ORGANIC
LETTERS

2000
Vol. 2, No. 15
2299−2301

[3 + 2]-Cycloaddition of Nonstabilized Azomethine Ylides. 10. An Efficient Strategy for the Construction of *x*-Azatricyclo[$m.n.0.0^{a,b}$]alkanes by Intramolecular Cycloaddition of Cyclic Azomethine Ylide[†]

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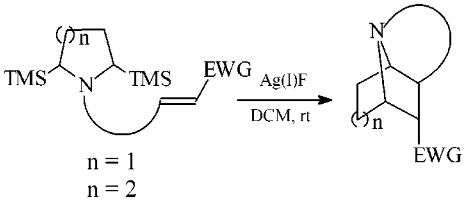
Received May 17, 2000

ABSTRACT



Various new structural entities related to *x*-azatricyclo[$m.n.0.0^{a,b}$]alkanes are constructed by the intramolecular [3 + 2] dipolar cycloaddition of nonstabilized cyclic azomethine ylides. The ylide is generated by the sequential double desilylation of *N*-alkyl α,α′-bis(trimethylsilyl)cyclic amines using Ag(I)F as a one-electron oxidant.

Owing to its facility of constructing two rings simultaneously, intramolecular 1,3-dipolar cycloaddition strategies have emerged as an important tool for the synthesis of structurally complex fused heterocyclic ring systems.[1−2] Particularly, several bicyclic[3−6] and polycyclic[7−9] fused pyrrolidine ring systems are synthesized by the intramolecular cycloadditions of stabilized acyclic azomethine ylides with tethered dipolarophiles.

Recently, our group has developed[10] a strategy of generating nonstabilized cyclic azomethine ylides by sequential double desilylation of *N*-alkyl α,α′-bis(trimethylsilyl)cyclic

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[†] For part 9, see ref 11.

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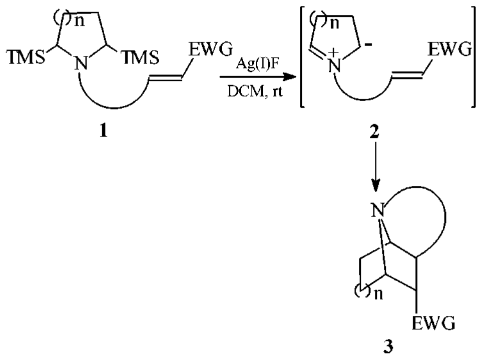
10.1021/ol006070s CCC: $19.00

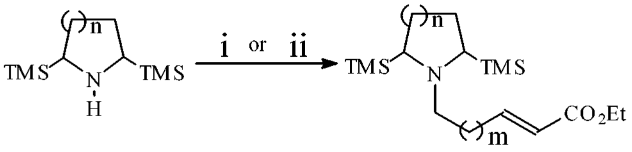
amines using Ag(I)F as a one-electron oxidant. We have also explored its application for the regio- and stereoselective construction of *x*-azabicyclo[*m*.2.1]alkane skeletons.[10,11] Biologically important alkaloids such as epibatidine[12] and epiboxidine[13] have also been synthesized using this strategy. Our continuing interest and the desire to explore the versatility of such ylides in the construction of complex polycyclic fused pyrrolidine ring systems led us to consider the intramolecular cycloaddition variant. Kozikowski's[14] recent disclosure that some compounds possessing structural features of skeleton **3** exhibit selective and high binding at dopamine transporter (DAT) further encouraged us to develop the intramolecular cycloaddition of cyclic azomethine ylides. We have constructed various new structural entities related to skeleton **3** through the strategy shown in Scheme 1 and are happy to delineate the preliminary results in this Letter.

Scheme 1



The precursors **7a** and **7b** were prepared by refluxing a mixture of 2,5-bis(trimethylsilyl)pyrrolidine (**4a**) with 6-iodo-(*E*)-2-hexenoate (**5a**) and 7-iodo-(*E*)-2-heptenoate (**5b**),[15] respectively, with K_2CO_3 in dry CH_3CN. Similarly, the substrates **7c** and **7d** were synthesized by reductive amination with 6-oxo-(*E*)-2-hexenoate (**6a**) and 7-oxo-(*E*)-2-heptenoate (**6b**),[16] respectively, with 2,6-bis(trimethylsilyl)piperidine (**4b**) (Scheme 2). We have already reported the synthesis of **4a**,**b**.[12] Reagents **5a** and **6a** were obtained utilizing simple reaction sequences starting from commercially available 1,4-butanediol.[15,17−19]

Scheme 2



4a n = 1

4b n = 2

7a n = 1, m = 2 65 %

7b n = 1, m = 3 67 %

7c n = 2, m = 2 73 %

7d n = 2, m = 3 75 %

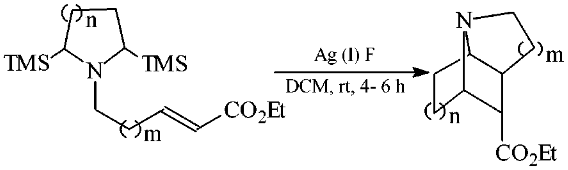
i) $ICH_2(CH_2)_mCH=CHCO_2Et$, **(5)**, K_2CO_3, CH_3CN, Δ, 24– 30 h.
ii) $OHC(CH_2)_mCH=CHCO_2Et$, **(6)**, ethanol, $NaBH_3CN$, rt, 6- 8 h.

The intramolecular cycloaddition reactions were at first initiated with **7a**. The general reaction procedure involved the slow addition of a solution of **7a** (1 equiv) in dry DCM to a stirred suspension of vacuum-dried Ag(I)F (2 equiv) at room temperature.

The color of the reaction mixture gradually turned dark brown, and the reaction was completed within 4−6 h with the concomitant formation of silver mirror on the surface of the reaction flask. The reaction mixture was filtered through a Celite pad, and usual purification by column chromatography using chloroform:methanol (7:3) as eluent afforded the single product **8a** in 61% yield which was characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral data.

The generality of the cycloaddition reaction was established by constructing a number of *x*-azatricyclo[*m*.*n*.0.0^{a,b}]-alkanes (**8b−d**) as depicted in Scheme 3.

Scheme 3



7a n = 1, m = 2	**8a** 61 %
7b n = 1, m = 3	**8b** 41 %
7c n = 2, m = 2	**8c** 69 %
7d n = 2, m = 3	**8d** 64 %

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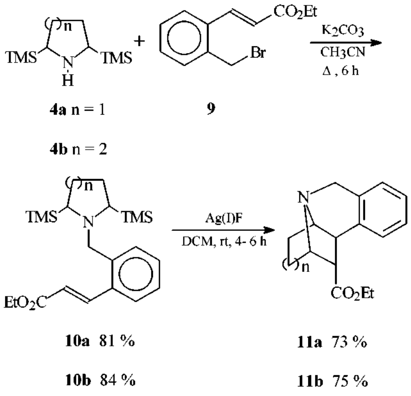
Detailed ^{1}H NMR decoupling and ^{1}H COSY experiments determined the stereochemistry of the cycloadducts. For illustration, in the cycloadduct **8a**, it was found that H_6 at δ 2.53 (m, 1H) coupled with H_7 at δ 2.95 (d, $J = 5.7$ Hz, 1H) and H_5 at δ 1.51−1.64 (m, 3H) but not with H_1 at δ 3.05−3.17 (m, 3H). This observation is found to be in conformity with the ^{1}H NMR patterns of the 7-azabicyclo[*m*.2.1]alkane skeletons[20] where no coupling is observed between bridgehead and adjacent *endo*-hydrogens. Therefore, H_6 is assigned an *endo*-orientation. In contrast, H_7 was found to couple H_6 and H_8 at δ 3.73 (t, $J = 4.6$ Hz, 1H), confirming the *endo*-orientation of the carbethoxy moiety. The stereochemistry of other cycloadducts **8b**−**d** was ascertained similarly.

To synthesize more rigid structures related to skeleton **3**, cycloadditions of **10a**,**b**, synthesized by refluxing **4** with **9**[21] in acetonitrile in the presence of K_2CO_3, were studied (Scheme 4). Reaction of **10** with Ag(I)F (as described for **8a**) gave cycloadducts **11a**,**b** in 73−75% yield. ^{1}H NMR, ^{13}CNMR, and mass spectral data characterized these cycloadducts, and stereochemical assignments were determined as described for **8a**.

Scheme 4



We have successfully synthesized a number of polycyclic *x*-azatricyclo[*m*.*n*.0.$0^{a,b}$]alkanes by employing the intramolecular [3 + 2] dipolar cycloaddition of nonstabilized cyclic azomethine ylides. We believe these rigid polycyclic structures may be of interest in natural product synthesis and medicinal chemistry. Studies related to the biological evaluation of **8** and **11** and their possible utilization in natural products synthesis are in progress.

Acknowledgment. A.K.S. thanks CSIR, New Delhi for the award of research fellowship. We are grateful to Dr. M. Vairamani (Indian Institute of Chemical Technology, Hyderabad) for providing HRMS data. Financial support from the Department of Science and Technology (New Delhi) is also gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data of starting materials (**7a**−**d**, **10a**,**b**) and cycloadducts (**8a**−**d**, **11a**,**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL006070S

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