The —NH—(C═)—Br Functionality of Heteroaromatic Compounds as a Synthon for Fused Dihydrooxazoles

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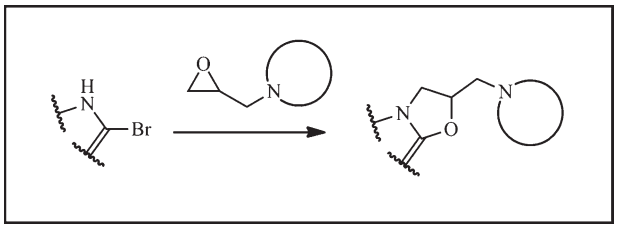

Fused dihydrooxazoles are produced by the reaction of 8-bromoteophylline (**1**), 6-bromo-2-pyridone (**7**), or 2-bromobenzimidazole (**11**) with an *N*-substituted *N*-(2,3-epoxypropyl)amine. The product derived from **1** undergoes rearrangement to a fused dihydrooxazine while the fused dihydrooxazoles derived from **7** and **11** are stable.

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INTRODUCTION

Recently, we have reported three examples of a synthesis of 7-(substituted aminomethyl)-6,7-dihydrooxazolo[2,3-*f*]purines by the reaction of 8-bromotheophylline with an *N*-substituted *N*-(2,3-epoxypropyl)amine [1,2]. The dihydrooxazole product can be isolated but heating of the crude mixture results in a rearrangement of the dihydrooxazole to a dihydrooxazine. This chemistry is exemplified in Scheme 1 by our previously unreported synthesis of the oxazine derivative **6** by treatment of 8-bromotheophylline (**1**) with 1-(2,3-epoxypropyl)-4-phenylpiperazine (**2**) followed by rearrangement of the intermediate dihydrooxazole **4**. In addition to the dihydrooxazole, such as **4**, the mechanism suggested previously postulates the formation of an open-chain intermediate **3** and a zwitterionic structure **5**. Additional studies on the formation of fused dihydrooxazoles are reported in this article.

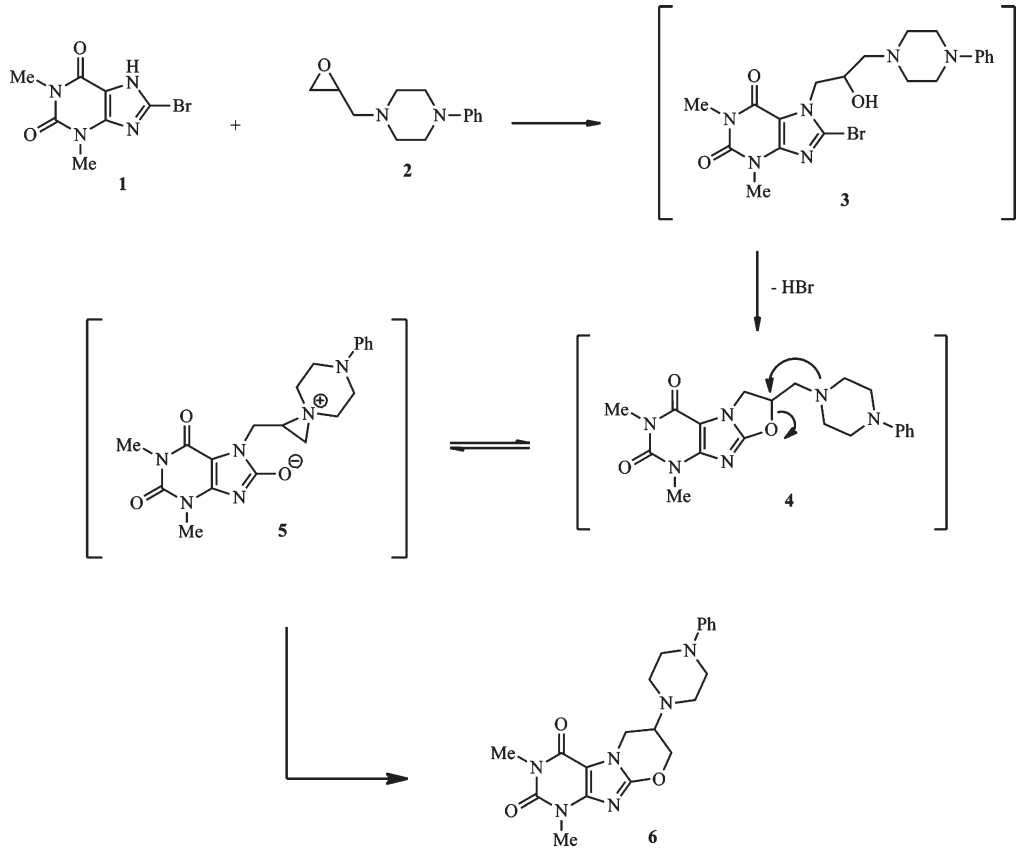
RESULTS AND DISCUSSION

The treatment of substrate **1** with various aminomethyloxiranes was conducted previously at room temperature and gave the corresponding dihydrooxazoles in high yields [1,2]. By contrast, a solution of the substrates **1** and **2** in ethanol did not show any changes when left at room temperature for 2 days either in the absence or in the presence of a catalytic amount of pyridine. We have shown previously that pyridine accelerates the chemistry mentioned above. On the other hand, heating of the mixtures of **1** and **2** resulted in the initial appearance of several products that were difficult to separate by chromatography. Heating under reflux for 6 h resulted in complete consumption of the substrate **1**, as observed by thin layer chromatography (TLC), and the formation of a major product **6**. After purification, the dihydrooxazine **6** was obtained in 65% yield. The intermediary of dihydrooxazoles, such as **4** in Scheme 1, has been noted previously, and these intermediate products have previously been isolated and characterized. Heating of pure dihydrooxazoles resulted in rearrangement to dihydrooxazines.

It was postulated that similar chemistry could be achieved by treatment with aminomethyloxiranes of other heterocyclic substrates containing the —HN—(C═)—Br functionality. Indeed, the reactions of 6-bromo-2-pyridone (**7**) with the aminomethyloxirane **2** and *N*-(2,3-epoxypropyl)morpholine (**9**) produced the respective dihydrooxazoles **8** and **10** as the major products (Scheme 2). These products did not show any instability (rearrangement to dihydrooxazines) on crystallization from heptanes. This feature is in a sharp contrast to the instability of dihydrooxazoles derived from 8-bromotheophylline.

The reaction of 2-bromobenzimidazole (**11**) with the aminomethyloxirane **9** is depicted in Scheme 3. Two

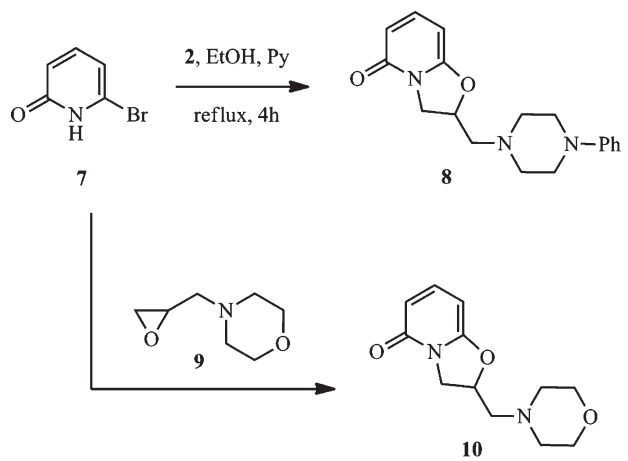
Scheme 1



products were observed by TLC, which were isolated and shown to be an open-chain product **12** and a dihydrooxazole **13**. Again, compound **13** is stable and does not undergo rearrangement upon heating. Compound **12** is a precursor to dihydrooxazole **13** because the intensity of **13** on TLC was increasing with time at the expense of the decreasing amount of **12**. Under the optimized conditions for **13**, its isolated yield was 85% and the intermediate product **12** was obtained in a 9% yield. Previously, we have postulated the intermediary of the open-chain products in the synthesis of dihydrooxazoles, resulting from opening of the oxirane ring of the aminomethyloxirane substrates. Compound **12** is the first example of the isolated and characterized intermediate product in these types of syntheses. This result is fully consistent with the proposed mechanism (see Scheme 1).

The zwitterionic intermediate compound **5** is the postulated direct precursor to the dihydrooxazine **6**. The

Scheme 2



Scheme 3

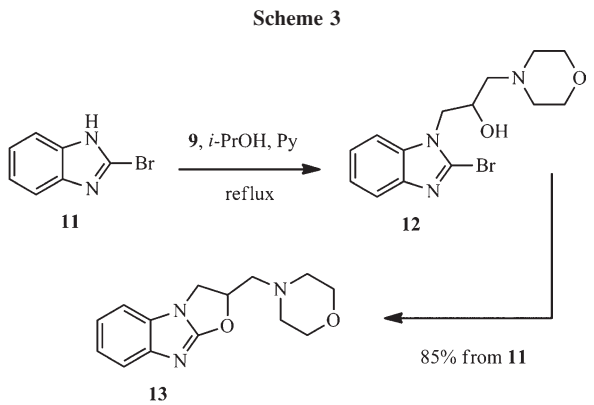
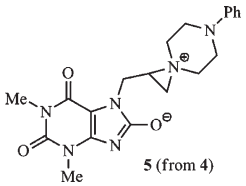
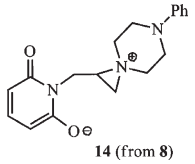
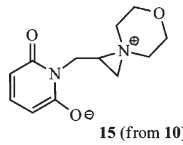
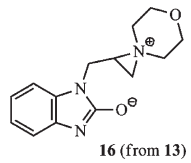


Table 1

Summary of the calculated charges on the oxygen atom of the zwitterionic intermediate product **5** and similar zwitterions **14–16** derived from **8**, **10**, and **13**, respectively.

No.	Mulliken	Natural	Electrostatic
5	−0.6051	−0.7014	−0.5587
 **5** (from **4**)			
14	−0.6291	−0.7109	−0.5876
 **14** (from **8**)			
15	−0.6275	−0.7082	−0.6011
 **15** (from **10**)			
16	−0.6577	−0.7670	−0.6963
 **16** (from **13**)			

facile rearrangement of dihydrooxazole **4** to dihydrooxazine **6** through the presumed intermediary of **5** and the observed stability of other dihydrooxazoles were approached by calculating charge densities on the oxygen atoms of **5** and analogous hypothetical structures **14–16** derived from stable dihydrooxazoles **8**, **10**, and **13**, respectively. The charges were calculated as Mulliken, natural, and electrostatic charges and are shown in Table 1. As can be seen, regardless of the method used, the partial charge is less concentrated in **5** than in the other structures analyzed. This result is consistent with good stabilization of the negative charge in the zwitterion **5** and, subsequently, facile ring opening of dihydrooxazole **4** to stable zwitterion **5**. Conversely, the corresponding zwitterions **14–16** would be less stable and, apparently, are not formed.

Finally, we wish to comment on the structure determination that was conducted by using a variety of spectral methods including HR-MS and ^{1}H-NMR and elemental analyses. The molecular composition of the synthesized compound, with the only exception of **12**, was supported by both the HR-MS data and elemental analysis. Although product **12** was characterized by HR-MS only, its ^{1}H- and ^{13}C-NMR spectra showed high purity. Analysis of the HR-MS data or elemental analysis results could not distinguish between dihydrooxazoles and isomeric dihydrooxazines. On the other hand, the ^{1}H-NMR spectra of these isomeric molecules are strikingly different. Especially diagnostic are chemical shifts for methine protons at the asymmetric carbons because the proton is adjacent to the methylene group in a dihydrooxazole and to an amino group in a dihydooxazine. The validation of this approach was obtained by comparison of ^{1}H-NMR spectra of the isomeric dihydrooxazoles and dihydrooxazines derived from 8-bromotheophylline. The chemical shifts of the previously synthesized isomers were rigorously assigned by using COSY, NOESY, HSQC, and HMBC techniques [1,2]. Similarly, these 2D NMR techniques were used to confirm chemical structure of newly synthesized compounds. Especially important for that purpose were NOESY and long-range ^{1}H and ^{13}C correlation spectra (HMBC), which show correlations signals between proper atoms of morpholine (compounds **10**, **13**) or piperazine (compound **8**) rings and atoms of oxazole moiety.

EXPERIMENTAL

Melting points (Pyrex capillary) are not corrected. Mass spectra and high resolution time-of-flight mass spectra were recorded using electron-spray ionization with 0.1% formic acid in methanol. ^{1}H- and ^{13}C-NMR spectra were obtained at 300 and 75 MHz, respectively, in deuteriochloroform solution with the solvent used as an internal standard. All commercial reagents were purchased from Aldrich or Fluka. The aminomethyloxiranes **2** and **9** were synthesized by the reaction of epichlorohydrin with morpholine and *N*-phenylpiperazine, respectively, by using a general method [3–5]. TLC analysis was conducted by using silica gel-coated plates.

For charge calculations, all structures were drawn in Hyperchem 8.0 (Hypercube) and imported to Spartan ′04 (Wavefunction). For each structure, the lowest energy conformation was determined with the equilibrium conformer module using a molecular mechanics force field. The equilibrium geometry of the lowest energy conformer was then calculated using B3LYP density functional theory and 6-31G* basis set. The partial charges were calculated from this geometry as Mulliken, natural, and electrostatic charges [6].

7-(4-Phenylpiperazino)-7,8-dihydro-6*H*-[1,3]oxazino[2,3-*f*]theophylline (6). A solution of 8-bromotheophylline (**1**, 0.26 g, 1 mmol), 1-(2,3-epoxypropyl)-4-phenylpiperazine (**2**, 0.44 g, 2 mmol), and pyridine (0.08 g, 1 mmol) in anhydrous ethanol (5 mL) was heated under reflux under a nitrogen

atmosphere for 6 h, after which time the TLC analysis (chloroform/triethylamine, 3:1) showed the absence of **1**. The solution was concentrated to 3 mL and refrigerated for 24 h. The resultant crystalline precipitate was filtered, washed with diethyl ether, and crystallized twice from *n*-butanol; yield 0.26 g (66%), mp 236–238°C; ^{1}H-NMR: δ 2.82 (m, 4H), 3.10 (pent, J = 5 Hz, 1H, C*H), 3.19 (m, 4H), 3.38 (s, 3H), 3.51 (s, 3H), 4.28 (d, J = 5 Hz, 2H), 4.56 (d, J = 5 Hz, 2H), 6.89 (m, 3H), 7.28 (m, 2H); ^{13}C-NMR (deuteriochloroform): δ 27.8, 29.8, 44.1, 49.3, 50.2, 54.2, 68.1, 102.9, 116.2, 120.2, 129.2, 147.1, 150.9, 151.7, 153.0, 154.5. High resolution ms. Calcd for $C_{20}H_{25}N_6O_3$ ($M^+ + 1$): *m/z* 397.1988. Found: *m/z* 397.1987. Anal. Calcd. For $C_{20}H_{24}N_6O_3$: C, 60.59; H, 6.10; N, 21.19. Found: C, 60.56; H, 6.18; N, 20.91.

General procedure for 8 and 10. A solution of 6-bromo-2-pyridone (**7**, 0.17 g, 1 mmol), 1-(2,3-epoxypropyl)-4-phenylpiperazine (**2**, 0.33 g, 1.5 mmol) or *N*-(2,3-epoxypropyl)morpholine (**9**, 0.22 g, 1.5 mmol), and pyridine (0.08 g, 1 mmol) in anhydrous ethanol (5 mL) was heated under reflux under a nitrogen atmosphere for 4 h. After concentration, the oily residue was subjected to silica gel chromatography eluting with chloroform/methanol (15:1). Product **8** was crystallized from *n*-heptane/toluene (3:1) and product **10** was crystallized from *n*-heptane.

2-[(4-Phenylpiperazino)methyl]-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyridin-5-one (8). This compound was obtained in a 40% yield (0.12 g), mp 135–136°C; ^{1}H-NMR: δ 2.80 (m, 6H), 3.20 (m, 4H), 4.08 (m, 1H), 4.38 (dd, J = 12 Hz, J = 8 Hz, 1H, CH), 5.09 (m, 1H, C*H), 5.61 (d, J = 7 Hz, 1H), 6.09 (d, J = 9 Hz, 1H), 6.87 (m, 3H), 7.33 (m, 3H); ^{13}C-NMR: δ 47.2, 49.1, 54.1, 60.6, 78.9, 83.5, 110.2, 116.1, 119.9, 129.1, 142.4, 151.1, 156.8, 161.0. High resolution ms. Calcd. for $C_{18}H_{22}N_3O_2$ ($M^+ + 1$): *m/z* 312.1712. Found: *m/z* 312.1707. Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.79; N, 13.49. Found: C, 69.09; H, 6.81; N, 13.46.

2-(Morpholinomethyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyridin-5-one (10). This compound was obtained in a 40% yield (0.09 g), mp 75–76°C; ^{1}H-NMR: δ 2.57 (m, 4H), 2.74 (m, 2H), 3.70 (m, 4H), 4.06 (dd, J = 12 Hz, J = 7 Hz, 1H), 4.35 (dd, J = 12 Hz, J = 8 Hz, 1H), 5.08 (m, 1H, C*H), 5.59 (d, J = 7 Hz, 1H), 6.09 (d, J = 9 Hz, 1H), 7.33 (dd, J = 9 Hz, J = 7 Hz, 1H); ^{13}C-NMR: δ 47.1, 54.4, 61.0, 66.8, 78.7, 83.5, 110.2, 142.3, 156.8, 161.0. High resolution ms. Calcd. for $C_{12}H_{17}N_2O_3$ ($M^+ + 1$): *m/z* 237.1240. Found: *m/z* 237.1245. Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.74; H, 6.82; N, 11.74.

Compounds 12 and 13. A solution of 2-bromobenzimidazole (**11**, 0.10 g, 0.51 mmol), *N*-(2,3-epoxypropyl)morpholine (**9**, 0.16 g, 1.1 mmol), and a few drops of pyridine in isopropanol (5 mL) was heated under reflux for 19 h, after which time the TLC analysis (chloroform/methanol, 9:1) showed the absence of **11**. After concentration under reduced pressure, the residue was subjected to silica gel chromatography eluting with hexanes/ethanol/triethylamine (5:1:1) (compound **13**) and then with dichloromethane/methanol (49:1) (additional purification of **12**).

2-Bromo-1-(2-hydroxy-3-morpholinopropyl)benzimidazole (12). This compound was obtained as an oil in a 9% yield (16 mg); ^{1}H-NMR: δ 2.50 (br s, exchangeable with D_2O, 1H), 2.70 (m, 2H), 2.84 (m, 2H), 3.60 (m, 5H), 3.87 (dd, J = 14 Hz, J = 8 Hz, 1H), 4.18 (m, 2H), 4.45 (dd, J = 14 Hz, J = 8 Hz, 1H), 7.27 (m, 3H), 7.69 (d, J = 8 Hz, 1H); ^{13}C-NMR: δ 38.1, 43.7, 49.0, 62.1, 67.2, 109.3, 119.6, 122.7, 123.2, 130.2, 135.4, 155.1. High resolution ms. Calcd. for $C_{14}H_{19}{}^{79}BrN_3O_2$ ($M^+ + 1$): *m/z* 340.0662. Found: *m/z* 340.0658.

2-(Morpholinomethyl)-2,3-dihydro-4H-[1,3]oxazolo[3,2-a]benzimidazole (13) This compound was obtained in an 85% yield (113 mg), mp 147–149°C; ^{1}H-NMR: δ 2.61 (m, 4H), 2.85 (m, 2H), 3.68 (m, 4H), 4.07 (dd, J = 9 Hz, J = 7 Hz, 1H), 4.31 (dd, J = 9 Hz, J = 8 Hz, 1H), 5.47 (m, 1H, C*H), 7.15 (m, 3H), 7.50 (m, 1H); ^{13}C-NMR: δ 45.2, 54.5, 61.1, 66.8, 85.7, 108.5, 118.8, 121.0, 121.9, 131.0, 146.6, 163.6. High resolution ms. Calcd. For $C_{14}H_{18}N_3O_2$ ($M^+ + 1$): *m/z* 260.1400. Found: *m/z* 260.1406. Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.65; H, 6.67; N, 15.94.

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