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Reactions of β-Diketone Compounds with Nitriles Catalyzed by Lewis Acids: a simple approach to β-enaminone synthesis

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Aluminium chloride selectively promoted the nucleophilic attack of β-diketone compounds with nitriles to give enaminones. Moreover a plausible mechanism for this transformation was given.

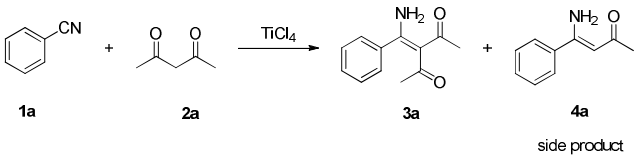
Introduction

Enaminones are important synthetic intermediates and building blocks for drug development[1] and natural product synthesis[2]. For example, they have been successfully used for synthesis of drug (anticonvulsants[3], anti-inflammatory agents[4], and antitumor agents[5]) and bioactive heterocycles (pyridinones, quinolones, pyrroles, isoxazoles, indole, and polyazaheterocycles) [6]. Moreover, they are widely applied in functional group transformation in the field of organic chemistry, including β-alkoxyvinyl ketone enamination[7], 1,2-aryl migration[8], 1,3-dicarbon enamination[9], dehydrogenation[10], lithiated enamine acylation[11], and the Sonochemical Blaise reaction[12]. In coordination chemistry, some β-enaminones can be used as good chelating ligands for main group and transition metals[13]. Therefore, the development of convenient and efficient methods for the synthesis of enaminones has attracted considerable attention. Over the past decades, numerous techniques have been developed for the construction of enaminones, which includes the direct condensation reaction of 1,3-dicarbonyl compounds with amines[14], and cleavage of heterocycles to some novel unconventional routes[15]. In addition, the metal-promoted reaction of 1,3-dicarbonyl compounds to activated nitrile compounds have been successfully employed in the synthesis of enaminones[16]. Despite the success of these approaches in obtaining various enaminones, these methods frequently suffer from certain disadvantages such as harsh reaction conditions, unsatisfactory yields, and the need to use special starting materials.

Results and discussion

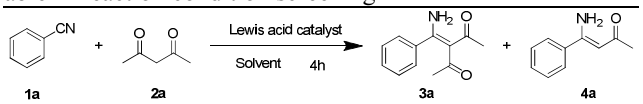
Recently, we reported the preparation of β-enaminodicarbonyl derivatives in the titanium(IV) chloride-promoted reactions of β-dicarbonyl compounds with nitriles[17]. However, when we examined benzonitrile **1a** with acetylacetone **2a** in the presence of titanium(IV) chloride, we found the yield of desired product **3a** was low because of a side product. After separation and confirmation of this side product, to our surprise, the side product was deacetylated product of **3a**, as show in Scheme 1. To the best of our knowledge, the addition reaction of β-diketone to activated nitriles to produce enaminones catalyzed by Lewis acid has not been systematically researched. These products could be a useful intermediate for the synthesis of bioactive heterocyclic molecules such as pyrazoles, isothiazole and isoxazole. However, poor reaction selectivity was found when a mixture of acetylacetone and aromatic nitrile was treated under titanium(IV) chloride conditions. We hypothesized that the reaction selectivity could be controlled by using an appropriate Lewis acid catalyst. Our own interest is looking for an efficient and general Lewis acid as a catalyst in synthesis of β-enaminones **4a**.

Scheme 1. Synthetic protocols of enaminone derivatives



Several Lewis acid catalyst systems were investigated to test this hypothesis. The reaction of benzonitrile **1a** with acetylacetone **2a** was chosen as a model to optimize the reaction conditions. The results are summarized in table 1. Various Lewis acid catalysts such as $SnCl_4$, $CuCl_2$, $AlCl_3$, $FeCl_3$, I_2, $BF_3{\cdot}Et_2O$, $TiCl_4$, $Ni(AcAc)_2$ and $Co(AcAc)_2$ were used. Among these catalysts, $AlCl_3$ and BF_3 exhibited the higher catalyst selectivity (Table 1, entries 5 and 10). In addition, the screening of different Lewis acid (Table 1, entries 1-15) led to the discovery that $AlCl_3$ was the most effective catalytic, forming the product **4a** in an encouraging yield (Table 1, entry 5). The temperature (Table 1, entries 16-20) and solvent (Table 1, entries 5, 21-28) were finally screened. Toluene and 100 ^oC were identified as the best solvent and reaction temperature, respectively. Therefore, in view of catalytic selectivity, higher yield and for environmental concern, the reactions of β-diketone compounds with nitriles were performed in the presence of $AlCl_3$ in toluene at 100 ^oC for 4 h.

Table 1 Reaction condition screening[a]

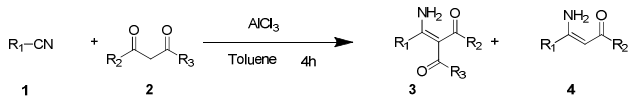


Entry	Catalyst	Solvent	Temperature	Yieldb (%) 3a	Yieldb (%) 4a
1	$SnCl_4$	Toluene	80°C	28	32
2	$NiCl_2$	Toluene	80°C	Trace	Trace
3	$CuCl_2$	Toluene	80°C	15	Trace
4	$ZnCl_2$	Toluene	80°C	Trace	Trace
5	$AlCl_3$	Toluene	80°C	10	70
6	$FeCl_3$	Toluene	80°C	35	10
7	I_2	Toluene	80°C	<10	<10
8	$CoCl_2$	Toluene	80°C	Trace	Trace
9	$PdCl_2$	Toluene	80°C	Trace	Trace
10	$BF_3{\cdot}Et_2O$	Toluene	80°C	68	Trace
11	$TiCl_4$	Toluene	80°C	60	13
12	$CeCl_3$	Toluene	80°C	Trace	Trace
13	$Ni(AcAc)_2$	Toluene	80°C	17	Trace
14	$Co(AcAc)_2$	Toluene	80°C	15	Trace
15	$Ce(BuAc)_2$	Toluene	80°C	Trace	Trace
16	$AlCl_3$	Toluene	60°C	<10	15
17	$AlCl_3$	Toluene	70°C	<10	55
18	$AlCl_3$	Toluene	90°C	10	75
19	$AlCl_3$	Toluene	100°C	12	78
20	$AlCl_3$	Toluene	110°C	<10	70
21	$AlCl_3$	DMSO	100°C	<10	Trace
22	$AlCl_3$	DMF	100°C	Trace	Trace
23	$AlCl_3$	EtOH	80°C	Trace	Trace
24	$AlCl_3$	DCM	40°C	<10	52
25	$AlCl_3$	THF	65°C	<10	38
26	$AlCl_3$	AcOH	80°C	Trace	Trace
27	$AlCl_3$	Dioxane	100°C	Trace	45
28	$AlCl_3$	Pyridine	100°C	Trace	Trace

[a] Reaction conditions: Lewis acid catalyst (1 mmol), benzonitrile **1a** (1 mmol), acetylacetone **2a** (1.2 mmol) and solvent (2ml) for 4 h. [b] Isolated yield.

The reactions of β-diketone compounds **2** with nitriles **1** were performed under optimized conditions to determine the scope of β-diketone substrates. The results are summarized in Table 2. The desired product enaminone **4a** was isolated in 75% yield from the reaction of **1a** with **2a** (Table 2, entry 1). Satisfactory yields similar to that of **4b**-**4f** were observed when 4-nitrobenzonitrile (**1b**), 2-nitrobenzonitrile (**1c**), 2-phenylacetonitrile (**1d**), cinnamonitrile (**1e**) and furan-2-carbonitrile (**1f**) were tested under optimized reaction conditions (Table 2, entries 2-6, 56-80%). The desired product enaminone **4g** was isolated in only 35% yield even prolonged the reaction time to 12 h (Table 2, entry 7). These results suggested that the reactivity of the nitrile substrate was remarkably influenced by the electronic property of the substituent of the benzene ring of nitrile. The reactivity of aromatic nitriles could be reduced by an electron-donating group linked to a benzene ring. Enaminone **4h** was obtained in a moderate yield when acetonitrile (**1h**) was tested (Table 2, entry 8, 68%). The reaction of unsymmetrical ketone **2j** regioselectively occurred on the less sterically hindered α-carbon atom (Table 2, entry 10). The enaminone products **4k** and **4l** were obtained in 70% and 67% yields, respectively (Table 2, entries 11-12). Therefore, these results clearly demonstrated that aluminium chloride serves as a useful Lewis acid catalyst for the addition reaction of ketones to activated nitriles to produce enaminones.

Table2. The reactions of β-diketone compounds with nitriles[a]

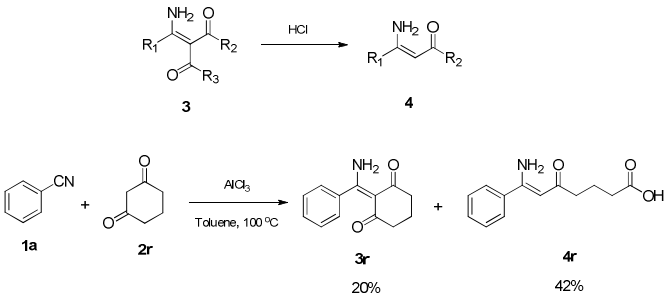


Entry		R_1	R_2	R_3	Yieldb (%) 3	Yield (%)[b] 4
1	a	Ph	Me	Me	12	78
2	b	4-$NO_2C_6H_4$	Me	Me	8	80
3	c	2-$NO_2C_6H_4$	Me	Me	11	71
4	d	Benzyl	Me	Me	15	67
5	e	Styryl	Me	Me	10	72
6	f	2-Furyl	Me	Me	18	56
7	g	2-$MeOC_6H_4$	Me	Me	20	35
8	h	Me	Me	Me	12	68
9	i	$C_2H_5OCOCH_2$	Me	Me	18	55
10	j	Ph	Ph	Me	16	38
11	k	Ph	t-Bu	t-Bu	Trace	70
12	l	Ph	Ph	Ph	Trace	67
13	m	2-ClC_6H_4	Me	Me	12	65
14	n	$BrCH_2CH_2$	Me	Me	8	71
15	o	4-HOC_6H_4	Me	Me	21	53
16	p	4-$HOC_6H_4CH_2$	Me	Me	27	45
17	q	$CH_3OCOC_6H_4$	Me	Me	20	61

[a] Reaction conditions: aluminium chloride (1 mmol), nitriles **1** (1 mmol), β-diketone **2** (1.2 mmol) and solvent (2ml) 100 °C for 4h. [b] Isolated yield.

Moreover, the product **3** could be also transformed to **4** in the presence of catalytic amounts of hydrochloric acid at room temperature[18]. And when benzonitrile **1a** was treated with cyclohexanedione **2m** under the optimized conditions, a mixture of enaminone **3r** (20%) and **4r** (42%) were obtained (Scheme 2).

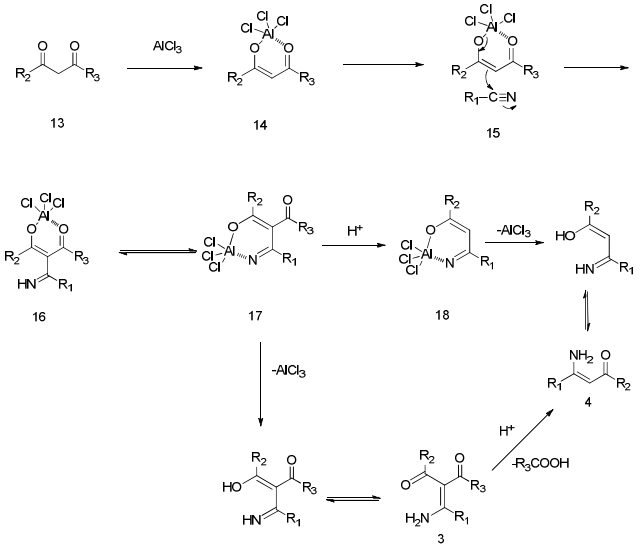
Scheme 2.



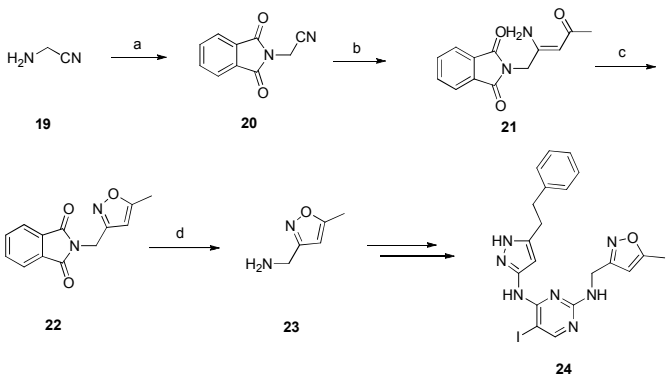
Therefore, a plausible reaction mechanism for aluminium chloride-promoted reactions of β-diketones was presented in Scheme 3. The first step of the mechanism involves the formation of an Al-enolate by interaction of $AlCl_3$ with β-diketone. Then the corresponding Al-enolate that formed will attack on the nitrile to generate a N-Al-O cyclic intermediate **17**. A part of intermediate **17** can be intercepted by the Al-enolate to produce the product **3**. At the same time, the acetyl groups in another part of intermediate **17** would leave first because of the existence of hydrogen ion to form intermediate **18**, which can be also intercepted by the Al-enolate to produce

the product **4**. Besides, with the influence of hydrogen ion, a part of product **3** could be transformed into product **4**.

Scheme 3.



Finally, application of this new Lewis Acids catalyzed method in the synthesis of heterocyclic frameworks was tested. The resulting β-enaminone derivatives can be transformed to various biologically active compounds. For example, the key intermediate **21**, prepared from commercially available 2-aminoacetonitrile **19** by two steps, proceeds smoothly under the optimized reaction conditions, affording the desired product **23** in 72% yield, which was an important building block for the synthesis of FGFR inhibitor derivatives (Scheme 4).



Scheme 4. (a) phthalic anhydride, TEA, $CHCl_3$, 60 ºC, 6 h; (b) acetylacetone, $AlCl_3$, 100 ºC, 4 h; (c) $NH_4OH{\cdot}HCl$, EtOH, 80 ºC, 1 h; (d) N_2H_4, EtOH, 80 ºC, 2 h.

Conclusions

In conclusion, we have successfully developed the Lewis acid catalyzed reaction of β-diketone compounds with nitriles using the readily available reagent $AlCl_3$. The reaction could be carried out under mild conditions and was compatible with many functional groups. This reaction will provide a straightforward, practically useful way to prepare various enaminones derivatives.

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Notes and references

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‡ the synthesis of **3** and **4**: To a solution of the benzonitrile (1 mmol) in toluene (2ml), $AlCl_3$ (1 mmol) and acetylacetone (1.2 mmol) were added at room temperature with stirring. The mixture was heated at 100 ºC with stirring for 4 h. Afer 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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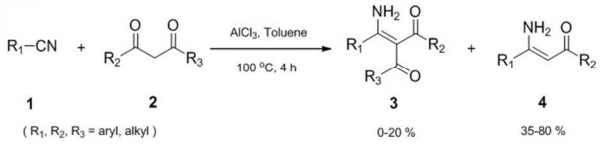

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