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SmCl$_3$-Catalyzed *C*-Acylation of 1,3-Dicarbonyl Compounds and Malononitrile

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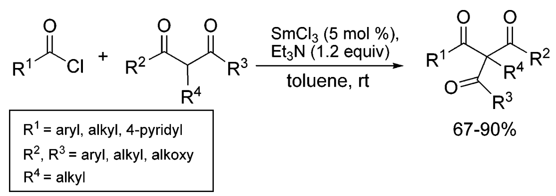
ABSTRACT



A recyclable, convenient, and efficient catalytic system for *C*-acylation of 1,3-dicarbonyl compounds and malononitrile with acid chlorides has been developed, giving moderate to excellent yields under mild conditions. This is the first catalytic example of such reactions. In addition, by applying this protocol as the key step, 3,5-disubstituted-1*H*-pyrazole-4-carboxylate can easily be synthesized in high yields in a one-pot procedure.

1,3,3′-Triketones are useful intermediates in organic synthesis, especially for the preparation of some biologically active compounds such as SR141716, phloroglucinols, and 5-deazaaminopterin.[1,2] Surprisingly, only a limited number of procedures for the synthesis of 1,3,3′-triketones have been developed. In most cases, 1,3,3′-triketones are prepared by *C*-acylation of 1,3-dicarbonyl compounds.[3−8] Nevertheless, these methods usually require the use of stoichiometric amounts of strong bases such as EtONa,[4] BaH_2,[5] EtMgBr,[6] *n*-BuLi,[7] or powerful reductive metals like Na,[8] which are not suitable for sensitive substrates. Notably, Rathke and Cowan developed a $MgCl_2$-promoted *C*-acylation of 1,3-dicarbonyl compounds.[9] Although these possess many potential advantages, the main limitation of this strategy is that a stoichiometric amount of Lewis acid and 2 equiv of tertiary amine additive are required. This is because an acylation product **3** is always a stronger acid than the corresponding dicarbonyl precursor **2** and thus may neutralize a portion of the β-diketonate intermediate (Scheme 1, route c). Therefore, the development of an alternative catalytic method for obtaining 1,3,3′-triketones represents a challenging but attractive subject from the viewpoints of operational simplicity, economy, and environmental impact.

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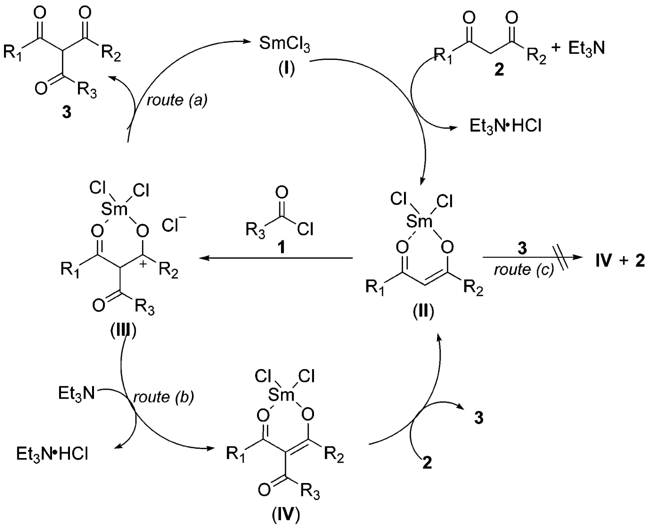
Scheme 1. Mechanistic Hypothesis



Taking into account those results, we considered that one way to avoid the competitive deprotonation of the acylation product would be to make the coordination between metal and β-diketonate more stable than that of the tricarbonyl counterpart. Lanthanide trichlorides are known to activate β-diketone in the presence of bases, forming lanthanide β-diketonate complexes.[10] Given the facts that the lanthanide−ligand bond strength predominantly depends on the electrostatic interaction and the degree of steric saturation, and that the introduction of an electron-withdrawning substituent could lead to decreased stabilization of lanthanide tri(β-diketonates),[11] we reasoned that it should be possible to control the preferential deprotonation of dicarbonyl compounds and intercept the resulting enolate intermediate with acyl chloride as an electrophile (Scheme 1, routes a and b). Herein, we wish to report a general, highly efficient, and catalytic method for *C*-acylation of 1,3-dicarbonyl compounds and malononitrile with acid chlorides.

Initially, we sought an effective catalytic system for the *C*-acylation of active methylene compounds, guided by the template reaction between benzoyl chloride **1a** and diethyl malonate **2a**. A range of reaction conditions were tested, and some of the results are listed in Table 1. As expected, lanthanide trichlorides proved to be efficient catalysts for the *C*-acylation of **1a** with **2a**. However, under the same conditions, for the other Lewis acids only very low yields of **3aa** were obtained even with longer reaction time (Table 1, entries 1−7). Among lanthanide trichlorides employed (Table 1, entries 8−14), the medium-sized $SmCl_3$ catalyzed the formation of **3aa** most efficiently. This is consistent with

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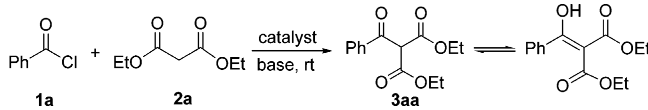
Table 1. Optimization of the Reaction Conditions for Acylation of Diethyl Malonate with Benzoyl Chloride[a]



entry	catalysts	solvent	time (h)	yield[b] (%)
1	$MgCl_2$	toluene	12	20
2	$AlCl_3$	toluene	10	24
3	$FeCl_3$	toluene	10	20
4	$BiCl_3$	toluene	12	18
5	$InCl_3$	toluene	12	32
6	H_3BO_3	toluene	12	21
7	$FeCl_3{\cdot}6H_2O$	toluene	10	16
8	$LaCl_3$	toluene	5	52
9	$NdCl_3$	toluene	5	56
10	$SmCl_3$	toluene	4	87
11[c]	$SmCl_3$	toluene	4	84
12	$DyCl_3$	toluene	5	78
13	$ErCl_3$	toluene	5	65
14	$YbCl_3$	toluene	5	50
15	$Yb(OTf)_3$	toluene	12	55
16	none	toluene	12	0
17	$SmCl_3$	THF	4	57
18	$SmCl_3$	n-C_6H_{14}	4	68
19	$SmCl_3$	CH_3CN	4	trace
20	$SmCl_3$	$ClCH_2CH_2Cl$	4	58
21[d]	$SmCl_3$	toluene	5	62

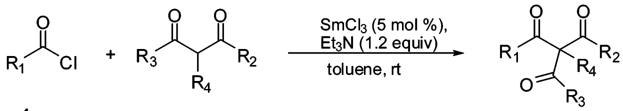
[a] Reaction conditions: diethyl malonate (1.0 mmol), benzoyl chloride (1.1 mmol), catalyst (10 mol %), solvent (4 mL), Et_3N (1.2 mmol), rt. [b] LC yield based on 1,3-dicarbonyl compound. [c] Catalyst (5 mol %). [d] Pyridine as base (1.2 mmol).

the upward trend of the stability of lanthanide β-diketonate complexes,[11] demonstrating that the coordination of the diketonate to lanthanide may play a key role in the equilibrium of the deprotonation of the acylation product and the substrate. No *C*-acylation reaction occurred in the absence of any catalyst (Table 1, entry 16).

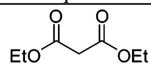
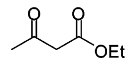
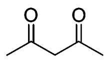
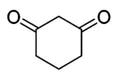
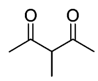
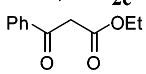
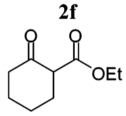
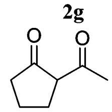
A screening of solvents for the $SmCl_3$ system revealed that toluene is a suitable solvent, and triketone **3aa** was formed in 87% yield (Table 1, entry 10). Less activity in CH_3CN and with pyridine as a base indicate that increased basicity of solvent or base may lead to preferential coordination of these reagents over β-diketonates, which resulted in lower yields (entries 19 and 21). In the $MgCl_2$ catalytic system,[9] where a stoichiometric amount of $MgCl_2$ and 2 equiv of tertiary amine additive were required, it was observed in the present case that 1 equiv of Et_3N was enough to effect complete conversion of the substrate in the presence of a catalytic amount of $SmCl_3$.

Having determined the optimum reaction conditions, we investigated the generality of this process. As can be seen from Table 2, a variety of 1,3-dicarbonyl compounds can be *C*-acylated by **1a** to give the corresponding products in moderate to excellent yields, depending on the steric hindrance at the methylene carbon and the nature of carbonyl functional groups (Table 2, entries 1−8). Interestingly, cyclic 1,3-diketones can also be employed in this $SmCl_3$-catalyzed

Table 2. $SmCl_3$-Catalyzed Acylation of Various 1,3-Dicarbonyl Compounds[a]



1a-g 2a-h 3

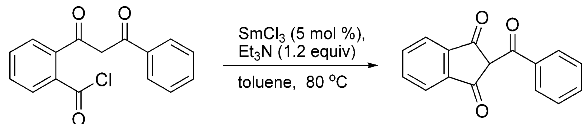
entry	R[1]	1,3-dicarbonyl compounds	time (h)	yield (%)[b]
1[c]	**C_6H_5 (1a)**	 **2a**	4	80 (**3aa**)
2	**1a**	 **2b**	2	84 (**3ab**)
3	**1a**	 **2c**	1	85 (**3ac**)
4	**1a**	 **2d**	1	90 (**3ad**)
5	**1a**	 **2e**	1	78 (**3ae**)
6	**1a**	 **2f**	1	80 (**3af**)
7	**1a**	 **2g**	1.5	75 (**3ag**)
8	**1a**	 **2h**	1	78 (**3ah**)
9	**4-ClC_6H_4 (1b)**	**2a**	2	81 (**3ba**)
10	**1b**	**2b**	1	82 (**3bb**)
11	**1b**	**2c**	0.5	87 (**3bc**)
12	**4-$NO_2C_6H_4$ (1c)**	**2b**	0.25	88 (**3cb**)
13	**3-$NO_2C_6H_4$ (1d)**	**2a**	0.75	76 (**3da**)
14	**1d**	**2b**	1	78 (**3db**)
15	**1d**	**2c**	1	80 (**3dc**)
16[d]	**4-$CH_3OC_6H_4$ (1e)**	**2a**	4	72 (**3ea**)
17	**1e**	**2b**	1.5	75 (**3eb**)
18	**$C_6H_5CH_2$ (1f)**	**2b**	2	67 (**3fb**)
19	**1f**	**2c**	1	72 (**3fc**)
20	**4-pyridyl (1g)**	**2b**	2	71 (**3gb**)

[a] Conditions: acyl choloride (1.1 mmol), 1,3-dicarbonyl compound (1.0 mmol), $SmCl_3$ (5 mol %), toluene (4 mL), Et_3N (1.2 mmol), rt. [b] Isolated yield. [c] 10 mol % of $SmCl_3$. [d] 10 mol % of $SmCl_3$.

acylation (Table 2, entries 4, 7, and 8). To our delight sterically hindered 2-substituted 1,3-dicarbonyl compounds can be acylated to a reasonable extent in the presence of $SmCl_3$ (Table 2, entries 5, 7, and 8). It is noted that diethyl malonate **2a**, which has a low acidity, also displayed high reactivity and reacted quickly with **1a** and **1e** to give the desired products in 80% and 72% yields, respectively (Table 2, entries 1 and 16), despite the need to extend the reaction time to 4 h, and using a higher catalyst loading of 10 mol % to increase the yield.

To the best of our knowledge, this is the first acylation of 1,3-dicarbonyl compounds promoted by a catalytic amount of Lewis acids. These successful results encouraged us to extend this method to application for the intramolecular *C*-acylation. Treatment of **4** with 5 mol % of $SmCl_3$ afforded the intramolecular acylation product **5** in 86% yield (Scheme 2).

Scheme 2. $SmCl_3$-Catalyzed Cyclization of 2-(3-Oxo-3-phenylpropanoyl)benzoyl Chloride

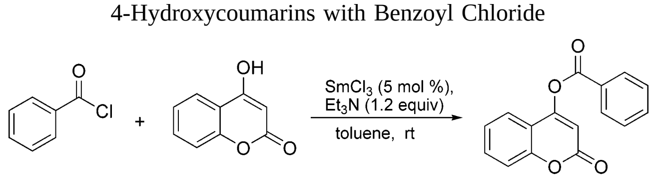


4 5 86%

Next, we set out to study the scope and limitation of the electrophilic coupling partner in more detail. As shown in Table 2, a number of different acid chlorides have been reacted with 1,3-dicarbony1 compounds. 4-Chlorophenyl acid chloride **1b** reacted comparably to **2a−c** providing the desirable products in 81−87% yields (Table 2, entries 9−11). The aromatic acid chloride **1c**, which has an electron-withdrawing substituent at the para-position, reacted more quickly and the triketone **3cc** was obtained in 88% yield (Table 2, entry 12). However, the aromatic acid chloride **1e**, bearing an electron-donating substituent at the para-position, reacted sluggishly and gave the corresponding triketone **3ea** in 72% yield (Table 2, entry 16). A nitro substituent in the meta-position of the aryl acid chloride **1d** had only a slight influence on the reactivity, as compared to the *p*-nitrophenyl acid chloride **1c** (Table 2, entries 12 and 13). Furthermore, we examined the reactions of aliphatic acid chlorides like 2-phenyl acetyl chloride **1f**. The reactions of **1f** with **2b** and **2c** proceeded smoothly to give **3fb** and **3fc**, respectively, in moderate yields (Table 2, entries 18 and 19). Importantly, this protocol can tolerate heteroatoms as found in isonicotinoyl chloride (Table 2, entry 20).

The development of new methods for the efficient and selective preparation of highly substituted coumarins is of great interest in organic chemistry because of the frequent existence of such structures in biologically active compounds and their role as valuable synthetic intermediates for potentially new pharmaceuticals.[12] Encouraged by the above results, we subsequently explored the reaction of 4-hydroxycoumarin (**2i**) with **1a**. However, only the *O*-acylation rather than *C*-acylation product (**3ai**) was obtained in 85% yield (Scheme 3).

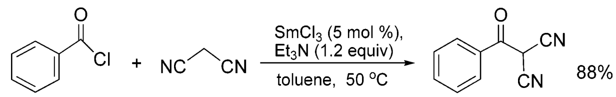
Scheme 3. $SmCl_3$-Catalyzed *C*-Acylation of 4-Hydroxycoumarins with Benzoyl Chloride



1a 2i 3ai

Until now, no example of the Lewis acid-catalyzed coupling of malononitrile with acid chlorides has been reported. After having established that $SmCl_3$ is an efficient catalyst for the inter- and intramolecular acylations of 1,3-dicarbonyl compounds, we were keen to explore the reaction of malononitrile with benzoyl chloride. $SmCl_3$ indeed led to the desired product **7** in good yield (Scheme 4), indicating

Scheme 4. $SmCl_3$-Catalyzed Acylation of Malononitrile with Benzoyl Chloride

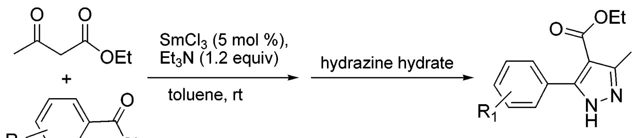


1a **6** **7**

that $SmCl_3$ is also highly effective in the catalytic acylation of malononitrile with acid chlorides as substrates.

Pyrazole-4-carboxylate derivatives possess important pharmacological properties including analgesic, antipyretic, and antiinflammatory properties.[13] Several methods to synthesize these compounds from 1,3-diketones have been reported in the literature.[14] However, they usually involve multistep processes and give the products only in poor to moderate yields. Having successfully developed an efficient acylation of 1,3-dicarbonyl compounds with acid chlorides, we finally turned our attention to the application of this method to the one-pot synthesis of highly substituted pyrazole-4-carboxylate building blocks, which can be further functionalized. Treatment of 1,3-dicarbonyl compounds **2** with acid chlorides **1** in the presence of 5 mol % of $SmCl_3$ and 1.2 equiv of Et_3N followed by reacting with hydrazine allowed the isolation of multisubstituted pyrazoles **8**−**11** in 72−81% yields. This provides a mild and straightforward route to pyrazole-4-carboxylate derivatives (Scheme 5).

Scheme 5. $SmCl_3$-Catalyzed One-Pot Synthesis of Pyrazole-4-carboxylate



R_1	isolated yield(%)
H (**8**)	80
p-Cl (**9**)	78
p-OMe (**10**)	72
m-NO_2 (**11**)	81

Finally, we checked the reusability of the $SmCl_3$ catalyst in the reaction of 8.8 mmo ofl **1a** with 8 mmo of l **2c** in toluene at room temperature. After the first experiment, the insoluble catalyst was readily recovered by filtrating the reaction mixture and then removing amine salt washed by acetonitrile for the next use. The results of seven runs showed that the recovered catalyst retains its activity in terms of yields (86%, 82%, 83%, 85%, 84%, 85%, and 82%, respectively) and rates.

In summary, a general and highly efficient $LnCl_3$-catalyzed intra- and intermolecular *C*-acylation of 1,3-dicarbonyl compounds and malononitrile with acid chlorides has been developed. This method provides significant advantages in cost, tolerance of functional groups, and simplicity of operation by obviating the use of strong bases and stoichiometric amounts of Lewis acids. Furthermore, the present catalyst is readily recovered and reused at least seven times for such reaction without visible loss of catalytic activity. Further investigations on the mechanism details and synthetic applications of this method are underway in our lab.

Acknowledgment. We thank the National Natural Science Foundation of China and the Natural Science Foundation of Shanghai.

Supporting Information Available: Experimental details and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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