A Convenient Synthesis of Nitrogen-Containing Heterocycles Bearing Amino Substituents from Heteroaryl Triflates

Sandro Cacchi,* Antonella Carangio, Giancarlo Fabrizi, Leonardo Moro, Paola Pace

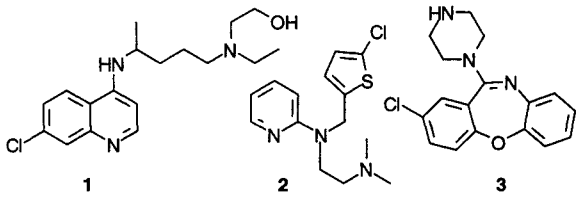
Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy

Fax: + 39 (6) 4991.2780; e-mail: cacchi@axrma.uniroma1.it

Received 5 August 1997

Abstract. Nitrogen-containing heterocycles bearing amino substituents were prepared by the reaction of the corresponding nitrogen-containing heteroaryl triflates with amines. The reaction affords good results with primary and secondary amines, and with aliphatic and aromatic amines. The whole triflation/amination process can also be conducted as a one-pot operation.

Nitrogen-containing heterocycles bearing amino substituents are of broad pharmaceutical interest[1] and this justifies continuing efforts in the development of structure-activity relationship of new compounds in this series and of new synthetic strategies.[2] Hydroxychloroquine **1**, Chlorothen **2**, and Amoxapine **3**, exhibiting respectively antimalarial, vasodilator, and antidepressant activities, are examples of this class of compounds.

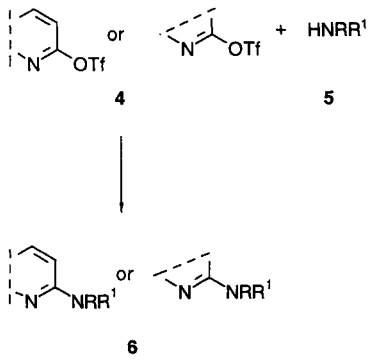


1 **2** **3**

During our ongoing studies on the utilization of vinyl and aryl triflates in organic synthesis,[3] we have found that quinoline-2-triflates react very cleanly, under mild conditions, with morpholine to afford the corresponding amino derivative through the displacement of the triflate function. The utilization of displacement reactions of the triflate group for the preparation of amino derivatives has been applied in the palladium-catalysed amination of aryl triflates;[4] in the uncatalysed amination of aryl triflates in refluxing acetonitrile or under high pressure (with triflates bearing electron-withdrawing substituents);[5] in the uncatalysed amination of aryl triflates proceeding through the intermediacy of arynes;[6] in the preparation of benzodiazepines;[7] in the preparation of N^2-alkylated deoxyguanosines.[8] The latter reaction, which produces amino derivatives of nitrogen-containing heterocycles, deals however with the chemistry of a very peculiar substrate, leaving room to the question of whether the presence of a single nitrogen in the heterocyclic ring can allow the substitution of the amino group for the triflate to occur under mild conditions and provide a general approach to the amination of nitrogen-containing heteroaryl triflates.

Therefore, because of the intense interest in nitrogen-based biologically active heterocycles, we decided to explore the scope of the reaction observed with quinoline-2-triflate. Here we report that the heteroaryl triflates **4** can be reacted with an excess of primary and secondary, aliphatic and aromatic amines, to afford the corresponding amino derivatives **6** in good yield (Scheme 1).[9]

No attempts have been made to optimize the reaction conditions for any example. Thus, further improvement for a particular case of importance appears likely. The starting triflates were readily prepared from hydroxy nitrogen-containing heteroaryls by reaction with N-phenyltrifluoromethanesulfonimide and sodium hydride. Nonaflates can



4 **5** **6**

Scheme 1

Table. The Reaction of Nitrogen-Containing Heteroaryl Triflates **4** with Amines **5** [a]

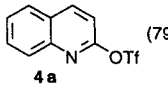
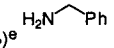
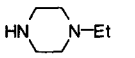
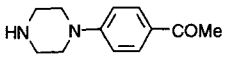
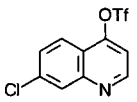
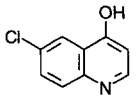
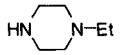
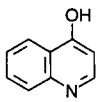
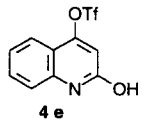
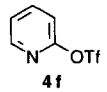
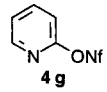
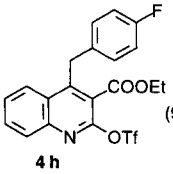
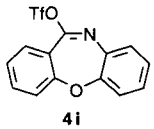
entry	hydroxy heteroaryl or heteroaryl triflate[b] or nonaflate[b]	amine **5**	reaction conditions: solv, temp (°C), time (h)	yield (%) of **6**[c]
1	 **4a** (79%)[e]		DMF, 40, 18	(**6a**) 56[d]
2			MeCN, 40, 89	(**6a**) 57[f]
3			DMSO, 40, 10	(**6a**) 80
4			DMSO, 40, 2	(**6b**) 96[g]
5			DMSO, 40, 20	(**6b**) 75[h]
6		$PhNH_2$	DMSO, 100, 42	(**6c**) 77
7			DMSO, 40, 1	(**6d**) 95
8			DMSO, 40, 3.5	(**6e**) 84
9	 **4b** (75%)		DMSO, 40, 1	(**6f**) 76
10	 **4c**		DMF, 25, 1[i] DMF, 40, 2.5[k]	(**6g**) 87[j]
11	 **4d**		DMF, 25, 1[i] DMF, 25, 19[k]	(**6h**) 75[j]
12			DMF, 25, 1[i] DMF, 40, 19[k]	(**6i**) 77[j]

Table. (continued)

entry	hydroxy heteroaryl or heteroaryl triflate[b] or nonaflate[b]	amine **5**	reaction conditions: solv, temp (°C), time (h)	yield (%) of **6**[c]
13	 **4e**	(86%)[l] 	DMF, 25, 0.2	(**6j**) 70[m]
14			DMF, 40, 2	(**6k**) 85
15	 **4f**	(45%) 	DMSO, 40, 22	(**6l**) 70[n]
16	 **4g**	(52%)[o] 	DMSO, 40, 20	(**6m**) 83
17			DMSO, 100, 24	(**6n**) 60[p]
18	 **4h**	(93%) $HNEt_2$	DMSO, 40, 1	(**6o**) 90
19	 **4i**	(34%) $HNEt_2$	DMSO, 40, 0.5	(**6p**) 59
20			DMSO, 40, 0.5	(**6q**) 63

[a] Reactions were carried out using the following molar ratios: **4**:**5** = 1:2.2. [b] Unless otherwise stated, yields of the starting triflates or nonaflates (figures in parentheses) refer to single, non optimized runs. Heteroaryl triflates were prepared from the corresponding hydroxy nitrogen-containing heteroaryls by reaction with N-phenyltrifluoromethane sulfonimide (1.2 equiv.) and sodium hydride (1.2 equiv.) in anhydrous DMF at room temperature. [c] Unless otherwise stated, yields refer to single runs and are given for pure, isolated products. All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures. [d] The corresponding N,N-dimethylamino derivative was isolated in 30% yield. [e] Average of three runs which gave **4a** in 75, 81, and 82% yield. [f] The starting triflate **4a** was recovered in 32% yield. [g] Average of three runs which gave **6b** in 97, 96, and 96% yield. [h] The reaction was carried out in the presence of K_2CO_3 using the following molar ratios: **4**:**5**:K_2CO_3 = 1:1.1:2.5. [i] Reaction conditions for the triflation step. [j] Overall yield, calculated on the hydroxy heteroaryl. [k] Reaction conditions for the amination step. [l] Average of two runs which gave **4e** in 85 and 87% yield. [m] The structure determination of **6j** and, indirectly, of **4e** was made on the basis of NOE studies. [n] **4f** was recovered in 9% yield. [o] **4g** was prepared from the corresponding hydroxy nitrogen-containing heteroaryl by reaction with perfluoro-1-butanesufonyl fluoride (2 equiv.) and sodium hydride (1.2 equiv.) in anhydrous DMF at room temperature. [p] The starting nonaflate **4g** was recovered in 17% yield

also be used as substrates, and were prepared from perfluoro-1-butanesulfonyl fluoride and sodium hydride. The amination reaction was usually carried out under mild conditions, typically at 40 °C. Aromatic amines or the utilization of nonaflates may require higher temperatures (entries 6 and 17). The reaction may be carried out in the presence of K_2CO_3, so as to decrease the excess of the amine. However, at least with the example we examined, longer reaction time and lower yield were observed (entry 5). The nature of the solvent may affect the reaction outcome (entries 1-3).

The whole process (triflation/amination) can also be conducted as a one-pot operation (entries 10-12).[10] This protocol may be of particular value with relatively unstable triflates.

To sum up, we have shown that the present amination can provide a facile and flexible approach to the important class of nitrogen-containing heterocycles bearing amino substituents from readily available starting materials.

Acknowledgment. The authors gratefully acknowledge the Ministero dell'Università e della Ricerca Scientifica (MURST) and the Consiglio Nazionale delle Ricerche (CNR) for financial support. The authors are also greatly indebted to Dr. Luciana Turchetto of the Istituto Superiore di Sanità for obtaining the mass spectra of new products.

References and Notes

1. The Merck Index, *An Encyclopedia of Chemicals, Drugs, and Biologicals*, twelfth edition, Merck & CO., Inc.; Whitehouse Station, NJ, 1996; Index Nominum: international drug directory, ed. by Swiss Pharmaceutical Society, 16th ed., Stuttgart: Medpharm Scientific Publ., 1995; Drug Evaluations Annual by American Medical Association, 1995.
2. For recent references, see for example: Leach, C.A.; Brown, T.H.; Ife, R.J.; Keeling, D.J.; Parsons, M.E.; Theobald, C.J.; Wiggall, K.J. *J. Med. Chem.* **1995**, *38*, 2748; Ife, R.J.; Brown, T.H.; Blurton, P.; Keeling, D.J.; Leach, C.A.; Meeson, M.L.; Parsons, M.E.; Theobald, C.J. *J. Med. Chem.* **1995**, *38*, 2763.
3. Cacchi, S. *Pure & Appl. Chem.* **1996**, *68*, 45.
4. Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* **1997**, *62*, 1264; Louie, J.; Driver, M.S.; Hamann, B.C.; Hartwig, J.F. *J. Org. Chem.* **1997**, *62*, 1268.
5. Kotsuli, H.; Kobayashi, S.; Suenaga, H.; Nishizawa, H. *Synthesis* **1990**, 1145.
6. Wickham, P.P.; Hazen, K.H.; Guo, H.; Jones, G.; Reuter, K.H.; Scott, W.J. *J. Org. Chem.* **1991**, *56*, 2045.
7. Kraus, G.A.; Liu, P. *Tetrahedron Letters* **1995**, *36*, 7595.
8. Steinbrecher, T.; Wameling, C.; Oesch, F.; Seidel, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 404.
9. Typical procedure for the reaction of **4** with **5**: to a solution of quinoline-2-triflate **4a** (0.150 g, 0.54 mmol) in DMSO (2 mL) was added 4-ethylpiperazine (0.15 mL, 1.19 mmol) and the reaction mixture was stirred at 40 °C for 1 h. After cooling, ethyl acetate was added and the resulting solution was washed with a saturated NaCl solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate/triethylamine 68/29/3 v/v/v) to give **6d** (0.123 g, 95% yield); mp: 74-76 °C; IR (nujol) 807, 754 cm^{-1}; ^1H NMR δ 7.85 (d, J = 7.0 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.60-7.48 (m, 2H), 7.21 (td, J = 7.3 Hz, J = 1.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 3.76 (t, J = 4.0 Hz, 4H), 2.56 (t, J = 4.0 Hz, 4H), 2.46 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 157.37, 147.81, 137.40, 129.49, 127.19, 126.56, 123.02, 122.32, 109.48, 52.75, 52.42, 45.00, 12.00; MS *m/e* (relative intensity) 241 (M^+, 11), 157 (100), 128 (19); Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.64; H, 7.94 N, 17.42 Found C, 74.74; H, 7.95, N, 17.38.
10. Typical procedure for the one-pot synthesis of **6**: NaH (60% dispersion in mineral oil) (0.066 g, 1.65 mmol) was washed three times with *n*-hexane (2 mL). Then, 4-hydroxyquinoline (0.200 g,

1.38 mmol) in anhydrous DMF (3 mL) was added dropwise under argon atmosphere. The reaction mixture was warmed at 40 °C and stirred for 30 min. After cooling, *N*-phenyl trifluoromethanesulfonimide (0.590 g, 1.65 mmol) was added, the reaction mixture was stirred at room temperature for 1 h, and piperidine (0.30 mL, 3.04 mmol) was added. The mixture was stirred for 19 h at room temperature. Ethyl acetate was added and the resulting solution was washed with a saturated NaCl solution, dried (Na_2SO_4), concentrated under reduced pressure and purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate/ triethylamine 88/9/3 v/v/v) to give **6h** (0.219 g, 75% yield); mp: 81-83 °C; IR 2932, 1572, 1399, 772 cm^{-1}; ^1H NMR δ 8.66 (d, J = 5.0 Hz, 1H), 8.03-7.94 (m, 2H), 7.59 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.42 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 6.74 (d, J = 5.0 Hz, 1H), 3.13-3.08 (m, 4H), 1.84-1.62 (m, 6H); ^{13}C NMR δ 157.88, 150.79, 149.47, 129.77, 128.79, 124.93, 123.85, 123.65, 108.53, 53.49, 26.00, 24.37; MS *m/e* (relative intensity) 212 (M^+, 77), 211 (100), 128 (13); Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60 N, 13.20; Found C, 79.29; H, 7.62, N, 13.24 .