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Synthesis of 1-indanones by intramolecular Friedel–Crafts reaction of 3-arylpropionic acids catalyzed by $Tb(OTf)_3$

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Abstract—Intramolecular Friedel–Crafts acylation reaction of 3-arylpropionic acids was efficiently catalyzed by $Tb(OTf)_3$ at 250 °C to give 1-indanones. Even deactivated 3-arylpropionic acids with halogen atoms on the aromatic ring can be cyclized in moderation to good yields.

1-Indanones are important synthetic intermediates for pharmaceuticals[1], ligands of olefin polymerization catalysts[2] and discotic liquid crystals.[3] Among various methods used for preparation of 1-indanones,[4] intramolecular Friedel–Crafts cyclization reaction of 3-arylpropionic acids or 3-arylpropionyl chlorides is one of the most general and useful methods. The direct dehydrative cyclization of 3-arylpropionic acids is less easier than the cyclization via acid chlorides, but preferable from environmental point of view because the former, one-step reaction produces water as the only by-product while the latter, two-step reaction produces large amounts of toxic and corrosive by-products. However, the direct cyclization has been performed by using an excess of protic acids (often as solvents) such as sulfuric acid,[5] hydrogen fluoride,[5] polyphosphoric acid,[6] methanesulfonic acid (MSA)[7] and a mixture of MSA and P_2O_5,[8] or Lewis acids such as $AlCl_3$ and $SnCl_4$,[5] and therefore forms a large amount of acid wastes after the reaction. Recently it was reported that Y-faujasite-type zeolite was an effective catalyst for dehydrative cyclization to form tricyclic ketones containing indanone structure, although it was not very effective for the synthesis of simple indanones.[9] Here we report some lanthanoid triflates, in particular $Tb(OTf)_3$ are useful catalysts for dehydrative cyclization of 3-arylpropionic acids to form 1-indanones.[10]

We have recently reported Lewis acid-catalyzed cyclization of 4-arylbutyric acids to form 1-tetralones.[11] It is known that formation of five-membered ring by Friedel–Crafts cyclization is more difficult than that of six-membered ring.[5] Indeed, $Bi(NTf_2)_3$[12] and some lanthanoid triflates, which were effective for 1-tetralone synthesis,[11] were proved not to catalyze the cyclization of 3-phenylpropionic acid (**1a**) under the conditions suitable for 1-tetralone synthesis at 180 °C. Similar results were reported for Nafion-H; it was effective for the cyclization of 4-phenylbutyric acid and gave 1-tetralone in 88–90% yields, while it did not catalyze the cyclization of 3-phenylpropionic acid efficiently and 1-indanone was obtained only in 0–5% yields.[13]

Survey of reaction conditions revealed that the cyclization of **1a** was highly influenced by reaction temperature, Lewis acid catalysts and concentration of **1a**. $Bi(NTf_2)_3$ afforded 1-indanone at 200 °C or higher (Table 1, entries 1–5). However, considerable side reactions took place and the yield of 1-indanone did not exceed 30%. Then, catalytic performance of commercially available $Ga(OTf)_3$, $In(OTf)_3$, lanthanoid triflates and $Hf(OTf)_4$ was examined at 240–250 °C (representative results are shown in Table 1). $Ga(OTf)_3$, $In(OTf)_3$, $Hf(OTf)_4$ and some lanthanoid triflates were not effective in this reaction, while 10 mol% of $Pr(OTf)_3$, $Nd(OTf)_3$, $Gd(OTf)_3$ and $Tb(OTf)_3$ produced 1-indanone in 58–70% yield (Table 1, entries 10, 11, 14, and

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Keywords: Indanone; Lewis acid; Friedel–Crafts reaction; Acylation; Dehydration; Lanthanoid; Cyclization.

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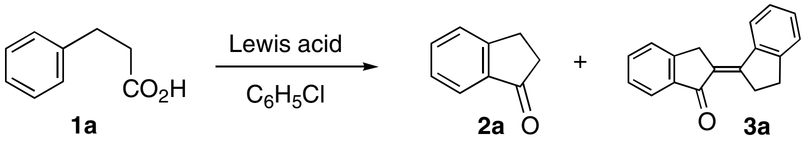
Table 1. Cyclization of 3-arylpropionic acid in the presence of Lewis acid catalysts[a]



Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)[b]	
				2a	**3a**
1	$Bi(NTf_2)_3$ (5)	200	10	16	nd
2	$Bi(NTf_2)_3$ (5)	220	8	29	nd
3	$Bi(NTf_2)_3$ (5)	240	8	29	nd
4	$Bi(NTf_2)_3$ (10)	240	6	Trace	nd
5	$Bi(NTf_2)_3$ (1)	240	12	24	nd
6	$Ga(OTf)_3$ (5)	240	2	3	0
7	$In(OTf)_3$ (5)	240	3	12	nd
8	$Sc(OTf)_3$ (10)	250	1	7	nd
9	$Ce(OTf)_3$ (10)	250	1	21	4
10	$Pr(OTf)_3$ (10)	250	3	70	14
11	$Nd(OTf)_3$ (10)	250	2	66	10
12	$Eu(OTf)_3$ (10)	250	1	44	nd
13	$Eu(NTf_2)_3$ (10)	250	1	25	nd
14	$Gd(OTf)_3$ (10)	250	1	65	11
15	$Tb(OTf)_3$ (10)	250	1	58	8
16[c]	$Tb(OTf)_3$ (10)	250	1	93	Trace
17[c]	$Tb(OTf)_3$ (5)	250	1.5	95 (83)	Trace
18[c]	$Tb(OTf)_3$ (1)	250	4.5	28	0
19[d]	$Tb(OTf)_3$ (5)	250	2	Trace	0
20[e]	$Tb(OTf)_3$ (5)	250	2	0	0
21	$Dy(OTf)_3$ (10)	250	1	40	11
22	$Yb(OTf)_3$ (10)	250	1	20	nd
23	$Lu(OTf)_3$ (10)	250	1	33	4
24[c]	$Hf(OTf)_4$ (5)	250	1.5	5	13
25[c]	TfOH (15)	250	1.5	8	10

[a] The reaction was performed using 0.25 mmol of **1a** in 2 mL of C_6H_5Cl in a sealed glass tube unless otherwise noted.

[b] GC yield using dodecane as an internal standard. Isolated yields are shown in parentheses. nd = not determined.

[c] C_6H_5Cl (6 mL) was used as a solvent.

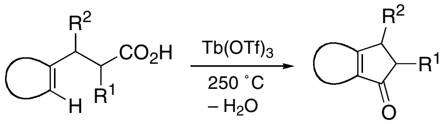
[d] Sulfolane (6 mL) was used as a solvent.

[e] Bu_2O (6 mL) was used as a solvent.

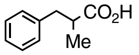
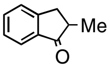
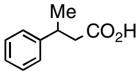
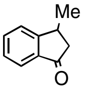
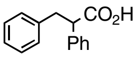
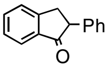
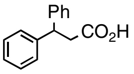
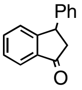
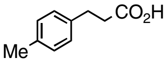
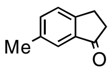
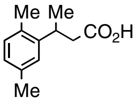
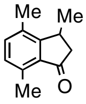
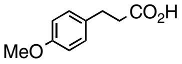
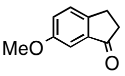
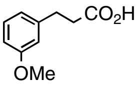
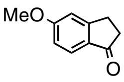
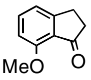
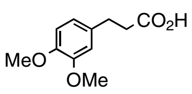
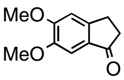
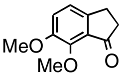
15). $Eu(NTf_2)_3$, which was effective for intermolecular Friedel–Crafts reaction using carboxylic acids as acylating agents,[14] was not suitable for this reaction (Table 1, entry 13). Although some of **1a** remained after the reaction in most cases, considerable side reactions also took place. One of the by-products was isolated and identified to be **3a**, an aldol condensation product of **2a**.[15] Therefore, we examined the effect of concentration of **1a** in order to suppress the self-condensation of **2a**. Generally lower concentration of **1a** decreased the formation of **3a** when $Pr(OTf)_3$, $Nd(OTf)_3$, $Gd(OTf)_3$ or $Tb(OTf)_3$ was used as a catalyst, while the degree of improvement in the yield of **2a** depended on the catalysts. The highest yield of **2a** was obtained when 0.04 M C_6H_5Cl solution of **1a** was heated at 250 °C in the presence of 5 mol% of $Tb(OTf)_3$ (Table 1, entry 17). Lower amount (1 mol%) of catalyst was not enough to complete the reaction (Table 1, entry 18) and other solvents such as sulfolane and Bu_2O completely stopped the reaction (Table 1, entries 19 and 20). TfOH did not effectively catalyze the cyclization of **1a** (Table 1, entry 25). Preliminary study on catalyst recycling showed that after the reaction at 250 °C in PhCl, $Tb(OTf)_3$ was still active (at least partially) and could be reused.[16]

Table 2 summarizes the scope and limitation of $Tb(OTf)_3$-catalyzed cyclization of 3-arylpropionic acids.[17,18] Substitution at α-position of aliphatic chain of propionic acid retarded the cyclization, and required longer reaction time and larger amount of catalysts (Table 2, entries 1 and 3), while substitution at β-position has little effect on the cyclization and 1-indanones were obtained in good yields (Table 2, entries 2, 4 and 6). 3-Arylpropionic acids with electron-donating substituents on the aromatic ring generally afforded 1-indanones in good yields (Table 2, entries 5–10). In the case of **1i** and **1j**, both of possible regio-isomers were produced (Table 2, entries 8 and 9). It is noteworthy that deactivated substrates, which have one or two halogen atoms on the aromatic ring, were successfully cyclized to give 1-indanones (Table 2, entries 11–13). However, CF_3-substituted **1o** could not be cyclized efficiently (Table 2, entry 14). The cyclization of indole derivative **1p** proceeded in moderate yield (Table 2, entry 15).

Table 2. Synthesis of 1-indanones and a related cyclic ketone[a]

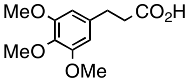
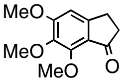
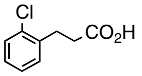
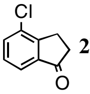
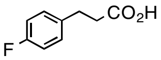
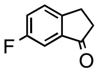
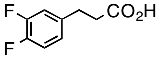
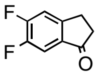
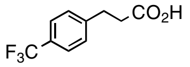
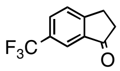
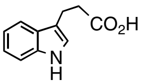
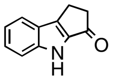


1b - 1p **2b - 2p**

Entry	Carboxylic acid	$Tb(OTf)_3$ (mol %)	Reaction time (h)	Product	Yield (%)[b]
1	 **1b**	10	8	 **2b**	83 (99)
2	 **1c**	5	4	 **2c**	88
3	 **1d**	15	14	 **2d**	52
4	 **1e**	5	10	 **2e**	71
5	 **1f**	5	2	 **2f**	74
6	 **1g**	5	3	 **2g**	91
7	 **1h**	10	2	 **2h**	58
8	 **1i**	5	3	 **2iA**	62
				 **2iB**	12
9	 **1j**	5	1	 **2jA**	65
				 **2jB**	5

(*continued on next page*)

Table 2 (*continued*)

Entry	Carboxylic acid	$Tb(OTf)_3$ (mol%)	Reaction time (h)	Product	Yield (%)[b]
10	 **1k**	5	0.5	 **2k**	72
11	 **1l**	20	24	 **2l**	(49)
12	 **1m**	10	11	 **2m**	64 (73)
13	 **1n**	20	8	 **2n**	(46)
14	 **1o**	10	8	 **2o**	Trace
15	 **1p**	5	3	 **2p**	42

[a] The reaction was performed using 0.25 mmol of carboxylic acids in 6 mL of C_6H_5Cl in a sealed glass tube.

[b] Isolated yields. GC yields using dodecane as an internal standard are shown in parentheses.

In summary, 1-indanones were efficiently synthesized by the intramolecular Friedel–Crafts acylation reaction of 3-arylpropionic acids using catalytic amounts of $Tb(OTf)_3$ at 250 °C. Further studies to improve the reaction efficiency at lower reaction temperature and on recycling of the catalyst are underway.

Acknowledgements

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15. A small amount of *Z*-isomer of **3a** was also produced. The structure of **3a** was unambiguously determined by X-ray analysis, which showed **3a** co-crystallized with a small amount of its *Z*-isomer. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-223357. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
16. After the reaction, the catalyst was recovered by extraction with water. Evaporation of water afforded crystalline nonahydrate $[Tb(H_2O)_9](OTf)_3$, whose structure was unambiguously determined by single crystal X-ray analysis.[19]Further drying under vacuum gave $Tb(OTf)_3$ (may be partially hydrated) as white powder in ca. 90% recovery.
17. Typical procedure: A mixture of $Tb(OTf)_3$ (7 mg), 3-phenylbutyric acid **1c** (41 mg, 0.25 mmol) and C_6H_5Cl (6 mL) in a sealed glass tube was heated in an oil bath at 250 °C for 4 h. Then the mixture was diluted with EtOAc (10 mL) and washed with a saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was separated by column chromatography on silica gel (hexane/EtOAc = 5/1) to give **2c** (32 mg, 88% yield).
18. All cyclic ketones reported in this paper are known compounds. However, for some compounds NMR data are not reported in the literature; **2k**: ^{1}H NMR (499.1 MHz, $CDCl_3$) δ 2.65–2.71 (m, 2H), 3.02 (quasi t, $J = 5.8$ Hz, 2H), 3.85 (s, 3H), 3.94 (s, 3H), 4.04 (s, 3H), 6.68 (s, 1H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 25.71, 37.20, 56.29, 61.41, 61.94, 103.78, 122.86, 140.63, 151.55, 153.32, 159.72, 203.31. **2m**: ^{1}H NMR (499.1 MHz, $CDCl_3$) δ 2.73–2.78 (m, 2H), 3.12 (quasi t, $J = 5.7$ Hz, 2H), 7.31 (td, $J = 8.5$, 2.4 Hz, 1H), 7.40 (dd, $J = 7.5$, 2.4 Hz, 1H), 7.45 (dd, $J = 8.5$, 4.4 Hz, 1H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 25.28, 37.00, 109.54 (d, $J = 22$ Hz), 122.33 (d, $J = 24$ Hz), 128.03 (d, $J = 8$ Hz), 138.79 (d, $J = 7$ Hz), 150.47, 162.28 (d, $J = 248$ Hz), 206.02. **2n**: ^{1}H NMR (499.1 MHz, $CDCl_3$) δ 2.73–2.75 (m, 2H), 3.13 (quasi t, $J = 5.3$ Hz, 2H), 7.28 (dd, $J = 9.5$, 6.7 Hz, 1H), 7.52 (quasi t, $J = 8.1$ Hz, 1H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 25.46 (d, $J = 2$ Hz), 36.51, 111.77 (dd, $J = 18$, 2 Hz), 114.94 (d, $J = 22$ Hz), 133.47 (dd, $J = 5$, 2 Hz), 150.68 (dd, $J = 251$, 15 Hz), 151.63 (dd, $J = 8$, 2 Hz), 156.18 (dd, $J = 259$, 15 Hz), 204.57. **2p**: ^{1}H NMR (499.1 MHz, $CDCl_3$) δ 3.02–3.04 (m, 2H), 3.11–3.14 (m, 2H), 7.19 (quasi t, $J = 8.5$ Hz, 1H), 7.40 (quasi t, $J = 8.5$ Hz, 1H), 7.49 (d, $J = 8.5$ Hz, 1H), 7.71 (d, $J = 8$ Hz, 1H), 9.03 (br s, 1H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 20.14, 41.02, 113.50, 120.73, 121.59, 123.59, 127.39, 138.70, 143.81, 147.28, 194.64.
19. (a) Harrowfield, J. M.; Kepert, D. L.; Patrick, J. M.; White, A. H. *Aust. J. Chem.* **1983**, *36*, 483–492; (b) Chatterjee, A.; Maslen, E. N.; Watson, K. J. *Acta Crystallogr., Sect. B.* **1988**, *44*, 381–386.