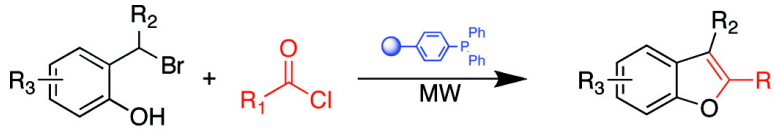
JOURNAL OF combinatorial CHEMISTRY

Article

Synthesis of Substituted Benzofurans via Microwave-Enhanced Catch and Release Strategy

Lidia De Luca, Giampaolo Giacomelli, and Giammario Nieddu

J. Comb. Chem., **2008**, 10 (4), 517-520• DOI: 10.1021/cc8000162 • Publication Date (Web): 29 May 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Synthesis of Substituted Benzofurans via Microwave-Enhanced Catch and Release Strategy

Lidia De Luca, Giampaolo Giacomelli,* and Giammario Nieddu

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

Received January 30, 2008

A microwave-enhanced procedure for the synthesis of substituted benzofurans starting from 2-(1-hydroxyalkyl)-phenols and using triphenylphosphine polystirene resin is reported. The benzofurans are isolated in good to high yields and purities by simple workup. The procedure can be applied to chiral α-alkyl-2-benzofuranmethanamines too.

The derivatives of benzofurans appear at a significantly lower amount in nature than the isoelectronic analogue indole. However, many 2-substituted benzofurans are well-known to exhibit a broad range of biological activities,[1] and therefore, the search for new biologically active compounds in this series is of interest. From this point of view, synthetic methods may be very useful in the production of specific structures characterized by given pharmacological qualities.

In recent years, many synthetic strategies were developed for this type of compound, and combinatorial approaches have also been a dynamic research area.[2] Many synthetic methodologies involve the condensation reactions between carbonyl compounds and different forms of nucleophiles.[3] Other synthetic approaches are based on the formation of furan rings from arene derivatives, involving dehydration of *o*-hydroxybenzyl ketones under acidic conditions,[4] base-mediated decarboxylation of *o*-acyl-phenoxyacetic acids or esters,[5] cyclofragmentation of oxiranes prepared from the corresponding *o*-hydroxybenzophenones,[6] dehydrative cyclization of phenoxy-alkyl ketones,[7] palladium(II)-catalyzed cyclization of aryl acetylenes,[8] *o*-alkenyl or alkynyl phenols,[9] or deprotonation of benzyl ethers under basic conditions.[10] However, several of these methods require strong acidic or basic conditions or cannot start from readily available materials for the introduction of different substituent patterns.

A valid alternative is based on the use of hindered nonionic phosphazene base P_4-*t*-Bu.[11] A synthetic approach to malibatol A,[12] featuring a novel benzofuran synthesis was described by Kraus.[13] A wide array of benzofurans were prepared through CuI-catalyzed ring closure of *o*-halobenzylketones in excellent yields.[14] A sustainable protocol for 2-alkyl- or 2-aryl-substituted benzofurans was reported to involve a copper-TMEDA complex that catalyzed the transformation of benzyl ketones into the corresponding benzofurans in high yields.[15] The particularity of the reaction consisted in the use of water as solvent. Water was the solvent used by Buchwald[16] who developed a one-pot protocol for the preparation of 2-substituted benzofurans from 2-chloroaryl alkynes via a palladium-mediated methodology.[17]

Chiral, non racemic 1-(benzofuran-2-yl)-arylamines have been achieved from enantiomerically pure or enriched arylpropargylamines by Botta, who extensively prepared these compounds for studies in the treatment of fungal skin infections.[18] Very recently, a Rh(I)-catalyzed demethylation−cyclization sequence for a direct transformation of *o*-anisole-substituted ynamides to chiral 2-amido benzofurans was described.[19]

All of these methods have some limitations, and therefore alternative methods are still desirable. A very attractive procedure for the preparation of a chiral 2-substituted benzofuran derivative was reported by Lee et al. in an approach to the total synthesis of kendomycin.[20] The synthesis of the benzofuranyl compound was accomplished using a two-stage method[21] in which a phenolic phosphonium bromide was merged through a Wittig process with the chiral nonracemic 5-benzyloxy-2, 4-dimethylpentanoic acid.

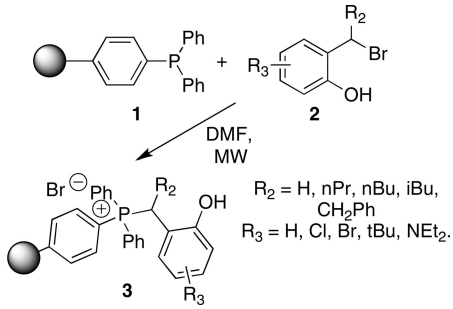
Following similar considerations, we have reported recently an effective route to chiral optically active 2-substituted benzofurans directly from carboxylic acids.[22] This procedure, which allowed the preparation of α-alkyl-2-benzofuranmethanamines from N-protected α-amino acids without sensible racemization phenomena, proceeded under mild conditions and in good yields. However, a drawback of this procedure was the recovery and purification of the final product because of the presence of triphenylphosphine oxide as byproduct.

To avoid this limitation, a "traceless" strategy has to be designed that would be compatible with the synthesis of heterocyclic systems. With recent advances in solid-phase synthesis, several combinatorial methods for the production of benzofuran libraries have been described.[6,23] To prepare a collection of benzofurans with a high degree of potential diversity and wide utility for drug discovery using solid-phase techniques, it also appeared to be important to develop a synthesis in which at least three substituents can be independently and readily varied. Simple considerations on

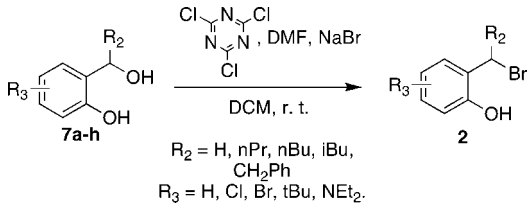
* To whom correspondence should be addressed. E-mail: ggp@uniss.it.

10.1021/cc8000162 CCC: $40.75
Published on Web 05/29/2008

Scheme 1. Preparation of Resin-Bound (2-Hydroxybenzyl)-triphenylphosphonium Bromide



Scheme 2. Preparation of Compounds **2**



solid-phase organic synthesis encouraged the transfer of the solution-phase reaction to the solid phase.

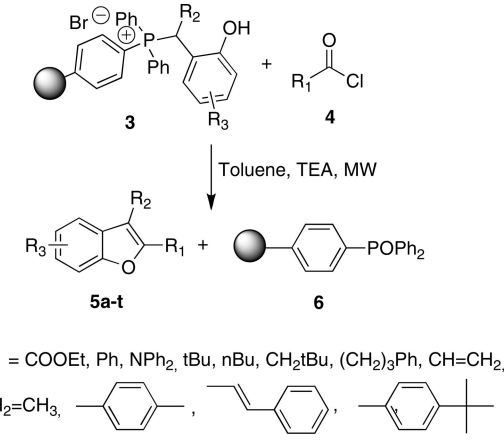
Therefore as a part of studies designed toward the development of new techniques for combinatorial heterocyclic synthesis under mild conditions,[24] we wish to report herein the use of triphenylphosphine polystirene resin for the synthesis of a library of benzofuran diversomers through a catch and release methodology.

Thus, triphenylphosphine polystirene resin **1** (0.16 mmol/g) was charged with the proper 2-(bromoalkyl)-phenol **2** in dry DMF (Scheme 1). The formation of the functionalized support **3** could be achieved only heating the mixture for too long, so the reactions were conducted under microwave irradiation to shorten the reaction time.[25] Thus the reaction mixture was heated in a sealed tube (CEM designed 10 mL pressure-rated reaction vial) and exposed to microwave irradiation for two cycles of 15 min at 85 °C.[26] Then the resin was washed thoroughly with portions of DMF, hexane, THF, hexane, and DCM in sequence.

Commercial 2-(1-hydroxyalkyl)-phenols **7** were used in the preparation of the 2-(bromoalkyl)-phenols **2**. Otherwise products **7** were obtained from 2-hydroxybenzaldehydes by reduction with $NaBH_4$ or through reaction with the proper Grignard reagent. The carbinols so obtained were successively converted into the corresponding 2-(bromoalkyl)-phenols **2** using a procedure, slightly modified, reported in the literature.[27] The method was based on the reaction of 2,4,6-trichloro[1,3,5]triazine (TCT) with DMF, followed by addition of 2 equiv of NaBr. After 12 h, a DCM solution of 1 mol equiv of 2-(1-hydroxyalkyl)-phenol **7** was added. At 25 °C, this system operates the quantitative conversion of the alcohols to the corresponding 2-(bromoalkyl)-phenols (Scheme 2), which can be recovered as sole products after a simple aqueous workup that removes the triazine byproducts.

It is to be noted that the reaction is totally chemoselective because under the reaction conditions adopted no reaction at the phenol hydroxyl was noted. The bromides **2** were directly anchored to the triphenylphosphine polystirene resin **1**, without any purification, avoiding therefore the storage because of the limited stability of the compounds.[28]

Scheme 3. Preparation of Benzofurans



Treatment of the resin **3** with an acyl chloride **4** and TEA afforded the isomerically pure benzofuran derivative **5** that can be recovered from the solution, leaving the triphenylphosphine oxide polystirene resin **6** (Scheme 3) as a solid residue.[29] The cyclization step was carried quantitatively in dry toluene. The reactions were carried out under microwave irradiation in a sealed tube, operating at 110 °C for two cycles of 30 min. The benzofurans **5** were recovered by filtration of the mixture and washing of the resin with toluene (Table 1). The residue acyl chloride was removed by treatment with $NaHCO_3$ aqueous solution.

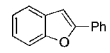
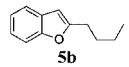
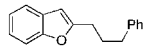
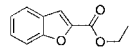
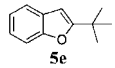
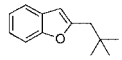
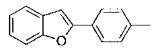
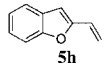
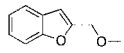
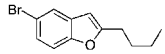
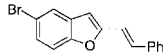
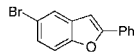
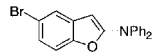
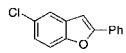
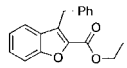
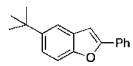
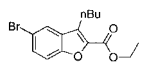
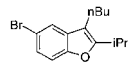
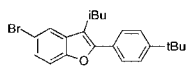
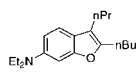
Yields are good in all cases examined, and the benzofurans can be recovered almost pure. Further, but simple, purification workup on column chromatography can be achieved to produce chemically pure products.

Finally we have tested the possibility of preparing optically active α-alkyl-α-(benzofuran-2-yl)-methanamines,[22] using the above-reported traceless procedure. Therefore, considering the difficulty of preparing and using N-protected amino acid chlorides,[30] we used 2,4,6-trichloro-1,3,5-triazine (TCT) in solid-phase procedures.

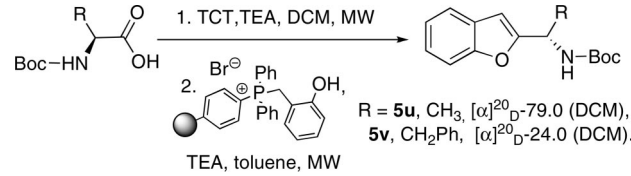
Thus, the optically active *N*-Boc amino acid was joined with TCT and TEA in DCM and MW irradiated to form the activated ester, and then the solvent was removed. The functionalized resin **3** (R_2=R_3=H) was added with toluene, and the mixture was irradiated at 110 °C for 60 min. After it was cooled to room temperature, the resin sample was collected by filtration, and the chiral optically active *tert*-butyl-1-(benzofuran-2-yl)-2-alkylcarbamates were recovered with the same specific rotatory powers of the samples obtained by the solution-phase approach (Scheme 4).[22] The results obtained have claimed that the use of TCT as activator of carboxylic moiety can be easily extended to the solid phase too.

In conclusion, the presented strategy, characterized by short reaction times, mild reaction conditions, and easy reaction workup, provides a facile preparation of substituted benzofurans even with a chiral stereocenter adjacent to the heterocycle directly from the carboxylic acid. This approach seems undoubtedly promising because of the possibility of also using derivatives of salicylaldehyde to extend the range

Table 1. Solid-Phase Synthesis of Benzofurans According Scheme 3

Entry	Compound	Yield (%)
1	 **5a**	65
2	 **5b**	71
3	 **5c**	70
4	 **5d**	69
5	 **5e**	85
6	 **5f**	74
7	 **5g**	66
8	 **5h**	55
9	 **5i**	88
10	 **5j**	81
11	 **5k**	91
12	 **5l**	73
13	 **5m**	75
14	 **5n**	77
15	 **5o**	85
16	 **5p**	85
17	 **5q**	74
18	 **5r**	74
19	 **5s**	79
20	 **5t**	81

Scheme 4. Solid-Phase Synthesis of (*S*)-*tert*-Butyl-1-(benzofuran-2-yl)-2-phenylethylcarbamate



of the final products by the appropriate choice of the chiral nonracemic carboxylic acid.

Experimental Section

General Procedure for Microwave-Assisted Benzofuran Synthesis. To a suspension of triphenylphosphine polystirene resin **1** (0.10 g, 0.160 mmol) swollen in dry DMF (1 mL) was added 2-(bromomethyl)phenol (0.12 g, 0.640 mmol). The resulting mixture was irradiated to 85 °C for 15 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 3 min; then 2-(bromomethyl)-phenol **2** (0.12 g, 0.640 mmol)was added again, and the mixture was irradiated to 85 °C for 15 min as above. After it was cooled to room temperature, the resin sample was collected by filtration using a sintered glass funnel. The resin was thoroughly washed with alternative portions of DMF (3 × 10 mL), hexane (3 × 10 mL), THF (3 × 10 mL), hexane (3 × 10 mL), and DCM (3 × 10 mL). The resin **3** was dried under reduced pressure and then suspended in dry toluene (1 mL). Benzoyl chloride (0.09 mL, 0.80 mmol) and TEA (0.33 mL, 2.4 mmol) were added, and the resulting mixture was irradiated to 110 °C for 60 min in a sealed tube. After it was cooled to room temperature, the resin was removed by filtration using a sintered glass funnel and successively washed alternatively with toluene (3 × 10 mL) and THF (3 × 10 mL). All the organic layers were combined, washed with aq $NaHCO_3$ (2 × 10 mL) and water (2 × 10 mL), and concentrated in vacuum. The crude 2-phenylbenzofuran **5a** (0.11 g, 65% yield) was further purified by chromatography (EtOAc/petroleum ether = 1:9) to obtained a white solid (global yield 61%) mp: 119−122 °C (ref 31 118−120 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.1 Hz, 2H), 7.55 (m, 2H), 7.44 (t, J = 7.1 Hz, 2H), 7.3 (m, 3H), 7.06 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 154.8, 130.4, 129.2, 128.7, 128.5, 124.9, 124.2, 122.9, 120.9, 111.1, 101.3.

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

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

References and Notes

(1) For selected papers on the pharmacological properties of benzofurans, see: (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. (e) 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. (f) 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. (g) Hocke, C.; Prante, O.; Lober, S.; Hubener, H.; Gmeiner, P.; Kuwert, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3963–3966. (h) 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. (i) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796–4805. (j) 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.

(2) (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) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498–6499.

(3) (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.

(4) (a) Adams, R.; Whitaker, L. *J. Am. Chem. Soc.* **1956**, *78*, 658–663. (b) Kalyanasundaram, M.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron Lett.* **1980**, *21*, 4391–4394.

(5) (a) Muller, A.; Meszaros, M.; Kormendy, K. *J. Org. Chem.* **1954**, *19*, 472–484. (b) Horaguchi, T.; Tanemura, K.; Suzuki, T. *J. Heterocycl. Chem.* **1988**, *25*, 39–43. (c) Horaguchi, T.; Kobayashi, H.; Miyazawa, K.; Hasegawa, E.; Shimizu, T. *J. Heterocycl. Chem.* **1990**, *27*, 935.

(6) Nicolaou, K. C.; Snyder, S. A.; Bigot, A.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1093–1096.

(7) (a) Wright, J. B. *J. Org. Chem.* **1960**, *25*, 1867–1872. (b) Royer, R.; Bisagni, E.; Hudry, C.; Cheutin, A.; Desvoye, M.-L. *Bull. Soc. Chim. Fr.* **1963**, 1003–1007. (c) Pene, C.; Demerseman, P.; Cheutin, A.; Royer, R. *Bull. Soc. Chim. Fr.* **1966**, 586–594. (d) Kawase, Y.; Takata, S.; Hikishima, E. *Bull. Soc. Chim. Jpn.* **1971**, *44*, 749–753. (e) Horaguchi, T.; Iwanami, H.; Tanaka, T.; Hasegawa, E.; Shimizu, T. *J. Chem. Soc., Chem. Commun.* **1991**, 44–46.

(8) (a) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803–11812. (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280–9288.

(9) (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. (e) Monteiro, N.; Arnold, A.; Blame, G. *Synlett* **1998**, 1111–1113. (f) Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1998**, *39*, 9605–9608.

(10) Dann, O.; Char, H.; Griessmeier, H. *Liebigs Ann. Chem.* **1982**, 1836–1869.

(11) Kraus, G. A.; Zhang, N.; Verkade, J. G.; Nagarajan, M.; Kisanga, P. B. *Org. Lett.* **2000**, *2*, 2409–2410.

(12) Dai, J. R.; Hallock, Y. F.; Cardellina, J. H.; Boyd, M. *J. Nat. Prod.* **1998**, *61*, 351–353.

(13) Kraus, G. A.; Kim, I. *Org. Lett.* **2003**, *5*, 1191–1192.

(14) Chen, C.-y.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964–6972.

(15) Carril, M.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2006**, *8*, 1467–1470.

(16) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695.

(17) Liao, Y.; Smith, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2005**, *7*, 2707–2709.

(18) Messina, F.; Botta, M.; Corelli, F.; Schneider, M. P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767–3769.

(19) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361–2364.

(20) (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. JP Patent 08231551 [A296090], 1996. (b) Su, M. H.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. US Patent 5728727 [A980317], 1998.

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

(22) De Luca, L.; Giacomelli, G.; Nieddu, G. *J. Org. Chem.* **2007**, *72*, 3955–3957.

(23) (a) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498–6499. (b) Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, 61–62. (c) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311–2314. (d) Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804–1809. (e) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678–5679. (f) Guthrie, E. J.; Macritchie, J.; Hartley, R. C. *Tetrahedron Lett.* **2000**, *41*, 4987–4990. (g) Smith, R. A.; Chen, J.; Mader, M. M.; Muegge, I.; Moehler, U.; Katti, S.; Marrero, D.; Stirtan, W. G.; Weaver, D. R.; Xiao, H.; Carley, W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2875–2878. (h) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 2607–2609. (i) McKiernan, G. J.; Hartley, R. C. *Org. Lett.* **2003**, *5*, 4389–4392. (j) Macloed, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, *68*, 387–401. (k) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909–912. (l) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235–2239. (m) Yao, T.; Yue, D.; Larock, R. C. *J. Comb. Chem.* **2005**, *7*, 809–812.

(24) (a) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M.; Taddei, M. *J. Comb. Chem.* **2003**, *5*, 465–471. (b) Porcheddu, A.; Giacomelli, G.; De Luca, L.; Ruda, A. M. *J. Comb. Chem.* **2004**, *6*, 105–111. (c) Porcheddu, A.; Giacomelli, G.; Chighine, A.; Masala, S. *Org. Lett.* **2004**, *6*, 4925–4927. (d) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Comb. Chem.* **2005**, *7*, 905–908. (e) Porcheddu, A.; Giacomelli, G. *J. Org. Chem.* **2006**, *71*, 7057–7059.

(25) For reviews on microwave-assisted combinatorial chemistry, see: (a) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105. (b) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314–320.

(26) The MW experiments were performed in a self-tuning single mode CEM Discover Focused Synthesizer apparatus. The instrument continuously adjusted the applied wattage to maintain the desired temperature.

(27) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553–555.

(28) We noted that the bromides darkened after about half an hour from recovery. It is however known that (halomethyl) phenols are chemically unstable and irritant compounds. Chauhan, M. S.; Dean, F. M.; McDonald, S.; Robinson, M. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, *35*, 9–363.

(29) Regeneration of the resin may be achieved via treatment with a clear solution of $LiAlH_4$ in THF according to literature in 80% yield. However, the regenerated resin is less efficient than the original and the yields are lowered. Sieber, F.; Wentworth Jr., P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, *64*, 5188–5192.

(30) Carpino, L. A.; Beyermann, M.; Wenschub, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268–274.

(31) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958–10964.

CC8000162