Remarkable [3+2] Annulations of Electron-Rich Olefins with Unstabilized Azomethine Ylides

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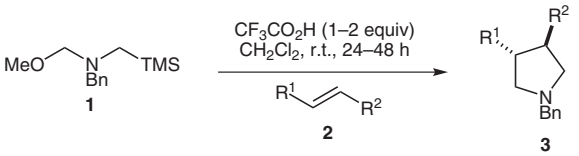
Abstract: Herein we would like to communicate that an unstabilized azomethine ylide generated from commercial trimethylamine *N*-oxide will undergo a remarkable 1,3-dipolar cycloaddition in good yield with electron-rich and unpolarized olefins. A broad range of substituents on the alkenes are tolerated provided they are compatible with excess LDA. This demonstration of novel reaction scope should encourage others to try trimethylamine *N*-oxide as an azomethine ylide precursor in the synthesis of challenging 3,4-disubstituted pyrrolidines.

Key words: 3,4-disubstituted pyrrolidine, cycloaddition, unstabilized azomethine ylide

Substituted pyrrolidines are common structural motifs present in a wide variety of natural products,[1] chiral ligands,[2] and biologically active compounds.[3] One of the most prevalent and reliable methods for the diastereoselective construction of 3,4-substituted architecture is the 1,3- dipolar cycloaddition reaction of an azomethine ylide and an appropriately substituted alkene.[4]

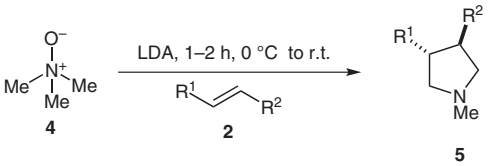
During the course of our research we became interested in constructing novel 3,4-disubstituted pyrrolidine ring systems. Since we did not require substitution on the 2- and 5-positions of the pyrrolidine ring, the azomethine ylide derived from the acid-catalyzed decomposition of commercial *N*-methoxymethyl-*N*-trimethylsilyl methyl phenyl methanamine (**1**)[5] was deemed a suitable choice (Scheme 1).



Scheme 1 Acid-catalyzed [3+2]-cycloaddition reaction

In general, with compatible substrates, we found this well-precedented chemistry to be operationally simple and scalable. In several cases we obtained multigram quantities of the corresponding *N*-benzyl pyrrolidine. A well-documented drawback of this method is that this type of unstabilized azomethine ylide does not readily undergo cycloaddition with unactivated dipolarophiles.[6]

Pyrrolidines whose requisite alkenes were unreactive under the acid-catalyzed conditions required a different preparation. A survey of the chemical literature unearthed a little used, but powerful method wherein a reactive unstabilized azomethine ylide can be generated by treating trimethylamine *N*-oxide **4** with lithium diisopropylamide at low temperature.[7] Under these strongly basic conditions, ylide formation is thought to proceed by deoxygenation of the *N*-oxide. The resultant intermediate is extremely reactive and can be trapped by simple alkenes such as hex-1-ene, cyclopentene, styrene, and stilbene.[8]



Scheme 2 Basic [3+2]-cycloaddition reaction

Herein we would like to report that this cycloaddition reaction furnished targeted *N*-methyl pyrrolidines in yields ranging from good to excellent in nearly all cases examined.[9] A broad range of substituents on the alkenes were tolerated in this transformation provided that functionalities were compatible with excess LDA. Among the successful dipolarophiles were several examples of electron-rich olefins including those that failed under the acid conditions (specifically products **8**–**10**, Table 1). We found this reaction to be operationally straightforward with cycloadditions generally reaching completion in less than one hour.

Despite its broad substrate scope, superior yields, and fast reaction times we presume that this reaction has gained only a modest following[10] among the synthetic community because the corresponding *N*-Me group on the pyrrolidine is difficult to remove. In our hands, we found 1-chloroethyl chloroformate (ACE-Cl) to be a useful reagent for this cleavage as its purification is operationally simple.[11] Furthermore, we found we could accelerate this N-demethylation to reach completion in just 30 minutes using microwave irradiation (Scheme 3).[12] For substrates like those in Table 1, the microwave ACE-Cl deprotection proceeded in low to moderate yield (Scheme 3).

In summary, we have demonstrated that the 1,3-dipolar cycloaddition between an unstabilized azomethine ylide and an unactivated olefin is not only possible, but can be

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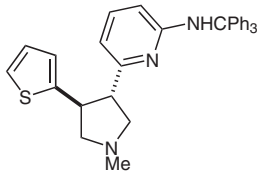
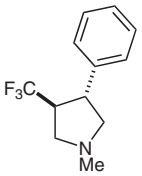
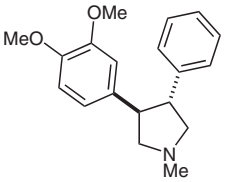
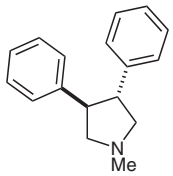
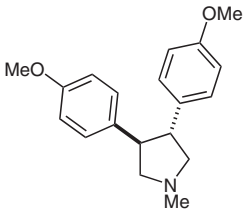
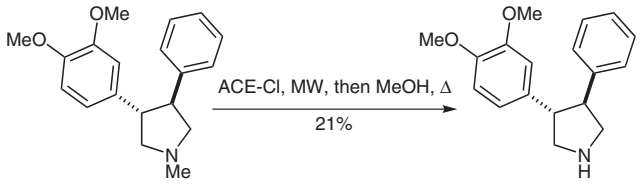
Table 1 Representative Trimethylamine-*N*-oxide [3+2]-Cycloaddition Products

Entry	Product	Yield (%)
1	 **6**	74
2	 **7**	90
3	 **8**	92
4	 **9**	63
5	 **10**	74



8 11

Scheme 3 Chemoselective *N*-methyl deprotection

high yielding. Electron-rich olefins that did not react under the more traditional acidic conditions[5] (Scheme 1), rapidly underwent a [3+2] cycloaddition in good yield under the basic conditions (Scheme 2) described herein. Use of this basic [3+2] cycloaddition enabled us to synthesize pyrrolidines whose assembly would be otherwise inaccessible by the acidic route. Application of this methodology to additional systems is on-going and will be reported in due time.

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References and Notes

(1) (a) Lewis, J. R. *Nat. Prod. Rep.* **2001**, *18*, 95. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
(2) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.
(3) For select recent examples, see: (a) Fish, P. V.; Andrews, M. D.; Fray, M. J.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2829. (b) Fish, P. V.; Fray, M. J.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2022. (c) Kohrt, J. T.; Bigge, C. F.; Bryant, J. W.; Casimiro-Garcia, A.; Chi, L.; Cody, W. L.; Dahring, T.; Dudley, D. A.; Filipski, K. J.; Haarer, S.; Heemstra, R.; Janiczek, N.; Narasimhan, L.; McClanahan, T.; Peterson, J. T.; Sahasrabudhe, V.; Schaum, R.; Van Huis, C. A.; Welch, K. M.; Zhang, E.; Leadley, R. J.; Edmunds, J. J. *Chem. Biol. Drug Des.* **2007**, *70*, 100.
(4) For recent reviews, see: (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.
(5) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235.
(6) Lown, J. W. *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1; Padwa, A., Ed.; Wiley: New York, **1984**, Chap. 6.
(7) Beugelmans, R.; Negron, G.; Roussi, G. *J. Chem. Soc., Chem. Commun.* **1983**, 31.
(8) (a) Beugelmans, R.; Benadjila-Iguertsira, L.; Chastanet, J.; Negron, G.; Roussi, G. *Can. J. Chem.* **1985**, *63*, 725. (b) Beugelmans, R.; Chastanet, J.; Roussi, G. *Heterocycles* **1987**, *26*, 3197. (c) Beugelmans, R.; Chastanet, J.; Roussi, G. *Heterocycles* **1987**, *26*, 3197.
(9) **Representative Procedure**
Commercial LDA (2.5 M in THF, 3.1 mL, 4.7 mmol, 4.5 equiv) was added to a solution of (*E*)-1,2-dimethoxy-4-styrylbenzene (250 mg, 1.0 mmol, 1 equiv) and trimethylamine *N*-oxide **4** (117 mg, 1.6 mmol, 1.5 equiv) in anhyd THF (10 mL) at 0 °C. After 1 h, the reaction was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with CH_2Cl_2–MeOH (95:5) to give 285 mg (92%) of *trans*-3,4-disubstituted pyrrolidine **8** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.12 (m, 5 H), 6.75–6.70 (m, 2 H), 6.68 (s, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.36–3.26 (m, 2 H), 3.12–3.06 (m, 2 H), 2.87–2.80 (m, 2 H), 2.44 (s, 3 H) ppm. LC-MS: *m/z* = 298.1 [M + 1].
(10) (a) De, B..; DeBernardis, J. F.; Prasad, R. *Synth. Commun.* **1988**, *18*, 481. (b) Negron, G.; Calderon, G.; Vazquez, F.; Lomas, L.; Cardenas, J.; Marquez, C.; Gavino, R. *Synth. Commun.* **2002**, *32*, 1977. (c) Kemperman, G. J.; Stuk, T. L.; Van Der Linden, J. J. M. WO2008003460, **2008**.
(11) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
(12) **Representative Procedure**
A solution of *N*-methylpyrrolidine **8** (255 mg, 0.9 mmol) in neat ACE-Cl (3 mL) was irradiated in a microwave reactor at 170 °C for 30 min. MeOH (3 mL) was added to the mixture and thermally refluxed for an additional 1 h. The

crude reaction mixture was purified by ion exchange on a MP-TsOH column to give 51 mg (21%) of pyrrolidine **11** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2 H), 7.18–7.12 (m, 3 H), 6.73–6.70 (m, 1 H), 6.70–6.66 (m, 1 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.66–3.54 (m, 2 H), 3.35–3.25 (m, 2 H), 3.24–3.14 (m, 2 H), 2.62 (br s, 1 H) ppm. LC-MS: *m/z* = 284.0 [M + 1].