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Amine-Catalyzed Addition of Azide Ion to α,β-Unsaturated Carbonyl Compounds

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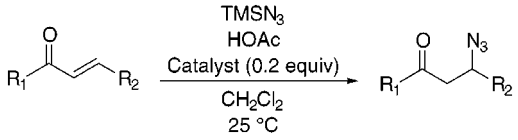
ABSTRACT



A new protocol for the β-azidation of α,β-unsaturated carbonyl compounds is described. The method employs tertiary amines as catalysts for azide addition. The azide source is a 1:1 mixture of $TMSN_3$ and AcOH. Tertiary amines, either in solution or bound to a solid support, are efficient catalysts for the reaction.

β-Amino acids represent important substructures in a variety of natural products.[1] In addition, their importance in natural and unnatural polymers represents an exciting new frontier in the realm of artificial protein structures that hold promise as biostable analogues of peptidomimetic pharmaceuticals.[2] As such, mild and efficient methods for their synthesis are of increasing importance.[3,4] While several impressive advances have been made in this area, there is a need for the development of flexible strategies that will accommodate a range of structural types. In addition, synthetic methods that are readily amenable to combinatorial catalyst and substrate screening may prove to be particularly valuable. In the present Letter, we report an exceedingly mild preparation of β-azido carbonyl compounds. Advantages of the protocol include high-yielding reactions that can be conducted at ambient temperature, the application of readily available amines as catalysts, and the use of readily available and stable trimethylsilyl azide ($TMSN_3$) as the azide source.

Our interest in studying this reaction was stimulated by the 1997 study of Lakshmipathi and Rama Rao who reported that triethylamine catalyzed the addition of hydrazoic acid (HN_3) to crotonate esters at elevated temperature (80 °C).[5−7] One drawback of the procedure includes the need to generate the highly toxic and explosive HN_3 as a stock solution. We speculated that premixing of $TMSN_3$ and acetic acid (AcOH) would initiate a disproportionation reaction leading to controlled stoichiometries of HN_3 with the production of trimethylsilyl acetate (TMSOAc) as a byproduct.[8] Introduction of the α,β-unsaturated ketone in the presence of an amine catalyst could then lead to conjugate addition. Indeed,

(1) For a review with an excellent bibliography, see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582 (refs 1−19).

(2) For representative studies in the field, see: (a) Appella, D. H.; Barchi, J. J.; Durrell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2309−2310. (b) Gademan, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem. Int. Ed.* . **1999**, *38*, 1223−1226. (c) Smith, A. B.; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Halcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947−9962. (d) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc*. **1992**, *114*, 6568−6570.

(3) For recent reviews, see: (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) See also: ref 1.

(4) For excellent recent advances, see: (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049−10053. (b) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (c) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. (d) Kim, B. J.; Park, Y. S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1705−1708.

(5) Lakshmipathi, P.; Rama Rao, A. V. *Tetrahedron Lett.* **1997**, *38*, 2551−2552.

(6) For a related azide conjugate addition employing Et_2AlN_3, see: Chung, B. Y.; Park, Y. S.; Cho, I. S.; Hyun, B. C. *Bull. Korean Chem. Soc.* **1988**, *9*, 269−270.

(7) For an alternative β-azidonation reaction involving conversion of a ketone to the corresponding silylenol ether, followed by treatment with PhI=O and $TMSN_3$, see: Magnus, P.; Lacour, J. Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406−3418.

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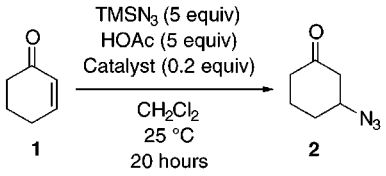
treatment of cyclohexenone (**1**) with 5 equiv of $TMSN_3$ and AcOH in the presence of catalytic quantities (0.2 equiv) of Et_3N (CH_2Cl_2, 25 °C) for 20 h resulted in clean conversion to azidoketone **2** in 90% isolated yield (eq 1).[9−11]

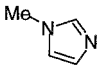
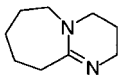
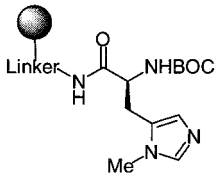


90% isolated yield (1)

A survey of Lewis bases revealed that there is reasonable generality with respect to the Lewis base that is employed (Table 1). Triethylamine and the aromatic heterocycle *N*-methylimidazole proved comparably competent as catalysts, resulting in 77% and 82% isolated yields, respectively, when the reactions were terminated after 5 h (entries 1 and 2). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) proved the most active of the catalysts we have screened, resulting in rapid, quantitative conversion to product (90% isolated yield), within the same 5 h period (entry 3). In contrast, pyridine and the non-amine base hexamethylphosphoramide (HMPA) were less efficient catalysts, allowing only 26% and 11% isolated yields, respectively, within the same period (entries 4 and 5). In a control experiment where the Lewis base was omitted completely, no product was formed (entry 6). Likewise, if the AcOH is omitted, no reaction occurs. Finally, in an experiment intended to prospect the feasibility of screening large numbers of catalysts for this reaction, a solid-support bound alkylimidazole was found to possess excellent activity,[12] producing a 90% isolated yield of the product after an 18 h period (entry 7).

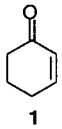
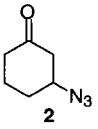
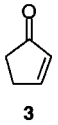
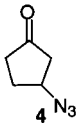
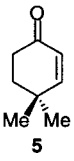
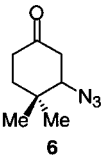
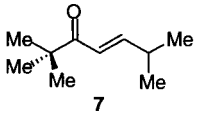
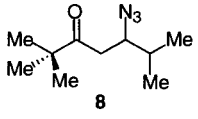
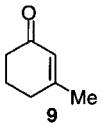
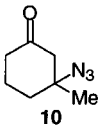
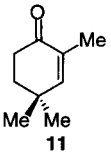
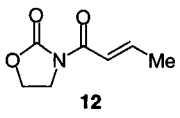
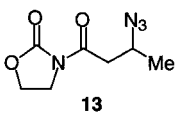
We then turned our attention to examining the substrate scope of these reaction conditions (Table 2). A number of cyclic and acyclic α,β-unsaturated ketones proved to be excellent substrates for these reactions. In addition to cyclohexenone (entry 1), cyclopentenone **3** was transformed

Table 1. Evaluation of Lewis Bases as Catalysts[a]

Entry	Catalyst	Isolated Yield
1	Et_3N	77%
2		82%
3		90%
4		26%
5	HMPA	11%
6	none	0%
7[b]		90%

[a] All reactions conducted in CH_2Cl_2 (0.2 M) at 25 °C for 5 h. Reactions were monitored by TLC, and then subjected directly to silica gel chromatography to afford analytically pure product. [b] Linker = (Phe)-(Aib)-(D-Pro). This reaction mixture was allowed to stir for 18 hours.

Table 2. Substrate Scope for Catalytic β-Azidation[a]

Entry	Substrate	Product	Isolated Yield
1	 **1**	 **2**	90%
2	 **3**	 **4**	70%
3	 **5**	 **6**	87%
4	 **7**	 **8**	90%
5	 **9**	 **10**	20%
6	 **11**	No Reaction	
7	 **12**	 **13**	95%

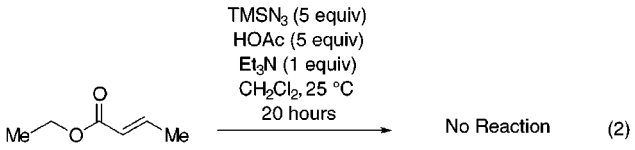
[a] All reactions conducted according to the optimized conditions (Table 1, Entry 1).

(8) Examination of this equilibrium by both ^1H NMR and IR spectroscopy reveals that the disproportionation reaction is extremely sluggish in the absence of an amine base. Introduction of Et_3N, however, results in the production of TMSOAc in an amount approximately equal to the amount of amine catalyst introduced. Thus, the bulk of the azide remains in the more stable $TMSN_3$ form, and the disproportionation appears to be initiated by Et_3N.

(9) Numbered products were characterized by ^1H NMR, ^{13}C NMR, and IR spectra, TLC R_f, and combustion analysis. Supporting Information for this Letter is available.

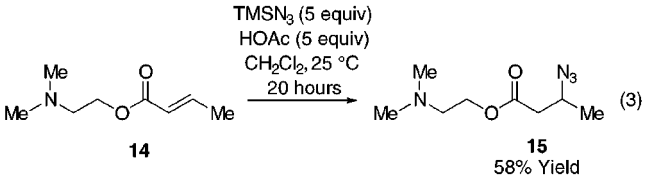
to the corresponding azidoketone **4** in reasonable yield (70%, entry 2). 4,4-Dimethylcyclohexenone (**5**) was transformed to the corresponding azide **6** in 87% yield, demonstrating that steric hindrance in the allylic position does not present any inherent problem (entry 3). Likewise, the *tert*-butyl-substituted ketone **7** proved to be an excellent substrate, undergoing transformation to azide **8** in 90% yield (entry 4). Trisubstituted cyclohexenones present a perhaps nonobvious reactivity profile. Whereas 3-methylcyclohexenone (**9**) underwent transformation to the corresponding quaternary azide **10** in 20% isolated yield under the standard conditions (entry 5), the 2-methyl variant **11** was inert under these reaction conditions (entry 6). While the reasons for this reactivity are not completely clear at this time, it is important to note that access to compounds with quaternary amine-functionalized centers may be possible with the present method. In addition, substrates other than ketones also function in the present reaction. For example, the crotonate derivative of 2-oxazolidinone (**12**) is processed under the conditions reported above to afford azide **13** in 95% yield (entry 7).

In the process of exploring other α,*β*-unsaturated carbonyl derivatives that might serve as suitable substrates for the conjugate addition, we found that ethyl crotonate did not undergo reaction under the above conditions, or even in the presence of a stoichiometric amount of amine base (eq 2);



(2)

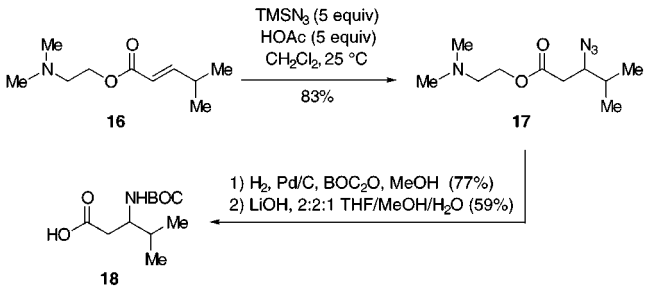
instead, complete recovery of the ester was observed. In contrast, the *N*,*N*-dimethylaminoethanol derivative **14** underwent a clean reaction to produce azide **15** in 58% isolated yield (eq 3), even when the external amine catalyst was omitted. The prospect of intramolecular activation represents a potential strategy for asymmetric versions of these processes employing chiral aminoester substrates.



(3)

Finally, *β*-azido carbonyl compounds represent useful surrogates for *β*-amino acids. For example, α,*β*-unsaturated ester **16** can be converted to *β*-azidoester **17** in 83% yield, employing the conditions above (Scheme 1). Subsequently,

Scheme 1



a two-step sequence transforms **17** into *N*-BOC-*β*-amino acid **18**. Thus, subjection of compound **17** to catalytic hydrogenation in the presence of BOC_2O (H_2, Pd/C, BOC_2O, MeOH, 25 °C, 3 h) afforded the intermediate protected aminoester (77%). Subsequent hydrolysis (LiOH, THF/MeOH/H_2O, 25 °C, 12 h) produced the protected amino acid **18** (recrystallized yield, 59%).[13]

In summary, we have reported a facile transformation of a range of α,*β*-unsaturated carbonyl compounds to the corresponding *β*-azidocarbonyl compounds. The reaction proceeds through catalysis by substoichiometric quantities of a tertiary amine base. While reactivity is excellent with ketones and oxazolidinone substrates, esters are less reactive unless a tertiary amine is incorporated as a component of the substrate. Finally, the successful application of intramolecular bases, as well as external bases bound to solid supports, bodes well for the development of chiral auxiliary processes and combinatorial screening of chiral bases for asymmetric catalysis, respectively. Current efforts are focused on these approaches.

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Supporting Information Available: Experimental procedures and characterization data for all compounds synthesized for this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **Caution:** Organic azides are potentially explosive compounds and should be handled with great care. We encountered no explosive behavior during these studies, however. In addition, differential scanning calorimetry (DSC) was performed on compounds **2**, **6**, and **13** at Science Resources, Inc. (Evansville, IN). In each case, the thermochemical transitions occurred at ≥130 °C. Full details of these measurements are reported in the Supporting Information (pp SI-9−SI-13).

(11)) For a discussion of the hazards associated with HN_3 and related azides, see: Bretherick, L. *Handbook of Reactive Chemical Hazards*; Butterworth: London, 1975; pp 775−776.

(12) For the preparation of this catalyst, see: Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784−6785.

(13) α-Azido ketones may also be converted to an α-amino acid. For example, see: Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 111−113.