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A new regio- and stereoselective synthesis of β-enamino ketones with 3-ethoxycyclobutanones and substituted amines

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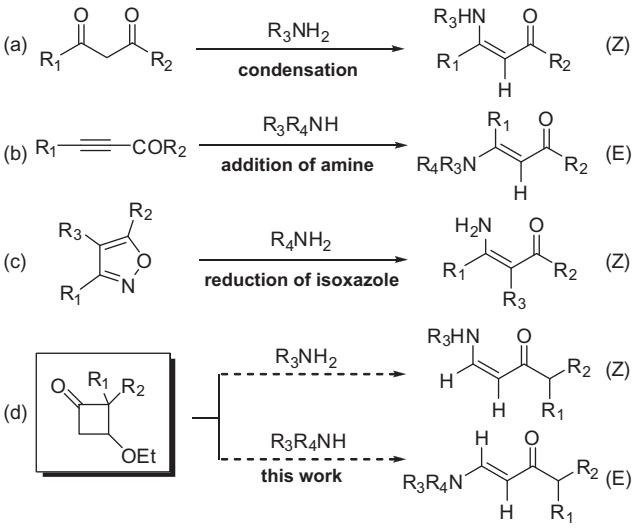
ABSTRACT

A new method toward regio- and stereoselective synthesis of β-enamino ketones is described. Through Lewis acid-catalyzed reactions between 3-ethoxycyclobutanones and substituted amines, a variety of cis and trans β-enamino ketone derivatives were prepared with complete regio- and stereoselectivity at room temperature.

β-Enamino ketone is an especially versatile class of intermediates for the synthesis of important heterocycles such as indole, pyrrole, pyridine, pyrimidine, pyrimidine, pyridinones, quinolines, oxazoles, and isoxazole derivatives, etc.[1,2] It has also been widely employed to prepare natural therapeutic molecules and biologically active analogs which include anti-inflammatory, antitumor, antimalarial, and antibacterial agents, etc.[3] 1,3-Amino alcohol can be readily synthesized via reduction of β-enamino ketone as well.[4] Additionally, chiral enaminones are used as ligands for diastereoselective synthesis.[5]

Owing to such important applications of β-enamino ketones, many efforts have been devoted to developing synthetic methods for the preparation of these compounds.[6] Among the current methods for synthesizing β-enamino ketones, three are most commonly used (Scheme 1a,b,c). One utilizes the direct condensation of 1,3-diketones with amines.[7] Another route involves the reaction of acid chlorides and acetylenes under Sonogashira condition followed by an attack of primary or secondary amines.[8] The third approach is through metal-mediated reduction of isoxazoles.[9] Although these methods are suitable for certain synthetic conditions, many of these procedures have one or more limitations which include low regioselectivity, circuitously synthetic steps, long reaction time, low yield, requirement of excess of reagents or catalysts, and harsh reaction conditions, etc. Therefore, an efficient and complementary method for β-enamino ketone synthesis is highly desired.

Serving as a versatile synthetic intermediate, 3-ethoxycyclobutanones have been used to prepare various types of compounds such as bicyclobutanes, silyloxy dienes, and six-membered cyclic compounds.[10] In those studies, 3-ethoxycyclobutanones were applied as a formal 1,4-dipole.[11] Recently our group reported the synthesis of pyrazoles through an annulation reaction between 3-ethoxycyclobutanones and substituted hydrazines.[12] Our studies



Scheme 1. General approaches for synthesis of β-enamino ketone.

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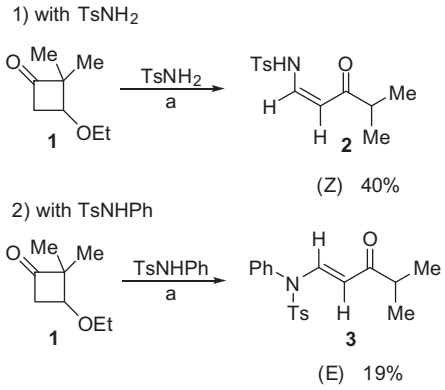


Scheme 2. Preliminary studies.

demonstrated, for the first time, 3-ethoxycyclobutanones can be employed as 1,3-dicarbonyl synthon for useful chemical transformations.

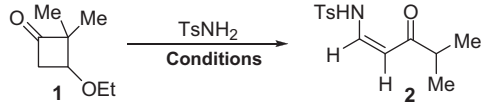
To date, there is no report in the literatures that 3-ethoxycyclobutanones could be operated as 1,3-dicarbonyl synthon to prepare β-enamino ketones. Herein we report the development of a new efficient one-step approach toward regio- and stereoselective syntheses of β-enamino ketone through Lewis acid-catalyzed reaction between 3-ethoxycyclobutanone and substituted amine (Scheme 1d).

In comparison with intramolecular trapping the zwitterionic intermediate resulted from activated 3-ethoxycyclobutanone by Lewis acid to afford a new five-member ring, we envisioned that intermolecularly approaching this in situ formed oxocarbonium intermediate with nucleophiles such as substituted amines, a variety of hemiaminal ethers could be generated respectively. After elimination of EtOH from hemiaminal ether intermediates, corresponding β-enamino ketones could be obtained eventually (Scheme 1d).

To test our hypothesis, a model study was initiated with $TsNH_2$ which is selected as the nitrogen nucleophile and 2,2-dimethyl 3-ethoxycyclobutanone (Scheme 2).[13] As a Lewis acid promoter, 0.5 equiv of $TiCl_4$ was added to the reaction mixture. The reaction was very fast and went to completion in 30 min at room temperature. Delightfully the desired product **2** was obtained in a 40% yield with complete regioselectivity. The double bond geometry of **2** was supported by the coupling constant between two olefinic protons which was 8.50 Hz. Interestingly, only *Z*-isomer product was obtained, which hints a potential hydrogen-bonding effect that may account for the stereochemistry outcomes of primary amines. However, as secondary amines such as TsNHPh was used as substrate, exclusively *E*-isomer product **3** was formed. The corresponding geometry of double bond of **3** was confirmed with a significant larger coupling constant of 13.70 Hz. This result suggests that more thermodynamic stable *E*-isomers are preferred products in the case of secondary amines.

Encouraged by these preliminary results, we started to optimize this reaction by screening different conditions (Table 1). In the case of $TsNH_2$, we found that besides $TiCl_4$, other Lewis acids, such as $BF_3.OEt_2$, $SnCl_4$ can catalyze β-enamino ketone formation with equal or higher levels of efficiency. In general, a small catalyst amount, like 0.05 or 0.1 equiv of $SnCl_4$ can promote the reaction more effectively than higher catalyst loadings. It was observed that the reaction also proceeded smoothly in various solvents, such as DCM, DCE, CH_3CN, and toluene, and gave β-enamino ketone **2** in moderate to excellent yields. Lower temperature only has a slight effect on yield and reaction time. Typically the reaction will proceed to completion within one hour in a fast and clean manner at ambient temperature. Entry 6 in Table 1 was found to be the best conditions for $TsNH_2$. Attempts to apply these conditions to secondary amines such as TsNHPh, were as successful as those to $TsNH_2$. After further screening the conditions, we discovered that

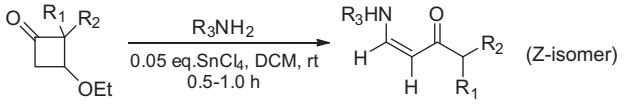
Table 1
Optimization of the reaction conditions

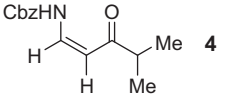
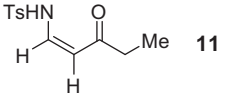
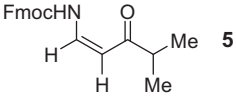
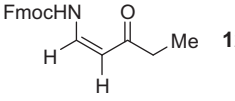
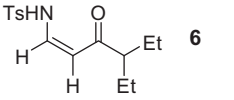
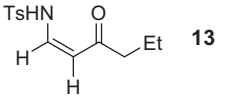
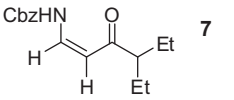
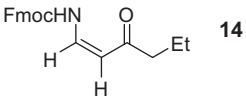
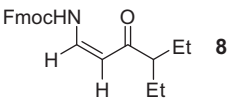
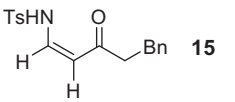
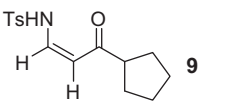
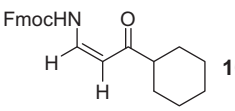
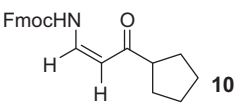
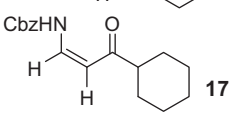


Entry	Catalyst	Condition	Yield[a] (%)
1	$TiCl_4$	0.1 equiv, DCM, rt, 0.5 h	51
2	BF_3OEt_2	0.1 equiv, DCM, rt, 0.5 h	75
3	$SnCl_4$	0.1 equiv, DCM, rt, 0.5 h	84
4	TfOH	0.1 equiv, DCM, rt, 0.5 h	68
5	TMSOTf	0.1 equiv, DCM, rt, 0.5 h	65
6	$SnCl_4$	0.05 equiv, DCM, rt, 0.5 h	96[b]
7	$SnCl_4$	0.3 equiv, DCM, rt, 0.5 h	68
8	$SnCl_4$	1.0 equiv, DCM, rt, 0.5 h	56
9	$SnCl_4$	0.1 equiv, DCE, rt, 0.5 h	81
10	$SnCl_4$	0.1 equiv, Toluene rt, 0.5 h	43
11	$SnCl_4$	0.1 equiv, CH_3CN, rt, 0.5 h	45
12	$SnCl_4$	0.1 equiv,DCM,0 °C, 1.5 h	87

[a] Conversion ratio.
[b] Isolated yield.

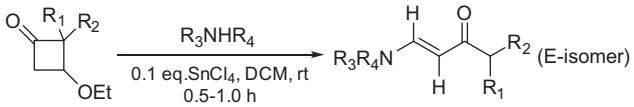
Table 2
Reaction scope with respect to primary amines

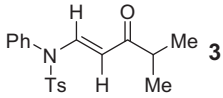
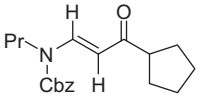
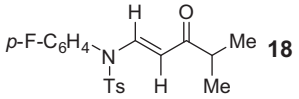
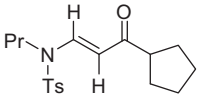
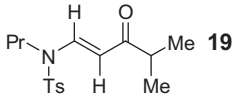
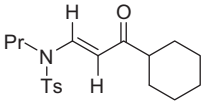
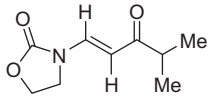
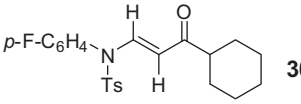
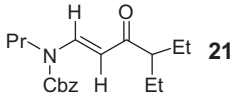
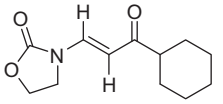
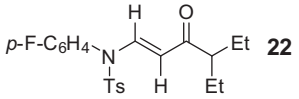
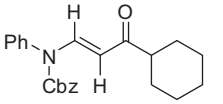
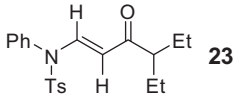
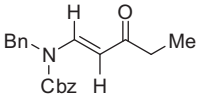
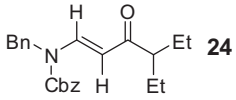
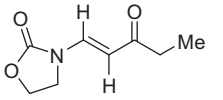
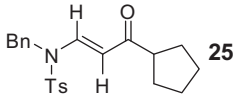
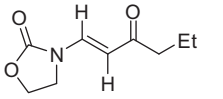
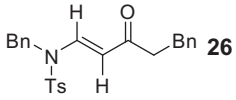


Product	Yield[a] (%)	Product	Yield[a] (%)
 **4**	84	 **11**	93
 **5**	78	 **12**	75
 **6**	94	 **13**	96
 **7**	82	 **14**	71
 **8**	78	 **15**	95
 **9**	95	 **16**	78
 **10**	75	 **17**	79

[a] Isolated yield.

Table 3
Reaction scope with respect to secondary amines



Product	Yield[a] (%)	Product	Yield (%)
 **3**	68	 **27**	73
 **18**	74	 **28**	70
 **19**	69	 **29**	68
 **20**	56	 **30**	73
 **21**	76	 **31**	46
 **22**	66	 **32**	55
 **23**	62	 **33**	65
 **24**	67	 **34**	52
 **25**	66	 **35**	48
 **26**	70		

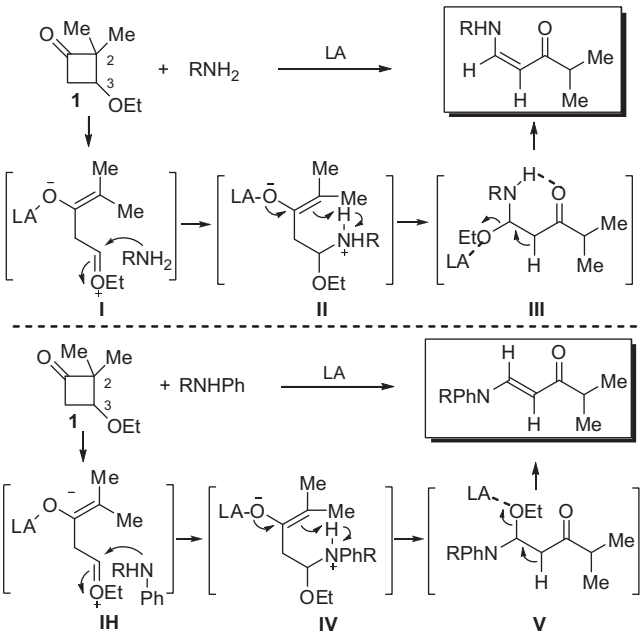
[a] Isolated yield.

0.1 equiv of $SnCl_4$ was the most suitable condition to form β-enamino ketone product **3** with TsNHPh.

With the optimal conditions in hand, we set out to explore the scope for this new reaction. As shown in Table 2, a variety of 3-ethoxycyclobutanones were reacted with different primary amines in the presence of 0.05 equiv $SnCl_4$. It was found that not only $TsNH_2$, but also $CbzNH_2$ and $FmocNH_2$ can react readily to furnish the corresponding (*Z*) geometric β-enamino ketone derivatives. Notably, all 3-ethoxycyclobutanones with varied 2-mono- or 2,2-di-substitutents produced the desired *Z*-isomer products smoothly in good to excellent yields (Compounds **4**–**17**, Table 2). In all cases, only one single product was isolated, no other regioisomer or stereoisomer was obtained.

As illustrated in Table 3, the optimum reaction conditions proved to be compatible with a variety of secondary amines which reacted with 3-ethoxycyclobutanones to readily provide (*E*) geometric β-enamino ketone derivatives in modest to good yields. Notably, as a secondary amine substrate, oxazolidin-2-one provided corresponding products in satisfactory yields as well (Table 3, compounds **20**, **31**, **34**, and **35**). Overall, in comparison with primary amines, secondary amines gave relatively lower yields, which may in part contribute to their more steric nature. In particular, the consistent complete regioselectivity and stereoselectivity of the reaction were observed. Only single isomers were obtained in all examples.

A plausible mechanism is demonstrated in Scheme 3. Upon activation of 2,2-dimethyl 3-ethoxycyclobutanone (**1**) with Lewis acids, the more substituted C2–C3 bond of 3-ethoxycyclobutanone **1** was broken down preferentially to form a zwitterionic intermediate II. Consequently intermolecularly approaching by either primary amine $TsNH_2$ or secondary amine TsNHPh provided the intermediates II or IV, respectively. Following this transforming



Scheme 3. Plausible mechanism.

step, a proton transfer generated hemiaminal ether intermediates III or V. Finally, elimination of one molecule of EtOH from III or V afforded corresponding *Z* or *E* geometric products.

In summary, an efficient one-step protocol has been developed for the rapid synthesis of β-enamino ketones from easily accessible starting materials at ambient temperature. To the best of our knowledge, this is the first report about regio- and stereoselective syntheses of both cis and trans β-enamino ketones by one single method. This method has been found to be generally useful for the preparation of a variety of β-enamino ketone derivatives some of which are difficult to make via conventional approaches. The reaction demonstrates excellent reactivity, complete regioselectivity and stereoselectivity, and high yields. By employing 3-ethoxycyclobutanones in this unique ring-opening reaction with substituted amines, we have shown, for the first time, that this masked 1,3-dicarbonyl synthon acts as a three-carbon synthon of 3-ethoxycyclobutanones in the preparation of β-enamino ketones. Further studies using 3-ethoxycyclobutanones as three-carbon components in other chemical transformations are currently in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.040.

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