ORGANIC LETTERS

2000
Vol. 2, No. 26
4265−4267

Versatile, Diastereoselective Additions of Silyl Ketene Acetals, Allyl Tributylstannane, and Me_3SiCN to *N*-Acyl Pyrazolines: Asymmetric Synthesis of Densely Functionalized Pyrazolidines

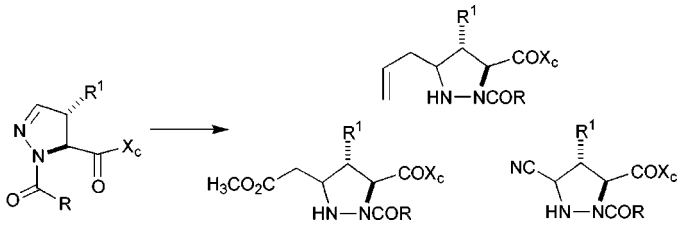
F. M. Guerra, M. R. Mish, and E. M. Carreira*

Laboratorium für Organische Chemie, ETH-Zentrum, Universitätrasse 16, CH-8092 Zürich, Switzerland

carreira@org.chem.ethz.ch

Received November 15, 2000

ABSTRACT



We report the diastereoselective addition of a wide range of nucleophiles to chiral pyrazolines to provide facile access to a range of useful densely functionalized building blocks for asymmetric synthesis. Coupled with the asymmetric cycloaddition reaction of Me_3SiCHN_2 to chiral acrylates, access to these chiral heterocycles is considerably expanded.

We have recently reported the diastereoselective dipolar cycloaddition reaction of trimethylsilyl diazomethane and camphorsultam-derived acrylates to provide optically active Δ^2-pyrazolines (Scheme 1, **1** → **3**).[1] A key advantage of this process is that all components necessary for the reaction are readily available and easily handled. We have also demonstrated that the pyrazolines may undergo C═N bond reduction to furnish the corresponding pyrazolidines lacking substitution at C-5. These heterocyclic adducts not only are versatile optically active building blocks for asymmetric synthesis[2] but also provide simple azaprolines as useful amino acid analogues.[3] The versatility of these optically active heterocycles would be greatly enhanced with access to 5-substituted pyrazolidines. However, their preparation using our cycloaddition strategy is hampered by the fact that the requisite synthesis and handling of substituted trimethylsilyl diazoalkanes would constitute a serious detraction from the overall simplicity and convenience of the cycloaddition methodology. Thus, we reasoned that development of a set of pyrazoline C═N addition reactions to accompany the cycloaddition of Me_3SiCHN_2 would furnish the corresponding 5-substituted pyrazolidines. We report herein the

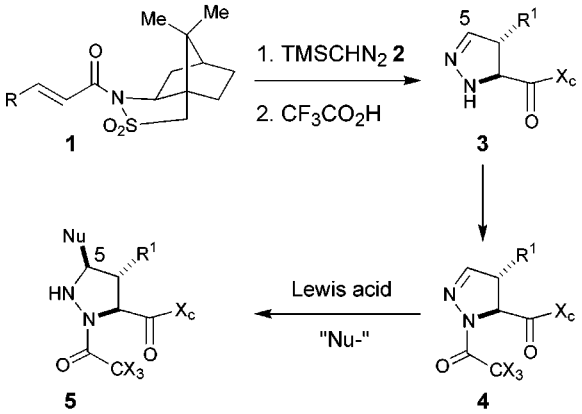
(1) Mish, M.; Guerra-Martinez, F.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379.

(2) (a) Whitlock, G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916. (b) Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *23*, 2007.

(3) (a) Yaron, A.; Naider, F. *Crit. Rev. Biochem. Mol. Biol.* **1993**, *28*, 31. (b) Eberhardt, E. S.; Panasik, N.; Raines, R. T. *J. Am. Chem. Soc.* **1996**, *118*, 12261. (c) Beausoleil, E.; L'Archveque, B.; Belec, L.; Aftani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447. (d) Dummy, P.; Keller, M.; Ryan, D. E.; Rohwedder, P.; Wohr, T.; Mutter, M. *J. Am. Chem. Soc.* **1997**, *119*, 918. (e) Travins, J. M.; Etzkorn, F. A. *J. Org. Chem.* **1997**, *62*, 8387. (f) For the synthesis of the six-membered ring analogues, namely, α-hydrazino acid derivatives, see: Rutjes, F. P. J. T.; Teerhuis, N. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1993**, *49*, 8605. (g) Sasaki, H.; Carreira, E. M. *Synthesis* **2000**, 135.

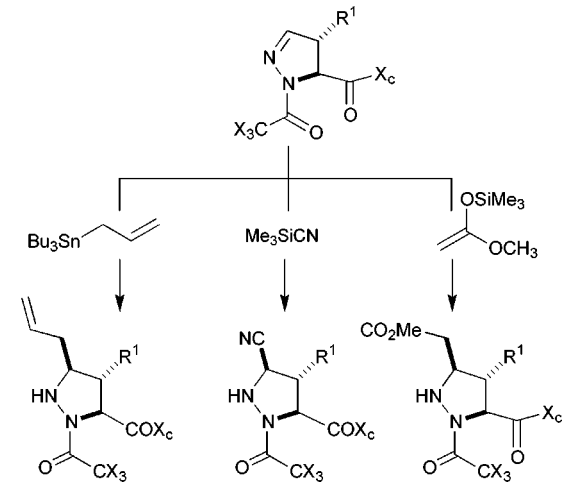
10.1021/ol006873f CCC: $19.00
Published on Web 12/06/2000

Scheme 1



Lewis acid promoted addition of allyl tributylstannane, trimethylsilyl cyanide, and the methyl acetate derived silyl ketene acetal to a number of chiral *N*-acyl pyrazolines (Scheme 2). The 5-substituted pyrazolidine adducts are

Scheme 2



isolated in good yield (60−91%) and in many cases are produced as single diastereomers, delivering enantiopure structures that are rich in functionality.

Although there is precedence for diastereoselective addition reactions to hydrazones, these typically involve unfunctionalized hydrazones and reagents that are strongly nucleophilic or basic,[4] with the exception of recent reports by Kobayashi.[5] Critically relevant to our own studies at the outset, additions to chiral pyrazolines had only been reported in a handful of cases and involved the use of strongly nucleophilic arylcerium or magnesium Grignard reagents. Moreover, because the substrates of interest in our study would be richly functionalized, it was paramount to develop mild nucleophilic conditions compatible with existing functionalilty, such as esters and imides, in the pyrazoline edducts under investigation.

The result of preliminary investigations led to the identification of a number of different *N*-acyl protected pyrazolines as substrates for the nucleophilic addition reactions of a diverse range of nucleophiles, such as the silyl ketene acetal derived from methyl acetate, allyltributylstannane, and trimethylsilyl cyanide (Scheme 2). *N*-Acetyl as well as *N*-trichloro and *N*-trifluoro acetyl groups were found to be ideally suited as protecting groups for a number of reasons: the acylated pyrazoline were activated toward nucleophilic addition in comparison to the parent pyrazoline, the adducts of nucleophilic addition would enjoy enhanced stability in contrast to the air-sensitive cyclic hydrazines that would otherwise be generated, and these *N*-protecting groups are conveniently removed (Figure 1).[6]

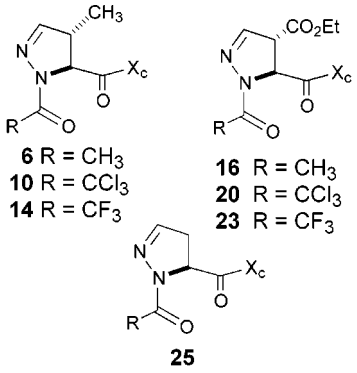


Figure 1. C═N substrates utilized in the study.

A range of Lewis acids ($BF_3{\cdot}Et_2O$, $SnCl_4$, $Ti(O^iPr)_4$, $TiCl_x(O^iPr)_{4-x}$) was screened in an attempt to find suitable promoters for the various nucleophilic addition reactions of interest. We were pleased to discover that $TiCl_4$ proved optimal, allowing for the broadest range of nucleophiles. Thus, as shown in Figure 2, *N*-acyl pyrazolines could be elaborated via addition of allyl tributylstannane (**7**, **11**, **17**, **21**, **26**), trimethylsilyl cyanide (**8**, **12**, **15**, **18**, **24**, **27**), and the silyl ketene acetal prepared from methyl acetate (**9**, **13**, **19**, **22**, **28**), providing for a wide latitude of functionality that can be introduced into a given heterocycle. Except for additions of substrates unsubstituted at C_3 (**26**−**28**), the products were generated as single diastereomers as determined by ^1H NMR analysis.[7] The fact that diastereomeric mixtures were only obtained when the β-position of the acyl hydrazone was unsubstituted suggests that the β-substituent plays a key role in directing the approach of the nucleophilic reaction component.

(4) (a) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 4563. (b) Denmark, S. E.; Kim, J.-H. *Synthesis* **1992**, 229. (c) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 224.

(5) (a) Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942. (b) Kobayashi, S.; Hasegawa, Y.; Ishitani, H. *Chem. Lett.* **1998**, 1131.

(6) The *N*-acetyl moiety, in combination with the pyrazoline C═N, provides functionality for potential activation of the substrate through chelation of a Lewis acid.

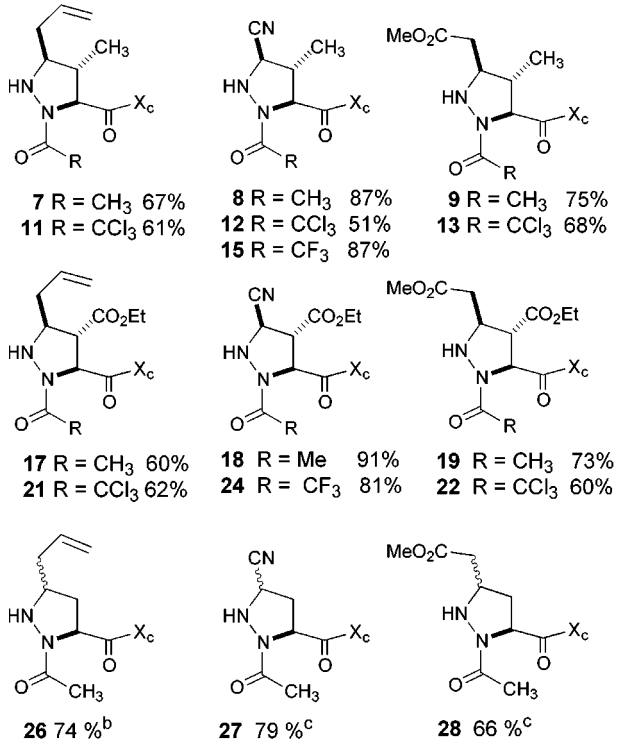
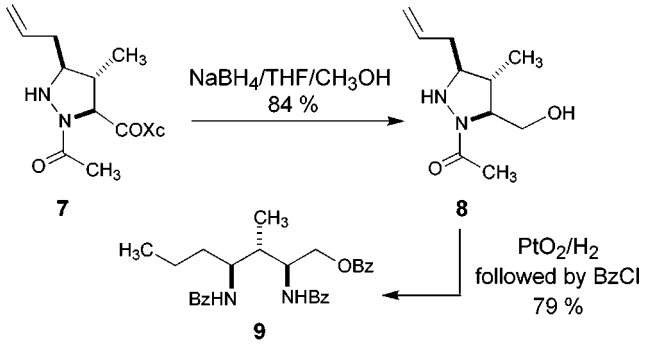


Figure 2. Products obtained in the addition reactions. Unless otherwise noted, products were isolated as single diastereomers, as determined by ^{1}H NMR analysis (b) Product isolated as a 1:1 ratio of diastereomers as determined by ^{1}H NMR spectroscopic analysis. (c) Product isolated as a 1.5:1 mixture of diastereomers as deteremined by ^{1}H NMR spectroscopic analysis.

The pyrazolidine adducts not only serve as potentially useful, novel proline surrogates but also are amenable to further synthetic elaboration in the service of complex molecule synthesis. For example, compound **7** was subjected to auxiliary removal and N−N bond cleavage as depicted in Scheme 3. Thus, treatment of **7** with sodium borohydride delivered alcohol **8** (84%).[8] Reduction of **8** with PtO_2 in 1.2 M methanolic HCl at 80 psi H_2,[9] followed by isolation of the bisammonium hydrochloride salt and subsequent treatment with excess benzoyl chloride provided **9** in 79% overall yield from **7** (two steps). This sequence typifies the range of highly functionalized acyclic molecules that could be accessed from the densely functionalized pyrazolines whose synthesis are now possible.

We have described the Lewis acid promoted nucleophilic additions of allyl tributylstannane, the methyl acetate derived silyl ketene acetal, and trimethylsilyl cyanide to a number

Scheme 3



of *N*-acyl pyrazolines to provide highly functionalized pyrazolidines in a highly diastereoselective fashion. Furthermore, subsequent auxiliary removal and reductive N−N bond cleavage can provide functionally rich, optically active ring-opened acyclic products that may serve as platforms for a variety of complex molecule syntheses. The development of the nucleophilic additions described herein substantively expands the scope of heterocycles available by the dipolar cycloaddition method we have described. Thus, pyrazolidines possessing substitution at every carbon of the heterocycle can be readily accessed while at the same time preserving the advantages (commercial availability, safety) inherent in the use of trimethylsilyl diazomethane as the initial cycloaddition 1,3-dipole. Further studies on the use of pyrazolidines as chiral building blocks for asymmetric synthesis are ongoing and will be reported in due time.

Acknowledgment. We are grateful to the Schweizerischer Nationalfonds, ETH-Zentrum, and Hoffman LaRoche for generous support, and additional generous research funds from Merck, Novartis, Pfizer, Astra-Zeneca are acknowleged.

Supporting Information Available: Full characterization and experimental procedures for adducts **7**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006873F

(7) The sense of induction for these reactions was established by single-crystal X-ray analysis of pyrazolidines **8** and **11** and by ^{1}H NOE analysis of pyrazolidines **7** and **9**. The remaining assignments were made by analogy.

(8) Katayiri, N.; Takebayashi, M.; Kokufuda, H.; Kaneko, C.; Kanehira, K.; Torihara, M. *J. Org. Chem.* **1997**, *62*, 1580.

(9) (a) Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927. (b) Dolle, R. M.; Branden, M. C.; Brennan, P. E.; Ahmed, G.; Tran, V.; Ho, D. M. *Tetrahedron Lett.* **1999**, *40*, 2907.