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Synthesis of 1-tetralones by intramolecular Friedel–Crafts reaction of 4-arylbutyric acids using Lewis acid catalysts

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Abstract—Intramolecular Friedel–Crafts reaction of 4-arylbutyric acids efficiently proceeded in the presence of catalytic amounts of Lewis acids such as $Bi(NTf_2)_3$ and $M(OTf)_3$ (M = Bi, Ga, In and rare-earth metals) to form 1-tetralones. Chroman-4-one and thiochroman-4-one were also obtained in good yields from 3-phenoxypropionic acid and 3-phenylthiopropionic acid, respectively.
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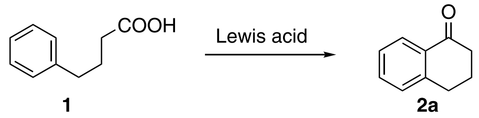
1-Tetralones are important intermediates for the preparation of pharmaceuticals[1] and also found in natural products.[2] One of the most important methods to prepare 1-tetralones is intramolecular Friedel–Crafts reaction of 4-arylbutyric acids or 4-arylbutyryl chlorides. The direct dehydrative cyclization of 4-arylbutyric acids is preferable to the cyclization via acid chlorides[3] because the former reaction formally produces only water as a by-product, which meets recent requirement for environmentally benign chemical processes. How-

Table 1. Cyclization of 4-phenylbutyric acid in the presence of Lewis acid catalysts[a]



Entry	Cat. (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$Bi(OTf)_3$ (10)	Toluene	90	20	8
2	$Bi(NTf_2)_3$ (10)	Toluene	90	20	Trace
3	$Bi(OTf)_3$ (10)	Toluene	Reflux	20	51
4	$Bi(NTf_2)_3$ (10)	Toluene	Reflux	20	59
5	$Bi(OTf)_3$ (1)	Toluene	180	7	74
6	$Bi(NTf_2)_3$ (1)	Toluene	180	7	97
7	$Bi(NTf_2)_3$ (1)	*p*-Xylene	180	7.5	Quant.
8	$Bi(NTf_2)_3$ (0.1)	*p*-Xylene	180	42	86
9	$Bi(NTf_2)_3$ (1)	Decane	180	7	Trace
10	$Bi(NTf_2)_3$ (1)	Decalin	180	7	Trace
11	$AlCl_3$ (3)	*p*-Xylene	180	6	0
12	$Ga(OTf)_3$ (1)	*p*-Xylene	180	7	57
13	$In(OTf)_3$ (1)	*p*-Xylene	180	7	80
14	$Sc(OTf)_3$ (1)	*p*-Xylene	180	10	71
15	$La(OTf)_3$ (10)	*p*-Xylene	180	6	67
16	$Nd(OTf)_3$ (1)	*p*-Xylene	180	7	90
17	$Sm(OTf)_3$ (1)	*p*-Xylene	180	7	96
18	$Eu(OTf)_3$ (10)	*p*-Xylene	180	6	50
19	$Yb(OTf)_3$ (1)	*p*-Xylene	180	7	39

[a] The reaction was performed using 0.25 mmol of 4-phenylbutyric acid in 2 mL of solvent. Entries 5–19 were conducted in a sealed glass tube.
[b] GC yield using dodecane as an internal standard.

Keywords: tetralone; Lewis acid; Friedel–Crafts reaction; bismuth; cyclization.

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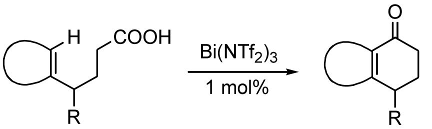
ever, the direct cyclization has been performed by using an excess of protic acids (often as solvents) such as sulfuric acid,[4] polyphosphoric acid (PPA),[5] polyphosphate ester (PPE),[6] methanesulfonic acid,[7] and hydrogen fluoride,[8] and therefore forms large amount of acid wastes after the reaction. To the best of our knowledge, only two catalytic examples, reactions using Nafion-H[9] and zeolites,[10] are known. Here we report that Lewis acids such as $Bi(NTf_2)_3$ and $M(OTf)_3$ (M = Bi, Ga, In and rare-earth metals) efficiently catalyze the cyclization of 4-arylbutyric acids.

First we studied the cyclization of 4-phenylbutyric acid (**1**) using $Bi(OTf)_3$ because it was known to catalyze Friedel–Crafts reaction of acid chlorides and acid anhydrides efficiently.[11] The reaction was found to be highly dependent on the reaction temperature and 1-tetralone (**2a**) was obtained in a good yield at 180°C by using only 1 mol% of catalyst (Table 1, entries 1, 3, 5). $Bi(NTf_2)_3$[12] was more efficient than $Bi(OTf)_3$ and gave **2a** quantitatively at 180°C in *p*-xylene (Table 1, entry 7). Even 0.1 mol% of $Bi(NTf_2)_3$ afforded **2a** in a good yield although a longer reaction time was required (Table 1, entry 8). The cyclization did not proceed in aliphatic hydrocarbon solvents such as decane and decalin (Table 1, entries 9–10).

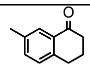
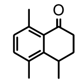
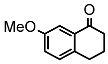
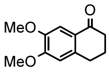
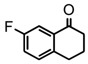
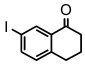
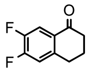
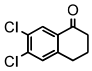
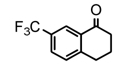
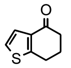
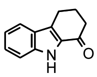
As expected, a catalytic amount of $AlCl_3$ did not promote the reaction at all in *p*-xylene at 180°C (Table 1, entry 11). On the other hand, various metal triflates those are known to catalyze Friedel–Crafts acylation reactions of acid chlorides and anhydrides[11c,13] also catalyzed the cyclization of **1** (Table 1, entries 12–19); in particular, $Sm(OTf)_3$ (1 mol%) afforded **2a** almost quantitatively.

Table 2 summarizes the scope and limitation of the dehydrative cyclization using $Bi(NTf_2)_3$.[14,15] 4-Arylbutyric acids with electron-donating substituents on the aromatic ring were easily cyclized in *p*-xylene at 180°C (Table 2, entries 1–4). In the case of 4-(4-iodophenyl)butyric acid, a small amount of by-product derived from the intermolecular reaction of the carboxylic acid with *p*-xylene used as solvent. Therefore, in the case of less-reactive substrates, chlorobenzene was used as solvent to minimize the reaction involving the solvent. The cyclization of 4-(4-fluorophenyl)- and 4-(4-iodophenyl)butyric acids efficiently proceeded at 200°C (Table 2, entries 5–6). It was reported that 4-(3,4-difluorophenyl)- and 4-(3,4-dichlorophenyl)butyric acids did not efficiently cyclize under the conventional conditions using PPA and 1-tetralones **2h** and **2i** were obtained in 39 and 36% yields, respectively,[5b] while the cyclization of them using 5 mol% of $Bi(NTf_2)_3$ gave **2h** and **2i** in good yields (Table 2, entries 7–8). Likewise the cyclization of 4-(4-trifluoromethylphenyl)butyric acid using PPA or PPE was reported not to give 1-tetralone **2j** at all and the cyclization of 4-(4-trifluoromethylphenyl)butyryl chloride using an excess of $AlCl_3$ afforded 7-trichloromethyl-1-tetralone, instead of **2j**, in 33% yield,[5b] while the present method furnished the desired tetralone **2j** in 46% yield (Table 2, entry 9).

Table 2. Synthesis of 1-tetralones and related cyclic ketones[a]



2b - 2l

entry	solvent	temp / °C	time / h	product	yield / %[b]
1	*p*-xylene	180	7	 **2b**	86 (99)
2	*p*-xylene	180	7	 **2c**	86
3	*p*-xylene	180	7	 **2d**	(93)
4	*p*-xylene	180	7	 **2e**	84 (92)
5	PhCl	200	15	 **2f**	81
6	PhCl	200	15	 **2g**	(89)
7[c]	PhCl	200	10	 **2h**	72 (80)
8[c]	PhCl	200	20	 **2i**	(81)
9[c]	PhCl	200	15	 **2j**	(46)
10	*p*-xylene	180	7	 **2k**	89
11	*p*-xylene	180	7	 **2l**	81

[a] The reaction was performed using 0.25 mmol of carboxylic acids in 2 mL of solvent in a sealed glass tube.

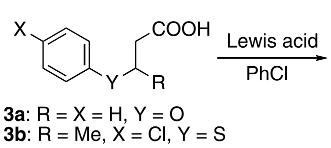
[b] Isolated yields. GC yields using dodecane as an internal standard are shown in parentheses.

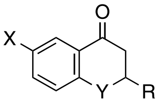
[c] 5 mol% of $Bi(NTf_2)_3$ was used.

Cyclization of heteroarylbutyric acids, 4-(2-thienyl)-butyric acid and 4-(3-indolyl)butyric acid, also proceeded efficiently (Table 2, entries 10–11).

Cyclization of 3-phenoxypropionic acid (**3a**) and 3-(4-chlorophenylthio)butyric acid (**3b**) to form chroman-4-one and thiochroman-4-one, respectively, was also efficiently promoted by Lewis acids (Table 3). Only 1 mol% of $Bi(NTf_2)_3$ was effective for both **3a** and **3b** (Table 3, entries 1 and 8). Cyclization of **3a** with $Ga(OTf)_3$ was slightly faster but less clean than that with $Bi(NTf_2)_3$, and prolonged heating decreased the yield of **4a** (Table 3, entries 2–3). Although $Eu(OTf)_3$ was less efficient than $Bi(NTf_2)_3$, an increase in the amount of the catalyst afforded **4a** quantitatively (Table 3, entries 6–7). $Sm(OTf)_3$, which was very effective for the cyclization of **1**, was not suitable for the

Table 3. Synthesis of chroman-4-one and thiochroman-4-one[a]





4a, 4b

Entry	3a/3b	Cat. (mol%)	Temp. (°C)	Time (h)	Yield (%)[b]
1	**3a**	$Bi(NTf_2)_3$ (1)	180	20	80
2	**3a**	$Ga(OTf)_3$ (1)	180	4	64
3	**3a**	$Ga(OTf)_3$ (1)	180	9	58
4	**3a**	$Sc(OTf)_3$ (1)	180	20	60
5	**3a**	$La(OTf)_3$ (10)	180	27	83
6	**3a**	$Eu(OTf)_3$ (1)	180	20	58
7	**3a**	$Eu(OTf)_3$ (10)	180	14	98
8	**3b**	$Bi(NTf_2)_3$ (1)	200	7	87
9	**3b**	$In(OTf)_3$ (1)	200	20	46
10	**3b**	$Sm(OTf)_3$ (1)	200	9	Trace
11	**3b**	$Sm(OTf)_3$ (10)	200	20	27
12	**3b**	$Yb(OTf)_3$ (1)	200	20	24
13	**3b**	$Yb(OTf)_3$ (10)	200	7	98

[a] The reaction was performed using 0.25 mmol of carboxylic acids in 2 mL of PhCl in a sealed glass tube.

[b] GC yield using dodecane as an internal standard.

cyclization of **3b**, while 10 mol% of $Yb(OTf)_3$ afforded **4b** quantitatively (Table 3, entries 10–13).

In summary, 1-tetralones and related cyclic ketones were efficiently synthesized by the intramolecular Friedel–Crafts acylation reaction of 4-arylbutyricacids and related carboxylic acids using catalytic amounts of Lewis acids such as $Bi(NTf_2)_3$ and $M(OTf)_3$ (M = Bi, Ga, In and rare-earth metals).

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References

1. For example, see: (a) Deshpande, M. N.; Cain, M. H.; Patel, S. R.; Singam, P. R.; Brown, D.; Gupta, A.; Barkalow, J.; Callen, G.; Patel, K.; Koops, R.; Chorghade, M.; Foote, H.; Pariza, R. *Org. Process Res. Dev.* **1998**, *2*, 351–356; (b) Vukics, K.; Fodor, T.; Fischer, J.; Fellegvári, I.; Lévai, S. *Org. Process Res. Dev.* **2002**, *6*, 82–85.
2. For example, see; (a) Wu, T. S.; Tsai, Y. L.; Damu, A. G.; Kuo, P. C.; Wu, P. L. *J. Nat. Prod.* **2002**, *65*, 1522–1525; (b) Quang, D. N.; Hashimoto, T.; Tanaka, M.; Baumgartner, M.; Stadler, M.; Asakawa, Y. *J. Nat. Prod.* **2002,** *65*, 1869–1874.
3. (a) Martin, E. L.; Fieser, L. F. *Org. Synth. Coll. Vol. II* **1943**, 569–571; (b) Johnson, G. D. *Org. Synth. Coll. Vol. IV* **1963**, 900–903.
4. (a) Krollpfeiffer, F.; Schäfer, W. *Ber. Dtsch. Chem. Ges.* **1923**, *56*, 620–632; (b) Caro, Y.; Masaguer, C. F.; Ravina, E. *Tetrahedron: Asymmetry* **2003**, *14*, 381–387.
5. (a) Snyder, H. R.; Werber, F. X. *Org. Synth. Coll. Vol. III* **1955**, 798–800; (b) Owton, W. M.; Brunavs, M. *Synth. Commun.* **1991**, *21*, 981–987.
6. (a) Rao, A. V. R.; Chanda, B.; Borate, H. B. *Tetrahedron* **1982**, *38*, 3555–3561; (b) Esteban, G.; Lopez-Sanchez, M. A.; Martinez, E.; Plumet, J. *Tetrahedron* **1998**, *54*, 197–212.
7. Premasagar, V.; Palaniswamy, V. A.; Eisenbraun, E. J. *J. Org. Chem.* **1981**, *46*, 2974–2976.
8. Fieser, L. F.; Hershberg, E. B. *J. Am. Chem. Soc.* **1939**, *61*, 1272–1281.
9. (a) Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 3955–3957; (b) Olah, G. A.; Mathew, T.; Farnia, M.; Prakash, G. K. S. *Synlett* **1999**, 1067–1068.
10. Kooti, M.; Zendehdel, M.; Amini, M. M. *J. Inclusion Phenom. Macrocyclic Chem.* **2002**, *42*, 265–268.
11. (a) Desmurs, J. R.; Labrouillere, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871–8874; (b) Repichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J. R. *Eur. J. Org. Chem.* **1998**, 2743–2746; (c) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181–200.
12. Picot, A.; Repicheta, S.; Le Roux, C.; Dubac, J.; Roques, N. *J. Fluorine Chem.* **2002**, *116*, 129–134.
13. (a) Kawada, A.; Mitamura, S.; Matsuo, J.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325–2333; (b) Matsuo, J.; Odashima, K.; Kobayashi, S. *Synlett* **2000**, 403–405; (c) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227–2302; (d) Prakash, G. K. S.; Yan, P.; Torok, B.; Bucsi, I.; Tanaka, M.; Olah, G. A. *Catal. Lett.* **2003**, *85*, 1–6.
14. Typical procedure: A mixture of $Bi(NTf_2)_3$ (3 mg) and **1** (41 mg, 0.25 mmol) in toluene (2 mL) was heated at

180°C for 7 h in a sealed glass tube. After the addition of dodecane (20 μL, an internal standard for GC analysis), the mixture was analyzed by GC to show the formation of **2a** in 97% yield. 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 = 10/1) to give **2a** (32 mg, 88% yield).

15. Selected data for new compounds: 7-iodo-1-tetralone (**2g**): yellow solid; mp 59.5–60°C; ^{1}H NMR (499.1 MHz, $CDCl_3$): δ 2.11–2.17 (m, 2 H), 2.65 (t, $J=6.7$ Hz, 2 H), 2.91 (t, $J=6.1$ Hz, 2 H), 7.02 (d, $J=7.9$ Hz, 1 H), 7.77 (dd, $J=7.9$ Hz, 1.8 Hz, 1 H), 8.35 (d, $J=1.8$ Hz, 1 H); ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 23.01, 29.33, 38.84, 91.68, 130.85, 134.25, 136.16, 141.97, 143.82, 196.99. Anal. calcd for $C_{10}H_9IO$: C, 44.14; H, 3.33. Found: C, 44.37; H, 3.11. 7-Trifluoromethyl-1-tetralone (**2j**): colorless oil; bp 95°C (2 mmHg, oven temperature for bulb-to-bulb distillation); ^{1}H NMR (499.1 MHz, $CDCl_3$): δ 2.15–2.21 (m, 2 H), 2.71 (t, $J=6.7$ Hz, 2 H), 3.04 (t, $J=6.1$ Hz, 2 H), 7.40 (d, $J=7.9$ Hz, 1 H), 7.70 (dd, $J=7.9$ Hz, 1.8 Hz, 1 H), 8.31 (s, 1 H); ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 22.85, 29.64, 38.88, 123.81 (q, $J=272$ Hz), 124.40–124.50 (m), 129.31 (q, $J=33$ Hz), 129.43–129.52 (m), 129.63, 132.86, 147.96, 196.97. Anal. calcd for $C_{11}H_9F_3O$: C, 61.68; H, 4.24. Found: C, 61.87; H, 4.00.