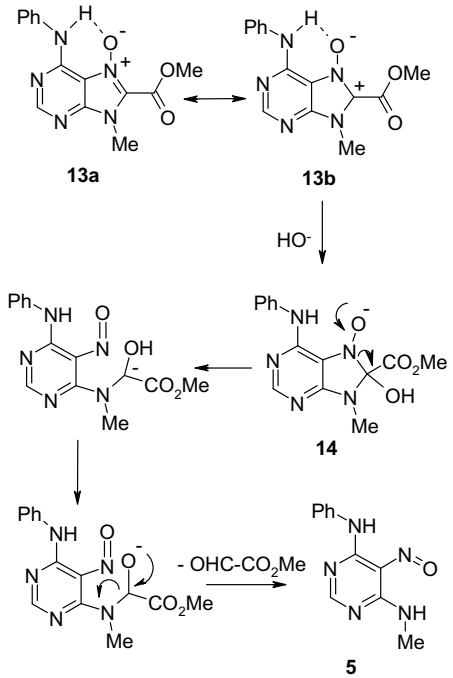
absorption of NH (3161 cm^{-1}) and CO (1736, 1720 cm^{-1}) groups. The mass spectrum of **10** exhibited a molecular ion peak with m/z = 251. The ^1H and ^{13}C NMR spectra showed the expected signals for the groups of **10**–**12**.[11]

The results obtained suggested that the transformations of *N*-methyl-*N*-(6-substituted-5-nitro-4-pyrimidinyl)aminoacetic acid methyl esters (**1**–**3** and **7**–**9**) into products of different structures proceeds via an intermediate **13** which is probably formed in the first step of cyclisation of **1**–**3** and **7**–**9**. *N*-Oxides **13** can react further in two directions differing in the site of attack of a hydroxide ion. The preference for the hydroxide ion to attack C8 of purine **13a** is probably determined by the increased reactivity of C8 towards nucleophiles due to the interaction of the substituent in position 6 of the purine with the oxygen of the 7-oxide group (Scheme 3).

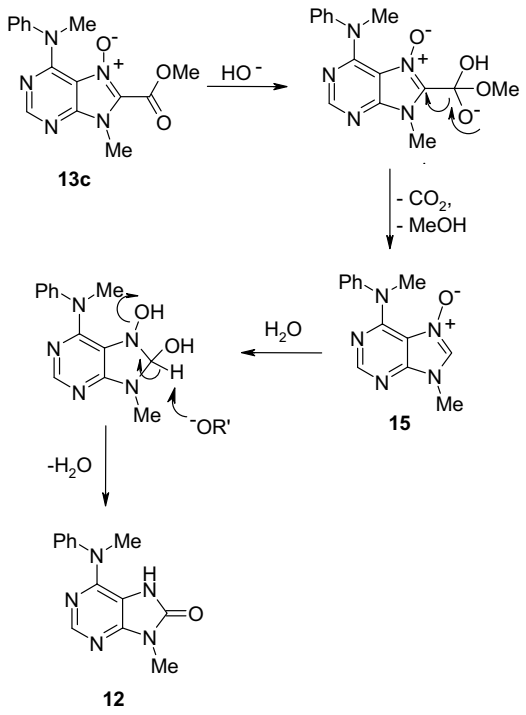
Thus, addition of hydroxide to **13** with formation of the intermediate **14** (Scheme 3) and elimination of OHC–COOMe leads to the 5-nitroso derivative **5**.

When the interaction between the substituent in 6 position and the *N*-oxide group by an intramolecular hydrogen bond is absent (intermediate **13c**), attack of the hydroxide ion takes place at the ester carbonyl group to form intermediate **15**. Rearrangement of **15** by an abnormal addition–elimination (AE_a) of water, similar to that proposed for conversion of benzimidazole *N*-oxides,[12] proceeds to give purin-8-one **12** (Scheme 4).

In conclusion, the present investigation provides unexpected and novel results on rearrangements of (6-substituted-5-nitro-4-pyrimidinyl)aminoacetates. The reaction



Scheme 3.



Scheme 4.

outcomes mainly depend on the substituent in the 6 position of the pyrimidine ring.

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7. *Representative procedure for the synthesis of compounds* **1**–**3** *and* **7**–**9**. To a suspension of 4-amino-6-chloro-5-nitropyrimidine (0.86 g, 5 mmol) and sarcosine methyl ester hydrochloride[13] (0.7 g, 5 mmol) in methanol (5 mL) a solution of triethylamine (1.01 g, 10 mmol) in methanol (3 mL) was added dropwise. The reaction mixture was refluxed for 30 min. The solution was cooled to room temperature, the precipitate was filtered off, washed with water and recrystallised to give 0.95 g (80%) of compound **1**, mp 149–150 °C (from methanol). IR (Nujol) ν_{max}/cm^{-1} 3325, 3187 (NH_2), 1758 (CO); δ_H (300 MHz, $CDCl_3$): 2.97 (3H, s, NCH_3); 3.78 (3H, s, OCH_3); 4.34 (2H, s, NCH_2); 7.00 (2H, br s, NH_2), 7.97 (1H, s, C2-H); (found: C, 39.90; H, 4.46; N, 29.19. $C_8H_{11}N_5O_4$ requires C, 39.84; H, 4.60; N, 29.04).
8. *General procedure for the synthesis of compounds* **4**–**6** *and* **10**–**12**. To a suspension of compounds **1**–**3** and **7**–**9** (5 mmol) in the corresponding alcohol (5 mL) a solution of the appropriate sodium alkoxide in alcohol, prepared from sodium (0.115 g, 5 mmol) and alcohol (3 mL), was added dropwise with stirring. The reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered off, washed with water and recrystallised to give compounds **4**–**6** and **10**–**12**.
9. *Spectral data of selected 4-methylamino-5-nitrosopyrimidines*. Compound **4**: yield 60% (using sodium methoxide in methanol), 55% (using sodium ethoxide in ethanol), 49% (using sodium propoxide in 1-propanol), mp 256 °C (dec) (from DMSO), IR (Nujol) ν_{max}/cm^{-1} 3320, 3329, 3331 (NH_2, NH); δ_H (300 MHz, DMSO-d_6): 2.91, 3.05 (3H, d, $J = 4.8$ Hz, NCH_3); 8.07 (1H, s, C2-H); 8.62, 8.51, 9.11, 10.23 (2H, br s, NH_2); 9.59, 11.11 (1H, q, $J = 4.8$ Hz, $NHCH_3$); δ_c (75 MHz, DMSO-d_6): 26.3, 27.7 (NCH_3), 139.99, 140.7 (C5), 145.5, 146.0 (C4 or C6), 163.05, 164.5 (C6 or C4), 164.7, 165.9 (C2); (found: C, 39.49; H, 4.56; N, 45.43. $C_5H_7N_5O$ requires C, 39.21; H, 4.61; N, 45.73). Compound **5**: yield 65% (using sodium methoxide in methanol), 58% (using sodium ethoxide in ethanol), 49% (using sodium propoxide in 1-propanol), mp 162–164 °C (from 2-PrOH), IR (Nujol) ν_{max}/cm^{-1} 3340, 3338 (NH); δ_H (300 MHz, CD_2Cl_2): 3.11, 3.30 (3H, d, $J = 4.8$ Hz, NCH_3); 7.29–7.89 (5H, m, ArH); 8.28, 8.34 (1H, s, C2-H); 9.93, 11.12 (1H, q, $J = 4.8$ Hz, $NHCH_3$); 11.46, 13.41 (1H, br s, NHC_6H_5); δ_c (75 MHz, CD_2Cl_2): 26.6, 28.1 (NCH_3), 122.6, 122.7 (C5), 125.3, 126.2, 129.2, 129.2 (Ar), 136.6, 137.8, (C4 or C6), 139.6, 139.7 (C6 or C4), 165.4, 165.7 (C2); (found: C, 57.59; H, 4.76; N, 30.39. $C_{11}H_{11}N_5O$ requires C, 57.63; H, 4.84; N, 30.55).
10. *Crystal data for compound* **4**: $C_5H_7N_5O$, M_w 153.16, orthorhombic, space group Pca21; $Z = 4$, $a = 16.4247(4)$, $b = 4.7518(2)$, $c = 8.3893(8)$ Å, $\alpha = \beta = \gamma = 90°$; $V = 654.8(3)$ Å^3, $F(000) = 320$, $D_x = 1.554$ g/cm^3. Crystallographic data for structure **4** have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 252806).
11. *Spectral data for the selected 9-methylpurin-8-ones*. Compound **11**: yield 52% (using sodium methoxide in methanol), mp 189 °C (from H_2O), IR (Nujol) ν_{max}/cm^{-1} 3155 (NH), 1717 (CO); δ_H (300 MHz, DMSO-d_6): 1.62 (8H, m, $(CH_2CH_2)_2$); 3.41 (3H, s, NCH_3), 3.81 (4H, m, $N(CH_2)_2$), 8.23 (1H, s, C2-H), 11.00 (1H, br s, NH). δ_C (75 MHz, DMSO-d_6): 24.6 (NCH_3), 25.5 (CH_2CH_2), 27.1 (CH_2CH_2), 47.1 ($N(CH_2)_2$), 102.0 (C5), 145.55 (C4 or

C6), 147.8 (C6 or C4), 149.5 (C2), 152.3 (CO); (found: C, 58.42; H, 6.86; N, 28.45. $C_{12}H_{17}N_5O$ requires C, 58.28; H, 6.93; N, 28.32). Compound **12**: yield 55% (using sodium methoxide in methanol), 42% (using sodium ethoxide in ethanol), mp 195–197 °C (from 2-PrOH), IR (Nujol) ν_{max}/cm^{-1} 3393 (NH); δ_H (300 MHz, $CDCl_3$): 3.39, (3H, s, NCH_3); 3.59, (3H, s, NCH_3); 5.86 (1H, br s NH); 7.29–7.51 (5H, m, ArH); 8.41 (1H, s, C2-H); δ_c (75 MHz, $CDCl_3$): 25.9 (NCH_3), 38.2 (NCH_3), 104.6 (C5), 126.4, 127.8, 129.1, 130.1 (Ar), 143.8 (C4 or C6), 145.5 (C6 or C4), 149.1 (C2), 152.1 (C8); (found: C, 61.49; H, 5.05; N, 27.55. $C_{13}H_{13}N_5O$ requires C, 61.16; H, 5.13; N, 27.43).

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