JOC*Note*

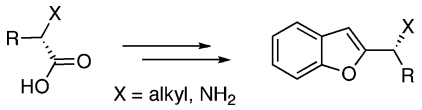
A Facile Approach to the Synthesis of Chiral 2-Substituted Benzofurans

Lidia De Luca, Giampaolo Giacomelli,* and Giammario Nieddu

Dipartimento di Chimica, Università degli Studi di Sassari, via Vienna 2, I-07100 Sassari, Italy

ggp@uniss.it

Received January 24, 2007



An effective route to chiral optically active 2-substituted benzofurans directly from carboxylic acids is reported. This procedure, which allows the preparation of α-alkyl-2-benzofuranmethanamines from *N*-protected α-amino acids without sensible racemization phenomena, proceeds in good yields under mild conditions with the help of microwave irradiation.

The benzofuran ring system features in a large number of naturally occurring biologically active compounds and in potential synthetic pharmacologic agents. For example, a variety of benzofuran derivatives have been investigated as estrogen receptor (ER) ligands,[1] H_3 receptor antagonists,[2] selective ligands for the dopamine D3 receptor subtype,[3] metalloproteinase-13 inhibitors,[4] and antifungal agents.[5]

For these reasons, many efforts have been directed for developing synthetic strategies for this privileged structure, and recently combinatorial approaches to this class of compounds have also been an active research area.[6] General synthetic methodologies may involve the condensation reactions between ketones (or aldehydes) and a number of different forms of nucleophiles, under acidic or basic conditions.[7] Among the reported synthetic strategies, the palladium-catalyzed heteroannulation reaction of *o*-alkenyl or -alkynyl phenols under relatively mild conditions has also been largely employed.[8] Most of them could not provide satisfactory results because of the requirement of strongly acidic or basic conditions or difficulties in the introduction of different substituent patterns starting from readily available materials.

Enantiomerically pure 2-substituted benzofurans might constitute starting materials for the production of biologically active compounds.[9] Considering the real tendency directed toward the development of enantiomerically pure drugs, there is a limited number of papers related to the preparation of enantiomers of benzofuran or more generally azole compounds, either by steroselective synthesis[10] or enantiomeric separation.[11]

Following our research on the synthesis of heterocyclic derivatives starting from relatively available compounds, we were therefore interested in the preparation of benzofurans and indole substrates. In this work, we wish to report development of a convenient method for the generation of 2-substituted benzofuran that could be easily adapted to the synthesis of homochiral derivatives.

The applied methodology starts from the improvement of an old procedure that reported the use of triphenylphosphine bromonium salt, triethyl amine, and acyl chloride under refluxing toluene for 8 h,[12] which was suitably modified to be cleanly applicable to *N*-protected amino acids for obtaining chiral enantiomerically pure α-alkyl-2-benzofuranmethanamines.

For our purposes, although acid chlorides could be used in the formation of simple optically active 2-alkyl benzofurans, such as, e.g., (*R*)-2-(1-phenylpropyl)benzofuran, this procedure did not allow the use of optically active amino acids, as racemization phenomena might be heavily involved.[13] Moreover many acid chlorides are dangerously toxic, irritating, and

* To whom correspondence should be addressed. Fax: +39-079-212069.

(1) (a) Halabalaki, M.; Aligiannis, N.; Papoutsi, Z.; Mitakou, S.; Moutsatsou, P.; Sekeris, C.; Skaltsounis, A.-L. *J. Nat. Prod.* **2000**, *63*, 1672−1674. (b) Von Angerer, E.; Biberger, C.; Leitchtl, S. *Ann. N.Y. Acad. Sci.* **1995**, *761*, 176−191. (c) Teo, C. C.; Kon, O. L.; Sim, K. Y.; Ng, S. C. *J. Med. Chem.* **1992**, *35*, 1330−1339. (d) Crenshaw, R. R.; Jeffries, A. T.; Luke, G. M.; Cheney, L. C.; Bialy, G. *J. Med. Chem.* **1971**, *14*, 1185−1190.

(2) (a) Gfesser, G. A.; Faghih, R.; Bennani, Y. L.; Curtis, M. P.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2559−2563. (b) Cowart, M.; Pratt, J. K.; Stewart, A. O.; Bennani, Y. L.; Esbenshade, T. A.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 689−693.

(3) Hocke, C.; Prante, O.; Lober, S.; Hubener, H.; Gmeiner, P.; Kuwert, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3963−3966.

(4) Hu, Y.; Xiang, J. S.; Di Grandi, M. J.; Du, X.; Ipek, M.; Laakso, L. M.; Li, J.; Li, W.; Rush, T. S.; Schmid, J.; Skotnicki, J. S.; Tam, S.; Thomason, J. R.; Wang, Q.; Levin, J. I. *Bioorg. Med. Chem.* **2005**, *13*, 6629−6644.

(5) (a) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796−4805. (b) Kawasaki, K.; Masubuchi, M.; Morikami, K.; Sogabe, S.; Aoyama, T.; Ebiike, H.; Niizuma, S.; Hayase, M.; Fujii, T.; Sakata, K.; Shidoh, H.; Stiratori, Y.; Aoki, Y.; Ohtsuka, T.; Stimma, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 87−91.

(6) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930. (b) Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804−1809. (c) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311−2314. (d) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498−6499.

(7) (a) Park, K. K.; Han, I. K.; Park, J. W. *J. Org. Chem.* **2001**, *66*, 6800−6802. (b) Katrintzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613−5615. (c) Nicolaou, K. C.; Snyder, S. A.; Bigot, A.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1093−1096.

(8) (a) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755−4757. (b) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 1861−1864. (c) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387−1390. (d) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101−5104. (d) Monteiro, N.; Arnold, A.; Blame, G. *Synlett* **1998**, 1111−1113. (f) Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1998**, *39*, 9605−9608.

(9) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720−14721.

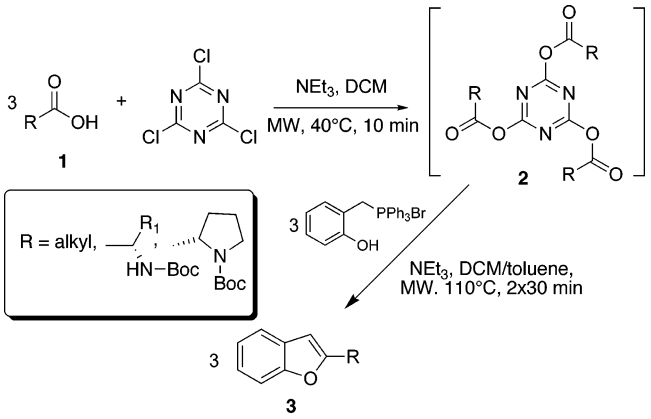
(10) (a) Botta, M.; Corelli, F.; Gasparrini, F.; Messina, F.; Mugnaini, C. *J. Org. Chem.* **2000**, *65*, 4736−4739. (b) Messina, F.; Botta, M.; Corelli, F.; Villani, C. *Tetrahedron: Asymmetry* **2000**, *11*, 1681−1685. (c) Messina, F.; Botta, M.; Corelli, F.; Mugnaini, C. *Tetrahedron Lett.* **1999**, *40*, 7289−7292. (d) Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263−1266.

(11) Tucker, R. P.; Fell, A. F.; Berridge, J. C.; Coleman, M. W. *Chirality* **1992**, *4*, 316−322.

(12) Hercouet, A.; Le Corre, M. *Tetrahedron Lett.* **1979**, *23*, 2145−2148.

10.1021/jo070142c CCC: $37.00
Published on Web 04/10/2007

SCHEME 1

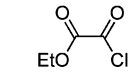
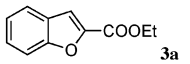
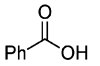
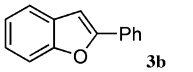
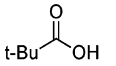
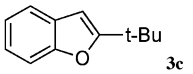
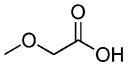
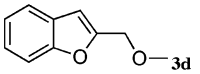
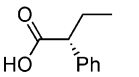
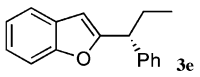
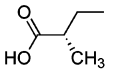
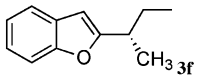
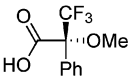
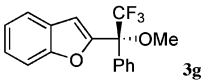
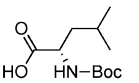
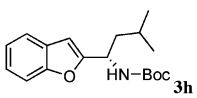
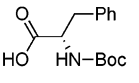
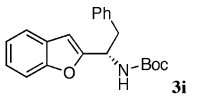
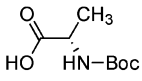
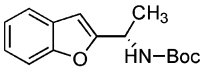
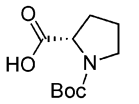
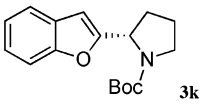
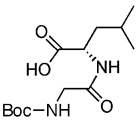
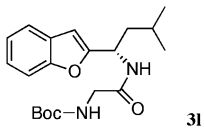
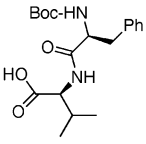
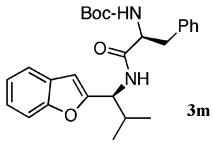


moisture-sensitive; in particular, *N*-protected amino acid chlorides may be also very unstable compounds.[13b]

Venkataraman and Wagle have reported the use of 2,4,6-trichloro-1,3,5-triazine (TCT) as a useful reagent for converting carboxylic acids into chloride, esters, amides, and peptides.[14] Following our interest in the use of 1,3,5-triazine derivatives in organic synthesis,[15] we have therefore tested the possibility to use TCT as an activator of the carboxylic function. An accurate study of all process parameters indicated that the more suitable experimental conditions were those reported in Scheme 1.[16]

Therefore 3 equiv of the acid or the optically active *N*-Boc amino acid (**1**) were treated with 2,4,6-trichloro-1,3,5-triazine (TCT) (1 equiv) and NEt_3 in DCM to form the activated ester **2**. Even if the reaction can be conducted at room temperature (24 h) or in refluxing DCM (12 h), we have preferred to carry out the reactions under microwave irradiation in a sealed tube in a self-tuning single mode CEM Discover Focused synthetizer, operating at 40 °C for 10 min, for drastically shortening the reaction times and avoiding the presence of significant amounts of byproducts. Successively, the cooled reaction mixture was transferred into an open flask having a reflux condenser. The mixture was added with toluene, 2-hydroxybenzyl triphenylphosphonium bromide (3 equiv), and NEt_3 and irradiated at 110 °C for two cycles of 30 min.[17] After removal of the precipitate, the compounds **3** were recovered from the solvent and further purified by silica gel column chromatography.

TABLE 1. Conversion of Carboxylic Acids into Benzofurans

entry	starting compound **1**	benzofuran **3**	Yields (%)
1		 **3a**	74[a]
2		 **3b**	79
3		 **3c**	75
4		 **3d**	78
5		 **3e**	70
6		 **3f**	75
7		 **3g**	73
8		 **3h**	63
9		 **3i**	58
10		 **3j**	66
11		 **3k**	74
12		 **3l**	72
13		 **3m**	69

[a] In this case the alkyl chloride was used following the standard procedure. Only the cyclization step was carried out under MW irradiation.

The results we have obtained are reported in Table 1. Yields are good in all cases examined notwithstanding the purification workup on column chromatography of the recovered crude products.

(13) (a) Falb, E.; Yechezkel, T.; Salitra, Y.; Gilon, C. *J. Peptide Res.* **1999**, *53*, 507−517. (b) Carpino, L. A.; Beyermann, M.; Wenschub, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268−274. (c) Smith, G. G.; Sivakus, T. *J. Org. Chem*. **1983**, *48*, 627−634.

(14) Venkastaran, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, 3037−3040.

(15) (a) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* **2004**, 2570−2572. (b) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *Synlett* **2004**, 2299−2302. (c) Giacomelli, g.; De Luca, L.; Porcheddu, A. *Tetrahedron* **2003**, *59*, 5437−5440. (d) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 6272−6274. (e) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553−555. (f) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907−7909. (g) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534−2537.

(16) The use of 2-chloro-4,6-dimethoxy-[1,3,5]triazine (CDMT) and *N*-methylmorpholine in THF or 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[15g] requires longer times and produces minor yields, owing to more complex purification workup.

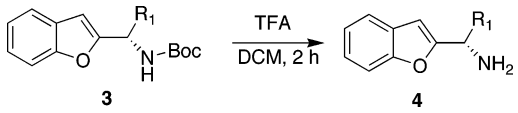
(17) The same reaction, carried out in refluxing toluene, required 10 h for completion. The yields of the recovered products were however comparable.

TABLE 2. Comparison of Conventional and Microwave Procedures for Benzofuran Synthesis

starting compound	% yield/purity[a] thermal reaction[b]	microwave-assisted reaction[c]
1b	60/95	74/98
1c	66/85	79/98

[a] Yield determined at the end of both steps. Average purity determined by NMR on the crude product. [b] Conditions: 24 h, 40 °C, then 10 h, 110 °C. [c] Conditions: 10 min, 40 °C, then 2 × 30 min, 110 °C.

SCHEME 2



3 **4**

With compounds **1b** and **1c** a comparison between classical heating (oil bath) and microwave irradiation was carried out, showing a better performance of the MW-assisted process as reported in Table 2.

All of the chiral benzofurans (**3e**−**l**) were optically active, and those derived from the α-amino acids (**3h**−**l**), recovered as *N*-Boc derivatives, were deprotected to the corresponding α-alkyl 2-benzofuranmethanamines with TFA in DCM (Scheme 2) with practically quantitative yields (>95%).

Significant racemization of the chiral center of the α-amino acids did not occur under the experimental conditions employed. The optical purity of (*S*)-1-(benzofuran-2-yl)-3-methylbutan-1-amine (**4h**) was in fact determined by the ^{19}F NMR spectrum of the reaction product with (+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MPTACl),[18] which showed that it consisted of a 98:2 mixture of the diastereomeric amides. From these data, an enantiomeric purity of about 96% can be calculated for **4h**, very close to that of the amino acid used as starting material. Moreover, both ^{1}H NMR and ^{19}F NMR spectra of the Mosher's amide derived from **4i** showed the presence of only one enantiomer, confirming that the process occurs without sensible racemization phenomena. Likewise in the case of benzofuran **3m**, derived from Boc-Phe-Val-OH, only one diastereisomer was recovered in both the ^{1}H NMR spectrum and the HPLC analysis.

In addition, it is worth noting that by this methodology it is possible to prepare 2-methoxymethyl-benzofuran (**3d**) in a one-pot procedure directly from 2-methoxyethanoic acid in high yield, rather than by multistage procedures earlier reported.[19]

In summary, the procedure reported herein appears to be simple and allows an easy preparation of 2-substituted benzofurans with a chiral stereocenter adjacent to the heterocycle directly from the carboxylic acid; in every case chemical yields were good with 100% optical yields. This method is characterized by short reaction times, mild reaction conditions, nontoxic byproducts, and easy reaction workup.

Experimental Section

Preparation of (*R*)-2-(1-Phenylpropyl)benzofuran, 3e. The procedure for (*R*)-2-(1-phenylpropyl)benzofuran (Table 1, entry 5) is representative for all cases. 2,4,6-Trichloro-[1,3,5]triazine (0.11 g, 0.61 mmol) and, dropwise, NEt_3 (0.24 mL, 1.83 mmol) were added at room temperature to a solution of (*R*)-2-phenylbutanoic acid {0.3 g, 1.83 mmol, $[\alpha]^{20}_D$ −93.1 (*c* 1.0, toluene)[20]} in DCM (2 mL). The resulting mixture was irradiated to 40 °C for 10 min in a sealed tube (CEM designed 10 mL pressure-rated reaction vial) in a self-tuning single mode CEM Discover Focused synthesizer. The mixture was cooled rapidly to room temperature, by passing compressed air through the microwave cavity for 1 min. After cooling to room temperature, the reaction mixture was transferred in a flask and was added with toluene (20 mL), (2-hydroxy-benzyl)-triphenylphosphonium bromide (0.82 g, 1.83 mmol), and NEt_3 (0.76 mL, 5.94 mmol). The open flask was irradiated at 110 °C for two cycles of 30 min, and then the solution was cooled rapidly to room temperature by passing compressed air through the microwave cavity for 3 min. The precipitate was removed by filtration, and the solvent was evaporated under reduced pressure to give a white oil. The crude product was purified by silica gel column chromatography (AcOEt/hexane = 1:9) to afford **3e** as a white oil, yield 70%. $[\alpha]^{20}_D$ −23.0 (*c* 1.17, DCM). ^{1}H NMR: δ 7.49 (m, 1 H), 7.4 (m, 1 H), 7.31 (m, 4 H), 7.24 (m, 1 H), 7.19 (m, 2 H), 6.46 (d, 1 H), 3.96 (m, 1 H), 2.27 (m, 1 H), 2.01 (m, 1 H), 0.96 (m, 3 H) ppm. ^{13}C NMR: δ 161.2, 154.7, 141.9, 128.6, 128.5, 127.9, 126.1, 123.3, 122.4, 120.4, 110.9, 102.3, 47.5, 27.6, 12.4 ppm. Anal. Calcd for $C_{17}H_{16}O$ (236.31): C, 86.40; H, 6.82. Found: C, 86.41; H, 6.84.

Acknowledgment. The work was financially supported by the University of Sassari and MIUR (Rome) within the project PRIN 2005.

Supporting Information Available: Synthetic procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070142C

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.
(19) Caruana, P.; Frontier, A. J. *Tetrahedron* **2004**, *48*, 10921−10926.
(20) Lardicci, L.; Menicagli, R.; Salvadori, P. *Gazz. Chim. Ital.* **1968**, *98*, 738−759.