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An Efficient Synthetic Approach to Polycyclic 2,5-Dihydropyrroles from α-Silyloxy Ketones

Cristian Draghici, Qiufeng Huang, and Matthias Brewer*

Department of Chemistry, The University of Vermont, 82 University Place, Burlington, Vermont 05405

matthias.brewer@uvm.edu

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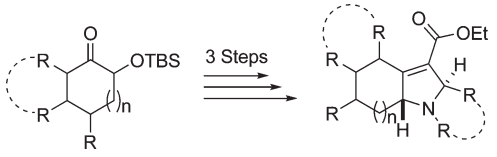
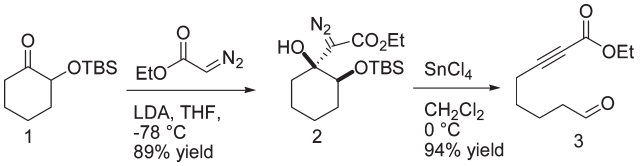


A three-step sequence to prepare polycyclic 2,5-dihydropyrroles from α-silyloxy ketones is presented. A Lewis acid-mediated ring fragmentation of cyclic γ-silyloxy-β-hydroxy-α-diazo esters provided tethered aldehyde ynoate intermediates which, when treated with amino acid silyl esters, underwent intramolecular azomethine ylide 1,3-dipolar cycloadditions. The 2,5-dihydropyrrole products were formed in good to excellent yield as single diastereomers.

Structurally complex nitrogen-containing heterocycles are ubiquitous in biologically active compounds[1,2] and synthetic chemists continually look for new ways to prepare these beneficial scaffolds.[3] Efficiency is an increasingly important consideration in the strategic planning of synthetic sequences in part because of the important role that environmental concerns have begun to play in the field of synthetic organic chemistry.[4] While there is a long history of research devoted to developing methods for the synthesis of nitrogen-containing heterocycles, polycyclic heterocycles are still challenging to prepare and more efficient and concise methods for the preparation of these important compounds are needed. In this Note we report an efficient 3-step route to polycyclic 2,5-dihydropyrroles from α-silyloxy ketones. 2,5-Dihydropyrroles are flexible synthetic intermediates because they lie at an intermediate oxidation state and can be easily oxidized to pyrroles[5] or reduced to pyrrolidines, which in turn are common motifs found in a diverse array of natural products and medicinal agents.

Our route to polycyclic 2,5-dihydropyrroles from α-silyloxy ketones derives from our recent discovery that cyclic γ-silyloxy-β-hydroxy-α-diazo esters (e.g., **2**, Scheme 1) fragment when treated with Lewis acid to provide tethered aldehyde ynoate products (e.g., **3**) in high yield.[6] Although seemingly complex, the requisite fragmentation precursors are simple to prepare by an aldol-type addition of ethyl lithiodiazoacetate to an α-silyloxy ketone (e.g., **1** → **2**, Scheme 1).[7−9] Overall, this route to tethered aldehyde ynoates appears to be quite general.

SCHEME 1. Ring Fragmentation Approach to Tethered Aldehyde Ynoates



The aldehyde ynoate functional group combination unmasked during this fragmentation is unique to this transformation. Recognizing that intramolecular reactions are a particularly efficient way to build structural complexity, and that azomethine ylides can be easily generated from aldehydes,[10] we sought to exploit the bifunctional fragmentation products in a subsequent intramolecular azomethine ylide 1,3-dipolar cycloaddition as a way to prepare polycyclic heterocycles. The cycloaddition of azomethine ylides and alkynes is known to provide 2,5-dihydropyrrole products.[11] However, the cycloaddition of azomethine ylides with ynoates has received less attention and to the best of our knowledge no examples of intramolecular 1,3-dipolar cycloadditions of ynoates with azomethine ylides generated by the decarboxylative condensation of α-amino acids and aldehydes have been reported.[12] With this in mind, we were

(1) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.

(2) (a) Macor, J. E., Ed. *Annu. Rep. Med. Chem.* **2008**, *43*. (b) Macor, J. E., Ed. *Annu. Rep. Med. Chem.* **2007**, *42*. (c) Landquist, J. K. Application as Pharmaceuticals. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 1, pp 143−183.

(3) (a) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401. (b) Javed, M. I.; Wyman, J. M.; Brewer, M. *Org. Lett.* **2009**, *11*, 2189.

(4) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, UK, 1998

(5) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2003**, *44* (46), 8417.

(6) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766.

(7) (a) Schoellkopf, U.; Frasnelli, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9* (4), 301. (b) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(8) Pellicciari, R.; Natalini, B.; Fringuelli, R. *Steroids* **1987**, *49*, 433.

(9) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998; Chapter 10.

(10) For reviews on the generation and reactivity of azomethine ylides see: (a) Padwa, A. *1,3-dipolar cycloaddition chemistry*; Wiley: New York, 1984. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, UK, 1991; Vol. 4, p 1069. (c) Coldhan, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (d) Najera, C.; Sansano, J. *Curr. Org. Chem.* **2003**, *7*, 1105.

(11) (a) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1988**, *44* (15), 4953. (b) Grigg, R.; Duffy, L. M.; Dorrity, M. J.; Malone, J. F.; Rajviroongit, S.; Thornton-Pett, M. *Tetrahedron* **1990**, *46*, 2213. (c) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2003**, *44*, 8417. (d) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2004**, *45*, 1567.

(12) For intramolecular reactions of ynoates with azomethine ylides generated from oxazolines see: (a) Vedejs, E.; Dax, S. L. *Tetrahedron Lett.* **1989**, *30*, 2627. (b) Vedejs, E.; Piotrowski, D. W. *J. Org. Chem.* **2002**, *58*, 1341. (c) Vedejs, E.; Naidu, B. N.; Klapars, A.; Warner, D. L.; Li, V.-s.; Na, Y.; Kohn, H. *J. Am. Chem. Soc.* **2003**, *125*, 15796. For an intramolecular reaction of an ynoate with an azomethine ylide generated by the alkylation of an imine see: Minguez, J.; Castellote, I.; Vaquero, J. J.; Garcia Navio, J.; Alvarez-Builla, J.; Castaño, O.; Andrés, J. *Tetrahedron* **1997**, *53*, 9341.

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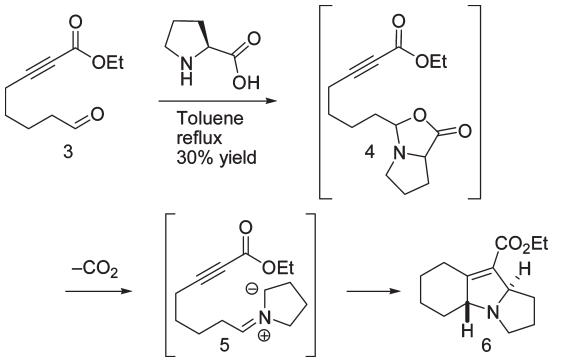
pleased to find that warming tethered aldehyde ynoate **3** and proline in toluene to reflux provided the desired tricyclic 2,5-dihydropyrrole **6**, albeit in a modest 30% yield (Scheme 2).

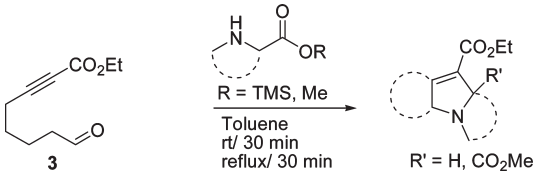
SCHEME 2. Intramolecular Azomethine Ylide 1,3-Dipolar Cycloaddition

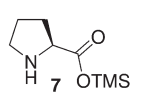
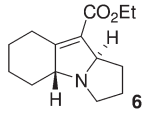
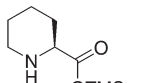
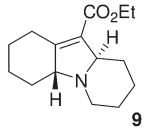
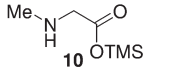
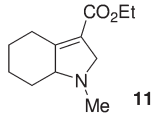
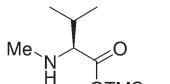
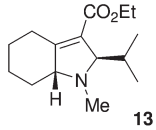
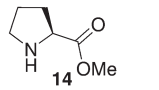
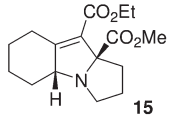


Silyl esters of amino acids are more soluble in organic solvents than amino acids and the use of these species has been shown in some cases to improve the outcome of azomethine ylide dipolar cycloaddition reactions.[13] We were pleased to find that substituting trimethylsilyl prolinate in place of proline increased the yield of dihydropyrrole **6** to 88% (Table 1). Under optimum conditions, the silyl amino acid ester[14] and tethered aldehyde ynoate were allowed to react at room temperature for 30 min and the mixture was then warmed to reflux for 30 min by immersing the reaction flask in a preheated oil bath. Interestingly, gradually warming the mixture to reflux tended to decrease product yields.

Using tethered aldehyde ynoate **3** as a substrate for intramolecular azomethine ylide 1,3-dipolar cycloadditions appears to be fairly general. The trimethylsilyl ester derivatives[14] of proline, pipecolinic acid, sarcosine, and valine each reacted with tethered aldehyde ynoate **3** to give good to excellent yields of the corresponding 2,5-dihydropyrrole products (Table 1, entries 1−4). Grigg and co-workers[15] have reported that the decarboxylative route to azomethine ylides typically leads to a dipole that has the *anti*-configuration (e.g., **5**, Scheme 2) via a stereospecific decarboxylation of an oxazolidinone intermediate (e.g., **4**). Stereomutation of the azomethine ylide dipole is usually slow, leading to cycloadditions with high diastereoselectivity. Our observations are in line with Grigg's findings; the dipolar cycloadditions shown in Table 1 were highly diastereoselective and returned only the diastereomers shown.[16] The methyl ester of proline also reacted with tethered aldehyde ynoate **3** via the stabilized azomethine ylide intermediate generated by a nondecarboxylative process to provide 2,5-dihydropyrrole **15** in 65% yield (entry 5, Table 1).

TABLE 1. 2,5-Dihydropyrroles Prepared from Tethered Aldehyde Ynoate 3



Entry	Amino Silylester	2,5-dihydropyrrole	% Yield
1			88
2			78
3			65
4			46
5[a]			65

a) The reaction was maintained at 0 °C for 30 min and then warmed to reflux for 1 h.

The ring fragmentation of γ-silyloxy-β-hydroxy-α-diazo esters is capable of providing a variety of tethered aldehyde ynoate products.[6] To test the ability of this sequence to provide structurally unique 2,5-dihydropyrroles we subjected several different fragmentation products to a subsequent dipolar cycloaddition reaction (Table 2). The conjugated enynonate tethered aldehyde **16** (entry 1) reacted readily with the silyl ester of pipecolinic acid to provide unsaturated 2,5-dihydropyrrole **17** in 78% yield. For reasons that are not clear, treating **16** with the silyl ester of sarcosine returned 2,5-dihydropyrrole **18** in only 20% yield (entry 2). The aryl-substituted ynoate **19** underwent productive cycloaddition with the silyl ester of pipecolinic acid to provide the tetracyclic indene derivative **20** in 67% yield (entry 3). Subjecting aldehyde ynoate **21** to 1,3-dipolar cycloaddition with the silyl esters of proline or pipecolinic acid provided a 44% yield each of 2,5-dihydropyrroles **22** and **23** in which new 7-membered rings have been formed (entries 4 and 5). Finally, steroid-derived tethered aldehyde ynoate **24** reacted efficiently with the silyl ester of proline to provide 2,5-dihydropyrrole **25** in 80% yield. This steroid derived dihydropyrrole

(13) (a) Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175. (b) Wang, C. L. J.; Ripka, W. C.; Confalone, P. N. *Tetrahedron Lett.* **1984**, *25*, 4613. (c) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153.

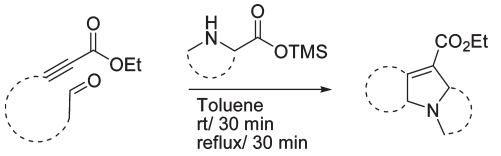
(14) (a) Smith, E. D.; Shewbart, K. L. *J. Chromatogr. Sci.* **1969**, *7*, 704. (b) Annunziata, R.; Ferrari, M.; Papeo, G.; Resmini, M.; Sisti, M. *Synth. Commun.* **1997**, *27*, 23. In some cases, the silyl ester was contaminated with the N,O-bissilyl amino acid derivative. These mixtures were equally effective in the cycloaddition reactions.

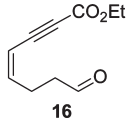
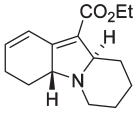
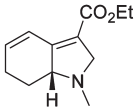
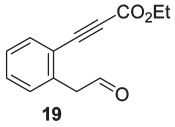
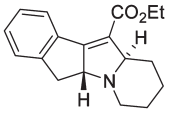
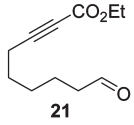
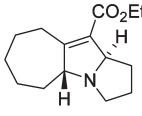
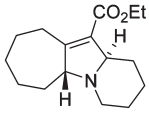
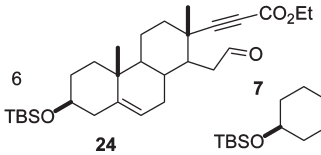
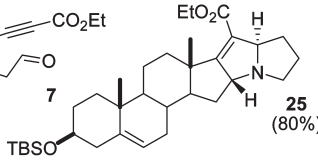
(15) (a) Grigg, R.; Idle, J.; Mcmeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49. (b) Grigg, R.; Idle, J.; Mcmeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703. (c) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2693.

(16) The relative configurations of compounds **6**, **9**, **15**, **20**, and **25** were determined through NOE studies. The relative stereochemistry depicted for the remaining compounds was based on analogy.

is structurally similar to several Solanum steroidal alkaloids. The 2,5-dihydropyrroles formed by this reaction sequence are stable products when stored under an inert atmosphere, but are prone to oxidize to the corresponding pyrroles upon standing in air.[17]

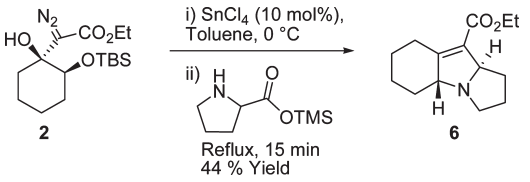
TABLE 2. 2,5-Dihydropyrroles Prepared from Various Tethered Aldehyde Ynoates



Entry	Tethered aldehyde ynoate	Amino Silylester	2,5-dihydropyrrole (Yield)
1	 **16**	**8**	 **17** (78%)
2	**16**	**10**	 **18** (20%)
3	 **19**	**8**	 **20** (67%)
4	 **21**	**7**	 **22** (44%)
5	**21**	**8**	 **23** (44%)
6	 **24**	**7**	 **25** (80%)

To render this approach to polycyclic 2,5-dihydropyrroles even more efficient, we briefly investigated the possibility of effecting a one-pot ring fragmentation 1,3-dipolar cycloaddition. Treating a toluene solution of diazo **2** (Scheme 3) with 1 equiv of $SnCl_4$ followed by the addition of trimethylsilyl prolinate and then warming the mixture to reflux provided little to no desired cycloaddition product. It seems likely that the amino acid silyl ester is incompatible with the Lewis acid since heating the fragmentation reaction to reflux without amino acid present did not result in decomposition of the aldehyde ynoate. We had previously determined that the fragmentation reaction could be effected with as little as 10 mol % of $SnCl_4$, albeit in slightly diminished yield (85% vs. 94% with 1 equiv of $SnCl_4$). We were pleased to find that using 10 mol % $SnCl_4$ in a one-pot fragmentation/1,3-dipolar cycloaddition sequence provided tricyclic 2,5-dihydropyrrole **6** (Scheme 3) in 44% yield.

SCHEME 3. One-Pot Ring Fragmentation/Intramolecular 1,3-Dipolar Cycloaddition



In summary, the ring fragmentation/1,3-dipolar cycloaddition sequence reported here is an efficient method to prepare polycyclic 2,5-dihydropyrroles from α-silyloxy ketones. A one-pot fragmentation/1,3-dipolar cycloaddition sequence also provided the desired 2,5-dihydropyrrole product, albeit in a diminished yield. This three-step sequence appears general and provided a variety of structurally unique products.

Experimental Section

2,5-Dihydropyrrole 6. From preformed tethered aldehyde ynoate 3: Trimethylsilyl prolinate[14] (0.086 mL, 0.30 mmol) was added dropwise to a solution of ethyl 8-oxooct-2-ynoate **3** (0.050 g, 0.274 mmol) in dry toluene (2.7 mL). After 5 min a pale green solution containing a white precipitate was observed. After 30 min the reaction flask was fitted with a dry condenser and transferred to an oil bath preheated to 120 °C. The mixture was heated at reflux for 15 min and then cooled to room temperature. The solvents were removed in vacuo and the resulting yellow oil was subjected to flash silica gel chromatography (99:1 CH_2Cl_2:MeOH/0.5% Et_3N) to provide 0.057 g (88% yield) of the title product (TLC eluent 92:8 CH_2Cl_2:MeOH; R_f 0.3): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (q, J = 6.2 Hz, 1H), 4.23 (dq, J = 10.8, 7.2 Hz, 1H), 4.17 (dq, J = 10.8, 7.2 Hz, 1H), 3.47−3.53 (m, 1H), 3.28−3.36 (m, 1H), 3.11 (dt, J = 10.3, 5.8 Hz, 1H), 2.63 (dt, J = 10.2, 6.7 Hz, 1H), 2.04−2.17 (m, 2H), 1.93 (td, J = 13.3, 5.4 Hz, 1H), 1.70−1.88 (m, 4H), 1.50−1.61 (m, 1H), 1.17−1.44 (m, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 156.6, 124.9, 75.9, 71.4, 59.8, 56.0, 37.1, 31.9, 27.2, 26.6, 25.5, 24.2, 14.3; MS (ESI) calcd for $[C_{14}H_{22}O_2N]^+$ 236.1651, found 236.1650.

One-pot protocol: $SnCl_4$ (0.029 mL of a 1 M solution in CH_2Cl_2, 0.029 mmol) was added in a continuous stream to a solution of γ-silyloxy-β-hydroxy-α-diazo ester **2** (0.100 g, 0.292 mmol) in toluene (3 mL) at which point the yellow solution turned colorless and gas evolution was observed. After 15 min trimethylsilyl prolinate **7** (0.092 mL, 0.321 mmol) was added and the solution became pale green and a white precipitate formed. After 30 min the reaction flask was fitted with a dry condenser and transferred to an oil bath preheated to 120 °C. The solution was heated at reflux for 15 min and then cooled to room temperature, at which point aqueous KOH (1.5 mL of a 1 N solution) was added with vigorous stirring. After 1 min the mixture was transferred to a separatory funnel with the aid of diethyl ether, the aqueous layer was removed, the organic layer was dried ($MgSO_4$), the solvents were removed in vacuo, and the residue was subjected to flash silica gel chromatography (99:1 CH_2Cl_2:MeOH/0.5% NEt_3) to provide 0.030 g (44% yield) of the title product.

(17) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2003**, *44* (46), 8417.

2,5-Dihydropyrrole 15. Methyl prolinate (0.164 mmol) in toluene (0.164 mL) was added dropwise to a 0 °C stirred solution of aldehyde ynoate **3** (25 mg, 0.137 mmol) and 4 Å molecular sieves (~120 mg) in toluene (1.5 mL). After 30 min at 0 °C the reaction flask was fitted with a dry condenser and transferred to an oil bath preheated to 120 °C. The progress of the reaction was monitored by TLC and upon completion (ca. 1 h) the mixture was cooled, filtered through a pad of Celite, the solvents were removed *in vacuo* and the residue was subjected to flash silica gel chromatography (Hexane: EtOAc = 10:1 to 5:1 to 1:1) to provide 25 mg (65% yield) of the title 2,5-dihydropyrrole; (TLC eluent 60:40 Hexane: EtOAc; Rf: 0.14) ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (q, J = 7.1 Hz, 2H), 3.95 (dd, J = 12.0, 5.8 Hz, 1H), 3.70 (s, 3H), 3.59 (m, 1H), 2.85−2.96 (m, 2H), 2.75 (dd, J = 9.6, 7.2 Hz, 1H), 2.14−2.21 (m, 1H), 2.03−2.13 (m, 1H), 1.84−2.01 (m, 3H), 1.70−1.80 (m, 2H), 1.32−1.53 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 164.4, 158.4, 125.4, 82.1, 68.6, 59.9, 52.3, 48.6, 34.3, 29.2, 26.7, 26.6, 25.6, 24.1, 14.2; MS (ESI): Calculated for $[C_{16}H_{24}O_4N]$: 294.1705 Found: 294.1710.

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Supporting Information Available: General experimental methods, detailed experimental procedures, product characterization data, and copies of product spectra. This material is available free of charge via the Internet at http://pubs.acs.org.