ORGANIC LETTERS

2002
Vol. 4, No. 23
4017−4020

Synthetic Applications of Azolium Ylides to a Traceless Solid-Phase Synthesis of 2-Substituted Azoles

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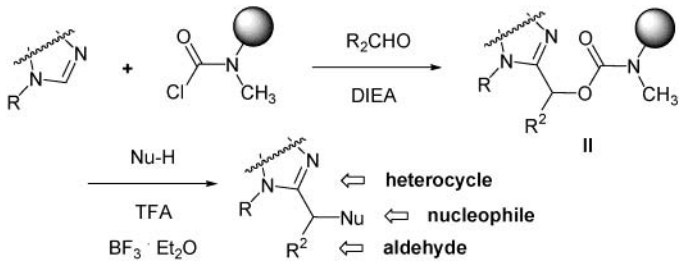
Received August 5, 2002

ABSTRACT



A new approach for the preparation of 2-substituted azole libraries using a polystyrene-carbamyl chloride resin in a traceless fashion is described. Azole substrates II are assembled in a one-pot condensation reaction of azoles and aldehydes with a resin-bound carbamyl chloride. Treatment of the azolyl-carbamate II with boron trifluoride etherate under thermal or microwave-assisted solvolysis conditions afforded 2-substituted azoles.

New methods for the solid-phase synthesis of organic molecules are needed in drug discovery to permit the continued expansion of compound collections with large numbers of druglike molecules.[1] The use of traceless solid-phase methods is a particularly effective strategy in library syntheses, because undesirable functional groups are not needed to link the substrates onto the resin support.[2] Azole derivatives are important components in many biologically active molecules.[3] Libraries of azole derivatives bearing a wide diversity of substitution patterns should then be a rich source of lead compounds when assayed in high-throughput screens against biological drug targets. We recently reported our results in developing a new method using imidazolium ylides/carbenes[4] in the preparation of 2-substituted azoles through a one-pot three-component reaction.[5] The simplicity and efficiency of this reaction is ideally suited for application to the traceless solid-phase synthesis of azole libraries. In two reaction steps, azoles are formed with three centers of diversity that are arrayed in a compact fashion around a single carbon atom.

Imidazoles are known to acylate at the 2-position, and the reaction of an imidazole with a benzoyl chloride is reported to initially form an imidazolium ylide as an intermediate. The ylide is proposed to react in a bimolecular fashion with a second benzoyl chloride to form a 2-benzoylimidazole on workup.[6] If a resin-bound acid chloride were substituted in this reaction, we expected that the intermediate ylide **I** would form; however, acylation should not occur at the 2-position,

(1) Balkenhol, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. Watson, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1903−1908. Ellman, J. A.; Gallop, A. *Curr. Opin. Chem. Biol*. **1998**, *2*, 317−319. Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127−1152.

(2) Wilson, L. J.; Klopfenstein, S. R.; Li, M. *Tetrhedron Lett*. **1999**, *40*, 3999−4002. van Maarseveen, J. H. *Comb. Chem. High Throughput Screening* **1998**, *1*, 185−214. Reitz, A. B. *Curr. Opin. Drug Discuss. Dev.* **1999**, *2*, 358−364. Paio, A.; Zaramella, A.; Feritto, R.; Conti, N.; Marchioro, C.; Seneci, P. *J. Comb. Chem*. **1999**, *1*, 317−325.

(3) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ress, C. W., Scrivn, E. F. V., Eds; Pergamon Press: Oxford, 1996; Vol. 3, pp 77−220.

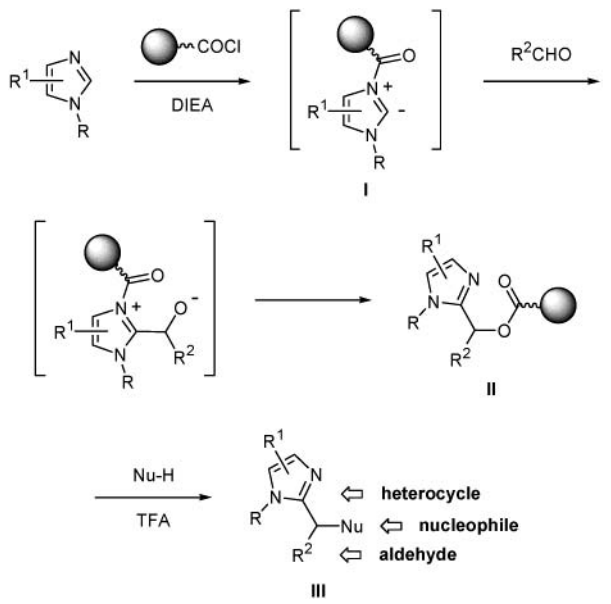
(4) A recent report describes the use of similar *N*-carbamyl-imidazolium carbenes/ylides as ligands for Pd(II) catalysts in the Sonogashira reaction. Batey, R. A.; Shen M.; Lough A. J. *Org. Lett.* **2002**, *4*, 1411−1414.

(5) Hlasta, D. J. *Org. Lett.* **2001**, 3, 157−159. Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189−192.

10.1021/ol0266727 CCC: $22.00
Published on Web 10/23/2002

since a second acid chloride on the resin surface would not be close enough to the reactive center (Scheme 1). Analogous

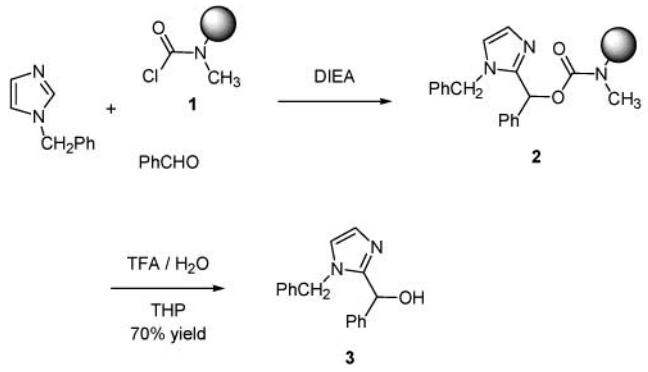
Scheme 1. Solid-Phase Synthesis of 2-Substituted Azoles



to our solution-phase method[5] the ylide would not be acylated but would be able to condense with an aldehyde that is present in the reaction media. After an intramolecular acyl transfer, the resin-bound 2-substituted imidazole **II** would be formed. Therefore in this key step the 2-substituted azoles **II** are assembled by the reaction of a resin-bound carbonyl chloride with an azole and an aldehyde (Scheme 1). Solvolysis of the resin-bound azole **II** results in cleavage of the azole off resin, presumably in the form of a carbonium ion, which is then trapped with a nucleophile. This two-step sequence would readily afford a library of 2-substituted azoles (**III**) with three centers of diversity.

This traceless solid-phase method was brought into practice. Initially, we chose polystyrene-carbonyl chloride as the resin-bound acid chloride.[7] In a one-pot reaction polystyrene-carbonyl chloride was generated in situ by treatment of carboxypolystyrene with a coupling reagent, 2-chloro-1,3-dimethylimidazolinium chloride, and *N*,*N*-diisopropylethylamine (DIEA).[8] After 4 h at room temperature, an excess of 1-benzylimidazole and benzaldehyde was added, and the resin-bound 2-substituted imidazole **II** was obtained.[9] The reaction of the resin-bound imidazole **II** with aqueous trifluoroacetic acid in tetrahydropyran at 60 °C for 16 h gave (1-benzyl-1*H*-imidazol-2-yl)phenylmethanol in 15−25% overall yields from the starting carboxypolystyrene resin. We found that more than 60% of the azole species that was loaded onto the resin was not cleaved off even under forcing conditions (based on elemental analysis). This result is consistent with the 2-acylation of the resin-bound ylide being the major pathway, unexpectedly following the same pathway as reported for the solution-phase reaction.[6] Our attempts to improve the overall yields by varying the reaction concentration and equivalents of reagents and using resin with lower loading were not successful.

Scheme 2. Polystyrene-Carbamyl Chloride in the Synthesis of 2-Substituted Imidazoles



We turned next to a carbamyl chloride, which should limit the cross-reaction as a result of the lower chemical reactivity of a carbamyl chloride compared to that of an acid chloride. Resin-bound carbamyl chloride was prepared by the treatment of *N*-methylaminomethyl polystyrene with phosgene or triphosgene in toluene.[10] The resulting resin-bound carbamyl chloride **1** is quite stable, unlike polystyrene carbonyl chloride, which is hygroscopic and water-sensitive. The dried carbamyl chloride resin **1** could be stored for more than 1 month in a drybox and still give good results. The one-pot reaction of the resin-bound carbamyl chloride **1** with benzaldehyde and 1-benzylimidazole in the presence of *N*,*N*-diisopropylethylamine or triethylamine yielded the resin-bound 2-substituted imidazole **2** in 70% yield.[11] Cleavage of the imidazole off resin with aqueous trifluoroacetic acid in tetrahydropyran at 60 °C for 16 h gave material that was 95% pure by LC/MS and after flash chromatography gave a 70% isolated yield of (1-benzyl-1*H*-imidazol-2-yl)phenylmethanol (**3**) (Scheme 2).

(6) Regel, E.; Buchel, K. H. *Liebig Ann. Chem.* **1977**, *145*−*158*; 159−168.

(7) Fyles, T. M.; Leznoff, C. C.; Weatherston, J. *Can. J. Chem.* **1978**, *56*, 1031−1041.

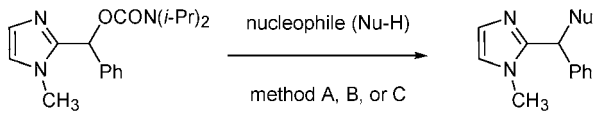
(8) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984−6988.

(9) **General Procedure.** To carboxypolystyrene resin (1 g, 1.10 mmol/g, from Novabiochem) in dichloroethane (20 mL) was added 2-chloro-1,3-dimethylimidazolinium chloride (3 equiv) and *N*,*N*-diisopropylethylamine (6 equiv). The resulting mixture was shaken at room temperature for 4 h, followed by addition of 1-benzylimidazole (3 equiv) and benzaldehyde (5 equiv) and shaken for another 24 h at room temperature. The solvent was drained, and the resin was washed three times with dichloromethane and dried under vacuum.

(10) Wang, G. T.; Chen, Y.; Wang, S.; Sciotti, R.; Sowin, T. *Tetrahedron Lett.* **1997**, *38*, 1895−1898. General procedure for preparing carbamyl chloride resin **1**: *N*-methylaminomethyl polystyrene (1 g, 1.38 mmol/g, from Novabiochem) was swelled in dichloromethane (20 mL) for 30 min at room temperature. To the resin suspension was added *N*,*N*-diisopropylethylamine (2.4 mL, 13.8 mmol), followed by portionwise addition of phosgene (10 equiv, 20% solution in toluene) or triphosgene (1.25 g, 4.2 mmol) under nitrogen at 0 °C. After the addition of phosgene was completed, the ice bath was removed, and the resulting mixture was shaken for 3 h at room temperature. The resin was washed with dry toluene and dichloromethane and dried under vacuum at 50 °C overnight. The dried carbamyl chloride resin was then stored in a sealed drybox for future use.

Previously we described solvolysis chemistry that was useful in the transformation of carbamates into various functionalized azole derivatives.[5] Following these conditions in cleavage reactions with the resin-bound imidazole **2** generally gave good results; however, little or no desired products were isolated in reactions with high pK_a amines. We found that amines with pK_a > 8.5, such as piperidine (pK_a 11.1), 1-methyl piperazine (pK_a 9.7), and primary amines, did not give good yields when using TFA as the only catalyst. To solve this problem we have further examined the solution-phase reaction to determine the best and most general reaction conditions to use in the resin cleavage reactions.

Table 1. Comparison of Thermal versus Microwave-Assisted Solvolysis of Carbamate



			method[a]		
entry	nucleophile	pK_a	A (%)	B (%)	C (%)
1	piperidine	11.1	trace[b]	85	87
2	1-methylpiperazine	9.7	trace[b]	80	85
3	morpholine	8.5	50	82	82
4	imidazole	7.1	55	78	80
5	aniline	4.7	85[c]	86	86

[a] Isolated yield. Method A: nucleophile (5 equiv), TFA (3 equiv), reflux in THF for 24 h. Method B: nucleophile (5 equiv), TFA (4.5 equiv), BF_3Et_2O (1.5 equiv), reflux in THF for 1 h. Method C: nucleophile (5 equiv), TFA (4.5 equiv), BF_3Et_2O (1.5 equiv), microwave in THP for 5 min at 120 °C in a Personal Chemistry, SmithSynthesizer. [b]Detected by LC/MS. [c] Reaction was refluxed for only 4 h.

Under our previously described solvolysis conditions (Table 1, method A) moderate to good yields of 2-substituted imidazoles were obtained with amines of pK_a = 8.5. Increasing the equivalents of TFA to equal piperidine or even to excess gave only a trace of the cleavage product. Lewis acids are known to mediate the solvolysis reactions of propargylic esters.[12] We examined the use of Lewis acids as an additive and found that addition of boron trifluoride etherate to the reaction media (method B) significantly improved the yield of the solvolysis reactions.[13] The desired products were obtained in good isolated yields, although refluxing reaction conditions were needed.

Microwave-assisted technology has been applied to various reactions as a practical method to reduce the reaction time, often by orders of magnitude.[14] Recently, microwave was used to accelerate automated library generation[15] and solid-phase reactions.[16] Using the same equivalents of reagents as in the thermal reaction (method B), the reactions on microwave irradiation to 120 °C internal temperature for 5 min gave similar isolated yields of products (Table 1, method C). These microwave-assisted reaction conditions also significantly reduced the reaction time for the solid-phase cleavage reactions. In Figure 1 are shown our results for the

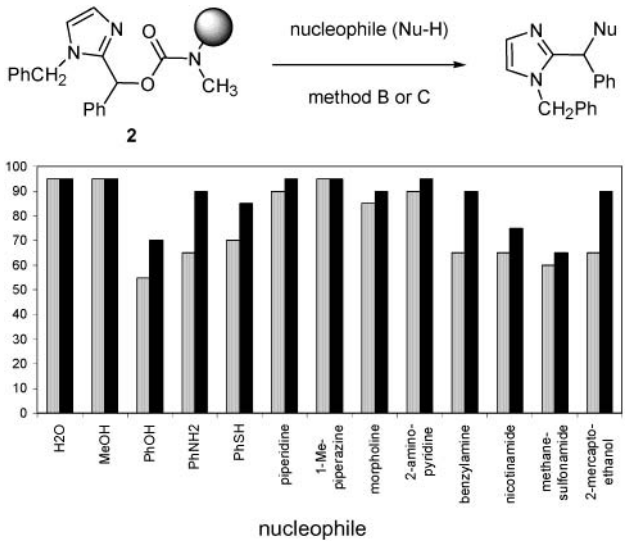


Figure 1. Comparison of HPLC purity of products from the nucleophilic cleavage of resin **2** by method B and method C. Results for method B are shown in gray bars, and results for method C are shown in black bars. Method B: nucleophile (5.0 equiv), TFA (4.5 equiv), BF_3Et_2O (1.5 equiv), THP, 60 °C for overnight. Method C: nucleophile (5.0 equiv), TFA (4.5 equiv), BF_3Et_2O (1.5 equiv), microwave in THP for 10 min at 120 °C in a Personal Chemistry, SmithSynthesizer.

cleavage reactions of resin **2** comparing the thermal reaction (method B) with the microwave-assisted reaction (method C). The purity as measured by LC/MS of the crude products was consistently improved under microwave-assisted reaction conditions compared to that of the thermal reaction. The isolated yields were similar for both methods and were in the range of 50−70%.[17] The reaction on solid phase required extended reaction times at elevated temperatures to obtain good yields, whereas the microwave-assisted reactions were complete in 10 min. Parallel synthesis using the microwave-

(11) General procedure for preparing resin-bound 2-substituted imidazoles **2**: To a suspension of the carbamyl chloride resin (1.0 g) in dichloromethane (20 mL), was added 1-benzylimidazole (300 mg, 3.6 mmol), benzaldehyde (650 mg, 6.4 mmol) and *N*,*N*-diisopropylethylamine (1.3 mL, 7.2 mmol), and then agitated for 24 h at room temperature. The resin was washed with dichloromethane (3x) and then MeOH (2x), and dried under vacuum. The loading was 0.9 mmol/g (70% overall from *N*-methylaminomethyl polystyrene) determined by elemental analysis for nitrogen content.

(12) Bartels, A.; Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **1999**, *40*, 5989−5990. Mahrwald, R.; Quint, S. *Tetrahedron* **2000**, *56*, 7463−7468.

(13) Lewis acids, including $ZnCl_2$, $ZnBr_2$, $ScOTf_3$, $TiCl_4$, Ti(O-*i*-Pr)$_4$, $SnCl_2$, $SnCl_4$, TMSOTf, and BF_3Et_2O were examined. The effect of the various Lewis acids and equivalents of reagents on the solvolysis conversion rate was monitored by LC/MS. BF_3Et_2O (1.5 equiv) gave the best results.

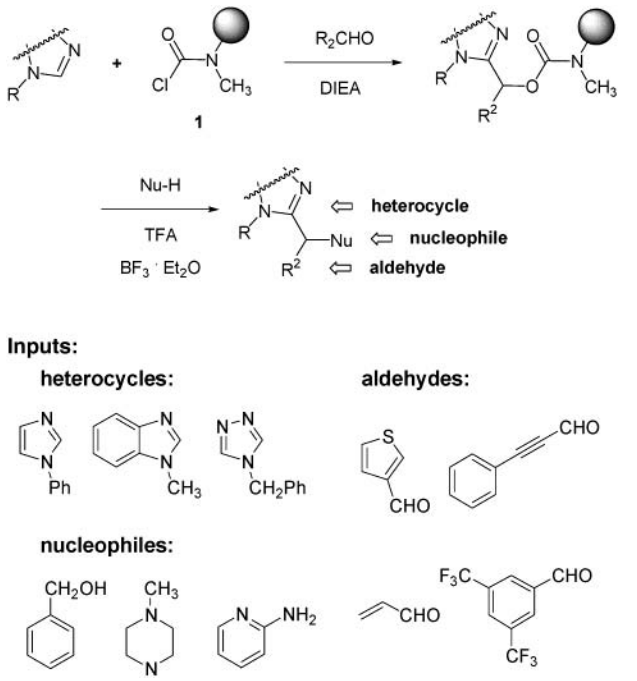
(14) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279−282. Caddick, S. *Tetrahedron* **1995**, *51*, 10403−10432.

(15) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624−630. Coleman, C. M.; MacElroy, J. M. D.; Gallagher, J. F.; O'Shea, D. F. *J. Comb. Chem.* **2002**, *4*, 87−93.

(16) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6(30)*, 314−320. Wilson, S. R.; Reinhard, K. *High-Throughput Synth.* **2001**, 55−64.

(17) The yield is based on the loading of **2** (70% determined by elemental analysis).

Scheme 3. Solid-Phase Synthesis of a 3 × 4 × 3 2-Substituted Azole Library



assisted reactions is limited to moderate-sized libraries, since sequential reactions are the most efficient with the current reactor systems.

We demonstrated the utility of this new traceless solid-phase reaction in the preparation of a 3 × 4 × 3 2-substituted azole library using the Bohdan Miniblock system (Scheme 3). We followed the reactions conditions described earlier for the formation of the resin-bound 2-substituted azoles,[11] and the thermal cleavage conditions (method B) resulted in the preparation of 34 of 36 of the desired compounds. After a solid-supported liquid−liquid extraction (SLE)[18] of the crude products, we found that 80% of the prepared compounds were ≥80% pure by LC/MS determination.

In conclusion, we have developed a traceless solid-phase method for the preparation of 2-substituted azole libraries. In one step, using a resin-bound carbamyl chloride, the azoles and aldehydes are loaded onto the solid phase to form resin-bound 2-substituted azoles. In a second step, reaction with nucleophiles under acid catalysis results in the formation of 2-substituted azoles. Our improved solvolysis conditions significantly broadened the range of nucleophiles that can be used in this chemistry. Therefore, in two reaction steps, azoles are formed with three centers of diversity that are arrayed in a compact fashion around a single carbon atom.

Acknowledgment. We thank the Johnson & Johnson Corporate Office of Science and Technology for postdoctoral fellowship funding for Y.D. through the Excellence in Science Award Program, and we thank Drs. Steven Coats, Kevin Pan, and Jung Lee for their helpful discussions on solid-phase methodology.

Supporting Information Available: General experimental details, isolated yields, and the characterization data of products showed in Figure 1 by ^{1}H NMR, ^{13}C NMR and MS. LC/MS results for the azole library in Scheme 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Breitenbucher, J. G.; Arienti, K. L.; McClure, K. J. *J. Comb. Chem.* **2001**, *3*, 528−533.