Pergamon

Tetrahedron Letters 43 (2002) 6391–6394

TETRAHEDRON
LETTERS

The catalytic Friedel–Crafts alkylation reaction of aromatic compounds with benzyl or allyl silyl ethers using $Cl_2Si(OTf)_2$ or $Hf(OTf)_4$

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Received 30 May 2002; revised 1 July 2002; accepted 5 July 2002

Abstract—The Friedel–Crafts alkylation reaction of various aromatic compounds with benzyl or allyl silyl ethers is effectively promoted under mild reaction conditions using Lewis acid catalysts. A mixture of the desired phenyltolylmethanes is obtained in 80% yield from toluene with benzyl dimethylsilyl or trimethylsilyl ether at 50°C in the presence of a catalytic amount of $Cl_2Si(OTf)_2$ or $Hf(OTf)_4$. © 2002 Elsevier Science Ltd. All rights reserved.

The Friedel–Crafts reaction is one of the most fundamental and useful reactions in synthetic organic chemistry and is widely applied to the synthesis of substituted arenes via the electrophilic addition of cationic species to aromatic compounds.[1] In the Friedel–Crafts alkylation reaction, alkyl halides have been employed as one of the suitable electrophiles for the synthesis of various aromatic compounds due to their appropriate stability and reactivity. Although benzyl or allyl alcohols have also been used for the synthesis of the corresponding alkylated compounds by the Friedel–Crafts alkylation reaction of aromatic compounds, there is an obvious limitation because the reaction employing alcohols usually requires a high temperature even if it is accelerated by acid catalysts such as $TeCl_4$,[2] Nafion-H,[3] and $Sc(OTf)_3$.[4,5] Furthermore, it is necessary to use an excess amount of ordinary Lewis acids except $Sc(OTf)_3$ to produce the alkylated compounds in high yields since free hydroxyl groups in the electrophiles sometimes deactivate the catalysts.

On the other hand, there have not been many trials for the development of the Friedel–Crafts alkylation reaction using alkyl silyl ethers as electrophiles since it is not predicted that siloxy groups work as effective leaving groups for the substitution reaction. However, it is expected that Lewis acid catalysts more efficiently promote the reaction under milder conditions by employing alkyl silyl ethers as electrophiles because the catalysts are not deactivated by the electrophiles in this case. From such a viewpoint, our laboratory developed an efficient esterification reaction of silyl carboxylates with alkyl silyl ethers using a catalytic amount of $Cl_2Si(OTf)_2$ in 1992.[6] In 1997, Mikami et al. reported the Friedel–Crafts alkylation reaction of anisole with three kinds of alkyl silyl ethers using $TMSNTf_2$ as a Lewis acid catalyst.[7] Though the benzylation of anisole with benzyl trimethylsilyl ethers and allylation of anisole with an allyl trimethylsilyl ether gave satisfactory yields, stoichiometric amounts of $TMSNTf_2$ were required in these cases.

Furthermore, Baba et al. developed the reductive Friedel–Crafts alkylation of aromatics using carbonyl compounds by the promotion of $InCl_3$ in 1998.[8] In this reaction, intermediary alkyl chlorodimethylsilyl ethers were generated in situ and the successive Friedel–Crafts reaction of the formed silyl ethers was carried out. However, it was mentioned in their reports that triethylsilyl ethers reacted with only very active nucleophiles such as anisole since the activity of the trialkylsilyl ethers is lower than that of chlorodimethylsilyl ethers when using $InCl_3$ as a catalyst.

As far as we know, there has not been a systematic study of the Friedel–Crafts alkylation reaction of aromatic compounds with alkyl silyl ethers. Therefore, we now report the development of an effective Friedel–Crafts alkylation utilizing benzyl or allyl silyl ethers

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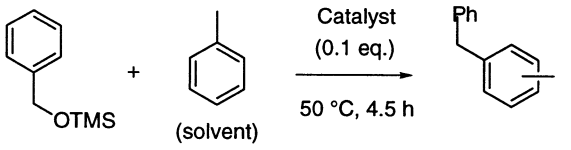
PII: S0040-4039(02)01376-X

which work as useful electrophiles under milder reaction conditions.

First, a solution of benzyl trimethylsilyl ether in toluene was heated at 50°C in the presence of a combined catalyst generated in situ from 10 mol% $AlCl_3$ and 30 mol% AgOTf, and a mixture of regioisomeric phenyltolylmethanes was obtained in only 3% yield after 4.5 h (Table 1, entry 1). Next, other Lewis acids containing the main and transition metals of groups III and IV were employed as catalysts for this reaction. It was found that $Cl_2Si(OTf)_2$,[6] the combined catalyst generated in situ from 10 mol% $SiCl_4$ and 20 mol% AgOTf, and $Hf(OTf)_4$[9] efficiently promoted the above reaction though $Sc(OTf)_3$ gave the corresponding alkylated compounds in moderate yields (entries 6, 10 and 4). On the other hand, it turned out that neither AgOTf, AgCl or TfOH was effective for the present coupling.

Second, benzyl alcohol and various benzyl silyl ethers were employed as electrophiles for the Friedel–Crafts alkylation reaction of toluene in the presence of a catalytic amount of $Cl_2Si(OTf)_2$. As shown in Table 2, it was observed that the yield decreased to 50% when benzyl alcohol was used as the electrophile. Though the yields decreased according to the bulkiness of the trialkylsiloxy groups, which are shown in entries 4–6, benzyl dimethylsilyl ether was proven as a suitable electrophile in this reaction and a mixture of the corresponding diarylmethanes was obtained with the best yield (entry 7).

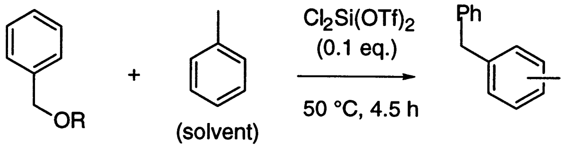
Table 1. Isolated yield of phenyltolylmethanes



Entry	Lewis Acid	Yield / %	(*o*-) / (*m*-)+(*p*-) [a]
1	$AlCl_3$ + 3AgOTf	3	42 / 58
2	$GaCl_3$ + 3AgOTf	14	38 / 62
3	$InCl_3$ + 3AgOTf	0	—
4	$Sc(OTf)_3$	47	39 / 61
5	$Yb(OTf)_3$	0	—
6	$SiCl_4$ + 2AgOTf	**73**	40 / 60
7	$GeCl_4$ + 2AgOTf	27	39 / 61
8	$SnCl_4$ + 2AgOTf	39	44 / 56
9	$Cl_2Ti(OTf)_2$	17	40 / 60
10	$Hf(OTf)_4$	**80**	40 / 60
11	TMSOTf	0	—
12	TfOH	0	—

[a] Determined by ^1H NMR.

Table 2. Isolated yield of phenyltolylmethanes



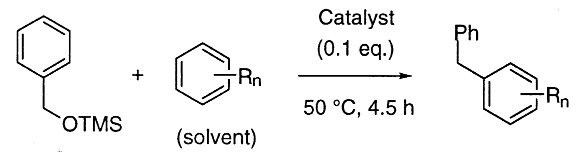
Entry	OR	Yield / %	(*o*-) / (*m*-)+(*p*-) [a]
1	OH	50	41/ 59
2	OMe	26	40 / 60
3	OTMS	73	40 / 60
4	OTES	54	42 / 58
5	OTBS	46	41 / 59
6	OTBDPS	34 (35)[b]	41 / 59
7	ODMS ($OSiHMe_2$)	80	39 / 61

[a] Determined by ^1H NMR. [b] Yield of recovered benzyl silyl ether.

The reaction conditions such as temperature and time were then examined in detail. When the reaction of toluene with benzyl dimethylsilyl ether was carried out at 50°C from 3 to 8 h, the desired arenes were afforded in almost the same yields (ca. 80%). It is noteworthy that the above reaction was catalyzed at even 40°C and a mixture of phenyltolylmethanes was produced in 70% yield while the Friedel–Crafts alkylation reaction using benzyl or allyl alcohols was generally carried out at higher temperature in the presence of Lewis acid catalysts. For example, the Friedel–Crafts alkylation reaction of toluene with benzyl alcohol using 10 mol% $Sc(OTf)_3$ gave a mixture of the desired compounds in 2% yield at 50°C and 4% yield at 60°C. On the other hand, the present reaction was promoted by using 10 mol% $Cl_2Si(OTf)_2$ at 60°C which produced a mixture of the corresponding diarylmethanes in 83% yield. When $Hf(OTf)_4$ was employed instead of $Cl_2Si(OTf)_2$ for the reaction of toluene with benzyl trimethylsilyl ether at 50°C, a mixture of phenyltolylmethanes was obtained in 80% yield.

Several examples of the present Friedel–Crafts alkylation reaction show that the desired substituted arenes are obtained in good yields using a catalytic amount of $Cl_2Si(OTf)_2$ or $Hf(OTf)_4$ under milder reaction conditions compared to those of the conventional severe conditions (see Table 3). Though some papers described better conversion yields of the reaction of benzene with benzyl alcohol analyzed by GLC,[3a,4] 64% is the best-isolated yield of diphenylmethane to the best of our knowledge (entry 1). The reactions of toluene and *o*-, *m*-, *p*-xylenes with benzyl dimethylsilyl ether smoothly proceeded when using $Cl_2Si(OTf)_2$ as a catalyst and the corresponding substituted arenes were formed in good

Table 3. Isolated yields of various diarylmethanes



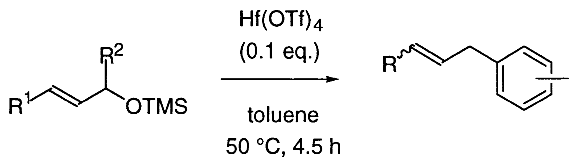
Entry	Rn	Yield / %	(*o*-) / (*m*-)+(*p*-)[d]
1[a,c]	H	64	—
2[b]	H	58	—
3[a,c]	Me	80	39 / 61
4[b]	Me	80	40 / 60[e]
5[a,c]	1,2-Me$_2$	78	34 / 66[f]
6[b,c]	1,2-Me$_2$	80	30 / 70[f]
7[a,c]	1,3-Me$_2$	80	22 / 78[g]
8[b]	1,3-Me$_2$	85	19 / 81[g]
9[a,c]	1,4-Me$_2$	80	—
10[b]	1,4-Me$_2$	73	—
11[a]	1,3,5-Me$_3$	80	—
12[b]	1,3,5-Me$_3$	83	—
13[a]	MeO	88[h]	41 / 59
14[b]	MeO	90[i]	41 / 59

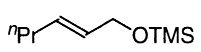
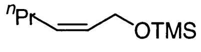
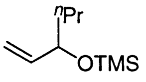
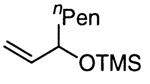
[a] $Cl_2Si(OTf)_2$ was used as a catalyst. [b] $Hf(OTf)_4$ was used as a catalyst. [c] Benzyl dimethylsilyl ether was used as an electrophile. [d] Determined by ^1H NMR. [e] Analysis of the product by GC gave the ratio of (*o*-) / (*m*-) / (*p*-) was 40 / 9 / 51. [f] The ratio of 1,2,3-trisubstituted benzene to 1,2,4-trisubstituted one [g] The ratio of 1,3,5-trisubstituted benzene to 1,2,4-trisubstituted one. [h] The reaction was carried out at rt for 8 h. [i] The reaction was carried out at rt for 3 h.

yields as shown in entries 3, 5, 7 and 9. Furthermore, the desired substituted aromatic compounds were produced in high yields from mesitylene or anisole with benzyl trimethylsilyl ether using either catalyst under quite mild reaction conditions (entries 11–14).

The present protocol using alkyl silyl ethers as electrophiles was successfully applied to the allylation of aromatic compounds. In the presence of a catalytic amount of $Hf(OTf)_4$, the reaction of toluene with (*E*)-1-(trimethylsiloxy)hex-2-ene was efficiently promoted at 50°C and a mixture of linear allylated *o*-, *m*- and *p*-toluenes was obtained in good yield (Table 4, entry 1). A regioisomeric mixture (*E*/*Z*=53/47) was produced in the case of employing (*Z*)-1-(trimethylsiloxy)hex-2-ene as the substrate (entry 2), whereas the reaction of toluene with 3-(trimethylsiloxy)hex-1-ene only produced the (*E*)-isomer (entry 3). When the $Sc(OTf)_3$-catalyzed allylation of toluene with (*E*)-hex-2-enol and (*Z*)-hex-2-enol was carried out under mild reaction conditions (50°C), the corresponding allylated toluenes were obtained in poor yields (12% and 10%).

Table 4. Isolated yields of several allylated toluenes



Entry	Substrate	Yield / %	(*o*-) / (*m*-)+(*p*-)[c]	*E* / *Z*[c]
1		83[a]	48 / 52	100 / 0
2		76[a]	48 / 52[d]	53 / 47
3		75[a]	47 / 53	100 / 0
4		88[b]	47 / 53	100 / 0

[a] R = ^{n}Pr. [b] R = ^{n}Pen. [c] Determined by ^1H NMR. [d] Isomer ratio indicated is for the mixture (*E* / *Z* = 53 / 47).

Thus, the catalytic Friedel–Crafts alkylation reaction of various aromatic compounds with benzyl or allyl silyl ethers was developed by employing 10 mol% $Cl_2Si(OTf)_2$ or $Hf(OTf)_4$. It is noteworthy that the reaction was efficiently promoted under mild reaction conditions (under 50°C) and various substituted diarylmethanes were obtained in good to high yields using alkyl silyl ethers as useful electrophiles.

A typical experimental procedure is described for the reaction of toluene with benzyl dimethylsilyl ether; to a suspension of silver trifluoromethanesulfonate (25.7 mg, 0.100 mmol) in toluene (1.0 mL) was added a solution of silicon tetrachloride (8.5 mg, 0.050 mmol) in toluene (0.5 mL) at room temperature. After having been stirred for 20 min, a solution of benzyl dimethylsilyl ether (83.0 mg, 0.500 mmol) in toluene (1.0 mL) was added. The reaction mixture was stirred for 4.5 h at 50°C and then saturated aqueous sodium hydrogencarbonate was added at 0°C. Usual work up and purification of the mixture by TLC on silica gel afforded 73.2 mg (80%) of a mixture of phenyltolylmethanes ((*o*-)/(*m*-)+(*p*-)=39/61).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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9. Hafnium tetrakis(trifluoromethanesulfonate) was prepared from $HfCl_4$ and TfOH. It was effectively employed in Friedel–Crafts acylation reaction, Fries rearrangement and Mannich-type reaction. See: (a) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2053–2060; (b) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 267–273; (c) Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* **1997**, 1099–1101. We had observed that $Cl_2Hf(OTf)_2$, generated in situ from 1 mol equiv. of $HfCl_4$ and 2 mol equiv. of AgOTf was effective catalyst for the synthesis of carboxylic esters in 1992. See: (d) Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* **1992**, 625–628; (e) Miyashita, M.; Shiina, I.; Miyoshi S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516–1527.