Communications

A Novel Trimethylsilyl Triflate-Promoted Annulation of N-Acetoacetylated Alkenyl Amides

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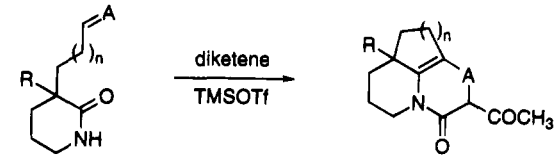
Silicon based reagents have found widespread application in organic synthesis.[1-3] (Trimethylsilyl)trifluoromethane sulfonate (TMSOTf), in particular, is frequently utilized as a highly electrophilic silylating agent,[4] and there are now a very large number of reactions that employ this reagent in either stoichiometric or catalytic quantities.[5-7] The virtually non-nucleophilic character of the triflate anion allows for the desired acid–base chemistry to occur without competitive trapping by the counterion.[8] As part of an ongoing program dealing with stereocontrolled approaches to heterocyclic ring systems, we have been interested in developing a 4 + 2-annulation strategy for heterocyclic synthesis which utilizes the intramolecular cycloaddition reaction of 1,4-dipoles.[9] Few approaches to six-ring heterocycles using this methodology have been reported.[10-13] We wish to disclose here that the reaction of a 3,3-disubstituted cyclic amide with diketene in the presence of 0.13 equiv of TMSOTf represents a convenient method for generating the equivalent of a cross-conjugated heteroaromatic betaine dipole.[14] The overall transformation is illustrated in Scheme 1. The details of this new reaction are the subject of this communication.

Although trimethylsilyl triflate is known to catalyze carbon–carbon bond forming reactions,[15] the generation of a zwitterionic species capable of undergoing dipolar cycloaddition has been reported only for 1,3-dipoles.[16] The present reaction involves the intramolecular cycloaddition of a 1,4-dipole synthon formed from the reaction of

Scheme 1



an N-acetoacetylated alkenyl amide in the presence of TMSOTf. In the initial studies, $BF_3{\cdot}OEt_2$ was utilized as the Lewis acid promoter for the annulation reaction. Subsequent studies demonstrated that these annulation reactions were capricious with variable yields of product being obtained. In addition, 1 full equiv of the Lewis acid was required, causing subsequent workup problems. In order to overcome these difficulties, a survey of diverse Lewis acids was carried out. Among the many Lewis acids tried, trimethylsilyl triflate gave the highest yield of the annulated product.

Stirring a sample of 3-ethyl-3-(buten-4-yl)piperidinone (**1**) and diketene with 0.13 equiv of trimethylsilyl triflate in benzene at ambient temperature initially generates the N-acetoacetylated amide **3** which is further converted to pyridone **5** (53% yield) under the reaction conditions. An independent synthesis of **3** was also carried out by heating a sample of **1** with 2,2,6-trimethyl-4*H*-1,3-dioxen-4-one in xylene at 140 °C.[17] Treatment of a pure sample of **3** with TMSOTf in benzene cleanly afforded pyridone **5**, with no signs of the initially formed dihydropyridone (*vide infra*).[18]

Control of ring size in the final product of the cycloaddition by variation of the dipolarophilic chain length is of appreciable interest. Introduction of a five-carbon chain was readily achieved by treating 3-ethylpiperidinone with 2 equiv of n-butyllithium followed by reaction with 5-bromopentene to give lactam **2**. Treatment of lactam **2** with diketene and TMSOTf (0.13 equiv) in benzene afforded pyridone **6** (26%) together with some of the N-acetoacetylated product **4**. Entry to the [6,6,5] and [6,6,6]-pyridone ring systems was also possible using the corresponding alkynyl substituted amides **7-10**. Thus, the reaction of **7** or **8** with diketene and TMSOTf in benzene at 25 °C gave pyridones **11** and **12** in 50% and 65% yield, respectively. It should also be noted that the reaction of the alkynyl-substituted lactams **9** and **10** afforded the same pyridones (**5** and **6**) as was obtained from lactams **1** and **2** in 53 and 50% yield.

Another aspect of the cycloaddition worth noting is the complete stereospecificity of the process. Treating a sample of the *E*-labeled lactam **13** with diketene and TMSOTf in benzene produced cycloadduct **14** in 63% yield. The stereochemistry of the substituent groups was established by single crystal X-ray diffractometry on the 2,4-dinitrophenyl hydrazone derivative.[19] Reaction of the *Z*-labeled lactam **15**, on the other hand, gave rise to a 2:1-mixture of cycloadducts **16** and **17** in 93% overall yield. The two tautomers were separated by silica gel

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(18) We assume that the initially formed cycloadduct is rapidly oxidized to the pyridone ring.
(19) The authors have deposited coordinates for structures **14**, **16**, and **17** with the Cambridge Data Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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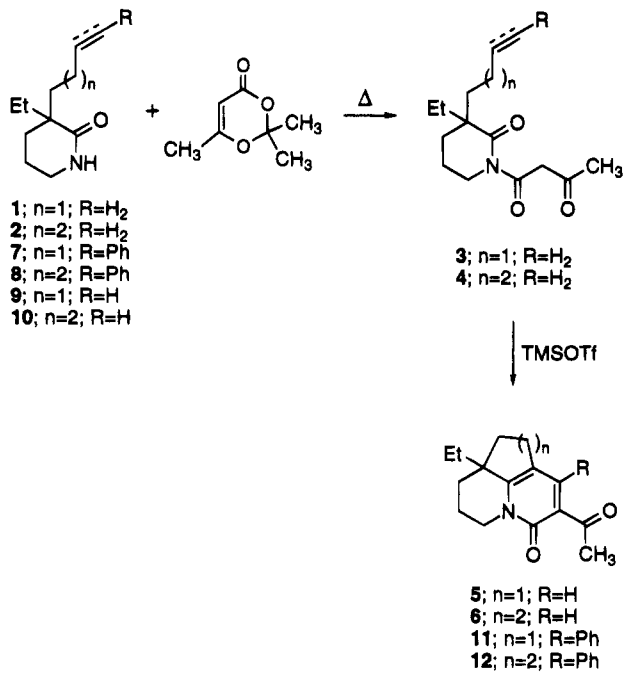
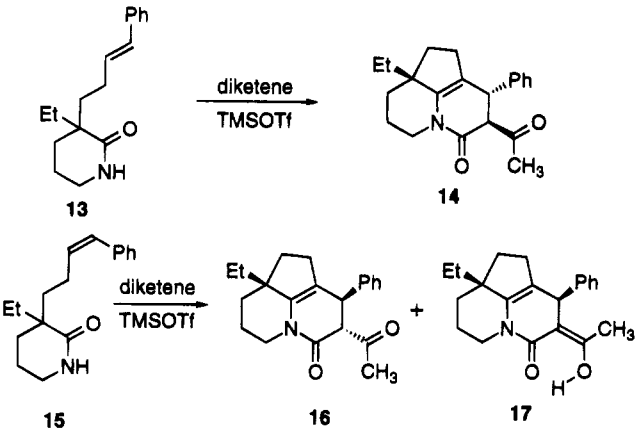
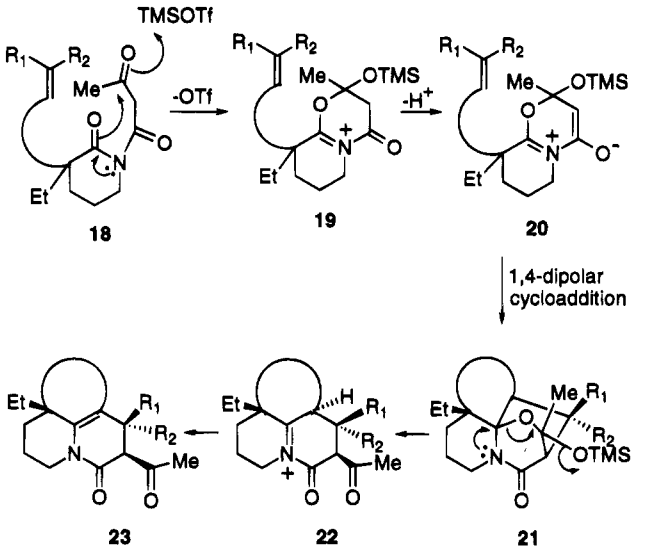


chromatography, and their structures were unequivocally assigned by single crystal X-ray diffractometry. Cycloadducts **16** and **17** were readily interconverted upon standing in solution.



The mechanism of this unusual annulation reaction has not been unequivocally established, but one reasonable possibility is outlined in Scheme 2. Here it is proposed that cyclization of the starting N-acetoacetylated amide (*i.e.*, **18**) occurs in the presence of TMSOTf to give the cyclized acyl iminium ion **19**. Removal of the acidic proton generates the cross-conjugated heteroaromatic betaine **20** which undergoes a subsequent intramolecular 1,4-dipolar cycloaddition. The resulting cycloadduct **21** proceeds on to the annulated product **23** *via* a nitrogen assisted C–O bond cleavage, ejection of $TMSO^-$ followed by a proton shift.[20,21] The observed

Scheme 2



stereochemistry of the annulation product **14** derived from lactam **13** is perfectly consistent with this mechanism. On the other hand, the expected stereoisomer derived from lactam **15** should have had all three substituent groups on the same side of the tricyclic skeleton, but this isomer was not found. In order to account for the stereochemistry actually encountered, we assume that the initially produced diastereomer is readily epimerized to the thermodynamically more stable epimer. Indeed, the isolation of **17** as a distinct tautomer from this reaction lends support to the presumed facility of epimerization.

In summary, TMSOTf promotes the intramolecular 4 + 2 annulation of N-acetoacetylated alkenyl amides. The overall convenience of the method, the ease of access to starting materials, and the complexity of the products obtained suggests its further application to the preparation of a number of polycyclic ring systems of interest in natural product chemistry. Work along these lines is in progress and will be reported in due course.

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Supplementary Material Available: Experimental procedures and characterization data (10 pages).

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(20) In order to account for the fact that the reaction proceeds smoothly using only 0.13 equiv of TMSOTf, we suggest that under the reaction conditions TMSOTf is regenerated, perhaps from the reaction of TMSOH and CF_3SO_3H.

(21) When **16** was allowed to stand in an oxygenated environment, it was readily oxidized to pyridone **11** thereby providing good support for the suggestion that the initial cycloadducts derived from **1** and **2** are easily oxidized to pyridones **5** and **6**.