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Synthesis of biologically active natural products by [3+2] cycloaddition of non-stabilized azomethine ylides (AMY): Concepts and realizations

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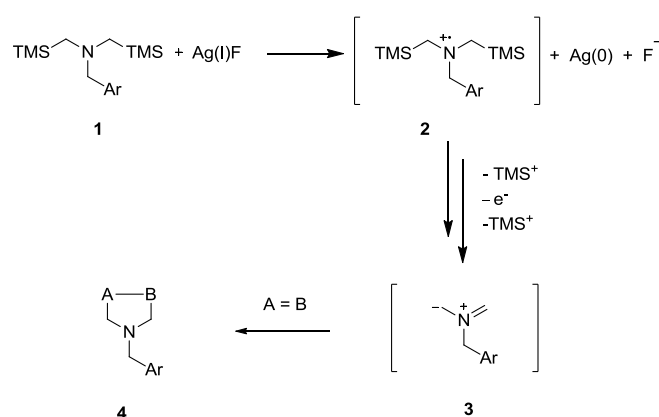
ABSTRACT

Non-stabilised azomethine ylides (AMY) which are represented as a zwitterionic form of a C-N-C unit having four electrons in three parallel atomic π orbitals perpendicular to the plane of the dipole, undergoes 1,3-dipolar cycloaddition to produce isolated as well as fused pyrrolidine ring system stereoselectively. Various new structural entities related to x -azatricyclo[$m.n.0.0a,b$]alkanes are constructed by the intramolecular 1,3-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. Various alkaloids such as (\pm)-pancracine, (\pm)-brunsvigine, (\pm)-maritidine, (\pm)-crinine, (-)-vincodifformine and (+)-aspidospermidine have been synthesized employing AMY cycloaddition strategy.

1. Introduction

Isolated as well as fused pyrrolidine rings are common scaffolds found in vast number of biologically active alkaloids,¹ therefore, their construction in an efficient manner has attracted attention of a large number of synthetic organic chemists. Although, there are many approaches known to construct substituted pyrrolidine rings in regio- and stereo-selective manner,^{2,3} [3+2]-cycloaddition reaction of azomethine ylides (AMY) with a suitable olefins is the most reliable and attractive approach.⁴ Azomethine ylides⁵ are represented by a zwitterionic structure with a C-N-C unit having four electrons in three parallel atomic π orbitals perpendicular to the plane of the dipole which reacts with another π system (olefins) involving a total of six π electrons [$\pi 4s + \pi 2s$] and is considered to proceed through a thermally allowed⁶ concerted process, though, non-concerted possibility is also suggested.⁷ A detailed account on the mechanistic discussion of AMY and its cycloaddition could be found in literature.⁸ Our group has developed⁹ an innovative concept to generate non-stabilized AMY **3** via one electron oxidation of N, N' -dialkylsilylamines **1** either by photoredox catalysis^{9a} or by using Ag(I)F as one electron oxidant.^{9b} Mechanistically, this reaction was rationalized considering sequential desilylation¹⁰ from the amine radical cation **2**, thus, generated after one electron oxidation of corresponding amine. The resultant AMY reacts inter-or intra-molecularly with an

activated olefin to generate fused or isolated pyrrolidine **4** scaffolds, respectively^{9a,b,11} as shown in **Scheme 1**.



Scheme 1: Pyrrolidine ring generation through 1,3 dipolar cycloaddition.

This strategy was utilized to construct indolizidine and pyrrolizidine skeletons by [3+2]-cycloaddition^{9b} of corresponding AMY **6**, generated by the sequential desilylation of **5**, with ethyl acrylate **7**. The cycloaddition provided two regeoisomeric pyrrolizidines **8** and **9** in 17:3 ratios. Since the isolation of pure diastereomers was difficult, the mixture was reduced by LAH to

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