Pergamon

Tetrahedron Letters, Vol. 37, No. 26, pp. 4447-4450, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00884-2

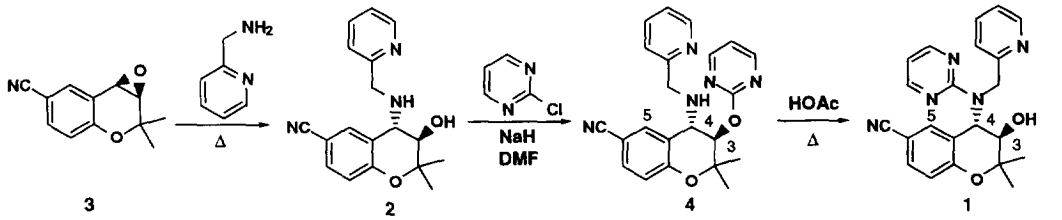
Synthesis of 4-(N-Alkyl-N-Heteroaryl)amino-3,4-Dihydro-3-Hydroxy-2,2-Dimethyl-2H-1-Benzopyran-6-Carbonitrile Derivatives via an Unusual 1,4-Oxygen to Nitrogen Heteroaryl Migration

Charles Z. Ding* and Arthur V. Miller
The Bristol-Myers Squibb Pharmaceutical Research Institute, P. O. Box 4000
Princeton, New Jersey 08543-4000

Abstract: Various heteroaryls were found to undergo 1,4-oxygen to nitrogen migration (e.g. **4**→**1**) under acidic conditions. This unprecedented migration provides a convenient access to 4-(N-alkyl-N-heteroaryl)amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile derivatives, which are otherwise difficult to prepare.

In an ongoing potassium channel opener program in our laboratory,[1] we were interested in the synthesis of 4-(N-alkyl-N-heteroaryl)amino-3,4-dihydro-3-hydroxyl-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile derivatives (e.g. **1**, Scheme 1). These compounds are usually prepared by the reaction of amines (e.g. **2**) with heteroaryls containing a leaving group (e.g. 2-chloropyrimidine).[2] However, the reaction of **2**, prepared from epoxide **3**, with 2-chloropyrimidine under a variety of conditions resulted in recovery of starting material.

Scheme 1

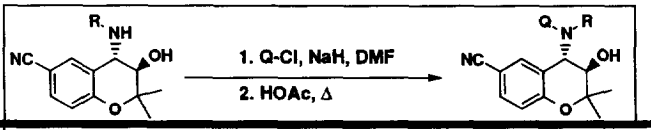


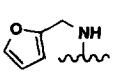
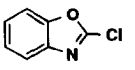
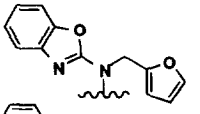
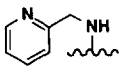
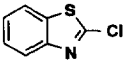
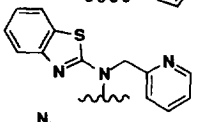
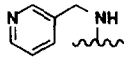
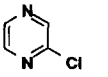
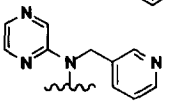
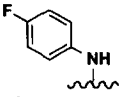
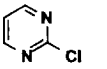
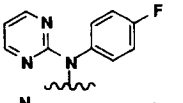
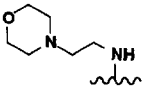
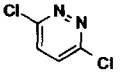
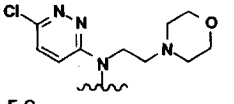
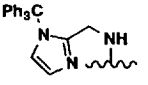
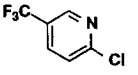
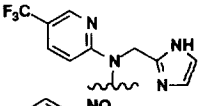
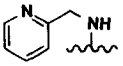
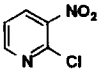
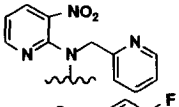
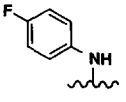
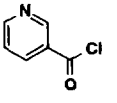
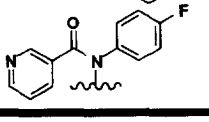
3 2 4 1

The failure of the reaction is probably due to steric hindrance and low nucleophilicity of the β-hydroxyamine moiety in **2**. When sodium hydride was used as a base (DMF, 0 °C), 2-alkoxypyrimidine **4** was cleanly produced (Scheme 1). Upon treatment of **4** with acetic acid at room temperature, the pyrimidine group underwent 1,4-oxygen to nitrogen migration to provide the desired product **1** (mp: 227-228 °C). The structural

integrity of compound **1** and **4** were established by NMR experiments. The presence of a free hydroxyl group at C-3 in compound **1** was confirmed by irradiation of H_3. This results in strong enhancement of the signal due to the hydroxyl group. For compound **4**, strong NOE to NH proton was observed upon irradiation of H_4 which confirms attachment of pyrimidine group to C-3 oxygen.

Table 1[3]



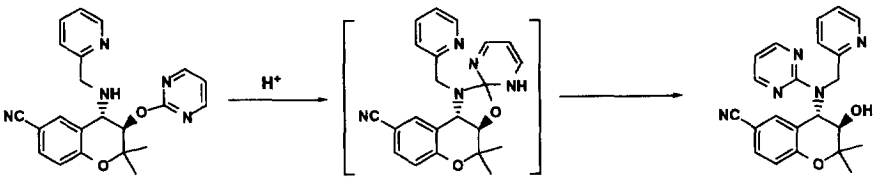
Entry	R, NH	Chloroheteroaryl Q-Cl	Q, N, R	Yield[a]	mp (°C)
1				83%	85
2				69%	134
3				42%	110-112[b]
4				76%	182-184[c]
5				45%	>200[c]
6				30%	205[c]
7				0%	-
8[d]				0%	-

a. The yields are isolated, overall yields. b. TFA salt. c. HCl salt. d. The nicotinate was not shown.

This migration is not limited to pyrimidine, as benzoxazole, benzothiazole, pyradiazine, pyrazine and pyridine also undergo 1,4-oxygen to nitrogen migration. These results are summarized in Table 1. The migration is facile with strongly electrophilic heteroaryls. For example, benzoxazole (entry 1) and pyrimidine (entry 4) migrate under the influence of acetic acid at room temperature. Migration of pyrazine (entry 3)

requires heating in acetic acid. The migration is somewhat retarded by steric factors. For example, the pyridine group (entry 7) does not undergo 1,4-migration despite prolonged heating in acetic acid. The failure of this migration is presumably due to steric effect of the ortho-nitro group. It is noteworthy that the pyrimidine group migrates to even the poorly nucleophilic aniline nitrogen (entry 4). No migration of the acyl group was observed under these conditions (entry 8). This serendipitous discovery of the 1,4-oxygen to nitrogen heteroaryl migration has allowed us to prepare various 4-(N-alkyl-N-heteroaryl)amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile derivatives.

Scheme 2



Acid promoted 1,4-nitrogen to oxygen migration of an acyl group is quite common, as is the base promoted 1,4-oxygen to nitrogen migration.[4,5] 1,4-Silyl group migration (oxygen→carbon; carbon→oxygen and oxygen→oxygen) is also frequently observed.[6] To our knowledge, the 1,4-oxygen to nitrogen heteroaryl migration described in this letter has not been previously observed. The exact reasons for this migration are not known. However, they may be related to the relief of steric strain in **4**, as the presence of a bulky C-2 gem-dimethyl group places the heteroaryloxy group in a sterically congested area. The intramolecular attack by the amino group is presumably facilitated by protonation of the heteroaryl nitrogen to give a spirocyclic intermediate **5** (Scheme 2) which collapses to form the observed product **1**. The failure of the acyl group to undergo migration (entry 8, Table 1) is consistent with this hypothesis.

In conclusion, we have shown that various heteroaryl groups undergo 1,4-oxygen to nitrogen migration. This migration allowed us to access various 4-(N-alkyl-N-heteroaryl)amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile derivatives which are otherwise difficult to prepare. The generality of this migration in non-benzopyran systems is not known at the present time.

Acknowledgment: Thanks are due to Ms. Yolanda Pan for her careful NMR experiments and Dr. Karnail S. Atwal for his insight during this investigation.

References and Notes:

1. (a) Atwal, K. S.; Grover, G, J.; Ahmed, S. Z.; Ferrara, F. N.; Harper, J. W.; Kim, K. S.; Sleph, P. G.; Dzwonczyk, S.; Russel, A. D.; Moreland, S.; McCullough, J. R.; Normandin, D. E. *J. Med. Chem.* **1993**, *36*, 3971-3974. (b) Atwal, K. S.; Grover, G, J.; Ferrara, F. N.; Ahmed, S. Z.; Sleph, P. G.; Dzwonczyk, S.; Normandin, D. E. *J. Med. Chem.* **1995**, *38*, 1966-1973. (c) Atwal, K. S.; Grover, G, J.; Ahmed, S. Z.; Sleph, P. G.; Dzwonczyk, S.; Baird, A. J.; Normandin, D. E. *J. Med. Chem.* **1995**, *38*, 3236-3245. (d)

Atwal, K. S.; Ferrara, F. N.; Ding, C. Z.; Grover, G, J.; Sleph, P. G.; Dzwonczyk, S.; Baird, A. J.; Normandin, D. E. *J. Med. Chem.* **1996**, *39*, 304-313.

2. (a) Overberger, C. G.; Kogan, I. C.; Minin, R. *Org. Synth.* **1955**, *35*, 58-59. (b) Chapman, N. B.; Clarke, K.; Wilson, K. *J. Chem. Soc.* **1963**, 2256-2266.

3. All new compounds gave satisfactory ^{1}H and ^{13}C NMR, MS, and elemental analyses. (3R-trans)-3,4-Dihydro-2,2-dimethyl-4-(heterocyclicalkylamino)-3-heteroaryloxy-2H-1-benzopyran-6-carbonitrile derivatives (e.g. **4**) are isolated, but not shown in the table.

A representative experimental procedure is provided. (3R-trans)-3,4-dihydro-2,2-dimethyl-4-[(2-pyridinylmethyl)amino]-3-pyrimidinyloxy-2H-1-benzopyran-6-carbonitrile (4): To a stirred solution of (3R-trans)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-[(2-pyridinylmethyl)amino]-2H-1-benzopyran-6-carbonitrile (310 mg, 1.0 mmol) in 4 mL of anhydrous DMF at 0 °C under argon was added NaH (100 mg, 60%, 2.5 mmol). The reaction was allowed to stir for 15 min, a solution of 2-chloropyrimidine (130 mg, 1.1 mmol) in DMF (0.5 mL) was added. The resultant solution was allowed to stir at 0 °C for 15 min and the reaction mixture was partitioned between ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (ethyl acetate) to give an oil (350 mg, 90%). MS (CI): 388 (M+H); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.47 (m, 2 H), 7.94 (d, J =1.2 Hz, 1 H), 7.60 (m, 1 H), 7.45 (dd, J = 1.2, 8.2 Hz, 1 H) 7.23 (d, J = 7.60, 1 H), 7.10 (m 1 H), 6.95 (m, 2 H), 5.75 (d, J = 8.8 Hz, 1 H), 4.23 (d, J = 8.8 Hz, 1 H), 4.05 (d, J =14.7 Hz, 1 H), 3.80 (d, J = 14.7 Hz, 1 H), 1.48 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 164.95, 159.33, 157.00, 148.97, 136.32, 133.59, 132.52, 124.03, 121.84, 119.30, 118.32, 115.56, 104.04, 78.61, 74.50, 55.03, 49.82, 26.06, 21.02.

(3R-trans)-3,4-dihydro-2,2-dimethyl-3-hydroxy-4-[(2-pyrimidinyl)(2-pyridinylmethyl)amino]-2H-1-benzopyran-6-carbonitrile (1): A stirred solution of (3R-trans)-3,4-dihydro-2,2-dimethyl-4-[(2-pyridinylmethyl)amino]-3-pyrimidinyloxy-2H-1-benzopyran-6-carbonitrile (**4**) (200 mg, 0.52 mmol) in acetic acid (2 mL) was heated at 60 °C for 18 h. The resultant solution was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic layer was separated and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography to give a white solid (180 mg, 90%; mp: 227-228 °C]. MS (CI): 388 (M+H); $[\alpha]_D$ = - 61.6 ° (c = 1.0, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.45 (d, J = 4.10 Hz, 1 H), 8.30 (bs, 2 H), 7.90 (bs, 1 H), 7.77 (m, 1 H), 7.50 (m, 2 H), 7.30 (s, 1 H), 7.25 (m, 1 H), 6.94 (d, J = 8.8 Hz, 1 H), 6.60 (t, J = 4.6 Hz, 1 H), 6.45 (d, J = 10 Hz, 1 H), 4.95 (d, J = 17.0 Hz, 1H), 4.10 (d, J = 17 Hz, 1 H), 3.85 (d, J = 10 Hz, 1 H), 1.64 (s, 3 H), 1.53 (s, 3 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 162.56, 158.98, 158.24, 157.75, 148.23, 137.27, 132.64, 131.63, 123.22, 123.05, 122.15, 119.48, 118.27, 111.27, 103.49, 80.92, 70.29, 55.75, 48.61, 27.44, 20.01. Anal. calc'd for $C_{22}H_{21}N_5O_2 \cdot 0.35H_2O$: C, 67.12; H, 5.55; N, 17.79. Found: 67.19; H, 5.25; N, 17.72.

4. (a) Fodor, G.; Bruckner, V.; Kiss, J.; Ohegyi, G. *J. Org. Chem.* **1949**, *14*, 337-345. (b) Fujino, M.; Wasahiko, M.; Shinagawa, S.; Kitada, C.; Yajima, H. *Chem. Pharm. Bull.* **1978**, *26*, 539-548. (c) Kinoshita, H.; Kotahe, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3609-3611. (d) Bernath, G.; Kovacs, K.; Lang, K. L. *Tetrahedron Lett.* **1968**, 2713-2716 and references cited. (e) Welsh, L. H. *J. Org. Chem.* **1967**, *32*, 119-122.

5. (a) Budziarek, R. *J. Chem. Soc. Chem. Commun.* **1968**, 1427-1429. (b) Mora-Lopez, G. A. *Ing. Cienc. Quim.* **1979**, *3*, 132-133; *Chem. Abstra.* **1979**, *92*, 75571v. (c) Tou, J. S.; Vineyard, B. D. *J. Org. Chem.* **1984**, *49*, 1135-1136.

6. (a) Mora, J. Costa, A. *Tetrahedron Lett.* **1984**, *25*, 3493-3496. (b) Hunig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062-2067. (c) Spinazze, P. G.; Keay, B. A. *Tetrahedron Lett.* **1989**, *30*, 1765-1768. (d) Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1990**, *55*, 4634-4638. (e) Beese, G.; Keay, B. A. *Synlett* **1991**, 33-34. (f) Coe, P. L.; Jones, A. S.; Walker, R. T. *Tetrahedron Lett.* **1988**, *29*, 835-836.

(*Received in USA* 26 *March* 1996; *revised* 26 *April* 1996; *accepted* 1 *May* 1996)