Pergamon

Tetrahedron Letters, Vol. 38, No. 13, pp. 2311-2314, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00301-8

Solid Phase Synthesis of 2-Substituted Benzofurans via the Palladium-catalysed Heteroannulation of Acetylenes

Daniele Fancelli[a]*, Maria Chiara Fagnola[b], Dino Severino[a], and Angelo Bedeschi[b].
[a]CNS Research, Med. Chem. Dept. and [b]Oncology Research

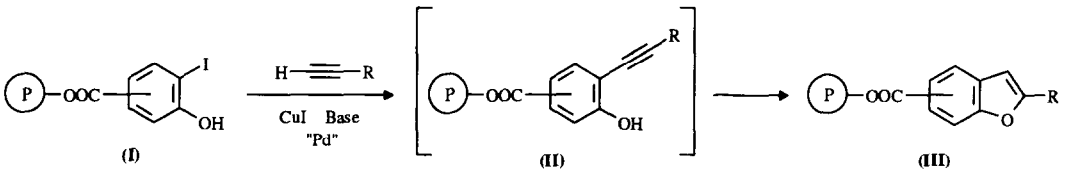
Pharmacia & Upjohn, via Pasteur 10, 20014 Nerviano, Milan, (Italy).

Abstract: The copper/palladium-promoted heteroannulation of terminal acetylenic compounds in the presence of resin bound ortho-hydroxy aryl iodides is described. The process produces 2-substituted benzofuran derivatives in good yield and high purity. © 1997 Elsevier Science Ltd.

Solid phase chemistry has recently gained much interest as an effective synthetic strategy for the building of combinatorial chemistry libraries of small organic molecules.[1] The high purity of the final products avoiding time consuming intermediate purifications, as well as the suitability for combinatorial methods and for automation, are considered the main attraction of this technique. On the other hand the synthetic repertoire on solid support is still inadequate, especially if compared with the traditional solution phase chemistry. For this reason a major effort is actually invested with the aim of increasing the variety of organic chemistry accessible on solid phase. The most common approach consists in the adaptation of well-established solution phase methodologies to the solid phase format, with particular attention to those applicable to a large range of readily available starting materials.

The benzofuran nucleus is present in a large number of biologically active natural[2] and synthetic compounds,[3] so its inclusion into combinatorial chemistry libraries could be of interest.[4]

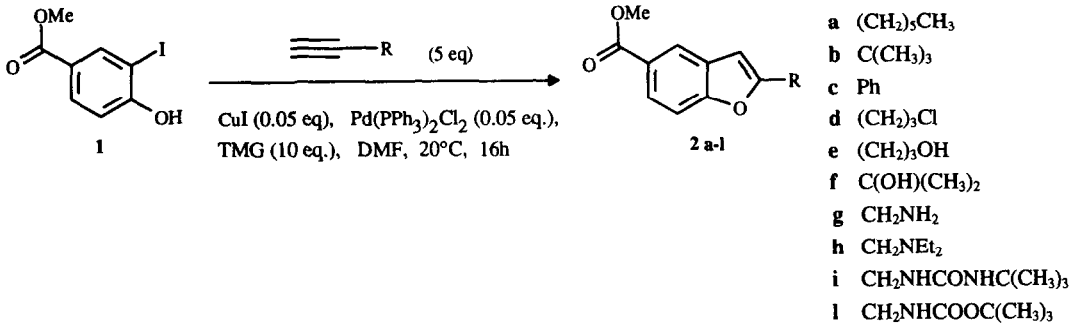
We wish to report here a procedure for the solid phase synthesis of 2-substituted benzofuran carboxylic acids, which utilises a Pd-catalysed heteroannulation of terminal acetylenes in the presence of resin bound *ortho*-hydroxy aryl iodides:



In solution phase the Pd-catalysed heteroannulation of acetylenes has become one of the most widely used methods for the preparation of benzofused heterocyclic compounds. Benzofurans,[5] indoles,[6] S-heterocycles,[7] furopyridines,[8] heterofused pyrroles[9] and chromones[10] have been synthesised using such methodology. As far as the benzofuran synthesis is concerned, the reaction is usually conducted at an elevated temperature in the presence of bases such as tertiary amines or potassium carbonate, but the use of the base tetramethylguanidine (TMG) has been reported to allow good yields and milder reaction conditions.[11]

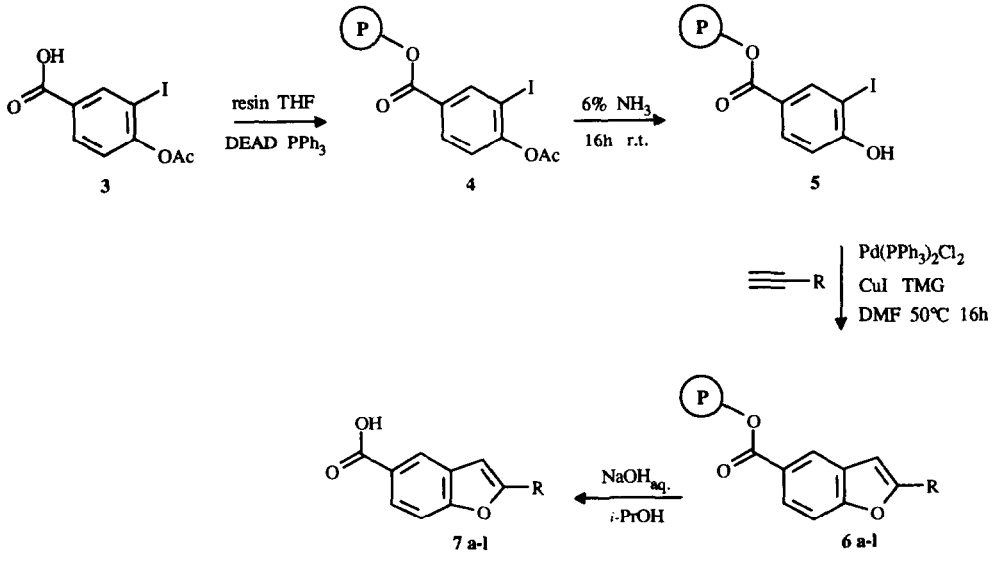
On the basis of this observation, we selected the reaction conditions outlined in Scheme 1 and tested the reaction on a number of acetylenic compounds bearing various functionalities. The 4-hydroxy-3-iodo-benzoic acid methyl ester (**1**) was used as the model.

Scheme 1



In each case the conversion of the starting iodo-phenol **1** exceeded 95% (HPLC) and the yields of isolated benzofurans **2** were in the range 67-90%. On the basis of this result we moved to the solid phase synthesis (Scheme 2).[12]

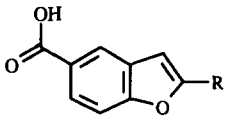
Scheme 2



The starting carboxylic acid **3** was directly linked to the commercial hydroxy resin TentaGel™ S-OH (particle size 130 μm, capacity 0.3 mmol/g) using the Mitsunobu reaction; during the coupling the hydroxyl was protected as an acetate to avoid self-condensations. The protective group was then removed by mild alkaline

hydrolysis and the resulting *ortho*-hydroxy iodide **5** reacted smoothly in the cyclization step to give the resin linked benzofurans **6**. Cleavage from the resin was performed with 1N aqueous sodium hydroxide / isopropyl alcohol. After neutralisation, HPLC quantitative assay[13] showed that benzofurans **7 a-l** were obtained as essentially pure compounds in overall yields ranging from 40 - 70% (Table 1).

Table 1



7 a-l

entry	R	yield (%)[a]	HPLC area %[b]
7 a	$(CH_2)_5CH_3$	53	89
7 b	$C(CH_3)_3$	40	94
7 c	Ph	71	88
7 d	$(CH_2)_3Cl$	61	71
7 e	$(CH_2)_3OH$	55	86
7 f	$C(OH)(CH_3)_2$	65	89
7 g	CH_2NH_2	not determined	90
7 h	CH_2NEt_2	42	88
7 i	$CH_2NHCONHC(CH_3)_3$	52	85
7 l	$CH_2NHCOOC(CH_3)_3$	55	85

a) Overall yields[13] based on the nominal capacity of the resin; b) normalised HPLC area.

To assess the suitability for automated combinatorial chemistry methodologies, the process was also carried out in a standard polypropylene 96 well-plate (1 ml capacity per well), loading 12 - 15 mg of **5** per well. In this case, after cleavage from the resin, the reaction mixtures were evaporated and the final products taken up and delivered in DMSO solution (750 µl) at 0.7 - 3.0 mM concentration.

In conclusion, the Pd-promoted heteroannulation of acetylenes has been proved as a valuable method for the solid phase synthesis of benzofurans; considering the mild reaction conditions and the large variety of acetylenic compounds commercially available, this method provides an efficient tool for increasing diversity in the design of combinatorial chemistry libraries of small organic molecules.

Acknowledgement The authors wish to thank M. Colombo and L. Franzoi for performing LC-MS analysis.

REFERENCES AND NOTES

1. For recent reviews, see: a) Hermkens, P. H. H. ; Ottenheijm, H. C. J. *Tetrahedron* **1996,** *13*, 4527-4554; b) Fruchtel, J. S. ; Jung, J. *Angew. Chem. Int. Ed. Eng.* **1996,** *35*, 17-42.
2. Cagniant, P. ; Cagniant, D. *Adv. Heterocycl. Chem.* **1975,** *18,* 337.
3. a) Manning, A.S. ; Bruyninckx, C. ; Hodeige, D. ; Ramboux, J. ; Chatelain, P. *Brit. J. Pharmacol.* **1992,** *107* (Suppl.) Abs. 270P; b) Middlemiss, D. ; *et al. BioMed. Chem. Lett.* **1993,** *3(4)* 589.; c) Morris, J. ; Wishka, D.G. ; Humphrey, W. R. ; Lin, A. H. ; Wiltse, A. L. ; Benjamin, C. W. ; Gorman, R. R. ; Shebuski, R. J. *BioMed. Chem. Lett.* **1994,** *4(21)* 2621; d) Halfpenny, P. R. ; Horwell, D. C. ; Hughes, J. ; Hunter, J. C. ; Rees, D. C. *J. Med. Chem.* **1990,** *33(1)* 286; e) Gammil, R. B. ; Bell, F. P. ; Bell, L. T. ; Bisaha, S. N. ; Wilson, G. J. *J. Med. Chem.* **1990,** *33(10)* 2685; f) Van Wijngaarden, I.. ; Kruse, C. G. ; van der Heiden, J. A. M. ; Tulp, M. T. M. *J. Med. Chem.* **1988,** *31(10)*1934;
4. For a recent work on the solid-phase synthesis of benzofurans see: Boehm, T. L.; Showalter, H. D. Hollis *J. Org. Chem.* **1996,** *61(19),* 6498.
5. a) Arcadi, A. ; Marinelli, F. ; Cacchi, S. *Synthesis* **1986,** 749; b) Kundu, N. G. ; Pal, P. ; Mahanti, J. S. ; Dasgupta, S. K. *J. Chem. Soc. Chem. Commun.* **1992,** 41; c) Larock, R.C. ; Yum, E. K. ; Doty, M. J. ; Sham, K. K. C. *J. Org. Chem.* **1995,** *60(11),* 3270.
6. a) Stephens, R. D. ; Castro, C. E. *J. Org. Chem.* **1963,** *28,* 3313; b) Sakamoto, T. ; Kondo, Y. ; Iwashita, S. ; Nagano, T. ; Yamanaka, H. *Chem. Pharm. Bull.* **1988,** *36,* 1305; c) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991,** *113(17),* 6689; d) Jeschke, T. ; Wensbo, D. ; Annby, U. ; Gronowitz, S. ; Cohen, L. A. *Tetrahedron Lett.* **1993,** *34,* 6471.
7. Spencer, J. ; Pfeffer, M. ; DeCian, A. ; Fisher, J. *J. Org. Chem.*. **1995,** *60*,1005.
8. Houpis, I.N. ; Choi, W.B. ; Reider, P.J. ; Molina, A. ; Churchill, H. ; Lynch, J. ; Volante, R.P. *Tetrahedron Lett.* **1994,** *35(50),* 9355.
9. Wensbo, D. ; Eriksson, A. ; Jeschke, T. ; Annby, U. ; Gronowitz, S. ; Cohen, L. A. *Tetrahedron Lett.* **1993,** *34,* 2823.
10. Kalinin, V. N. ; Shostakovsky, M. V. ; Ponomaryov, A. B. *Tetrahedron Lett.* **1990,** *31(28),* 4073.
11. Candiani, I. ; DeBernardinis, S. ; Cabri, W. ; Marchi, M. ; Bedeschi, A. ; Penco, S. *Synlett* **1993,** *3*, 269.
12. Typical experimental conditions:

    Resin bound ortho-acetoxy aryl iodide 4 4-Acetoxy-3-iodo-benzoic acid (0.46 g, 1.5 mmol), THF (50 ml), TentaGel™ hydroxy resin (1.00 g, 0.3 mmol) and Ph_3P (0.80 g, 3.0 mmol) were sequentially added under argon atmosphere to a dry 100 ml peptide reaction flask. To this mixture, a solution of diethylazodicarboxylate (0.54 ml, 3 mmol) in THF (5 ml) was added dropwise at 5°C. After shaking the resulting mixture for 16 hours at room temperature, the solvent and excess reactants were filtered off and the resin was washed with THF, MeOH, and Et_2O. The coupling cycle was repeated twice, and the resulting resin was vacuum dried to afford 1.07 g of **4**. A loading of 0.23 meq/g was determined by quantitative HPLC measurement of an aliquot of cleaved material.[13]

    Resin bound ortho-hydroxy aryl iodide 5 The above obtained dry resin (1.0 g) was treated with 60 ml of tetrahydrofuran, 20 ml of methanol, and 20 ml of 30% ammonia aqueous solution. The reaction mixture was kept at 20°C with occasional shaking for 16 hours. Afterwise the resin was collected, sequentially washed with THF, MeOH, and Et_2O, and vacuum dried.

    Resin bound benzofuran derivative 6c The resin **5** (80 mg), DMF (5 ml), phenylacetylene (100 µl), tetramethylguanidine (300 µl), Pd $(PPh_3)_2Cl_2$ (10 mg), and CuI (5.0 mg), were sequentially added to a round bottom reaction flask. The reaction flask was then stoppered and the reaction mixture was heated at 50°C for 16 hours with occasional stirring. The solvent and excess reactants were then removed by filtration, and the remaining light brown solid support was washed with DMF, MeOH, Et_2O and dried *in vacuo*.

    2-Phenyl-benzofuran-5-carboxylic acid 7c The resin bound benzofuran derivative **6c** was treated with *i*-PrOH (1.3 ml) and 1N aqueous NaOH (3.3 ml). The resulting mixture was heated at 50°C for 8 hours with occasional shaking, and then left at room temperature overnight. The solid support was removed by filtration, the pH of the residual hydroalcoholic solution was adjusted to about 7 with 5N aqueous HCl, and the 2-phenyl-benzofuran-5-carboxylic acid **7c** quantitatively assayed.

13. Analytical samples of compounds **7a**, **7c**, **7d**, **7f**, and **7i** were prepared, and their HPLC response factors were used for quantitatively assaying or for estimating the 2-substituted benzofuran-5-carboxylic acids **7**.
    HPLC conditions: 4.7 X 110 mm Whatman PartiSphere 5 C18 column; flow rate 1.5 ml/min; gradient elution 20 - 70% acetonitrile / 0.05M KH_2PO_4 buffer solution for 10 min, then 70% acetonitrile / 0.05M KH_2PO_4 buffer solution for 10 min; area integration at 220 nm.

(*Received in UK* 18 *November* 1996; *revised* 12 *February* 1997; *accepted* 14 *February* 1997)