



Lewis acid-catalyzed Friedel–Crafts acylation reaction using carboxylic acids as acylating agents

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Abstract—Rare-earth metal Lewis acids, in particular $\text{Eu}(\text{NTf}_2)_3$, were found to be efficient catalysts for Friedel–Crafts acylation reaction using aliphatic as well as aromatic carboxylic acids as acylating agents at high temperature.
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Friedel–Crafts acylation reaction is one of the most important methods to prepare aromatic ketones.¹ The conventional method, which uses acid chlorides or acid anhydrides as acylating agents and a stoichiometric or an excess amount of reaction promoter such as AlCl_3 or HF, suffers from severe corrosion, waste, and safety problems and does not meet recent requirement for environmentally benign chemical processes. Direct use of carboxylic acids, precursors for acid chlorides and anhydrides, as acylating agents with a catalytic amount of and a reusable reaction promoter produces water as the only by-product and will be a cleaner alternative to the conventional Friedel–Crafts acylation. Zeolites,² heteropoly acids and their salts,³ clay,⁴ and Lewis acids⁵ are reported to catalyze Friedel–Crafts acylation using carboxylic acids as acylating agents. However, the catalytic efficiency and/or applicable substrate range are very limited.

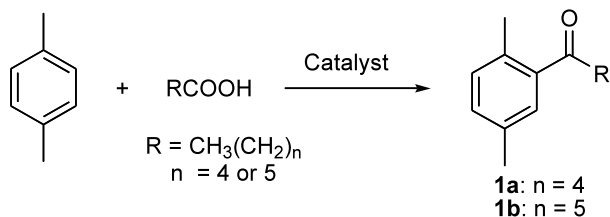
Recently many reports described a catalytic amount of Lewis acids efficiently promote Friedel–Crafts acylation reactions using acid chlorides or acid anhydrides as acylating agents.⁶ However, only a few reports are published on the Friedel–Crafts acylation reactions using carboxylic acids as acylating agents with a catalytic amount of Lewis acids without stoichiometric additives. In 1996, Kobayashi's group reported Friedel–Crafts acylation of phenols and naphthols with carboxylic acids using a catalytic amount of Lewis acids such as $\text{Hf}(\text{OTf})_4$, $\text{Zr}(\text{OTf})_4$ and $\text{Sc}(\text{OTf})_3$.^{5b} During the

course of our research, a patent using rare-earth metal triflates as catalysts with azeotropic removal of water has appeared, although the catalytic efficiency seems not to be very high, and scope and limitation of the procedure are not clear.⁷ As our initial approach to the Friedel–Crafts acylation reactions using carboxylic acids as acylating agents, we examined the catalytic efficiency of metal triflates and bis(trifluoromethanesulfonyl)amides to know their scope and limitation.⁸ Here we report that $\text{Eu}(\text{NTf}_2)_3$ is efficient catalysts when the reaction is performed at high temperature.⁹

The reaction of *p*-xylene with hexanoic and heptanoic acids was examined using various rare-earth metal Lewis acids with excess of *p*-xylene (50–65 equiv. to carboxylic acids) in a sealed glass tube without azeotropic removal of water. Table 1 shows representative results. At 180°C, $\text{Sc}(\text{OTf})_3$ (20 mol%) afforded 1-(2,5-dimethylphenyl)-1-hexanone **1a** in the highest yield, 39%, among 12 commercially available rare-earth metal triflates tested (Table 1, entry 1). $\text{Eu}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$ also afforded **1a** but in lower yields (Table 1, entries 2 and 3). Although even at 180°C conversions of the carboxylic acid were much higher than the yields of **1a** (Table 1, entries 1–3), which suggested considerable side-reactions, higher reaction temperature, 250°C, unexpectedly improved the yield of ketone significantly; in particular, $\text{Yb}(\text{OTf})_3$ afforded **1b** in 83% yield (Table 1, entry 6). Further improvement was attained by using $\text{Eu}(\text{NTf}_2)_3$;¹⁰ **1b** was obtained nearly quantitatively (Table 1, entry 8). $\text{Sc}(\text{NTf}_2)_3$ ¹¹ also afforded ketone in higher yield than $\text{Sc}(\text{OTf})_3$ (Table 1, entry 7) while $\text{Yb}(\text{NTf}_2)_3$ ¹² showed poorer results than $\text{Yb}(\text{OTf})_3$ (Table 1, entry 11). $\text{Bi}(\text{NTf}_2)_3$,¹³ which is an excellent catalyst for the intramolecular Friedel–Crafts cycliza-

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Table 1. Reaction of *p*-xylene with hexanoic and heptanoic acids^a

entry	catalyst (mol%)	temp (°C)	time (h)	conv. (%) ^b	yield (%) ^c
1	Sc(OTf) ₃ (20)	180	45	>99	39
2	Eu(OTf) ₃ (20)	180	45	>99	29
3	Yb(OTf) ₃ (20)	180	45	76	14
4	Sc(OTf) ₃ (20)	250	12	>99	49
5	Eu(OTf) ₃ (20)	250	12	83	52
6	Yb(OTf) ₃ (20)	250	12	>99	83
7	Sc(NTf ₂) ₃ (15)	250	12	98	75
8	Eu(NTf ₂) ₃ (20)	250	12	>99	96
9	Eu(NTf ₂) ₃ (15)	250	12	>99	91
10	Eu(NTf ₂) ₃ (10)	250	12	>99	73
11	Yb(NTf ₂) ₃ (15)	250	10	>99	64
12	Bi(NTf ₂) ₃ (15)	250	8	>99	80

^a Entries 1–3: hexanoic acid was used. Entries 4–12: heptanoic acid was used. The ratio of *p*-xylene/carboxylic acid was 65/1 for entries 1–6 and 8 and 50/1 for entries 7 and 9–12.

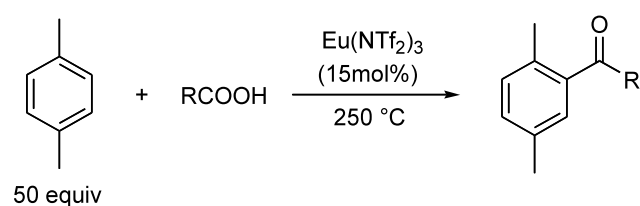
^b Conversion of carboxylic acids determined by GC analysis using naphthalene (for entries 1–3) or docosane (for entries 4–12) as an internal standard.

^c Yields are based on carboxylic acids and were determined by GC analysis using naphthalene (for entries 1–3) or docosane (for entries 4–12) as an internal standard.

tion of 4-arylbutyric acids,⁹ was also effective although less efficient than Eu(NTf₂)₃ (Table 1, entry 12).

Tables 2 and 3 summarize the preliminary scope and limitation of Eu(NTf₂)₃-catalyzed Friedel–Crafts acylation of aromatic compounds with carboxylic acids.¹⁴ As seen in Table 2, this procedure is effective for a wide range of aliphatic carboxylic acids with various chain lengths as well as aromatic carboxylic acids although the yields decreased to some extent in the case of short chain carboxylic acids such as acetic acid and propionic acid (Table 2, entries 1 and 2) as well as branched carboxylic acids, in particular at the α -position (Table 2, entries 4, 6, 8). This wide applicability is the advantage of this procedure over previously reported zeolite² and heteropoly acid salts catalysts.³

Table 3 shows the reaction of several aromatic compounds with heptanoic acid. Monoalkylbenzenes are efficiently acylated with good *p*-selectivity (Table 3, entries 1 and 2). *m*-Xylene was also efficiently acylated (Table 3, entry 3) while benzene afforded acylation

Table 2. Reaction of *p*-xylene with aliphatic and aromatic carboxylic acids catalyzed by Eu(NTf₂)₃

entry	R	time (h)	conv. (%) ^a	yield (%) ^b
1	CH ₃	8	94	48
2	C ₂ H ₅	8	>99	56
3	<i>n</i> -C ₃ H ₇	9	>99	61
4	<i>i</i> -C ₃ H ₇	16	91	34
5	<i>n</i> -C ₄ H ₉	9	98	70
6	<i>i</i> -C ₄ H ₉	11	>99	55
7	<i>n</i> -C ₅ H ₁₁	7	96	65
8	<i>i</i> -C ₅ H ₁₁	10	>99	61
9	<i>n</i> -C ₇ H ₁₅	12	>99	80
10	<i>n</i> -C ₈ H ₁₇	12	nd ^c	86
11	<i>n</i> -C ₁₁ H ₂₃	14	>99	72
12	Ph	14	>99	66
13	4-MePh	13	94	76

^a Conversion of carboxylic acids determined by GC analysis using docosane as an internal standard.

^b Isolated yields.

^c Not determined.


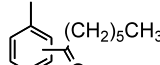

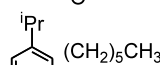

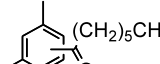

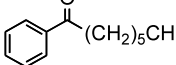

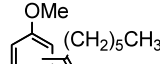
product only in 4% yield under the same reaction conditions (Table 3, entry 4). As expected, acylation of anisole is faster than that of alkylbenzenes and gave the acylated product in high yield with >97% *p*-selectivity (Table 3, entry 5).

Eu(NTf₂)₃ was found still active after the reaction at 250°C. After the reaction of *p*-xylene with heptanoic acid at 250°C (isolated yield of **1b** was 78%), Eu(NTf₂)₃ was recovered in 77% yield by the extraction of the reaction mixture dissolved in hexane with water. The recovered Eu(NTf₂)₃ catalyzed the same reaction without decrease in catalytic activity (isolated yield of **1b** was 78%).

It is noteworthy that the acylation using aliphatic carboxylic acids was successful despite high reaction temperature because Friedel–Crafts acylation reaction of aliphatic acid chlorides with a catalytic amount of Lewis acids is often only successful for highly reactive aromatic compounds such as anisole.¹⁵ At higher reaction temperature, side-reactions of ketone products are suggested.^{6d,e}

In summary, we have examined the scope and limitation of Lewis acid catalysts for Friedel–Crafts acylation

Table 3. Reaction of various aromatic compounds with heptanoic acid catalyzed by $\text{Eu}(\text{NTf}_2)_3$

$\text{ArH} + \text{CH}_3(\text{CH}_2)_5\text{COOH} \xrightarrow[250^\circ\text{C}]{\text{Eu}(\text{NTf}_2)_3 \text{ (15 mol\%)}} \text{Ar}-\text{C}(=\text{O})-(\text{CH}_2)_5\text{CH}_3$ 50 equiv				
entry	ArH	product	time (h)	yield (%) ^a
1			17	78 ^b
2			19	71 ^c
3			12	74 ^d
4			24	4
5			6	87 ^e

^a Isolated yield. The ratios of regioisomers were determined by GC analysis using docosane as an internal standard unless otherwise noted.

^b *o*-/*m*-/*p*-isomers = 22/5/73.

^c (*o*- + *m*-)/*p*-isomers = 15/85.

^d 1-(2,4-dimethylphenyl)-1-heptanone/other regioisomers = 96/4 by GC-MS.

^e The ratio of *p*-/*o*-isomers was determined to be >97/3 by ¹H NMR analysis.

reaction using carboxylic acids as acylating agents and found $\text{Eu}(\text{NTf}_2)_3$ is an efficient catalyst at high reaction temperature. Further studies to clarify the side reactions and to improve the reaction efficiency at lower reaction temperature are underway.

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