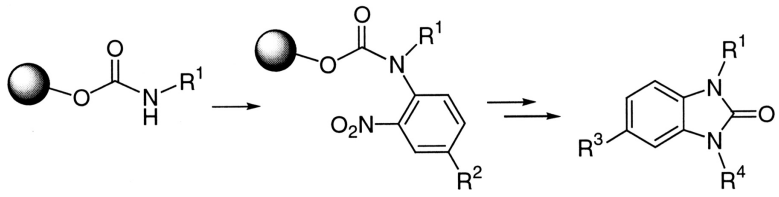
JOURNAL OF combinatorial CHEMISTRY

Article

Traceless Solid-Phase Synthesis of Substituted Benzimidazolones

Chih-Chung Wang, and Wen-Ren Li

J. Comb. Chem., **2004**, 6 (6), 899-902• DOI: 10.1021/cc049926j • Publication Date (Web): 11 September 2004



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

Traceless Solid-Phase Synthesis of Substituted Benzimidazolones

Chih-Chung Wang and Wen-Ren Li*

Department of Chemistry, National Central University, Chung-Li, Taiwan 32054

Received April 2, 2004

Introduction. Drug discovery in modern bioorganic and medicinal chemistry has been accelerated with the application of combinatorial and parallel synthesis techniques for developing compound libraries. The successful applications of these approaches facilitate speedy availability of closely related analogues for biological-activity evaluation. Recent reviews on the survey of combinatorial library synthesis[1−8] and several reports of combinatorial synthesis of wide range of bioactive compounds[9−14] revealed the burgeoning interest of researchers in this technique. The concept of solid-phase synthesis came to the forefront in 1963 with Merrifield's publication of the synthesis of L-leucy-L-alanylglycyl-L-valine via attachment of the intermediate to the polymer backbone.[15] The major advantages of solid-phase synthesis that make it superior to standard solution-phase technique are (i) isolation of products is by simple filtration, (ii) an excess of reagents can be used to drive reactions to completion, (iii) the process is economic with respect to time and cost, and (iv) the method can be automated. The traceless solid-phase synthesis, in which the group used for the attachment to solid supports is not left with the final target molecule, holds great importance because it is established fact that the functional group has a dramatic effect on the biological efficacy of the molecule.[16−18] In some cases, the functional group left on the target molecule may not be desired for bioactivity and may limit final the structural optimization.

Benzimidazolones and other related cyclic urea derivatives are useful heterocyclic building blocks and have been shown to possess significant biological properties, including inhibition of aldose reductase, antagonism of neurotransmitter receptors, antiulcer activity, antimicrobial activity,[19] and modulation of ion channels.[20,21] Such a spectrum of biological activity has attracted considerable attention to these compounds, and recently, researchers have reported several solid- and solution-phase synthesis approaches toward benzimidazolones and related derivatives.[18,22−28] A common feature of these approaches is the attachment of the heterocycle to the support through an ester linkage, thus resulting in a carboxylic acid residue on the final product upon cleavage. Herein, we report a versatile route to substituted benzimidazolones involving a cyclative cleavage of a carbamate linkage and also having the extra advantage of leaving no trace of the resin linker.

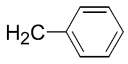
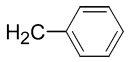
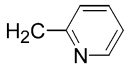
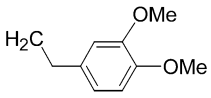
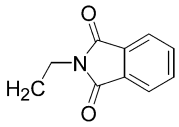
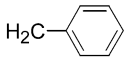
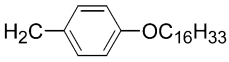
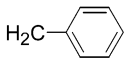
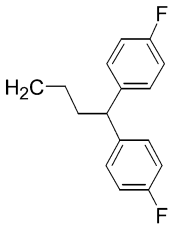
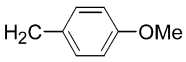
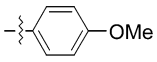
Results and Discussion. A new approach to substituted benzimidazolones is shown in the Scheme 1. The key step of the sequence involved the introduction of one of the nitrogens by nucleophilic addition of a carbamate to an *o*-fluoronitrobenzene. Spontaneous cyclization and detachment of the benzimidazolones from the resin occurred in high yields under reductive conditions on solid supports. To further expand the scale and incorporate a third element of diversity into the library of target molecules, the benzimidazolones were treated with NaH and various alkyl halides in DMF to afford fully functionalized benzimidazolones. Representative products were prepared on solid supports in excellent yields and purities by the protocol described above, and these results are summarized in Table 1. Each compound was fully characterized by ^{1}H, ^{13}C NMR, and mass spectrometric techniques.

In the first step, the Wang resin was activated in the presence of diisopropylethylamine using *p*-nitrophenyl chloroformate.[10,29,30] The activated resin **2** was then reacted with various amines in DMF yielding the desired carbamate **3**. There are various reports of substitution of aryl fluoride with phenoxide or primary alkoxide,[31−35] amine,[22,26,36] or thio[33,37] groups; however, the reports on the substitution of fluoride with carbamate moiety on the solid support were not found in our literature survey. To effect this unique transformation, we tried different bases using various reaction conditions. The bases *n*-BuLi, *t*-BuLi, and $NaNH_2$ failed to afford the desired product, and NaH and *t*-BuOK gave products with low yields; however, after a considerable number of experiments, we found LHMDS (lithium hexamethyldisiliylamide) to be an effective base giving excellent yield when used at −78 °C (reaction time 5 h). The best effective ratio of reactants, that is, amide/aryl fluoride/LHMDS, was also optimized to 1:1:1 when benzylamines and straight-chain alkylamines were used. However, in the cases of aniline and *p*-methoxy aniline (entry 12), it gave only <15 and 48% yields, respectively. Presumably, this may be due to the low nucleophilicity of acyl derivatives of anilines. Further, we attempted to reduce the nitro group by selectively using a $Cu(acac)_2$,[36] thus avoiding a simultaneous cyclization; however, this attempt was not successful. Hence, we used a widely adopted method[9,11,23,26] of applying $SnCl_2$ (route 1). For this reaction, the solvent DMF was found to give ∼10% higher yields, as compared to yields with the solvent EtOH. In the workup, the use of $NaHCO_3$ and Na_2CO_3 to quench the $SnCl_2$ resulted in the formation of an inseparable emulsion of organic and aqueous phases. The use of aqueous NaOH with pH adjustment to 10, however, gave clear separation and extraction. In route 2, reducing the methyl ester selectively while avoiding the reduction of associated carbamate posed a challenge. Reduction with $NaBH_4$ gave products with low yields, and the use of $LiBH_4$ and even $NaBH_4$/LiCl[38] resulted in the reduction of carbamate. While

* To whom correspondence should be addressed. Fax: +886-3-427-7972. E-mail: ch01@ncu.edu.tw.

10.1021/cc049926j CCC: $27.50
Published on Web 09/11/2004

Table 1. Benzoimidazolones Generated on Solid Support

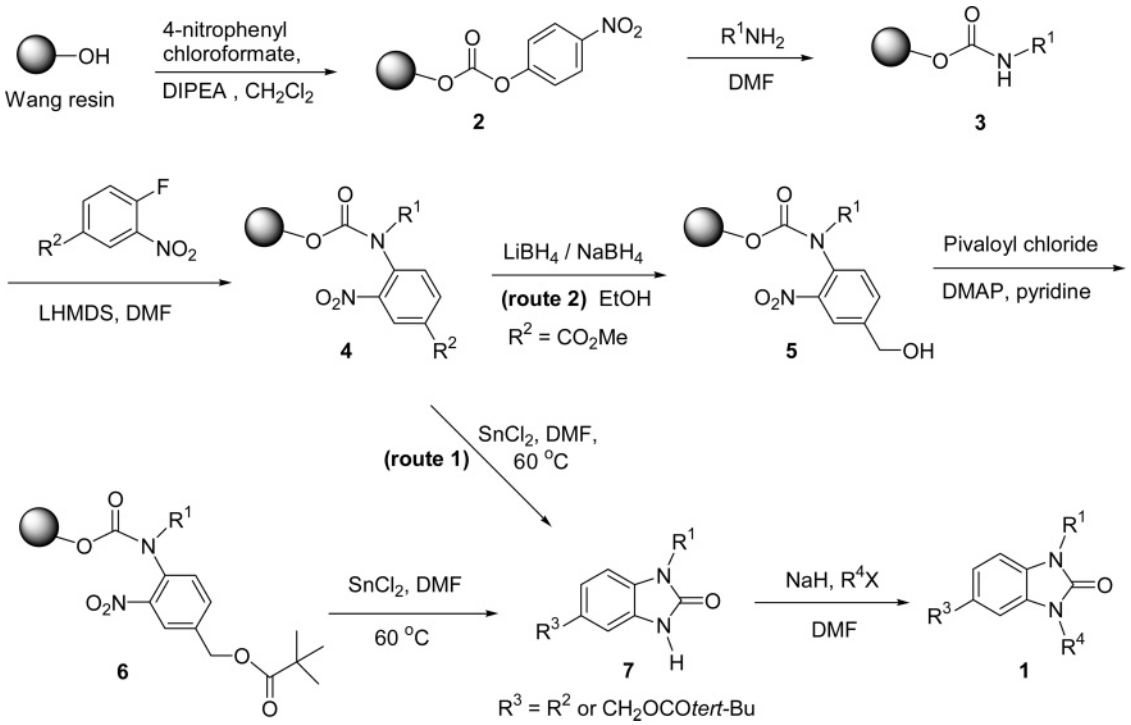
entry	1	R^1	R^3	R^4	purity[a]	yields[b]
1	**1a**		CO_2CH_3	H	89%	82%
2	**1b**	C_6H_{13}	CO_2CH_3	H	86%	81%
3	**1c**		CF_3	H	92%	85%
4	**1d**	C_6H_{13}	CF_3	H	95%	88%
5	**1e**		CF_3	H	92%	83%
6	**1f**		$CO_2CH_2CH_3$	H	83%	73%
7	**1g**	C_6H_{13}	CF_3		75%	68%
8	**1h**		$CH_2OCOtert$-Bu		89%	81%
9	**1i**		CF_3		76%	65%
10	**1j**	C_6H_{13}	CF_3	CH_3	81%	71%
11	**1k**		CO_2CH_3	H	86%	79%
12	**1l**		CO_2CH_3	H	57%	48%

[a] Confirmed by HPLC−UV detection. [b] Reported yields are isolated yields after flash chromatography on silica gel. The overall yields are based on the initial loading of the Wang resin.

optimizing a reducing agent for this transformation, the combination of $NaBH_4$ and $LiBH_4$ (1:1) was found to be the most suited in the solvent EtOH, giving resin **5**. Attempts to react pivolyl chloride with the resulting alcohol **5** using base K_2CO_3 or pyridine was unsuccessful. Alcohol **5** was reacted with pivaloyl chloride using DMAP as a catalyst with solvent pyridine, affording resin **6**. Then reduction of the nitro group of ester **6** was affected in an manner similar to that in route 1, obtaining the compound **7**. Further, to add the third element of diversity, some of the compounds **7** were subjected to alkylation using NaH in solvent DMF[26], giving the corresponding compounds **1**. The yields of the final compounds were ~80%, with the exception of compounds **1g**, **1i**, and **1l**. Low yields of these compounds (**1g** and **1i**) might be due to poor leaving potency of the chloride group of the alkyl halides used. In these cases, NaI was also used in alkylation reaction that boosted the yields to some extent, however, not to the level that was found in the cases in which alkyl bromides or alkyl iodides were used.

In summary, a new methodology for the parallel synthesis of benzimidazolones with a 3-fold functional diversity has been developed using a combination of solid- and solution-

Scheme 1



phase strategies. The 3-fold diversity aids in the development of the broad range of analogues. That, in turn, facilitates generation of effective structure−activity relationship data for different kinds of substitutions through evaluation of such closely related compounds. The uniqueness of this methodology is the substitution of aromatic fluoride with the carbamate moiety on the solid support. To the best of our knowledge, this has not been found reported in the literature. In general, solid-phase combinatorial approaches to benzimidazolone or benzopiperazinone[11] derivatives mostly leave a polar support attachment, namely, COOH, COOMe, or $CONH_2$ functionality,[22−25] onto the benzene nucleus after the final cleavage of the product from the resin. The present approach eliminates this limitation of necessarily leaving certain functionality that may not be desired in the target molecule to have a high bioactivity profile. Although the commercial availability and reactivity of nitrofluorobenzenes possessing additional groups is limited, the present traceless synthetic approach still enables one to prepare benzimidazolones with 3-fold diversity. With the high yields and purities, this method is the versatile approach to develop combinatorial library of benzimidazolone analogues with 3-fold diversity.

Acknowledgment. The authors are grateful to the National Science Council, Taiwan, for financial support (91-2113-M-008-012) of this work.

Supporting Information Available. Representative experimental procedures, spectral data of benzoimidazolones-(**1a**−**1l**) in Table 1, and ^1H and ^{13}C NMR spectra for compounds **1a**−**1i**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477.
(2) Dolle, R. E. *J. Comb. Chem.* **2002**, *4*, 369.
(3) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125.
(4) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549.
(5) Manimala, J. C.; Anslyn, E. V. *Eur. J. Med. Chem.* **2002**, 3909.
(6) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(7) Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61.
(8) Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415.
(9) Wang, F.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 8651.
(10) Li, W.-R.; Yang, J. H. *J. Comb. Chem.* **2002**, *4*, 106.
(11) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172.
(12) Laborde, E.; Peterson, B. T.; Robinson, L. *J. Comb. Chem.* **2001**, *3*, 572.
(13) Ermann, M.; Simkovsky, N. M.; Roberts, S. M.; Parry, D. M.; Baxter, A. D. *J. Comb. Chem.* **2002**, *4*, 352.
(14) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874.
(15) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2419.
(16) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607.
(17) Comely, A. C.; Gibson, S. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1012.
(18) Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665.
(19) Goker, H.; Tuncbilek, M.; Ayhan, G.; Altanlar, N. *Farmaco* **1998**, *53*, 415.
(20) Baragatti, B.; Biagi, G.; Calderone, V.; Giorgi, I.; Livi, O.; Martinotti, E.; Scartoni, V. *Eur. J. Med. Chem.* **2000**, *35*, 949.
(21) Remond, G.; Portevin, B.; Bonnet, J.; Canet, E.; Regoli, D.; De Nanteuil, G. *Eur. J. Med. Chem.* **1997**, *32*, 843.
(22) Pan, P.-C.; Sun, C.-M. *Tetrahedron Lett.* **1999**, *40*, 6443.
(23) Raju, B.; Nguyen, N.; Holland, G. W. *J. Comb. Chem.* **2000**, *4*, 320.
(24) Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 201.
(25) Yeh, C.-M.; Tung, C.-L.; Sun, C.-M. *J. Comb. Chem.* **2000**, *2*, 341.
(26) Wei, G. P.; Phillips, G. B. *Tetrahedron Lett.* **1998**, *39*, 179.
(27) Yeh, C.-M.; Sun, C.-M. *Tetrahedron Lett.* **1999**, *40*, 7247.

(28) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2000**, *41*, 5419.
(29) Li, W.-R.; Yo, Y.-C.; Lin, Y.-S. *Tetrahedron* **2000**, *56*, 8867.
(30) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937.
(31) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem.* **1998**, *63*, 9594.
(32) Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535.
(33) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J. I. *J. Org. Chem.* **1998**, *63*, 6338.
(34) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721.
(35) Zhu, J.; Laib, T.; Chastanet, J.; Beugelmans, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2517.
(36) Phillips, G. B.; Wei, G. P. *Tetrahedron Lett.* **1996**, *37*, 4887.
(37) Smith, A. B. I.; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738.
(38) Hamada, Y.; Shiori, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921.

CC049926J