Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4789–4792

Synthesis of 2-(α-substituted-amidoalkyl)-imidazoles

Craig A. Zificsak and Dennis J. Hlasta*

Combinatorial Chemistry Team, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 8 Clarke Drive, Cranbury, NJ 08512, USA

Received 20 April 2005; accepted 10 May 2005
Available online 31 May 2005

Abstract—The addition reaction of imidazolium ylides to electron-deficient imines affords orthogonally protected 2-(α-substituted-amidoalkyl)-imidazoles. This reaction serves as a method to incorporate the imidazole nucleus into amine-containing substrates under mild reaction conditions. Microwave-accelerated synthesis provides rapid and general access to a breadth of derivatives.

Imidazoles are common heterocyclic components in biologically important small molecules, from histidine containing peptides to pharmaceuticals and investigational drugs.[1] As such, new methods for the preparation of functionalized imidazoles is of general interest.[2] Previous work from this laboratory introduced the use of 1,3-azolium ylides as nucleophiles in addition reactions to aldehydes.[3,4] This method for the preparation of 2-substituted 1,3-azoles (e.g., imidazoles, thiazoles) is a mild and general alternative to the classical metalation chemistry that is often employed for the synthesis of this type of substrate. A natural extension of this chemistry was to investigate additional electrophiles in this addition reaction.

Electron-deficient imines have widespread use as synthons for the incorporation of nitrogen functionality in addition reactions.[5] Electron-deficient imines are readily prepared from aromatic aldehydes and are usually stable to purification and long-term storage, making them excellent building blocks for the preparation of chemical libraries.[6] The nitrogen of the addition products also presents an additional site for functionalization, a key attribute for the preparation of diversity-enrichment libraries. In this letter, we describe a method for the preparation of 2-(α-substituted-amidoalkyl)-imidazoles such as **4**. The use of orthogonal protecting groups permits differential *N*-substitution leading to a method that can be applied to diversity-enrichment libraries for use in high-throughput screening of novel drug targets.

When *N*-benzylimidazole is treated with a carbamoyl chloride or di-*tert*-butyldicarbonate (Boc_2O), a 1,3-imidazolium intermediate **1** is generated.[3,4] This intermediate activates the C2 hydrogen for deprotonation by a tertiary amine base such as triethylamine or DIEA, or in the case of Boc_2O, by the *tert*-butylate anion, which is generated as a result of the initial *N*-acylation of the imidazole. This ylide intermediate **2** was found to readily add to *N*-sulfonyl imines with mild heating, furnishing the *N*-Boc-*N*-sulfonyl adduct **4** in 87% yield (Fig. 1).

Further exploration of the reaction lead to the utilization of microwave heating as a convenient method for conducting the addition reaction. Under optimized conditions, combining the three reaction components in dry DCE and heating under microwave conditions at 100 °C for 5–15 min allowed for complete consumption of the limiting imine component. The addition of TFA to the reaction mixture then allows for the isolation of the desired monoprotected amine (Table 1). Attempts to catalyze the reaction of benzylimidazole using various Lewis acids did not affect an increase in reactivity.[7]

As shown in Table 1, isolated yields range from modest to excellent, and are dependent on the nucleophilicity of the imidazolium intermediate. For benzylimidazole and other simple alkyl imidazoles, the yield is generally high (entries 1–4). The incorporation of a single withdrawing group onto the imidazole ring is tolerated, but accompanied by a decrease in yield (entries 5 and 6). Variation of the aryl portion of the imine is tolerated (entries 7–9) as

Keyword: Imidazolium ylide.
* Corresponding author: Tel.: +1 (609) 655 6908; fax: +1 (609) 655 6913; e-mail: dhlasta@prdus.jnj.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.05.026

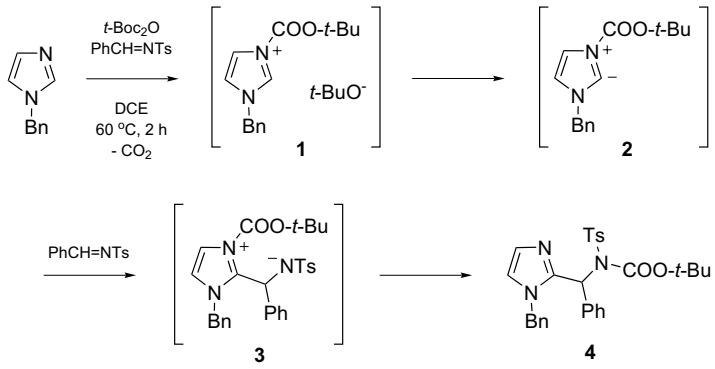
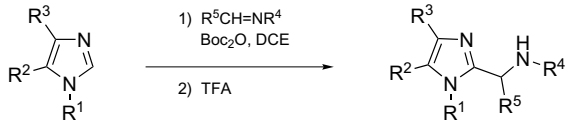


Figure 1. Proposed mechanism for the addition of *N*-benzylimidazole to an *N*-tosyl-imine.

Table 1. Addition of imidazolium ylides to imines and subsequent deprotection[a]



5

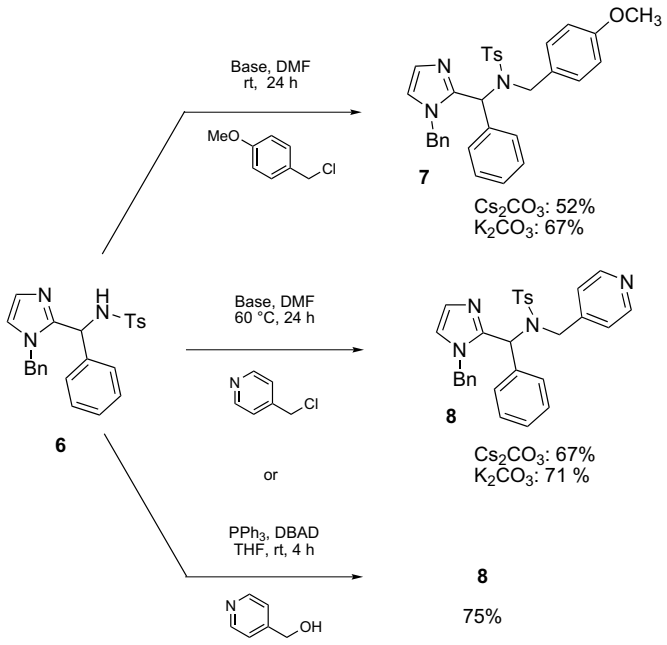
Entry	R^1	R^2	R^3	R^4	R^5	Yield[b]
1	Bn	H	H	Ts	Ph	85
2	Me	H	H	Ts	Ph	75
3	Allyl	H	H	Ts	Ph	93
4	Me	CH=CH	CH=CH	Ts	Ph	95
5	Me	Cl	H	Ts	Ph	53
6	Me	CO_2Me	H	Ts	Ph	45
7	Bn	H	H	Ts	4-MeOPh	75
8	Bn	H	H	Ts	3-Pyr	69
9	Bn	H	H	Ts	CH=CHPh	80
10	Bn	H	H	$PO(OPh)_2$	Ph	95[c]
11	Bn	H	H	Boc	Ph	84[c,d]
12	Bn	H	H	Cbz	Ph	47
13	Bn	H	H	Mtr[e]	Ph	89[c]

[a] Conditions: (i) 1.0 equiv imine, 1.1 equiv imidazole derivative, 1.6 equiv Boc_2O, 0.5 M in DCE, 5–15 min, 100 °C (CEM Explorer microwave); (ii) then add 25% v/v TFA, 60 °C, 15 min (oil bath).
[b] Isolated yield, characterized by HRMS, ^1H NMR, and ^{13}C NMR.
[c] These reactions were run at 65 °C in an oil bath for 2 h.
[d] Isolated as the bis-Boc adduct without TFA treatment.
[e] Mtr = 4-methoxy-2,3,6-trimethylphenylsulfonyl.

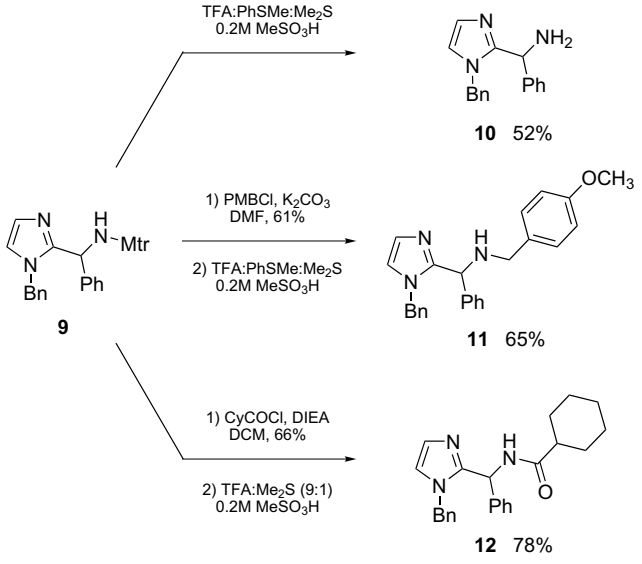
is the use of alternative activating groups (entries 10–13).[6] For entry 11, the TFA deprotection step was not conducted, leading to the bis-Boc adduct. The modest yield of the Cbz-derivative is attributable to the sensitivity of the imine starting material, which suffered from hydrolysis in handling and resulted in the *O*-Boc adduct of benzaldehyde as a major side product. The use of less electron-rich imidazoles (i.e., 4,5-dichloro- or 4,5-dicyano-1-methylimidazole, or caffeine) does not lead to addition products. Two azoles that were productive in the addition to aldehydes, thiazole, and 1-methyl-1,2,4-triazole, afforded less than 5% conversion to the addition product as measured by LCMS.[4] No addition products were observed for oxazole or 5-phenyloxazole, consistent with the aldehyde series. Electron-rich imines (e.g., *N*-benzylidene diphenylmethylamine or *N*-benzylidene-*o*-anisidine) did not afford any addition products.

The incorporation of an additional point of diversity was accomplished by *N*-alkylation of **6**[8] (Table 1, entry 1). Benzyl halides in the presence of either cesium or potassium carbonate gave good yields of *N*-benzyl adducts. Additionally, the Mitsunobu reaction was equally effective in the generation of disubstituted sulfonamides (Scheme 1).

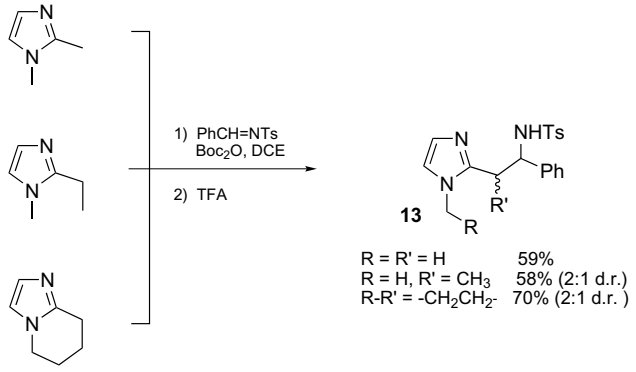
We next investigated the use of the Mtr-protecting group as a readily cleaved sulfonamide protecting group that would permit the installation of a third point of diversity. Originally developed as a protecting group for the guanidine side chain of arginine and lysine, the Mtr group has seen limited use as an amine protecting group.[9,10] The addition of benzylimidazole to the Mtr-benzaldehyde imine was straightforward to afford the Mtr amide **9**[11] (Table 1, entry 13) after TFA removal



Scheme 1. Functionalization of sulfonamide adducts.



Scheme 2. Functionalization of sulfonamide adducts. Mtr = 4-methoxy-2,3,6-trimethylphenylsulfonyl.



Scheme 3. 2-Alkylimidazoles as azolium ylide precursors.

of the *N*-Boc, as was functionalization of the sulfonamide (Scheme 2). The use of Fujino's deprotection protocol (TFA:PhSMe:Me_2S 0.2 M $MeSO_3H$)[9] cleanly provided the deprotected amines, even in the presence of the acid-labile PMB protecting group.

Lastly, the use of 1,2-dimethylimidazole in addition to benzaldehyde was previously accomplished via the azolium ylide reaction,[4] and extension of this reaction to sulfonylimines was also successful. As shown in Scheme 3, 1,2-dimethylimidazole, 2-ethyl-1-methylimidazole, and the tetrahydroimidazo[1,2-*a*]pyridine[12] afforded the homologated 2-alkylimidazole adducts when treated with benzaldehyde sulfonylimine and Boc_2O. The generation of diastereomeric mixtures for the latter two examples was independent of the reaction temperature (rt, 60 °C, or 100 °C/microwave) and the relative configuration was not determined.

Acknowledgements

We thank the Johnson & Johnson Corporate Office of Science and Technology for postdoctoral fellowship funding for C.A.Z. through the Excellence in Science Award Program. We also thank Julie Innocent for assistance with sample purification.

References and notes

1. Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 3, pp 77–220.
2. Zificsak, C. A.; Hlasta, D. J. *Tetrahedron* **2004**, *60*, 8991–9016.
3. Hlasta, D. J. *Org. Lett.* **2001**, *3*, 157–159.

4. (a) Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189–192; (b) Deng, Y.; Hlasta, D. J. *Org. Lett.* **2002**, *4*, 4017–4020.
5. Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131–184.
6. For imine preparations, see: (a) Jennings, W. B.; Lovely, C. J. *Tetrahedron Lett.* **1988**, *29*, 3725–3728; (b) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238–1240.
7. Lewis acids screened were: $Cu(OTf)_2$, $MgBr_2$, $Ti(O\textit{i}\text{-}Pr)_4$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, and $TiCl_4$. No improvement in conversion or purity was observed.
8. Spectral data for imidazole **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H, J = 8.3 Hz), 7.25 (m, 3H), 7.17 (m, 3H), 7.06 (m, 2H), 7.02 (d, 2H, J = 8.3 Hz), 6.94 (d, 1H, J = 1.2 Hz), 6.81 (br d, 1H, J = 7.5 Hz), 6.72 (d, 1H, J = 1.2 Hz), 6.69 (br s, 1H), 5.49 (br s, 1H), 4.82 (d, 1H, J = 15.5 Hz), 4.70 (d, 1H, J = 15.5 Hz), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 142.7, 138.1, 137.4, 135.2, 129.1, 128.9, 128.6, 128.1, 128.1, 127.8, 127.6, 127.0, 126.9, 120.8, 54.0, 49.4, 21.4; HRMS (TOF) *m*/*z* 418.1587 (calcd for $C_{24}H_{24}N_3O_2S$ 418.1589).
9. Saito, K.; Higashijima, T.; Miyazawa, T.; Wakimasu, M.; Fujino, M. *Chem. Pharm. Bull.* **1984**, *32*, 2187–2193, and references cited therein.
10. (a) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811–2820; (b) Bachand, B.; Tarazi, M.; St. Denis, Y.; Edmunds, J. J.; Winocour, P. D.; Leblond, L.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 287–290; (c) Costanzo, M. J.; Yabut, S. C.; Almond, H. R., Jr.; Andrade-Gordon, P.; Corcoran, T. W.; De Garavilla, L.; Kauffman, J. A.; Abraham, W. M.; Recacha, R.; Chattopadhyay, D.; Maryanoff, B. E. *J. Med. Chem.* **2003**, *46*, 3865–3876.
11. Spectral data for imidazole **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 3H), 7.07 (m, 3H), 6.98 (m, 3H), 6.79 (m, 2H), 6.71 (d, 1H, J = 1.3 Hz), 6.49 (d, 1H, J = 6.8 Hz), 6.38 (s, 1H), 5.39 (d, 1H, J = 6.8 Hz), 4.79 (d, 1H, J = 15 Hz), 4.70 (d, 1H, J = 15 Hz), 3.80 (s, 3H), 2.56 (s, 3H), 2.45 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 145.9, 138.7, 138.2, 137.9, 135.4, 129.9, 128.9, 128.3, 128.1, 127.9, 127.5, 127.4, 126.9, 124.9, 120.9, 111.8, 55.5, 53.8, 49.4, 24.2, 17.9, 11.8; HRMS (TOF) *m*/*z* 476.2017 (calcd for $C_{27}H_{30}N_3O_3S$ 476.2008).
12. Lattrell, R.; Blumbach, J.; Duerckheimer, W.; Fleischmann, K.; Kirrstetter, R.; Klesel, N.; Mencke, B.; Scheunemann, K.-H.; Schwab, W.; Seliger, H.; Stache, U.; Winkler, I. *J. Antibiot.* **1988**, *41*, 1395–1408.