A Novel and Efficient Synthesis of 6-Dialkylamino-9-benzyl-8-methoxypurines and 6-Dialkylamino-9-benzylpurin-8-ones by Reaction of Methyl *N*-Benzyl-*N*-(6-dialkylamino-5-nitropyrimidin-4-yl)glycinates with Sodium Alkoxides

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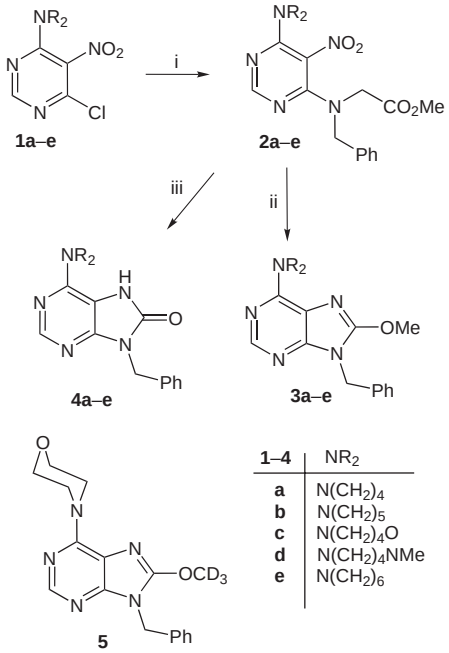
Abstract: A novel and simple synthesis of 6-dialkylamino-9-benzyl-8-methoxypurines and 6-dialkylamino-9-benzylpurin-8-ones by reaction of methyl *N*-benzyl-*N*-(6-dialkylamino-5-nitropyrimidin-4-yl)glycinates with sodium alkoxides is described.

Key words: methyl *N*-benzyl-*N*-(6-dialkylamino-5-nitropyrimidin-4-yl)glycinates, 8-methoxypurines, purin-8-ones, cyclisation, rearrangement

Due to interest in synthetic purines as mediators of various biological processes[1] a number of solution and solid-phase synthesis procedures have recently been advanced.[2] A literature survey revealed that 5-aminopyrimidines with suitable substituents are the most often used starting compounds for this purpose.[3] However, to the best of our knowledge, no work has been done on the synthesis of purines from 5-nitropyrimidines under non-reductive conditions. Recently, we have reported on the unexpected transformations of methyl *N*-methyl-*N*-(5-nitropyrimidin-4-yl)glycinates into 5-nitroso-4-methylaminopyrimidines or purinones.[4a] As continuation of our ongoing program aimed on the study of reactions of 5-nitropyrimidines[4] we report herein on a novel and very simple synthesis of 6-dialkylamino-9-benzyl-8-methoxypurines and 6-dialkylamino-9-benzylpurin-8-ones from the corresponding methyl *N*-benzyl-*N*-(5-nitropyrimidin-4-yl)glycinates.

The starting materials – methyl *N*-benzyl-*N*-(6-dialkylamino-5-nitropyrimidin-4-yl)glycinates **2a**–**e** – were synthesised by the reaction of the readily available 4-dialkylamino-6-chloro-5-nitropyrimidines **1a**–**e**[5] with methyl *N*-benzylglycinate in the presence of triethylamine[6] (Scheme 1). Treatment of **2a**–**e** with an equivalent amount of sodium methoxide in methanol at room temperature led to the formation of corresponding 8-methoxy-9*H*-purines **3a**–**e** in good yields,[7] whereas sodium ethoxide in ethanol caused a transformation of **2a**–**e** into 6-dialkylamino-9-benzylpurin-8-ones **4a**–**e**.[7] This rather unexpected result emboldened to study the reaction of **2a**–**e** with various alkoxides as it is exemplified by the results of reaction **2c** with various bases in Table 1. The data obtained indicate that only methoxides in methanol gave 6-dialkylamino-9-benzyl-8-methoxypurines **3** (entries 1–3), other alkoxides such as EtONa, EtOLi, EtOK, PrONa or $NaOCH_2CH_2F$ in the appropriate alcohols cause the transformation of **2c** into purin-8-one **4c** (entries 6–9, 12). However, potassium *tert*-butoxide in *t*-BuOH and sodium 2,2,3,3-tetrafluoropropoxide in 2,2,3,3-tetrafluoropropanol – the most and least basic alkoxides among the employed ones (entries 10, 13) did not initiate the transformations of **2c**. Performing the reaction in aprotic solvents (MeONa in benzene or DMF at room or elevated temperature or LDA in THF; entries 4, 5, 11) also did not give satisfactory results: in all cases after the work-up of the reaction mixtures the initial compounds were recovered.



Scheme 1 *Reagents and conditions*: i) $PhCH_2NHCH_2CO_2Me$ (1 equiv), Et_3N (1 equiv), MeOH, reflux, 1 h; ii) NaOMe (1 equiv), MeOH, 2 h, r.t.; iii) NaOEt (1 equiv), EtOH, 2 h, r.t.

The reaction of **2c** sodium deuteriomethoxide in deuterated methanol gave the labeled product **5** (Scheme 1), what indicates that methoxy group in **3a**–**e** comes from the solvent and not from an ester group of compounds **2a**–**e**.

These data indicate that protic solvents – alcohols (exception is *t*-BuOH) and rather strong, sterically unhindered

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Table 1 Reaction of Compound **2c** with Bases[a]

Entry	Base	Time (h)	Product	Yield (%)[b]
1	NaOMe/MeOH	2	**3c**	91
2	LiOMe/MeOH	5	**3c**	57
3	KOMe/MeOH	0.5	**3c**	83
4	NaOMe/C_6H_6		No reaction	
5	NaOMe/DMF		No reaction	
6	NaOEt/EtOH	2	**4c**	81
7	LiOEt/EtOH	5	**4c**	45
8	KOEt/EtOH	0.5	**4c**	79
9	NaOPr/PrOH	2	**4c**	60
10	KO*t*-Bu/*t*-BuOH		No reaction	
11	LDA/THF		No reaction	
12	$NaOCH_2CH_2F/FCH_2CH_2OH$	2	**4c**	78
13	$NaOCH_2CF_2CHF_2/CHF_2CF_2CH_2OH$		No reaction	

[a] 1 Equiv of base is used at r.t.
[b] Isolated yield.

bases – have to be used to perform the observed transformations of methyl *N*-benzyl-*N*-(6-dialkylamino-5-nitropyrimidin-4-yl)glycinates **2** into the purine derivatives **3** and **4**. Counterion in alkoxides does not have influence on the reaction direction. Nevertheless, reactions with lithium alkoxides appeared to be slower and with potassium alkoxides – faster than using the corresponding sodium alkoxides. For example, duration of the reaction of **2c** with MeOLi in methanol to give **3c** is 5 hours, while the same reaction using MeOK and MeONa is over already after 30 minutes and two hours, respectively. The synthesis of the title compounds using sodium alkoxides seems to be more economic and convenient than the synthesis using lithium or potassium alkoxides.

Formation of compounds **3a**–**e**, probably, proceeds during Dieckmann's type cyclisation of **2a**–**e** and subsequent reactions of intermediates – purine 7-oxides with methanol.[4a] Transformation of **2a**–**e** into purin-8-ones **4a**–**e** can occur by two competitive mechanisms: by an abnormal addition and elimination of water to purine 7-oxides[4a] or by bimolecular rearrangement of purine 7-oxides analogously to that proposed for benzimidazole *N*-oxides.[9]

In conclusion, we have developed a very simple, efficient, and straightforward synthesis of 6-dialkylamino-9-benzyl-8-methoxy-9*H*-purines and 9*H*-purin-8-ones through reactions of methyl *N*-benzyl-*N*-(6-dialkylamino-5-nitropyrimidin-4-yl)glycinates with sodium alkoxides. This is the first example for preparing of the title compounds from nitropyrimidines under non-reductive conditions. Taking into account that benzyl, oxo and methoxy groups in the molecules can be removed or undergo further transformations this method for the synthesis of the title compounds should be useful for the preparation of various biologically important 6,8,9-trisubstituted purine derivatives.

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(6) **Typical Procedure for the Preparation of Methyl *N*-Benzyl-*N*-(6-dialkylamino-5-nitropyrimidin-4-yl)glycinates 2a–e.**

A solution of compound **1a**–**e** (5 mmol), benzylamino acetic acid methyl ester (0.9 g, 5 mmol), Et_3N (0.5 g, 5 mmol) in MeOH (10 mL) was refluxed for 1 h. After cooling to r.t. the precipitate was filtered off and recrystallised to give **2a**–**e**.

Compound **2a**: yield 80%, mp 98–100 °C (from MeOH). IR (nujol): ν_{max} = 1748 (CO_2Me), 1563 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.88–1.92 [4 H, m, $(CH_2)_2$], 3.37–3.41 [4 H, m, $N(CH_2)_2$], 3.76 (3 H, s, OMe), 4.23 (2 H, s, NCH_2CO), 4.96 (2 H, s, NCH_2Ph), 7.30 (5 H, s, ArH), 8.02 (1 H, s, C_2-H) ppm. Anal. Calcd for $C_{18}H_{21}N_5O_4$: C, 58.21; H, 5.70; N, 18.86. Found: C, 58.37; H, 5.67; N, 18.79.

Compound **2c**: yield 87%, mp 140–142 °C (from MeOH). IR (nujol): ν_{max} = 1747 (CO_2Me), 1567 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.30–3.34 [4 H, m, $N(CH_2)_2$], 3.48–3.52 [4 H, m, $O(CH_2)_2$], 3.71 (3 H, s, OMe), 4.51 (2 H, s, NCH_2CO), 4.96 (2 H, s, NCH_2Ph), 7.30 (5 H, s, ArH), 7.97 (1 H, s, C_2-H) ppm. Anal. Calcd for $C_{18}H_{21}N_5O_5$: C, 55.81; H, 5.46; N, 18.08. Found: C, 55.89; H, 5.27; N, 18.15.

Compound **2e**: yield 83%, mp 125–126 °C (from *i*-PrOH). IR (nujol): ν_{max} = 1762 (CO_2Me), 1578 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.48 [8 H, m, $(CH_2)_2$], 3.20–3.51 [4 H, m, $N(CH_2)_2$], 3.76 (3 H, s, OMe), 4.36 (2 H, s, NCH_2CO), 5.00 (2 H, s, NCH_2Ph), 7.24–7.29 (5 H, m, ArH), 7.91 (1 H, s, C_2-H) ppm. Anal. Calcd for $C_{20}H_{25}N_5O_4$: C, 60.14; H, 6.36; N, 17.53. Found: C, 60.29; H, 6.28; N, 17.71.

(7) **Typical Procedure for the Preparation of 6-Dialkylamino-9-benzyl-8-methoxypurines (3a–e) and 6-Dialkylamino-9-benzylpurin-8-ones (4a–e).**

To a suspension of the corresponding compound **2a**–**e** (5 mmol) in an alcohol (5 mL) a solution of the sodium alkoxide, prepared from sodium (0.115 g, 5 mmol) and appropriate alcohol (3 mL), was added dropwise under stirring. The reaction mixture was stirred at r.t. for 2 h. The precipitate was filtered off and recrystallised to give **3a**–**e** or **4a**–**e**.

Compound **3a**: yield 80%, mp 139–140 °C (from EtOH).[8]

Compound **3b**: yield 79%, mp 143–145 °C (from *i*-PrOH).[8]

Compound **3c**: yield 91%, mp 142–144 °C (from MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79–3.81 [4 H, m, $N(CH_2)_2$], 4.12 (3 H, s, OMe), 4.17–4.20 [4 H, m, $O(CH_2)_2$], 5.17 (2 H, s, NCH_2Ph), 7.29 (5 H, s, ArH), 8.30 (1 H, s, C_2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 43.6, 45.1, 57.0, 66.0, 115.0, 127.0, 127.4, 128.4, 136.3, 150.2, 150.3, 151.2, 153.4 ppm. MS (%): *m/z* = 325 (30) [M^+]. Anal. Calcd for $C_{17}H_{19}N_5O_2$: C, 62.75; H, 5.89; N, 21.52. Found: C, 62.86; H, 5.74; N, 21.17.

Compound **3d**: yield 85%, mp 150–151 °C (from hexane).[8]

Compound **3e**: yield 76%, mp 127–128 °C (from *i*-PrOH).[8]

Compound **4a**: yield 82% (using NaOEt in EtOH). Yield 62% (using NaOPr in PrOH), mp 254–255 °C (from MeOH).[8]

Compound **4b**: yield 80% (using NaOEt in EtOH), mp 215–216 °C (from MeOH).[8]

Compound **4c**: yield 81% (using NaOEt in EtOH), mp 259–260 °C (from MeOH). IR (nujol): ν_{max} = 3116 (NH), 1715 (CO) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 3.52–3.56 [4 H, m, $N(CH_2)_2$], 3.68–3.71 [4 H, m, $O(CH_2)_2$], 4.98 (2 H, s, NCH_2Ph), 7.32 (5 H, s, ArH), 8.19 (1 H, s, C_2-H), 11.16 (1 H, br s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 43.1, 46.6, 66.7, 105.9, 128.1, 128.2, 129.2, 137.7, 147.7, 149.7, 150.9, 153.5 ppm. MS (%): *m/z* = 311 (40) [M^+]. Anal. Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.87; H, 5.47; N, 22.52.

Compound **4d**: yield 82% (using NaOEt in EtOH), mp 222–223 °C (from MeOH).[8]

Compound **4e**: yield 77% (using NaOEt in EtOH), yield 59% (using NaOPr in PrOH), mp 249–250 °C (from *i*-PrOH).[8]

Compound **5**: yield 93%, mp 128–129 °C (from MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.78–3.80 [4 H, m, $N(CH_2)_2$], 4.19–4.21 [4 H, m, $O(CH_2)_2$], 5.17 (2 H, s, NCH_2Ph), 7.28 (5 H, s, ArH), 8.29 (1 H, s, C_2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.7, 45.9, 56.2, 67.3, 116.3, 127.8, 127.9, 128.9, 136.5, 150.9, 151.2, 152.3, 154.2 ppm. Anal. Calcd for $C_{17}H_{16}D_3N_5O_2$: C, 62.18; H/D, 6.75; N, 21.33. Found: C, 62.05; H/D, 6.74; N, 21.52.

(8) Compounds **2b**,**d**, **3a**,**b**,**d**,**e** and **4a**,**b**,**d**,**e** were also fully characterised by IR, ^1H NMR, ^{13}C NMR spectroscopic and microanalytical data.

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