Three-step synthesis of an array of substituted benzofurans using polymer-supported reagents

Jörg Habermann, Steven V. Ley * and René Smits

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW

Received (in Cambridge, UK) 2nd June 1999, Accepted 27th July 1999

An efficient combinatorial route to substituted 3-phenylbenzofurans, is achieved by the bromination of acetophenones to α-bromoacetophenones by polymer-supported pyridinium bromide perbromide (PSPBP). The subsequent clean substitution of the obtained bromides by phenols using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD-P) and cyclodehydration of the resulting α-phenoxyacetophenones using Amberlyst 15, affords pure products without the need for any chromatographic purification step.

The continuous identification of new pharmacological targets by biological screening has led to the synthesis of a large number of substances using combinatorial techniques. In general, chemical libraries containing large numbers of compounds may be prepared either on polymeric supports or in solution.[1a] The use of supported reagents combines the advantages of solution (*e.g.* the ease of monitoring the progress of the reactions by applying LC-MS, TLC or NMR techniques) and solid phase chemistry (*e.g.* allowing the employment of an excess of reagent without the need for additional purification steps). Solid supported reagents have been heavily investigated since 1970. Despite the fact that an overwhelming number of reagents and sequestering agents have been developed on solid phase[1] only a few of these have found an application in combinatorial chemistry.[2] Recent work in our group has focussed on the application of polymer-supported reagents in the *multi-step synthesis* of chemical libraries and natural products.[3] In this communication we wish to report a further example using various supported reagents for the efficient construction of heterocyclic derivatives.

Benzofuran derivatives are an important class of heterocyclic compounds that are known to possess important biological properties. Substituted benzofurans find application as antioxidants, brightening agents, a variety of drugs and in other fields of chemistry and agriculture.[4] Therefore, the development of a simple, fast and flexible method to generate libraries of such compounds was desirable. 3-Substituted benzofurans, which are difficult to obtain as the aryl group easily rearranges from the 3- to 2-position,[5] could be synthesised conveniently from α-phenoxyacetophenones in the presence of zeolites, although the yields were quite low and a tedious cleaning procedure was required.[6] Toluene-*p*-sulfonic acid has also been used to cyclise an aryloxyketone to yield a substituted benzofuran in the synthesis of benzopsoralenquinone derivatives.[7] We have designed a route to 3-phenylbenzofurans using an orchestrated sequence of polymer-supported reagents. In the key step, the cyclodehydration, the polymer-bound equivalent of toluene-*p*-sulfonic acid, Amberlyst 15 is used.

Starting from a range of commercially available acetophenones **1a**–**h** (Fig. 1) an α-bromination was carried out, using polymer-supported pyridinium bromide perbromide (PSPBP)[8] in toluene at 5 °C (**1a**–**e**), −10 °C (**1f**, **g**) and −15 °C (**1h**).[9] The major problem was the formation of the undesired dibromination product. Therefore, the process needed careful control of the reaction temperature, especially when using activated acetophenones. When using deactivated ketones the reaction could not be driven to completion (see Table 1). Similar

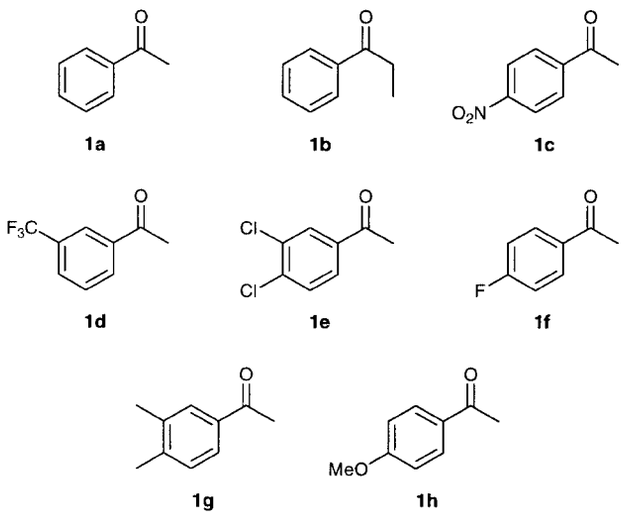
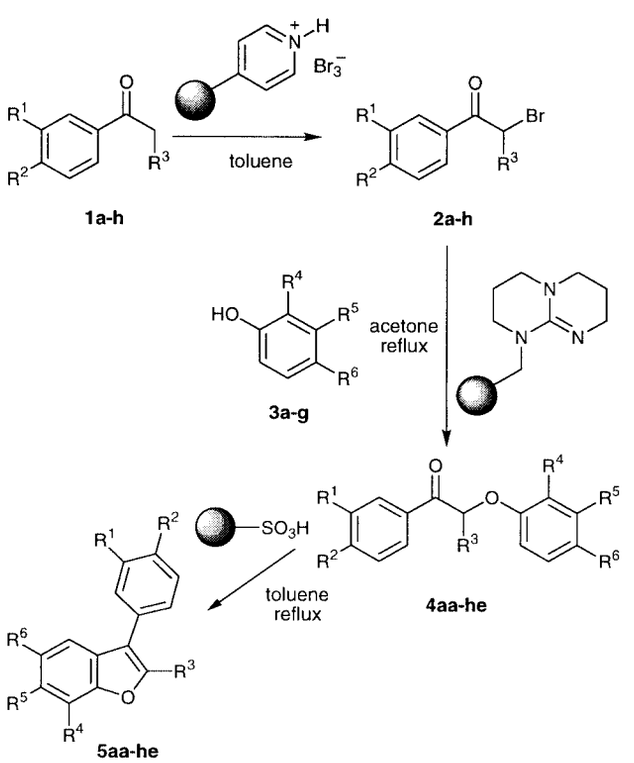


Fig. 1 Acetophenones brominated to α-bromoacetophenones by PSPBP.



Scheme 1

brominations using Amberlyst resins have also been described.[10a–d] The α-bromoacetophenones **2a**–**h** (Scheme 1) were then reacted with a range of commercially available phenols

Table 1 Summary of polymer-supported reactions

	Yield (%)[16]	Purity (%)[17]	ES-MS[18]		Yield (%)[16]	Purity (%)[17]	ES-MS[18]
2a	87	>95	201.10 (+)	**4hc**	86	95	293.19 (+)
2b	60	95	215.10 (+)	**4hd**	83	95	323.09 (+)
2c	84	87	243.81 (−)	**4he**	61	>95	273.23 (+)
2d	92	93	266.91 (−)	**5aa**	96	95	194.10[19]
2e	93	95	218.00 (+)	**5ab**	97	95	209.22 (+)
2f	80	>95	227.12[19]	**5ac**	95	90	245.12 (+)
2g	quant.	70	218.00 (+)	**5ad**	99	95	292.29 (+)
2h	89	93	231.05 (+)	**5ae**	quant.	95	224.10[19]
4aa	71	95	213.01 (+)	**5ba**	quant.	95	209.23 (+)
4ab	59	95	227.19 (+)	**5bb**	91	>95	223.20 (+)
4ac	95	90	263.13 (+)	**5bc**	98	>95	259.26 (+)
4ad	89	95	293.10 (+)	**5bd**	94	>95	288.50 (+)
4ae	67	95	243.23 (+)	**5be**	89	95	239.15 (+)
4af	76	95	281.02 (+)	**5da**	61	>95	262.10[19]
4ag	62	>95	258.30 (+)	**5db**	58	>95	276.98 (+)
4ba	75	>95	227.25 (+)	**5dc**	85	87	353.12 (+)
4bb	76	>95	241.17 (+)	**5dd**	quant.	87	360.45 (+)
4bc	92	95	227.20 (+)	**5de**	77	75	292.10[19]
4bd	87	>95	305.07 (−)	**5fa**	86	90	235.18 (+)
4be	76	>95	257.16 (+)	**5fb**	81	95	227.20 (+)
4da	54	87	281.17 (+)	**5fc**	92	90	262.10[19]
4db	42	93	295.21 (+)	**5fd**	quant.	95	292.00[19]
4dc	82	87	352.12 (+)	**5fe**	89	95	243.23 (+)
4dd	85	93	359.01 (−)	**5ha**	79	95	223.66 (−)
4de	30	75	311.13 (+)	**5hb**	80	95	239.25 (+)
4fa	57	90	231.23 (+)	**5hc**	quant.	95	275.10 (+)
4fb	55	95	244.99 (+)	**5hd**	quant.	95	302.00[19]
4fc	83	90	281.10 (+)	**5he**	57	>95	255.27 (+)
4fd	73	95	311.00 (+)	**6a**	66	>95	238.22 (+)
4fe	56	95	261.20 (+)	**6d**	89	93	306.13 (+)
4ha	64	95	243.23 (+)	**6f**	73	>95	256.19 (+)
4hb	52	95	257.18 (+)	**6h**	65	95	268.19 (+)

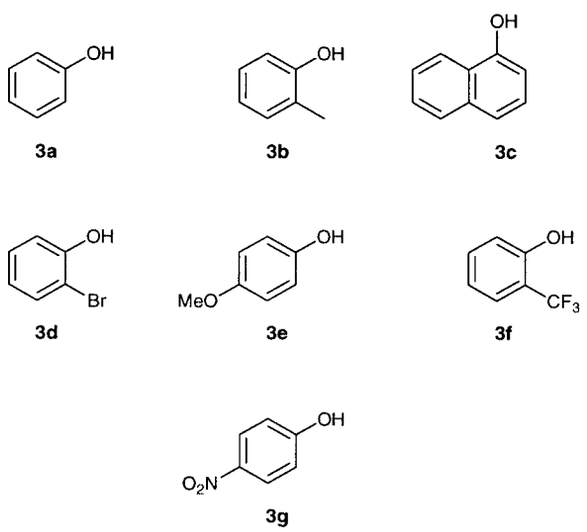
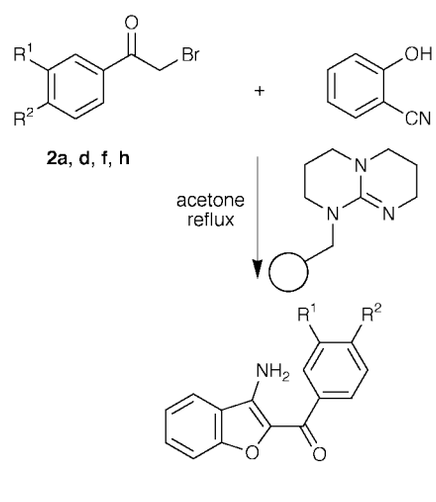


Fig. 2 Phenols used in the substitution reaction to α-phenoxyacetophenones using TBD-P.

3a–**g** (Fig. 2) in refluxing acetone using 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD-P)[11] as a base to effect the substitution reaction. Excellent yields and purities of the corresponding α-phenoxyacetophenones were obtained with electron-rich and electron-deficient bromides and phenols. When using α-bromo-3,4-dichloroacetophenone **2e** some by-products were formed and the purity was found to be below 50%. No reaction could be observed using α-bromo-4-nitroacetophenone **2c**, although the polymer went black after the addition of the bromide.

The heterocyclic benzofuran ring system was then constructed by a clean cyclodehydration of the α-phenoxyacetophenones in toluene under reflux for seven hours, using Amberlyst 15 as a cyclising agent. When α-(1-bromophenoxy)-acetophenones **4(a**–**h)d** were cyclised, longer reaction times were observed. It is assumed that this is due to increased steric hindrance of the reactive center. When using α-(4-methoxy-phenoxy)acetophenones **4(a**–**h)e**, mixtures of 2- and 3-phenyl isomers were obtained. The presence of the methoxy group on the acyl ring lowers the reaction temperature for the cyclo-dehydration and facilitates the acid catalysed migration of the phenyl group. The reaction could be controlled by reducing the temperature to 80 °C and in one case (**5hd**) to 100 °C;[12] only the desired 3-phenyl isomers were formed. The reaction works well with unsubstituted α-phenoxyacetophenones and with compounds containing activating substituents in the phenoxy ring. The cyclisation of aryloxyketones that carry electron deficient phenoxy groups was not possible under these conditions. An electron withdrawing group attached to the acetophenone moiety causes the yields/purities to decrease.

It was also possible to synthesise 3-aminobenzofurans (**6a**–**d**) from α-bromoacetophenones in one step. The bromides were refluxed with 2-cyanophenol and TBD-P in acetone (Scheme 2). 3-Aminobenzofurans are important precursors of tricyclic



Scheme 2

compounds that are of interest in many pharmaceutical products.[13]

In conclusion, we have generated an array of 3-phenylbenzofurans **5** and 3-aminobenzofurans **6** without any chromatographic purification step to demonstrate the versatility of sequentially applying polymer-supported reagents in synthetic sequences. Many further analogues could, in principle, be generated by this route. All reactions produced essentially clean products, as determined by LC-MS and NMR spectroscopy. All intermediates could also be isolated by intercepting part of the reaction streams and used in other synthetic programmes, *e.g.* α-bromoacetophenones may be used in the synthesis of 2-hydroxy-2-aryl-1,4-benzodioxanes, which exhibit a wide range of biological activity,[14] or in the synthesis of 4-phenylthiazoles, some of which are Interleukin inhibitors.[15]

Acknowledgements

We gratefully acknowledge financial support from the Erasmus Fellowship (to R. S.), the *Stiftung Stipendien-Fonds des Verbandes der Chemischen Industrie* (Germany, Post Doctoral Fellowship to J. H.), Cambridge Combinatorial, the BP endowment and the Novartis Research Fellowship (to S. V. L.).

Notes and references

1 (*a*) L. A. Thompson and J. A. Ellman, *Chem. Rev.*, 1996, **96**, 555; (*b*) A. Akelah and D. C. Sherrington, *Chem. Rev.*, 1981, **81**, 557; (*c*) S. J. Shuttleworth, S. M. Allin and P. K. Sharma, *Synthesis*, 1997, 1217; (*d*) S. W. Kaldor and M. G. Siegel, *Curr. Opin. Chem. Biol.*, 1997, **1**, 101.

2 (*a*) M. J. Suto, L. M. Gayo-Fung, M. S. S. Palanki and R. Sullivan, *Tetrahedron*, 1998, **54**, 4141; (*b*) L. M. Gayo and M. J. Suto, *Tetrahedron Lett.*, 1997, **38**, 513; (*c*) J. J. Parlow, *Tetrahedron Lett.*, 1996, **37**, 5257; (*d*) S. W. Kaldor, M. G. Siegel, J. E. Fritz, B. A. Dressman and P. J. Hahn, *Tetrahedron Lett.*, 1996, **37**, 7193; (*e*) D. L. Flynn, R. V. Devraj and J. J. Parlow, *Curr. Opin. Drug Discovery Dev.*, 1998, **1**, 41; (*f*) D. H. Dewry, D. M. Coe and S. Poon, *Med. Res. Rev.*, 1999, **19**, 97; (*g*) S. F. Oliver and C. Abell, *Curr. Opin. Chem. Biol.*, 1999, **3**, 299; (*h*) J. J. Parlow, R. V. Devraj and M. S. South, *Curr. Opin. Chem. Biol.*, 1999, **3**, 320.

3 (*a*) B. Hinzen and S. V. Ley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 1; (*b*) F. Haunert, M. H. Bolli, B. Hinzen and S. V. Ley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2235; (*c*) S. V. Ley, M. H. Bolli, B. Hinzen, A.-G. Gervois and B. J. Hall, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2239; (*d*) M. H. Bolli and S. V. Ley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2243; (*e*) J. Habermann, S. V. Ley and J. S. Scott, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 3127; (*f*) M. Caldarelli, J. Habermann and S. V. Ley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 107; (*g*) S. V. Ley, A. W. Thomas and H. Finch, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 669; (*h*) S. V. Ley, O. Schucht, A. W. Thomas and P. J. Murray, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1251; (*i*) J. Habermann, S. V. Ley and J. S. Scott, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1253; (*j*) M. Caldarelli, J. Habermann and S. V. Ley, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2049.

4 See for example: N. P. Ph. Buu-Hoï, E. Bisagni, R. Royer and C. Routier, *J. Chem. Soc.*, 1957, 625.

5 W. Davies and S. Middleton, *J. Chem. Soc.*, 1959, 3544.

6 Z. Chen, X. Wang, W. Lu and J. Yu, *Synlett*, 1991, 121.

7 A. Chilin, G. Pastorini, A. Castellin, F. Bordin, P. Rodighiero and A. Guiotto, *Synthesis*, 1995, 1190.

8 M. Fréchet, M. J. Farrel and L. J. Nuyens, *J. Macromol. Sci. Chem.*, 1977, **11**, 507.

9 During the synthesis of **2h** the polymer was added in small portions.

10 (*a*) S. Cacchi, L. Caglioti and E. Cernia, *Synthesis*, 1979, 64; (*b*) A. Bongini, G. Cainelli, M. Contento and F. Manescalchi, *Synthesis*, 1980, 143; (*c*) F. Rahaingoson, B. Kimpiobi-Ninafiding, Z. Mouloungui and A. Gaset, *Synth. Commun.*, 1992, **22**, 1923; (*d*) J. J. Parlow, *Tetrahedron Lett.*, 1995, **36**, 1395.

11 W. Xu, R. Mohan and M. M. Morrissey, *Tetrahedron Lett.*, 1997, **38**, 7337.

12 Longer reaction times were observed.

13 (*a*) V. P. Vaidya, S. B. Mahajan and Y. S. Agasimundin, *Ind. J. Chem. B*, 1981, **20**, 391; (*b*) B. Viti, D. Gianotti, R. Nannicini, R. Ricci and V. Pestellini, *J. Heterocycl. Chem.*, 1991, **28**, 379; (*c*) W. W. K. R. Mederski, M. Osswald, D. Dorsch, M. Christadler, C. J. Schmitges and C. Wilm, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 619.

14 T. Ganesh, C. Harish Kumar and G. L. David Krupadanam, *Synth. Commun.*, 1999, **29**, 2069.

15 K. Yamaguchi, M. Yada, T. Tsuji, Y. Hatanaka, K. Goda and T. Kobori, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 957.

16 Yield determined by weight for reaction from precursor compound.

17 Purity as estimated from ^{1}H NMR spectroscopy.

18 Masses given are obtained in the mode denoted in brackets. Mass ions are generally [M + H] or [M − H], in some case [M+NH_4] or [M+Na].

19 No mass ion could be observed under ES-MS conditions; EI-MS conditions were applied.

Communication 9/04384E