Friedel–Crafts Benzylation and Phenethylation Reactions Using Benzyl and Phenethyl Benzothiazol-2-yl Carbonate Derivatives

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Friedel–Crafts benzylation and phenethylation reactions of several aromatic compounds with benzyl and phenethyl benzothiazol-2-yl carbonate derivatives were carried out in the presence of scandium triflate ($Sc(OTf)_3$) as a catalyst. Suitable combinations of the leaving group of carbonates and acid promoters that generate cationic alkyl species were examined.

Friedel–Crafts alkylation reactions are very useful tools for introducing alkyl groups into aromatic compounds.¹ A standard Friedel–Crafts alkylation is generally carried out by using an alkyl halide and a Lewis acid catalyst such as aluminum chloride. In some cases, however, undesirable side reactions such as poly-alkylations and skeletal rearrangements take place to decrease their yields. Therefore, various methods for catalytic Friedel–Crafts alkylations which proceed under mild and controlled conditions have been studied extensively.²

In the meantime, the use of esters for alkylating agents has been reported^{1,3} as the alternatives of alkyl halides. These esters were dialkyl carbonates and alkyl sulfates, sulfites, phosphates, silicates, and borates which were activated by using more than a stoichiometric amount of a Lewis acid. Then the carbonates having one alkyl and one good leaving group which were activated by acids were considered. The carbonates having one alkyl and one benzothiazol-2-yl group would generate active species and react with nucleophiles such as aromatic compounds to form the alkylated products along with synchronous formation of CO_2 and benzothiazolinone by the application of acids. These carbonates are prepared via alkyl chloroformates formed from alcohols and $COCl_2$, and subsequent treatment of the chloroformates with benzothiazolinones in the presence of Et_3N or pyridine.

First, benzylation of an aromatic compound with benzyl carbonates **1a–c** in the presence of Sc(OTf)₃, one of the active Lewis acid catalysts,⁴ was chosen as a model reaction in order to find a suitable carbonate which has an excellent leaving group (Table 1). In the case of the benzylation of anisole (1.0 equiv.) in dichloromethane, benzyl 6-nitrobenzothiazol-2-yl carbonate **1c** gave mono-benzylated anisole in 55% yield along with dibenzylated anisole in 29% yield (Entry 1) while benzyl 4-nitrophenyl carbonate **1a** and benzothiazol-2-yl carbonate **1b** were not reactive enough to give benzylated products (Entries 2 and 3). When the reaction was carried out in a large excess amount of anisole, however, mono-benzylated products were obtained in high yields without accompanying dibenzylated products (Entries 4 and 5).

Next, Friedel–Crafts phenethylation of an aromatic compound with phenethyl carbonate derivatives **2** having similar structures to benzyl carbonate **1c** was examined (Table 2). AlTable 1. Friedel–Crafts benzylation with benzyl carbonate 1^a



1a:R¹=4-nitrophenyl; **1b**:R¹=benzothiazol-2-yl; **1c**:R¹=6-nitrobenzothiazol-2-yl

Entry	1	\mathbb{R}^2	Solvent	Temp. / °C	Time / h	Yield /% (<i>o</i> : <i>p</i>)
1 ^b	1a	OMe	CH_2Cl_2	reflux	1	N. R.
2 ^b	1b	OMe	CH_2Cl_2	reflux	1	trace
$3^{b,c}$	1c	OMe	CH_2Cl_2	reflux	1	55 (22:33)
4	1a	OMe	anisole	120	0.5	98 (45:53)
5	1c	OMe	anisole	120	0.5	95 (38:57)
6	1a	Me	toluene	reflux	2	88 (36:52)
7	1c	Me	toluene	reflux	1	82 (33:49)
8	1a	1,3-diMe	<i>m</i> -xylene	120	1.5	91 (72:19) ^d
9	1c	1,3-diMe	<i>m</i> -xylene	120	0.5	92 (73:19) ^d
10	1c	Н	benzene	reflux	1.5	85 (77:8) ^e
$11^{\rm f}$	1c	Cl	chlorobenzene	reflux	1.5	69 (23:46)

^aA mixture of **1** (0.2 mmol), an aromatic compound (0.8 mL), and Sc(OTf)₃ (5 mol%) was stirred unless otherwise noted. ^bAnisole (1.0 equiv.) was used. ^c2,4-Dibenzyl-1-methoxybenzene was also obtained in 29% yield. ^dRatio of (2,4-dimethylphenyl)phenylmethane : (2,6-dimethylphenyl)phenylmethane. ^eRatio of diphenylmethane : dibenzylbenzene. ^fSc(OTf)₃ (3 mol%) was used.

though the phenethylation of anisole with **2** in the presence of 20 mol% of TfOH resulted in incomplete consumption of **2** (Entries 1–8), thiocarbonate **2h** gave the best yield of the desired product (Entry 8). The combined use of **2h** and at least 50 mol% of TfOH or Sc(OTf)₃ completed the reaction to produce phenethylated anisoles in good yields (Entries 11 and 13) without any skeletal rearrangements, probably by the S_N1 type reaction via a non-aromatic symmetrical intermediate as mentioned by McMahon et al.⁵ The result indicated that the present phenethylation reaction was completed by using less stoichiometric but rather catalytic amounts of the acid. The use of 16 mol% of Sc(OTf)₃, however, again resulted in incomplete consumption of **2h** after the reaction mixture was stirred at 120 °C for 4 h. In this case, additional refluxing for 5 h caused formation of a side-product of 2-phenethyloxybenzothiazole in

Table 2. Effects of substituents of phenethyl carbonate **2** on the Friedel–Crafts phenethylation of anisole^a

x=<0^	√ ⟨N→ Y→ 2		+ (Z		TfOH o Sc(OTf 120 °C, s	$\frac{br}{5h}$	OMe
Entry	2	Х	Y	Ζ	TfOH / mol%	Sc(OTf) ₃ / mol%	Yield /% (<i>o</i> : <i>p</i>)
1	2a	0	0	NO_2	20		trace
2	2 b	0	0	Н	20		10 (5:5)
3	2c	0	S	NO_2	20		trace
4	2d	0	S	Н	20		22 (10:12)
5	2e	S	0	NO_2	20		10(5:5)
6	2f	S	0	Н	20		N. R.
7	2g	S	S	NO_2	20		33 (14:19)
8	2h	S	S	Н	20		39 (19:20)
9	2g	S	S	NO ₂	100		63 (34:29)
10	2h	S	S	Н	100		73 (35:38)
11	2h	S	S	Н	50		71 (34:37)
12 ^b	2h	S	S	Н		100	84 (42:42)
13 ^c	2h	S	S	Η		50	83 (40:43)
14 ^d	2h	S	S	Н		16	31 (16:15)

^aA mixture of **2** (0.2 mmol), anisole (0.8 mL), and TfOH or $Sc(OTf)_3$ was stirred at 120 °C for 5 h unless otherwise noted. ^bReaction time was 1 h. ^cReaction time was 2 h. ^dThe reaction mixure was stirred at 120 °C for 4 h and then under reflux for 5 h. 2-Phenethyoxybenzothiazole was obtained as a by-product in 26% yield.

26% yield, which was apparently the result of decomposition of **2h**. It seems that the generation of a phenethyl cation is much more difficult than the benzyl one due to its lower cationic stability. For instance, according to the conventional Friedel–Crafts reaction conditions using aluminum chloride⁶ (1.0 equiv.) in anisole (at 50 °C for 2 h and then at 80 °C for 3.5 h), phenethylated anisoles were obtained in only 16% combined yield (*ortho:para* = 1:1) via McMahon's intermediate.⁵

The effects of Lewis acids on the model phenethylation reaction of anisole with 2h are shown in Table 3. Among the Lewis acids examined, Sc(OTf)₃ gave the best result.

Thus, the use of the above mentioned active carbonate derivatives in the presence of a catalytic amount of $Sc(OTf)_3$ effectively worked in Friedel–Crafts benzylation and phenethylation reactions of aromatic compounds to give the corresponding alkylated products in good yields.

Further investigations to develop more effective systems of catalytic Friedel–Crafts alkylations are now in progress.

A typical experimental procedure for the Friedel–Crafts benzylation of anisole is as follows (Table 1, Entry 5): to a mix-

 Table 3. Effects of Lewis acids on the Friedel–Crafts phene-thylation of anisole with 2h



Entry	Additive	Temp. / °C	Time / h	Yield /% (<i>o</i> : <i>p</i>)
1	TfOH	120	5	73 (35:38)
2	Sc(OTf) ₃	120	1	84 (42:42)
3	$Sn(OTf)_2$	100-150 ^a	3	43 (17:26)
4	$Zn(OTf)_2$	120	5	N. R.
5	CuOTf	100	3	N. R.
6	$Cu(OTf)_2$	100	3	28(14:14)
7	AgOTf	80-120 ^b	5	30(15:15)
8	$AgB(C_6F_5)_4$	80-120 ^b	5	47 (31:16)

^aThe reaction mixure was stirred at 100 °C for 1 h and then at 150 °C for 2 h. ^bThe reaction mixure was stirred at 80 °C for 2 h and then at 120°C for 3 h.

ture of **1c** (66.0 mg, 0.20 mmol) and Sc(OTf)₃ (4.9 mg, 5 mol%) was added anisole (0.66 mL) at room temperature. The mixture was stirred at 120 °C for 0.5 h and then was cooled down to room temperature. Then, it was poured into 10% of aqueous so-dium hydrogencarbonate solution and was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtrated, and concentrated in vacuo. The crude product was purified by preparative TLC to give 2-benzyl-1-methoxybenzene (15.2 mg, 38%) and 4-benzyl-1-methoxybenzene (22.7 mg, 57%).

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