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Lewis Acid Catalyzed Benzylic Bromination

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

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Abstract

Lewis acid catalyzed bromination on aromatic side chain was achieved efficiently by using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a bromination reagent under mild conditions. Zirconium(IV) chloride showed the highest catalytic activity for the benzylic bromination. It was revealed that the present Lewis acid catalysis proceeds via the radical generation pathway. In contrast to Lewis acid catalysis, Brønsted acid promoted aromatic ring bromination without any benzylic bromination. Monobromination of tetramethylsilane was also demonstrated with zirconium(IV) chloride and DBDMH to provide desired product in good yield.

Keywords

bromination; Lewis acid; Brønsted acid; radical; Wohl-Ziegler

Introduction

The bromination of aromatic compounds is a highly useful transformation because resulting brominated aromatics are widely used in the fields of synthetic organic chemistry and materials science. Especially, recent progress of transition metal catalyzed cross coupling reaction has been extending the utility of bromoarenes and benzylic bromides. Although *N*-bromoimides have been widely used both for benzylic bromination and electrophilic aromatic ring brominations, harsh reaction conditions or electron rich substrate are usually required.^[1,2] For example, Wohl-Ziegler bromination, which is one of the most popular method to obtain α -brominated alkylarenes, is usually performed with *N*-bromosuccinimide (NBS) in the presence of radical initiator under high temperature. Surprisingly little attention has been given to allowing this reaction to proceed under lower temperature.^[1] Recently we reported that zirconium(IV) chloride catalyzed aromatic ring brominations quite efficiently with NBS as an electrophilic bromination reagent.^[1c] In that paper, we also mentioned that the ZrCl₄/NBS system promoted Wohl-Ziegler type benzylic bromination of toluene derivatives without bromination on the aromatic ring. Herein, we wish to report an even more efficient Lewis acid catalyzed benzylic brominations under mild conditions in contrast to Brønsted acid catalyzed aromatic ring brominations (Eq. 1).

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Results and Discussion

In the course of our previous studies on Lewis acid catalyzed electrophilic halogenations, we found that zirconium(IV) chloride catalyzed the benzylic bromination of toluene with NBS at room temperature to provide benzylbromide.^[1c] Further optimization of reaction conditions revealed that the use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as bromination reagent increased the reaction rate dramatically to afford benzylbromide exclusively (Table 1, Entries 1-3). Some other metal halides also catalyzed the benzylic bromination selectively (Entries 4-8). In marked contrast to Lewis acid catalysis, the use of Brønsted acid promoted the ring bromination of toluene to provide a mixture of *o*- and *p*-bromotoluene with excellent yield without the generation of benzylbromide. The use of trifluoromethanesulfonic acid and perfluorinated alkanesulfonimides showed almost the same reactivity and selectivity (Entries 9-11).

We assume that this sharp contrast between Lewis acid and Brønsted acid catalysis can be explained by differences of the reaction pathways. Thus, Lewis acid would assist the generation of benzyl radical^[3] from DBDMH to promote a Wohl-Ziegler benzylic bromination while Brønsted acid would activate DBDMH by protonations^[4] to accelerate Friedel-Crafts type electrophilic ring brominations. To ensure a radical pathway in the course of Lewis acid catalysis, the light effect was investigated (Scheme 1). Zirconium(IV) chloride catalyzed bromination of ethylbenzene under room light afforded (1-bromomethyl)benzene (**6**) with 98% yield while the reaction did not proceed in the dark. In addition, the irradiation by green laser^[5] dramatically accelerated the reaction to afford the desired product even under -78°C . These results clearly show that this reaction involves the generation of radical species.

Next, the general scope of the reaction was probed by application to a series of alkylated aromatics with zirconium(IV) chloride or trifluoromethanesulfonimide. The results are presented in Table 2. In all examples except for reactions with electron rich substrate, Lewis acid catalysis carried out benzylic brominations while Brønsted acid catalysis carried out ring brominations specifically. In contrast, when the reactions were carried out with electron rich aromatic substrates, Lewis acid catalysis afforded a ring brominated products as well as the use of Brønsted acid (Entries 6-9). Benzylic chlorination of ethylbenzene was performed by using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as a chlorination reagent to afford (1-chloroethyl)benzene (**7**) in good yield (Entry 2). A substrate having pinacolborate **16** also underwent the benzylic bromination by Lewis acid catalyst to provide a desired benzylbromide derivative **17** (Entry 10) while the use of Brønsted acid gave a complicated mixture.

Finally, our method was applied to α -bromination of silane.^[6] The treatment of tetramethylsilane (**18**) with DBDMH in the presence of 10 mol% of zirconium(IV) chloride successfully afforded bromomethyltrimethylsilane (**19**) in 70% yield (Scheme 2).

Conclusions

We have disclosed highly effective Lewis acid catalyzed side chain brominations of aromatic compounds with DBDMH as a bromination reagent. In particular, the use of zirconium(IV) chloride catalyst showed excellent catalytic activity to provide various benzyl bromide derivatives. In contrast to Lewis acid catalysis, Brønsted acid promoted aromatic ring bromination without any benzylic bromination. Monobromination of tetramethylsilane was also demonstrated with zirconium(IV) chloride and DBDMH. The present bromination system could thus be one of the most powerful methods for Wohl-Ziegler type radical

bromination under mild reaction conditions as well as it could be more atom economical process than that using NBS.

Experimental Section

General

All reactions were carried out in flame-dried glassware under argon atmosphere and stirred by magnetic stir-plates. Flash column chromatography for the isolation of products was performed according to the method of Still using silica gel 60 (mesh 230-400) supplied by E. Merck. All reactions were carried out with anhydrous dichloromethane which was dried with a M BRAUN solvent purification system (A2 Alumina). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 (500 MHz ^1H , 125 MHz ^{13}C). Chemical shift values (δ) are reported in ppm (tetramethylsilane δ 0.00 ppm for ^1H ; residual chloroform δ 77.0 ppm for ^{13}C).

Materials

All starting compounds were purchased from Aldrich or Boron Molecular Inc and used without further purification. All acid catalysts were purchased from Aldrich or Strem and also used without further purification. Zirconium(IV) chloride, aluminum(III) chloride and bistrifluoromethanesulfonimide were handled in a glove box. All products were characterized by the comparison of ^1H NMR spectra with commercially available authentic samples. Green laser pointer (wavelength 532 nm, max output power < 5 mW) for Scheme 1 was purchased from Leadlight Technology, Inc.

Typical procedure for Table 1 and 2

To a suspension of zirconium(IV) chloride (0.05 mmol) in dichloromethane (2 mL), was added a solution of toluene (**1**) (0.5 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH; 0.25 mmol) in dichloromethane (2 mL) at room temperature. The mixture was stirred for 2 h at room temperature under room light. The reaction was quenched with saturated aqueous NaHCO_3 solution and extracted by diethyl ether. The organic layer was subjected to GC analysis using 1,2-dichlorobenzene as an internal standard. The yield of benzylbromide (**4**) was determined to be 86%.

Compound 17

^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, J = 7.0 Hz, 1H), 7.42-7.37 (m, 2H), 7.30-7.26 (m, 1H), 4.92 (s, 2H), 1.37 (s, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.2, 136.4, 131.3, 130.4, 127.6, 83.8, 33.9, 24.8.

Reaction procedure for Scheme 1

Reactions were carried out with ethylbenzene (**5**) (0.5 mmol) as a substrate by the similar procedure as used for Table 1. Yields of (1-bromoethyl)benzene (**6**) were determined by ^1H NMR analysis of the crude mixture. A reaction vessel was covered with aluminum foil when the reaction was carried out in the dark. A laser pointer was set on the top of a reaction vessel and the entire piece of equipment was covered with aluminum foil when the reaction was carried out under the irradiation by green laser.

Reaction procedure for Scheme 2

To a suspension of zirconium(IV) chloride (0.1 mmol) in dichloromethane (4 mL), were added tetramethylsilane (**18**) (4 mmol) and DBDMH (1 mmol) at room temperature. The mixture was stirred for 36 h at room temperature under room light. A yield of bromomethyltrimethylsilane (**19**) was determined by ^1H NMR analysis of the reaction

mixture to be 70% (1.4 mmol, based on 1/2 DBDMH); ^1H NMR (500 MHz, CDCl_3) δ 2.46 (s, 2H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 18.2, -2.5.

(1)

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Scheme 1.

Light effect for benzylic bromination of ethyl benzene.

Scheme 2.

Lewis acid catalyzed radical bromination of tetramethylsilane.

Table 1

Acid catalyzed bromination of toluene. ^[a]

Entry	Acid (mol%)[^b]	Yield [%][^c]		
		2	3	4
1	none	0	0	0
2[^d]	ZrCl ₄ (10)	0	0	39
3	ZrCl ₄ (10)	0	0	86
4	Zr(O ^{<i>i</i>} Pr) ₄ •H ₂ O (10)	0	0	32
5	TiCl ₄ (10)	2	2	71
6	AlCl ₃ (10)	5	4	70
7	Tf ₂ NAICl ₂ (10)	1	1	76
8	Cy ₂ BCl (10)	0	0	71
9	TfOH (50)	49	45	0
10	Tf ₂ NH (50)	48	46	0
11	(C ₄ F ₉ SO ₂) ₂ NH (50)	44	42	0

[^a] Reactions were carried out in dichloromethane at room temperature for 2 hours with 0.5 equivalent of DBDMH under room light unless otherwise noted.

[^b] Cy = cyclohexyl, Tf = trifluoromethanesulfonyl.

[^c] Yields were determined by GC analysis.

[^d] 1.0 equivalent of NBS was used instead of DBDMH.

Table 2

Acid catalyzed halogenation of aromatic compounds ^[a]

Entry	Substrate	Acid (mol%)	Time [h]	Product	Yield [%]
1		ZrCl ₄ (10)	2		98/ ^{b/}
2/ ^{c/}		ZrCl ₄ (10)	24		76/ ^{b/}
3		Tf ₂ NH (50)	4		93/ ^{b/} o/p = 1/1.3
4		ZrCl ₄ (10)	6		89/ ^{d/}

Entry	Substrate	Acid (mol%)	Time [h]	Product	Yield [%]
5		TF ₃ NH (50)	10		45[d]
6		ZrCl ₄ (10)	1		99[b]
7		TF ₃ NH (50)	1.5		95[b]
8		ZrCl ₄ (10)	1		95[d]

Entry	Substrate	Acid (mol%)	Time [h]	Product	Yield [%]
9		Tf ₂ NH (50)	1		90 ^[d]
10		ZrCl ₄ (10)	6		84 ^[d]

^[a] Reactions were carried out in dichloromethane at room temperature with 0.5 equivalent of DBDMH unless otherwise noted.

^[b] Yields were determined by ¹H NMR.

^[c] 0.5 equivalent of DCDMH was used instead of DBDMH.

^[d] Isolated yield.