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Synthesis of β-enaminodicarbonyl derivatives in the Titanium (IV) chloride-promoted reactions of β-dicarbonyl compounds with nitriles

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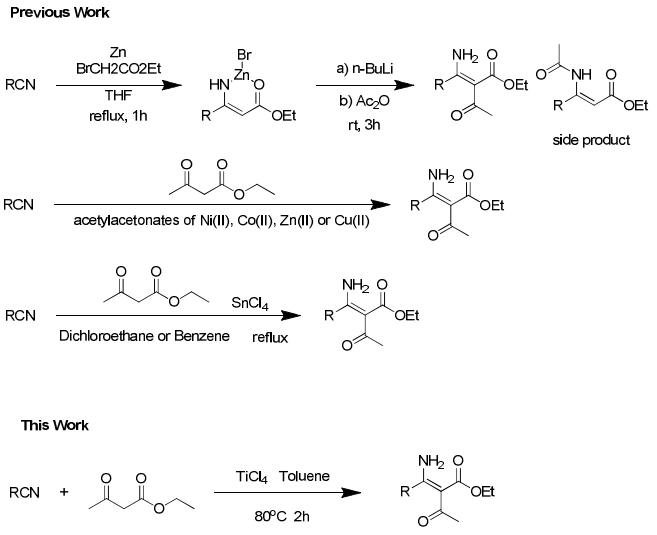
Abstract: Titanium (IV) chloride selectively promoted the nucleophilic attack of ethyl acetoacetate with nitriles to give enaminoketoesters, which were valuable intermediates for the syntheses of 2, 3, 4-substituted heterocyclic. Moreover a plausible mechanism for this transformation was given.
Keywords: Titanium (IV) chloride /β-enaminodicarbonyl / 2, 3, 4-substituted heterocyclic

Introduction

It is believed that β-enaminodicarbonyl derivatives have many potential applications as biologically active compounds and as precursors of substituted β-amino acids, heterocyclic systems, and other classes of valuable compounds [1]. As a consequence, much attention has been paid to the development of an appropriate method for the synthesis of β-enaminodicarbonyl derivatives. Conceptually, many of these β-enaminodicarbonyl derivatives should be available by the addition of appropriate carbon nucleophiles to nitriles. In the past few years, promising progress has been made in this area. Lee and coworkers[2,3] demonstrated that the Blaise reaction, the addition of zinc enolates derived from a-halo esters to nitriles, proceeded via a zinc bromide complex of a β–enamino ester. However, this reaction was quite limited due to the competitive amino-acylated side product, as show in Scheme 1. So far, the most popular route to β-enaminodicarbonyl derivatives is the reaction of β-ketoesters with nitrile by using catalytic amounts (1-5 mol%) of acetylacetonates of Ni(II), Co(II), Zn(II) or Cu(II)[4-9], whereas tin(IV) chloride also promotes C-C bond formation[10-13]. Therefore, in view of higher yield and for environmental concern, the development of a direct synthetic method for β-enaminodicarbonyl derivatives in the presence of Lewis acids would be highly desirable. In this paper we reported a direct Titanium（IV) chloride-promoted method for β-dicarbonyl compounds with nitriles providing β-enaminodicarbonyl derivatives and their conversion to 3,4,5-substituted heterocyclic.

Scheme1. Synthetic Protocols of Enaminodicarbonyl Derivatives

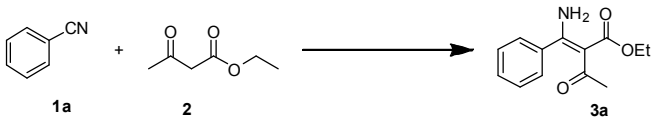


Results and Discussion

Our study began with the C-C bonds formation of nitriles with ethyl acetoacetate. Initially we examined direct benzonitrile and

acetoacetate in the presence of different kinds of Lewis acid as a catalytic in toluene at 110□. To our surprise, the screening of different Lewis acid (Table 1, entries 1-8) led to the discovery that $TiCl_4$ was an effective catalytic, forming the product in an encouraging yield of 65% (Table 1, entry 7). Other additives such as $SnCl_4$ (Table1, entry3) and I_2 (Table1, entry4) also promoted exclusive generation of the product, but the yields are lower than when $TiCl_4$ used. However, $FeCl_3$ (Table1, entry1), $ZnCl_2$ (Table1, entry2), $CoCl_2$ (Table1, entry5), $HgCl_2$ (Table1, entry6), $CuBr_2$ (Table1, entry8) did not activate the reaction efficiently affording the product. With the aim of improving the desired product yield, the equivalent of $TiCl_4$ was examined, and a stoichiometric amount of $TiCl_4$ gave the best yield compared with others (Table 1, entries 9-12). Increase or decrease the equivalent of $TiCl_4$ would reduce the reaction yield. Given that temperature might play an important role in this reaction, we tested the temperature from 50□ to 100□ (Table 1, entries 13-18). It was found out that this reaction could provide the most efficient yield of 82% at 80□. At higher temperatures the by-products would show up, however, the remaining ingredients were the key factors affecting the yield at lower temperatures. Interestingly, the choice of solvent exerted great influence on the reaction yield (Table 1, entries 19-22). Evaluation of various organic solvents in the presence of $TiCl_4$ revealed that toluene provided the best yield. Polar aprotic solvents, such as DMF and DMSO did not effectively improve the reaction yields. Running the reaction in polar protic solvent such as ethanol only afforded a small amount of desired product.

Table1. Optimization of the Reaction Conditions[a]



1a 2 3a

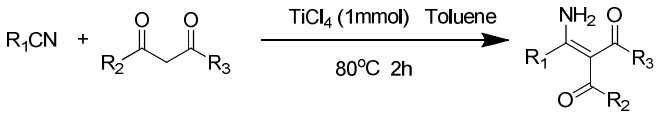
Entry	Catalytic(mol)	Temperature	Solvent	Yield[b](%)
1	$FeCl_3$ (1.5)	110□	Toluene	NR[c]
2	$ZnCl_2$ (1.5)	110□	Toluene	NR[c]
3	$SnCl_4$ (1.5)	110□	Toluene	57
4	I_2 (1.5)	110□	Toluene	23
5	$CoCl_2$ (1.5)	110□	Toluene	NR[c]
6	$HgCl_2$ (1.5)	110□	Toluene	NR[c]
7	$TiCl_4$ (1.5)	110□	Toluene	65
8	$CuBr_2$ (1.5)	110□	Toluene	NR[c]
9	$TiCl_4$ (0.5)	110□	Toluene	45
10	$TiCl_4$ (1.0)	110□	Toluene	72
11	$TiCl_4$ (2.0)	110□	Toluene	40
12	$TiCl_4$ (3.0)	110□	Toluene	18
13	$TiCl_4$ (1.0)	50□	Toluene	NR[c]
14	$TiCl_4$ (1.0)	60□	Toluene	25
15	$TiCl_4$ (1.0)	70□	Toluene	66
16	$TiCl_4$ (1.0)	80□	Toluene	82
17	$TiCl_4$ (1.0)	90□	Toluene	80
18	$TiCl_4$ (1.0)	100□	Toluene	75
19	$TiCl_4$ (1.0)	80□	DMSO	52
20	$TiCl_4$ (1.0)	80□	DMF	NR[c]
21	$TiCl_4$ (1.0)	80□	EtOH	30
22	$TiCl_4$ (1.0)	40□	DCM	45

[a] The reaction were carried out with 1 (1 mmol), 2 (1.2 mmol), solvent (2 mL). [b] Isolated yield based on 1a. [c]No reaction.

With these optimized conditions in hand, we proceeded to investigate the substrates of nitriles. Aromatic nitriles (Table 2, entries 1–8) as well as aliphatic nitriles such as benzyl cyanide acetonitrile, and 3-bromopropanenitrile (Table 2, entries 9–12) were converted to their corresponding β-enaminodicarbonyl derivatives **1a–14n** in moderate to excellent yield. Electron-deficient aryl nitriles gave the expected β-enaminodicarbonyl products in good-to-excellent yield, which was much better than electron-rich one (Table 2, entries 2-7). Many synthetically important functional groups, such as alkoxy, alkyl, nitro and halogen were well-tolerated under the optimal conditions. Moreover, adjacent heteroatom substituted aryl nitriles reacted with ethyl acetoacetate under our conditions to give the products in higher yield, up to 85% (Table 2, entries 8). In the case of other active β-dicarbonyl compounds such as acetyl acetone and diethyl malonate, the yield was also desirable (Table 2, entries 13-14). Therefore, these results clearly demonstrated that Titanium (IV) chloride serves as a useful

Lewis acid catalyst for the reaction of nucleophilic attack of ethyl acetoacetate with nitriles.

Table2. $TiCl_4$-Promoted Reactions of β-dicarbonyl Compounds with Nitriles[a]



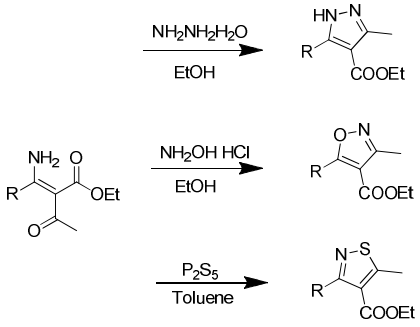
1 2 3

Entry		R_1	R_2	R_3	Yield[b] (%)
1	a	Ph	CH_3	OC_2H_5	82
2	b	2-$NO_2C_6H_4$	CH_3	OC_2H_5	88
3	c	4-$NO_2C_6H_4$	CH_3	OC_2H_5	92
4	d	2-$MeOC_6H_4$	CH_3	OC_2H_5	74
5	e	2, 4 – Dimethoxy Phenyl	CH_3	OC_2H_5	56
6	f	2-ClC_6H_4	CH_3	OC_2H_5	68
7	g	2-Methoxy-3-Pyridyl	CH_3	OC_2H_5	70
8	h	2-Furly	CH_3	OC_2H_5	85
9	i	Benzyl	CH_3	OC_2H_5	76
10	j	Styryl	CH_3	OC_2H_5	78
11	k	Me	CH_3	OC_2H_5	70
12	l	$BrCH_2CH_2$	CH_3	OC_2H_5	65
13	m	Ph	CH_3	CH_3	60
14	n	Ph	OC_2H_5	OC_2H_5	80

[a] The reaction were carried out with 1 (1 mmol), 2 (1.2 mmol), solvent (2 mL). [b] Isolated yield.

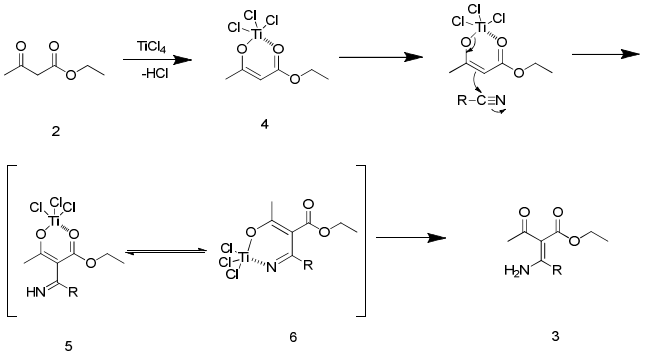
Finally, application of this new metal-promoted method in the synthesis of heterocyclic was tested. The resulting β-enaminodicarbonyl derivatives were transformed to pyrazoles, isoxazoles and isothiazoles, which are important pharmacophores in various biologically active compounds [14]. As show in Scheme 2, reaction of 3 with hydrazine hydrate, hydroxylamine hydrochloride and phosphorus pentasulfide in appropriate solvent afforded the corresponding 3,4,5-trisubstituted pyrazoles, isoxazoles and isothiazoles in good to excellent yields. These encouraging results indicated that the present method provided an efficient approach for the preparation of diverse 3,4,5-trisubstituted heterocyclic.

Scheme 2.Transformation of **3** to 3,4,5-substituted Heterocyclic



A plausible reaction mechanism for Titanium (IV) chloride-promoted reactions of β-dicarbonyl compounds was presented in Scheme 3. The first step of the mechanism involves the formation of a Ti-enolate by interaction of $TiCl_4$ with ethyl acetoacetate and in this step the HCl will go out first. Then corresponding Ti-enolate that formed will attack on the nitrile to generate a N-Ti-O cyclic intermediate **6**, which is intercepted by the Ti-enolate to produce the final product **3**.

Scheme3. A Possible Mechanism for the $TiCl_4$-promoted Reaction



Conclusions

In conclusion, we have successfully developed the metal-promoted reaction of β-dicarbonyl compounds with nitriles

using the readily available reagent $TiCl_4$. The reaction could be carried out under mild conditions and was compatible with many functional groups. This reaction provides a straightforward, practically useful way to prepare various β-enaminodicarbonyl derivatives.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Copies of the 1H NMR and 13C NMR spectra are REQUIRED for all key intermediates and final products; additional information as needed.. See DOI: 10.1039/b000000x/

A representative procedure for the synthesis of 3a: To a solution of the benzonitrile (1mmol), $TiCl_4$ (1mmol) and ethyl acetacetate (1.2mmol) were added at room temperature with stirring. The mixture was refluxed with stirring for 2h. After cooling to room temperature, saturated sodium carbonate solution was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel.

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