Scope of the Intramolecular Imidotitanium−Alkyne [2 + 2] Cycloaddition−Azatitanetine Acylation Sequence. An Efficient Procedure for the Synthesis of 2-(2-Keto-1-alkylidene)tetrahydropyrroles and Related Compounds

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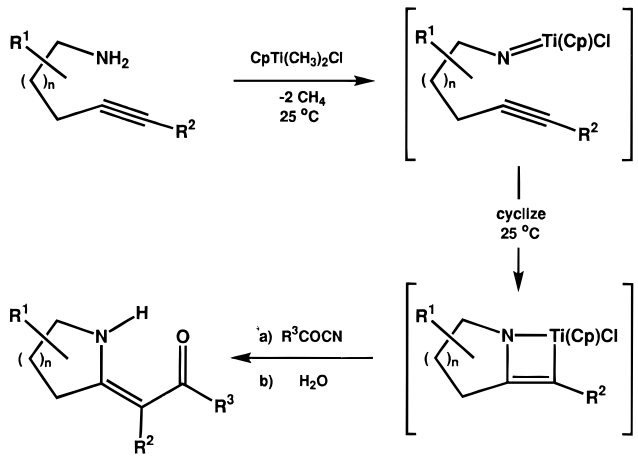
Summary: Sequential [2 + 2] cycloaddition of transient imidotitanium complexes to tethered alkynes followed by C-acylation of the resulting azatitanetines with acyl cyanides has been shown to provide a range of functionalized tetrahydropyrroles and related derivatives in good to excellent yields. The selectivity of product formation is correlated to the pattern of alkyne substitution.

Introduction

Transient organotransition metal complexes have experienced increasing popularity as vehicles for effecting chemical synthesis and molecular stitching. Noteworthy examples that have recently appeared include instances in which the reactive metal center propagates cascade cyclizations,[3] mediates multicomponent annulation,[4] or serves as part of a "living" intermediate that can subsequently be functionalized in a convergent manner.[5] Our interests in the synthetic utilization of *monocyclopentadienyl* imidotitanium complexes and the corresponding zirconium analogs have previously led to the disclosure of the first examples of heteroannulation mediated by these species[6] as well as the use of this methodology in concise, stereocontrolled syntheses of (−)-preussin[7a] and (±)-monomorine.[7b] As part of our initial report,[6] one example was provided which suggested the predisposition of acyl cyanides to take part in chemoselective *C*-acylation of azatitanetines generated via [2 + 2] cycloaddition of transient Ti−imido complexes with alkynes (Scheme 1). Herein we expand on the scope, substrate dependence, and synthetic utility of this reaction sequence.

Scheme 1



Results and Discussion. The alkynyl amines that were utilized in this study were prepared by three complementary procedures. Amines **1a** and **1b** were conveniently synthesized in 56% and 43% overall yield, respectively, via the sequential alkylation of 1-bromo-3-chloropropane **(2)** with the appropriate alkynyllithium reagent (THF−HMPA, −78 to 0 °C), followed by potassium phthalimide-mediated displacement (K^+PHT^-, DMF, 100 °C) and final PHT cleavage ($N_2H_4 \cdot H_2O$, EtOH, reflux). Amines **1c** and **1d** were prepared from the *O*-THP oximes of 2-hexanone, **3b**, and 2-propanone, **3a**, respectively, via alkylation of the corresponding lithio derivatives with 3-bromo-1-(trimethylsilyl)-1-propyne, followed by $LiAlH_4$-mediated reduction and *C*-desilylation (in the case of **1d**, 74% overall), or with 1-bromo-2-heptyne and subsequent oxime reduction (in the case of **1c**, 71% overall).[7b] Amines **1e**, **1f**, **1g**, and **1h** were readily prepared in 72%, 88%, 69%, and 65% overall yields, respectively by sequential lithiation−alkylation of the appropriate nitrile with the corresponding propargyl bromide, followed by $LiAlH_4$-mediated reduction **(**Scheme 2).[8]

The conversion of alkynylamines **1a**−**h** to the corresponding azametalletines was conducted as described previously.[6a,7a] Specifically, treatment of $CpTiCl_3$[9] or $CpZrC1_3 \cdot DME$[10] in THF with CH_3Li (2 equiv, 0 °C, 30 min) provided solutions of $CpTi(CH_3)_2Cl$ (**5a**) or $CpZr(CH_3)_2Cl$ (**5b**), which were used directly for azametalletine generation. Accordingly, addition of the alkynyl-

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(3) (a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421. (c) Negishi, E.-i.; Jensen, M. D.; Kondakov, D. Y.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 8404.
(4) (a) Boese, R.; Harvey, D. F.; Malaska, M. J.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1994**, *116*, 11153. (b) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (c) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667.
(5) (a) Lipshutz, B. H.; Masahito, S. *Tetrahedron* **1995**, *51*, 4407. (b) Dennehy, R. D.; Whitby, R. J. *J. Chem Soc., Chem. Commun.* **1990**, 1060.
(6) (a) McGrane, P. L.; Jensen, M. D.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459. (b) For the use of various di(cyclopentadienyl) lanthanide complexes in catalytic aminoalkyne cyclizations, see: Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295 and references therein.
(7) (a) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485. (b) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323.
(8) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1988**, *110*, 3994.
(9) Cardoso, A. M.; Clark, R. J. H.; Moorhouse, S. *J. Chem. Soc. Dalton Trans.* **1980**, 1156.
(10) Lund, E. C.; Livinghouse, T. *Organometallics* **1990,** *9*, 2426.

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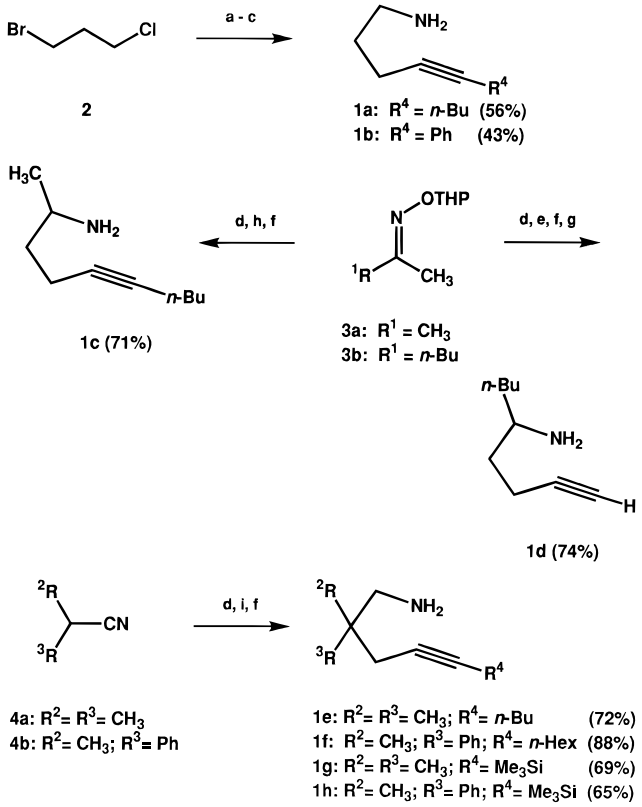
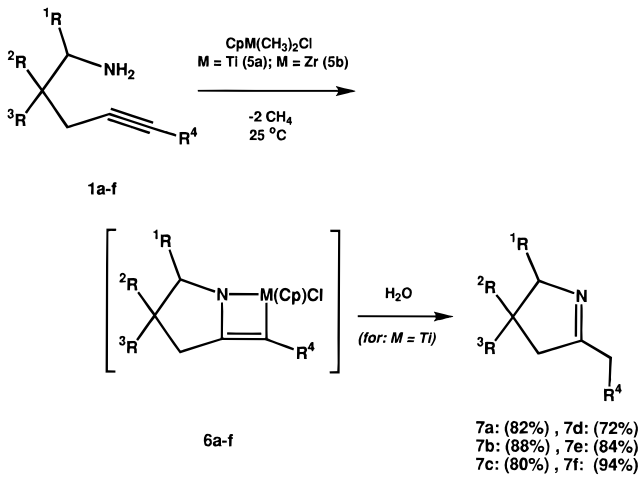
Scheme 2[a]



[a] Legend: (a) $R^4C{\equiv}C-Li$, THF−HMPA; (b) K^+PHT^-, DMF; (c) $N_2H_4{\cdot}H_2O$, EtOH; (d) LDA, THF; (e) $Me_3SiC{\equiv}CCH_2Br$; (f) $LiAlH_4$, THF; (g) NaOH (catalyst), CH_3OH; (h) n-$BuC{\equiv}CCH_2Br$; (i) $R^4C{\equiv}CCH_2Br$.

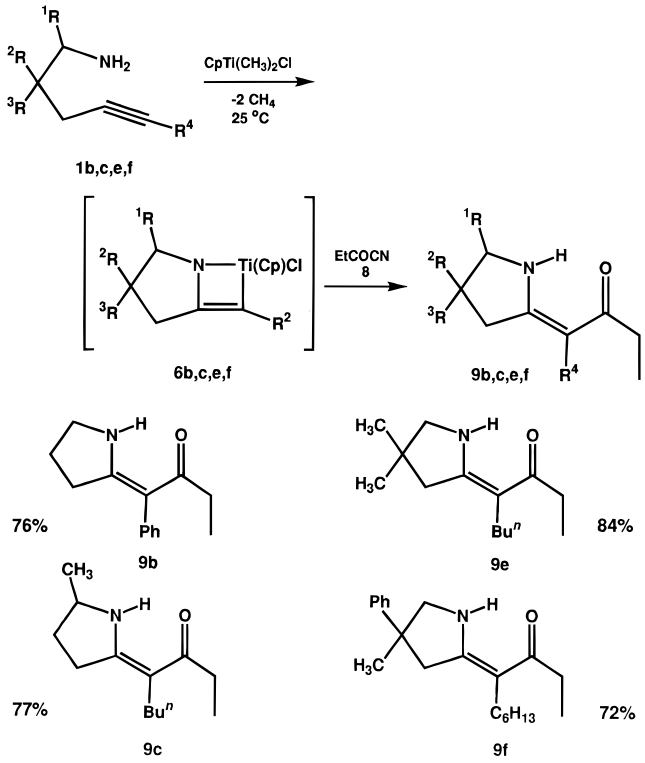
Scheme 3



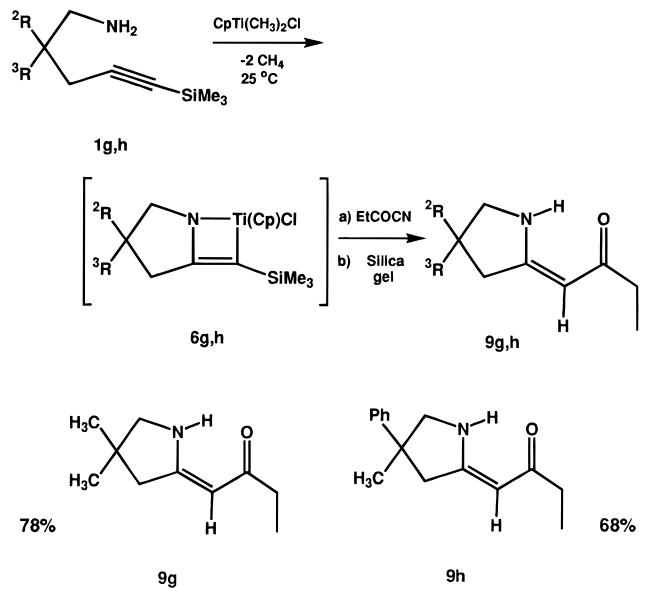
amine of interest to the preformed solution of $CpM(CH_3)_2Cl$ (M = Ti or Zr) in the dark resulted in an immediate evolution of CH_4 with concomitant formation of the corresponding azametalletine **6** by way of the putative group IV metal−imido complex R−N═M(Cp)-Cl. In all instances that were studied (e.g., **1a**−**f**), protonolysis of the resulting azametalletine solutions (H_2O, 0 °C, M = Ti or Zr) gave rise to the corresponding 2-*H*-pyrroles **7** in excellent isolated yields, Scheme 3.[11]

Acylation Studies. Given the abundance of bioactive azacycles possessing a functionalized carbon chain

Scheme 4



Scheme 5



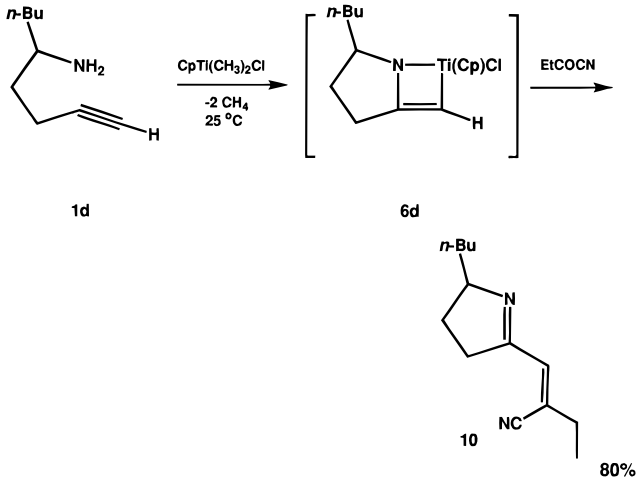
at the 2-position, the elucidation of electrophilic re agents predisposed toward chemoselective *C*-acylation of azametalletines became a priority. At the outset, it was discovered that common acylating reagents (e.g., acyl chlorides and anhydrides) displayed high selectivities for *N*-acylation of azametalletines (M = Ti or Zr, *vide infra*). Fortunately, it was soon determined that the use of acyl cyanides gave rise to efficient *C*-functionalization of *azatitanetines*. Accordingly, simple addition of the appropriate acyl cyanide (1.1 equiv) to a preformed solution of the azatitanetine (THF, 0 °C), followed by stirring at room temperature for 72 h and final protonation (CH_3OH), afforded the corresponding 2-(2-keto-1-alkylidene)tetrahydropyrroles in good to

(11) In the instances of **6f** and **6h**, spontaneous *C*-desilylation of the initial Δ^1-pyrrolines occurred during the standard work-up procedure.

(12) For an early and suggestive example of azatitanetine cyanoalkylidenation, see ref 7a.

(13) Jensen, M. D. Ph.D. Dissertation, University of Minnesota, Minneapolis, MN, 1991.

Scheme 6



excellent isolated yields from the starting alkynyl amines. Interestingly, efforts to effect the *C*-acylation of azazirconetines under conditions analogous to those used for the corresponding titanium derivatives gave unsatisfactory results. In these instances, Δ^1-pyrrolines (ultimately derived from *C*-protonation) were frequently isolated as the major products. In light of this apparent limitation, the structurally diverse series of alkynylamines **1b**−**h** was converted to the corresponding set of azatitanetines via the standard protocol ($CpTi(CH_3)_2Cl$, THF, 0 °C to room temperature) for use in representative *C*-acylation reactions. In order to acquire an accurate comparison of [2 + 2] cycloaddition−*C*-acylation over the range of organometallic intermediates derived from **1b**−**h**, electrophilic interception was effected using propanoyl cyanide (**8**) as a common trapping agent (Schemes 4 and 5).

Several features of the foregoing examples are worthy of comment. Irrespective of the pattern of substitution, all 5-amino-1-alkynes examined as part of this study undergo sequential cyclization−acyl-cyanide-mediated functionalization with very good to excellent efficiency. Azatitanetines derived from substrates possessing nonterminal alkynes as [2 + 2] addends invariably undergo conventional *C*-acylation to furnish vinylogous amides as products (Scheme 4). As expected, products derived from 1-(trimethylsilyl)alkynes undergo facile *C*-desilylation mediated by wet silica gel to provide products formally derived from *terminal* alkynylamines (Scheme 5). By way of contrast, exposure of azatitanetines derived from terminally unsubstituted alkynylamines to acyl cyanides gives rise to products derived from formal cyanoalkylidenation (e.g., **10**) (Scheme 6).[12]

As indicated previously, the use of acyl chlorides for the electrophilic functionalization of azametalletines leads to products derived from preferential *N*-acylation, albeit in a less-than-predictable manner. Accordingly, exposure of **6b** to methyl chloroformate or butanoyl chloride, followed by methanolysis in the presence of silica gel, gave enamide **11**[6a] or ketoamide **12**[13] in 88% and 93% yields, respectively. Surprisingly, acylation of **6a** with octanoyl chloride provided alkynylamide **14**. Since direct hydrolysis of **6a** affords pyrroline **7a** in 94% isolated yield (*vide supra*), the formation of **14** is, in all likelihood, a consequence of eliminative-cycloreversion involving the organometallic intermediate **13** prior to protonation (Scheme 7).

In conclusion, this study has shown that intramolecular imidotitanium−alkyne [2 + 2] cycloaddition−azatitanetine acylation is a reasonably general and highly efficient sequence for the convergent synthesis of pyrrolidine derivatives. The utilization of this synthetic protocol for the preparation of compounds of biological interest will be the topic of future accounts from this laboratory.

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Supporting Information Available: Text giving experimental procedures and spectral data for pyrrole derivatives **9b**−**h**, **10**, enamide **11**, and ketoamide **12** (7 pages). Ordering information is given on any current masthead page.

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Scheme 7