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Novel rearrangement of 7-(substituted aminomethyl)-6,7-dihydrooxazolo[2,3-*f*]purines to 7-(substituted amino)-7,8-dihydro-6*H*-[1,3]oxazino[2,3-*f*]purines

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Abstract—Oxazinopurines were obtained in high yield by the reaction of 8-bromotheophylline with morpholinomethyl-, piperidinomethyl- or indolinomethyl-substituted oxiranes without isolation of the intermediate oxazolo[2,3-*f*]purine.

Currently there is an immense interest in substituted purines as anticonvulsants[1] and as drugs for heart therapy and for improving peripheral blood circulation.[2–4] It has also been reported that several derivatives are potent adenosine receptor ligands.[1] Oxazolo[2,3-*f*]theophyllines, highly bioactive agents, are conveniently synthesized by the reaction of an 8-halotheophylline with an oxirane.[1,5–7] The construction of this ring system is illustrated in Scheme 1 by our preparation of compounds **3a–c** by condensation of 8-bromotheophylline[8] (**1**) with the respective aminomethyloxiranes[5] **2a–c**. For example, a mixture of **1** (0.39 g, 1.5 mmol), **2a** (0.31 g, 2 mmol) and pyridine (80 mg, 1 mmol) in ethanol (5 mL) was stirred at 23 °C for 10 days to give a precipitate of **3a** in 85% yield.

Attempts to accelerate the synthesis by heating the mixture resulted in a lower yield of **3a** and observation of a new major product, identified as **6a** (vide infra). Analysis of the mixture by TLC (silica gel, chloroform/triethylamine, 9:1) revealed that as the reaction progressed the amount of **3a** initially increased, and then the new product **6a** was observed, which was followed by a decrease in the amount of **3a** with a concomitant increase in the amount of **6a**. Continued heating for several hours resulted in the formation of **6a** as the sole product. Since these results suggested that **3a** undergoes rearrangement to **6a**, a sample of pure **3a** was heated in solution. The isomerization of **3a** in 2-methoxyethanol under reflux (125 °C) was virtually quantitative after 45 min, and it was accelerated to 15 min in the presence of a catalytic amount of pyridine. Heating a similar solution to 140 °C, in xylenes in the absence of pyridine, required 18 h for complete conversion.

Similar results were obtained for the reactions of **1** with piperidinomethyl- and indolinomethyl-substituted oxiranes **2b** and **2c**. The respective oxazolo[2,3-*f*]theophyllines **3b** and **3c** were the only products for the reactions conducted at 23 °C; mixtures of **3b**/**6b** and **3c**/**6c** were obtained upon heating for a short period of time, and continued heating resulted in the formation of **6b** and **6c** as the sole products. However, the reaction times for **6a–c** varied considerably. Under optimized conditions, a mixture of **1** (1.5 mmol), **2** (2 mmol), and pyridine (1 mmol) in an alcohol (3 mL) was heated under reflux until TLC analysis showed the absence of **1**. Cooling of the mixture resulted in crystallization of **6**. Compound **6a** was obtained in a 90% yield after 1 h of reflux in *n*-propanol (100 °C), the synthesis of **6b** (95%) was accomplished after 20 min of reflux in *n*-propanol and the preparation of **6c** (80%) required 41 h of reflux in *n*-butanol (120 °C) under otherwise identical conditions. As can be seen, the order of increasing reaction time, **6b** > **6a** > **6c**, parallels the order of decreasing nucleophilicity of the respective amines: piperidine > morpholine > indoline.

Keywords: 6,7-Dihydrooxazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-dione; Rearrangement; 6,7-Dihydro[2,3-*f*]purine-2,4(1*H*,3*H*)-dione.

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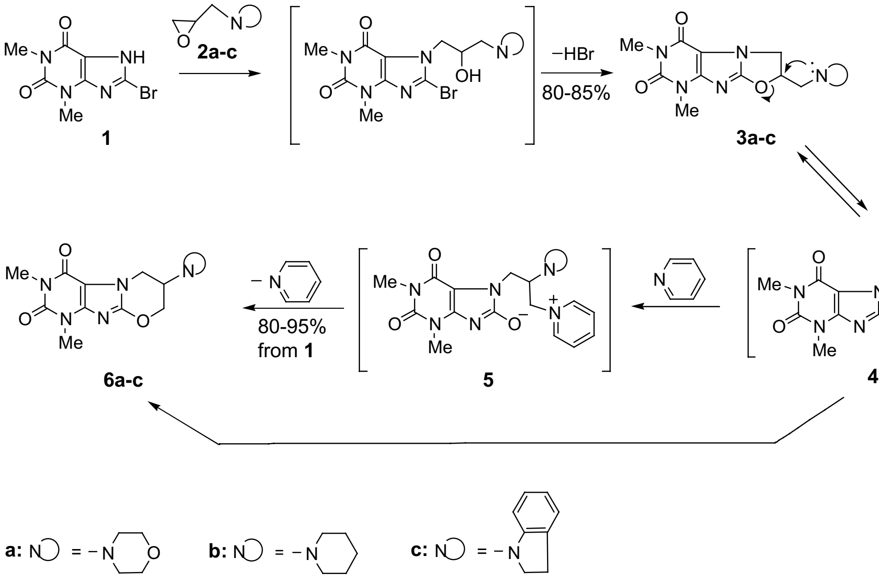
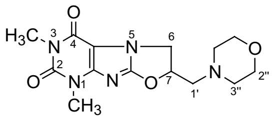
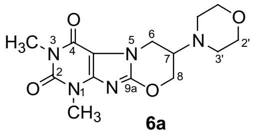


Scheme 1.

Products **3a**,**b** were purified by silica gel chromatography (chloroform/triethylamine, 9:1) as attempted crystallization from a variety of solvents always resulted in partial isomerization to **6a**,**b**. On the other hand, compound **3c**, containing the least nucleophilic indolinomethyl group, and all oxazinopurines **6** were successfully crystallized from *n*-propanol. The crystallization yield was virtually quantitative in all cases demonstrating that highly pure products precipitated directly from crude mixtures. Compounds **3** and **6** all gave satisfactory elemental analysis results. The melting points are as follows: **3a**, 230–232 °C; **3b**, 210–212 °C; **3c**, 203–204 °C; **6a**, 234–235 °C; **6b**, 226–228 °C; **6c**, 265–266 °C.

Molecular ion peaks were observed in the electron impact-induced mass spectra of all the products. The ^{1}H NMR spectra [9] of **3a**–**c** and **6a**–**c** gave similar absorption patterns for the protons of the 6,7-dihydrooxazolo-[2,3-*f*]theophylline and 7,8-dihydro-6*H*-[1,3]oxazino-[2,3-*f*]theophylline ring systems, respectively. Detailed

Table 1. NMR data for compounds **3a** and **6a**

Protons	^{1}H, δ	COSY	^{1}H–^{13}C HMBC	NOESY
 **3a**				
H6	4.48 (m)	H7	C7, C1′	
H6	4.24 (m)	H7	C7, C1′	H1′
H7	5.50 (m)	H6, H1′		H1′
N1Me	3.50 (s)		C2	
N3Me	3.38 (s)		C2, C4	
H1′	2.82 (m)	H7	C6, C7, C3″	H6, H7, H3″
H2″	3.63 (t, J = 4.4 Hz)	H3″	C3″	
H3″	2.60 (t, J = 4.4 Hz)	H2″	C2″, C1′	H1′
 **6a**				
H6	4.35 (m)	H7	C7, C8, C9a	H7, H3′
H7	2.98 (m)	H6, H8	C3′	H6, H8, H3′
H8	4.50 (m)	H7	C6, C7, C9a	H7, H3′
N1Me	3.46 (s)		C2, C10a	
N3Me	3.32 (s)		C2, C4	
H2′	3.66 (t, J = 4.4 Hz)	H3′	C2′	
H3′	2.62 (t, J = 4.4 Hz)	H2′	C3′	H6, H7, H8

NMR studies were conducted on **3a** and **6a** for direct comparison, and the results are summarized in Table 1. Unambiguous proton assignments were made using 2 D NMR methods including COSY, gradient versions of HSQC and HMBC experiments and NOESY. In particular, the results of HSQC experiments together with long range ^{1}H–^{13}C correlations derived from HMBC spectra were especially informative. For compound **6a**, the methylene protons at positions 6 and 8 were correlated to carbon atoms at positions 7 and 9a, and a methine proton C7*H* showed a correlation to *C*3′ of the morpholine. Such a pattern of HMBC signals is only possible for the 7,8-dihydro-6*H*-[1,3]oxazino[2,3-*f*]purine substituted with the morpholino group at position 7. The NOESY spectrum of **6a** is in full agreement with this analysis.

A mechanism consistent with the observations discussed above is given in Scheme 1. It takes into account the fact that 6,7-dihydrooxazolo[2,3-*f*]purines lacking the aminomethyl functionality at the 7 position do not undergo the rearrangement. It is suggested that the intramolecular, amine mediated opening of the dihydrooxazole ring in **3** generates an internal oxide/aziridinium salt **4**. A subsequent intramolecular nucleophilic attack by the oxide anion at the less sterically hindered methylene portion of the aziridinium cation furnishes the observed product **6**. Due to the polar nature of the intermediate product **4**, the rearrangement should be strongly affected by solvent polarity, as observed during the isomerization of **3a** conducted in 2-methoxyethanol and xylenes. Since the isomerization of **3** to **6** is greatly accelerated in the presence of pyridine, it appears that pyridine-mediated opening of the aziridinium ring in **4** generates an adduct **5** which is a more reactive precursor to **6**. This suggestion is fully consistent with our molecular modeling work on **4** and **5** (AM1 molecular orbital, Spartan software). Specifically, in the computed low-energy conformation of **4** the methylene moiety of the aziridinium cation is positioned away from the oxide anion and, as a result, the formation of **6** is slow. By contrast, the transformation of the suggested intermediate product **5** to **6** is faster because the pyridinium methyl moiety is in close proximity to the nucleophilic center.

In summary, a novel, quantitative isomerization of 6,7-dihydrooxazolo[2,3-*f*]theophyllines to 7,8-dihydro-6*H*-[1,3]oxazino[2,3-*f*]theophyllines is described. The substituted oxazinotheophyllines **6** are the first examples of a new class of compounds. The practical synthesis of **6** is conveniently conducted as a one-pot procedure by reacting 8-bromotheophylline with an aminomethyloxirane without isolation of the intermediate oxazolopurine derivative. Currently, we are studying the scope and limitations of this efficient transformation. Specifically, it can be suggested that this is a general reaction between 2-haloimidazoles, their *C*-substituted or fused analogs and aminomethyloxiranes possessing a primary, secondary or tertiary amino function.

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9. The NMR spectra were recorded at 300 MHz in $CDCl_3$ solution at 29 °C. Chemical shifts were referenced against the solvent lock signal. Standard Varian pulse sequences were used for 2D experiments. Heteronuclear correlations experiments were conducted with 16 repetitions each of 256 t_1 increments. The NOESY spectra were acquired with a mixing time of 0.2 s and 32 repetitions each of 200 t_1 increments.