Asymmetric Dipolar Cycloadditions of Me_3SiCHN_2. Synthesis of a Novel Class of Amino Acids: Azaprolines

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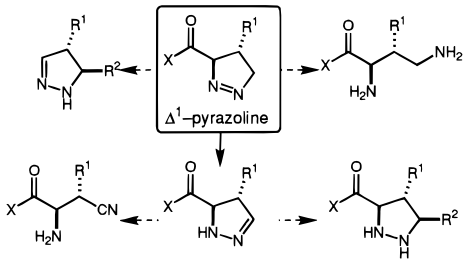
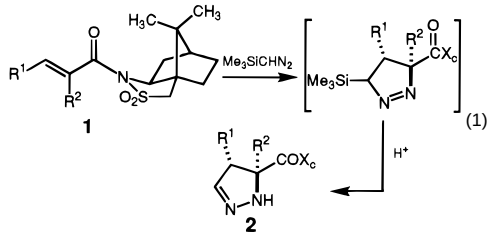
Dipolar cycloadditions are a powerful class of synthetic reactions for the construction of diversely functionalized five-membered heterocycles.[1] In particular, cycloadditions involving nitrile oxides, azomethine ylides, carbonyl ylides, nitrones, and nitronates as dipoles have been well studied and applied toward several elegant complex-molecule syntheses.[2−4] The use of diazoalkanes, however, has not been extensively examined. Synthetic applications of these dipoles have typically been limited to the preparation of the derived cyclopropanes or pyrazoles obtained by nitrogen extrusion or aromatization of the initial [3 + 2] adduct, respectively.[5] However, the pyrazoline cycloadducts which result from the reaction of diazoalkanes with chiral α,*β*-unsaturated carboxylic acid derivatives can serve as useful optically active, functionalized intermediates that in turn are amenable to further synthetic elaboration (Scheme 1). Herein, we describe the novel diastereoselective cycloaddition of Me_3SiCHN_2, an item of commerce, and camphor sultam-derived dipolarophiles **1** to furnish Δ^2-pyrazolines **2** following acidic work-up (eq 1). Additionally, using this method, we delineate the asymmetric synthesis of a novel class of α-amino acids: azaprolines. Given the prominence of prolines in biologically important peptide sequences relevant to metallopeptidase activity (e.g., ACE inhibitors such as captopril and enalopril), immunomodulation, coagulation, and protein−ligand interactions (SH3−domains),[6−8] the amino acid analogs reported herein should find important applications as proline surrogates.

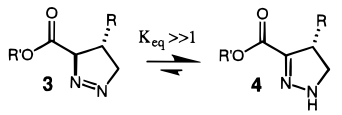
Scheme 1





(1)

The lack of synthetic methodology involving the use of diazoalkanes in asymmetric dipolar cycloadditions may be a consequence of the fact that diazoalkanes (1) have not been readily available, (2) are not typically amenable to prolonged storage, and (3) may be thermally unstable.[9] The recent availability of Me_3SiCHN_2 as an easily handled, stable item of commerce permits the examination of its use for asymmetric synthesis. At the outset of our investigations, however, we were aware of a potential problem (eq 2): prior studies on the cycloadditions of diazoalkanes with α,*β*-unsaturated esters had



(2)

indicated that the Δ^1-pyrazolines **3** initially formed in such cycloadditions readily isomerized to the corresponding conjugated pyrazoline **4**.[5a,b] The result of such an isomerization in the system of interest would be the loss of the desired α-amino stereocenter.

In our initial investigations, we observed that *N*,*N*-dialkyl acrylamides were unreactive toward Me_3SiCHN_2.[10] In contrast, *N*-tosyl acrylamides proved sufficiently reactive, providing quantitative yields of cycloadducts (23 °C, 4−6 h). Our interest in studying diastereoselective diazoalkane cycloaddition reactions led us to examine the reaction of dipolarophiles derived from the camphor sultam auxiliary.[2,11] The dipolarophile substrates **5**−**8** were readily synthesized from the commercially available (*R*)-camphor sultam chiral auxiliary and the corresponding acid chlorides. When solutions of substrates **5**−**8** in hexane/toluene were treated at 23 °C with a solution of Me_3SiCHN_2 (2 M in hexane, 1−3 equiv), 3-trimethylsilyl-substituted-Δ^1-pyrazolines could be isolated in quantitative yields following evaporation of the volatiles; exposure of these adducts to acid (CF_3CO_2H/CH_2Cl_2) furnished Δ^2-pyrazolines **9**−**12** (Table 1). Analysis of the unpurified reaction mixtures by HPLC revealed

(1) For general references, see: (a) Carruthers, W. *Cycloaddition Reactions in Organic Sythesis*; Pergammon: Oxford, 1990; p 269. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Wiley: New York, 1991; Vol. 4, p 1069. (c) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Wiley: New York, 1991; Vol. 4, p 1111. (d) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Wiley: New York, 1991; Vol. 5, p 239.

(2) For an excellent review, see: Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293.

(3) For recent references, see: (a) Curran, D. P.; Yoon, M. H. *Tetrahedron* **1997**, *53*, 1971. (b) Fernández−Mateos, A.; Coca, G. P.; González, R. R.; Hernández, C. T. *J. Org. Chem.* **1996**, *61*, 9097. (c) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346. (d) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108. (e) Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett.* **1991**, *32*, 4893.

(4) (a) Cinquini, M.; Cozzi, F. In *Stereoselective Synthesis*; Helmchen, G., Hoffman, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; p 2953. (b) Denmark, S. E.; Parker, D. L.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 435. (c) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125. (d) Padwa, A.; Brodney, M. A.; Marino, J. P.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1997**, *62*, 67. (e) Padwa, A.; Brodney, M. A.; Marino, J. P.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78. (f) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (g) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (h) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (i) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598. (j) Roush, W. R.; Walts, A. E. *J. Am. Chem. Soc.* **1984**, *106*, 721.

(5) (a) Galley, G.; Pätzel, M.; Jones, P. G. *Tetrahedron* **1995**, *51*, 1631. (b) Bartels, A.; Liebscher, J. *Tetrahedron: Asymm.* **1994**, *5*, 1451. (c) Aoyama, T.; Nakano, T.; Nishigaki, S.; Shioiri, T. *Heterocycles* **1990**, *30*, 375. (d) Lappert, M. F.; Poland, J. S. *J. Chem. Soc. (C)* **1971**, 3910. (e) Seyferth, D.; Menzel, H.; Dow, A. W.; Flood, T. C. *J. Chem. Soc.* **1968**, *90*, 1081. (f) The cycloaddition of vinyl boronates and ethyl diazoacetate has been shown to give the corresponding non-conjugated Δ^2-pyrazoline following hydrolysis of the boronate adduct, see: Matteson, D. S. *J. Org. Chem.* **1962**, *27*, 4293.

(6) Attwood, M. R.; Hassall, C. H.; Kröhn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1011.

(7) (a) Vanhoof, G.; Goossens, F.; De Meester, I.; Hendriks, D.; Scharpe, S. *The FASEB Journal* **1995**, *9*, 736. (b) Kini, R. M.; Evans, H. J. *Biochem. Biophys. Res. Commun.* **1995**, *212*, 1115.

(8) Simon, J. A.; Schreiber, S. L. *Chem. Biol.* **1995**, *2*, 53.

(9) *Prudent Practices for Handling Hazardous Chemicals in Laboratories*; National Academy Press: Washington, D.C., 1981; p 65.

(10) We have observed that unreactive dipolarophiles may be activated toward cycloaddition upon treatment with Lewis acids.

(11) For a review, see: (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.

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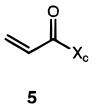
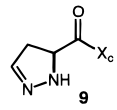
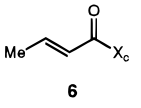
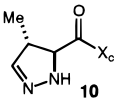
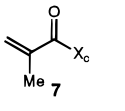
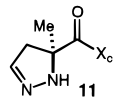
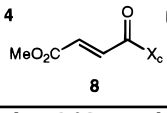
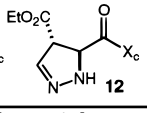
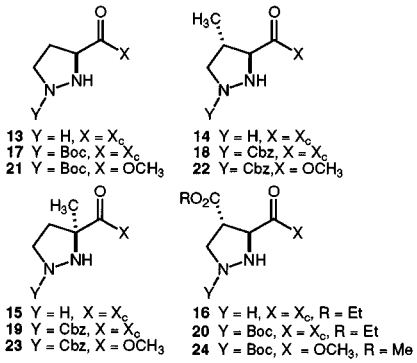
Table 1. Asymmetric Synthesis of Δ^2-Pyrazolines[a]

Entry	Dipolarophile[b]	Product	Yield	ds[c]
1	 **5**	 **9**	72%	90:10[d]
2	 **6**	 **10**	67%	90:10[d]
3	 **7**	 **11**	65%	94:6[d]
4	 **8**	 **12**	78%	91:9[e]

[a] Conducted at 23 °C in 1:1 hexane/toluene, 1−3 equiv of Me_3SiCHN_2. Upon completion, volatiles were removed and the residue treated with CF_3CO_2H/CH_2Cl_2. [b] Xc = (1*R*)-(+)-2,10-camphorsultam. [c] Diastereoselectivity was assayed by HPLC, see Supporting Information. All diastereomeric products were fully characterized. [d] The absolute configuration was established by X-ray crystallography. [e] Configuration assigned by analogy.

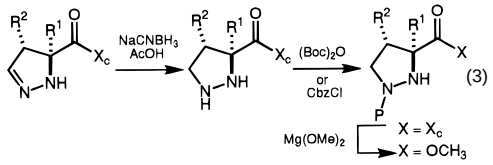
Chart 1



that **9**−**12** had been formed in 90−94% diastereoselectivity as single regioisomers. In all cases the diastereomeric products were readily separated by chromatography on silica gel. The configuration of the diastereomers was confirmed by single crystal X-ray crystallographic analysis of **9**−**11**, consistent with the typical facial selectivity observed for such camphor sultam-derived systems.[12] Surprisingly, the conjugated pyrazolines such as **4** (eq 2) were not observed as products of the reaction.

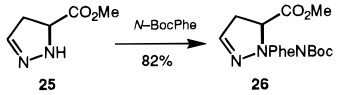
The optically active Δ^2-pyrazolines isolated provide novel substituted proline analogs, which have not previously been prepared. In order to demonstrate the utility of the methodology described herein as a means of providing access to synthetically useful azaproline analogs, we have studied reactions that result in C=N reduction, auxiliary removal, chemoselective protection, and peptide bond formation.

Reduction of the Δ^2-pyrazolines was readily effected upon treatment with $NaCNBH_3$ in acetic acid to give the pyrazolidines **13**−**16** (eq 3, and Chart 1) which were most effectively handled following protection as the corresponding *N*-Cbz or *N*-Boc



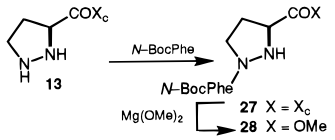
(3)

carbamates **17**−**20** isolated in 50−70% yield two steps.[13,14] Protection proved to be highly chemoselective, providing only the carbamates **17**−**20** for all of the pyrazolidines examined.[15] Cleavage of the chiral auxiliary was readily carried out upon treatment of **17**−**20** with $Mg(OCH_3)_2$ in methanol (0−23 °C) and afforded **21**−**24** (51−67%).[14,16] Both the Δ^2-pyrazolines and pyrazolidines participate in peptide coupling reactions. For example, treatment of **9** (entry 1, Table 1) with $Mg(OMe)_2$ furnished the corresponding Δ^2-pyrazoline-5-carboxylic acid methyl ester **25**, which was coupled with *N*-Boc-(*L*)-Phe (DCC, DMAP, THF) giving dipeptide **26** in 82% yield (eq 4). Condensation of pyrazolidine **13** with *N*-Boc-(*L*)-Phe (DCC,



(4)

DMAP, THF) furnished dipeptide **27**, which was subsequently converted to **28** upon treatment with $Mg(OMe)_2$ (eq 5).[17]



(5)

The dipolar cycloaddition reaction of Me_3SiCHN_2 with chiral acrylates provides access to optically active Δ^2-pyrazolines. This asymmetric process has several salient features: (1) the starting materials (camphor sultam auxiliary and Me_3SiCHN_2) are commercially available; (2) the products are furnished in good yields with useful levels of regioselectivity and diastereoselectivity; and (3) these heterocyclic products are amenable to synthetic transformations including reduction, chemoselective peptide coupling reactions, and auxiliary removal. The methodology described not only documents the asymmetric dipolar cycloadditions of Me_3SiCHN_2 but also, importantly, provides access to analogs of proline, an amino acid for which there are few readily synthesized congeners. Recent studies have demonstrated dramatic conformational changes in peptides incorporating proline analogs, with a concomitant alteration of biological response. Azaprolines may prove to be important surrogates due to the variability of ring substitution afforded by both the choice of the acryloyl moiety used in the dipolar cycloaddition as well as the capacity to diversely functionalize the C_γ-N^δ of the pyrazolidine.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (8 pages). See any current masthead page for ordering and Internet access instructions.

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(12) To the best of our knowledge, the absolute configuration of dipolar cycloadducts derived from the α-methacryloyl sultam **7** has not been unambiguously established previously. We have obtained an X-ray crystal structure that indicates the cycloadduct formed from the same diastereoface as acryloyl sultams **5**, **6**, and **8**.

(13) The unprotected pyrazolidines proved to be unstable, necessitating their derivatization as *N*-Boc and *N*-Cbz protected derivatives.

(14) To determine if steroisomerization had occurred in the formation of **17** and **21**, both **21** and *ent*-**21** were coupled to *N*-Boc-(*L*)-Phe. ^{1}H NMR analysis of the unpurified reaction products established that racemization does not occur upon auxiliary removal, as dipeptide diasteromer mixtures were not observed. See Supporting Information.

(15) ^{1}H NMR data for **17**−**20** are consistent with peptide bond formation at C_γ−N^δ.

(16) Esters **22**−**24** were observed as the only diastereomers of the reaction as determined by ^{1}H and ^{13}C NMR spectroscopy.

(17) Experiments similar to those in ref 14 using *ent*-**13** and *ent*-**25** established the absence of stereoisomerization in carbamate formation, auxiliary removal, and peptide coupling reactions. See Supporting Information.