

VCl₃ catalysed efficient synthesis of β -enamine esters and ketones from β -keto esters

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VCl₃ is a useful and efficient catalyst for the synthesis of β -enamine esters and ketones from β -keto esters with primary amines.

Keywords: vanadium (III) chloride [VCl₃], β -enamine esters, β -keto esters, amines, amination

β -Enamine esters and ketones are an important class of valuable intermediates,¹ particularly in the construction of bioactive heterocyclic compounds such as dihydropyridines,²⁻⁵ pyrimidines,⁶ pyridines,^{7,8} isothiazoles,⁹ indoles,¹⁰ α - and β -amino acids,¹¹⁻¹² γ -aminols,^{12a} alkaloids,¹³ and peptides.¹⁴

Several methods for the synthesis of β -enamine esters and ketones have been developed and these compounds can be successfully obtained from direct condensation of β -keto esters with amines in benzene or toluene with azeotropic removal of water.¹⁵⁻¹⁶ Moreover, these compounds can be obtained via addition of metallic esters or amide enolates to nitriles,¹⁷ tosyl imines,¹⁸ and indolyl halides,¹⁹ and via addition of enamines to activated carboxylic acids.²⁰ However, most of the currently available methods requires a large excess of amine and suffer from limitations such as low chemical yields, higher reaction times and lack of general applicability. In the fast few years some successful modifications have been reported such as the use of Lewis acids like BF₃·Et₂O,²¹ neutral alumina,²² Montmorillonite-K-10,²³ as solid catalyst in benzene or as solid supports.²⁴⁻²⁵ Herein we describe an efficient method²⁶ for the preparation of β -enamine esters and ketones in very high yields at room temperature from β -keto esters or ketones and amines by VCl₃ as an efficient catalyst precursor.

In anhydrous conditions, one mole equivalent of amines with respect to the β -keto esters at room temperature in dichloromethane furnished the β -enamine esters and ketones by using a catalytic amount of VCl₃. VCl₃ is very active but stable in anhydrous conditions only. It can be recovered in anhydrous conditions by filtration, but it is not possible in this method since the liberated water hydrolyses the VCl₃ to V(OH)₃ and HCl. The formed V(OH)₃ also acts as a Lewis acid hence this reaction completes in less time than other methods.²¹⁻²⁵

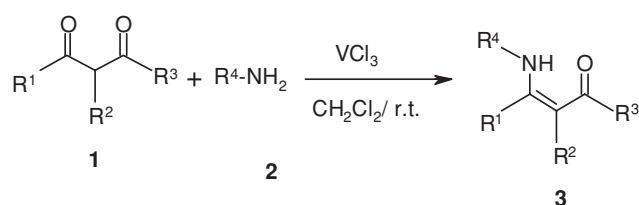
Experimental

Synthesis of 3-phenylamino-but-2-enoic acid methyl ester (**3a**). Aniline (10 mmol) was added into the suspension of VCl₃ (10 mol %) in the ethyl aceto acetate (10 mmol). The resulting mixture was stirred at room temperature for 3–5 h (monitored by TLC). After addition of 10 ml of CH₂Cl₂, the catalyst filtered off and the solution was concentrated to dryness under reduced pressure. Pure products were obtained by purification on a silica gel column.

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Scheme 1

Table 1 VCl₃ catalysed efficient synthesis of β -enamine esters and ketones^a

Entry	R ¹	R ²	R ³	R ⁴	Product ^b	Time /h	Yield /%
1	Me	H	–OEt	Ph	3a	3	82
2	Me	Cl	–OEt	Ph	3b	5	98
3	Me	H	–OEt	<i>p</i> -OMe-Ph	3c	3	97
4	Me	H	–OEt	<i>n</i> -But	3d	4	96
5	Et	Cl	–OEt	Ph	3e	3	88
6	Et	H	–OEt	PhCH ₂	3f	4	89
7	Et	H	Et	Ph	3g	3	87
8	Ph	H	OEt	Ph	3h	5	89
9	Ph	H	OEt	PhCH ₂	3i	3	90
10	Et	H	–OEt	Ph	3j	3	88
11	Me	H	Me	Ph	3k	4	89
12	Me	Cl	Me	Ph	3l	4	92
13	Et	H	Me	Ph	3m	5	93
14	Me	H	Me	Ph	3n	4	92

^aYields refer to pure products and all products were characterised by comparison of their physical and spectral data with those of authentic samples.

^bAll the β -enamine esters and ketones are known compounds

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