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A practical and convenient Blanc-type chloromethylation catalyzed by zinc chloride under solvent-free conditions

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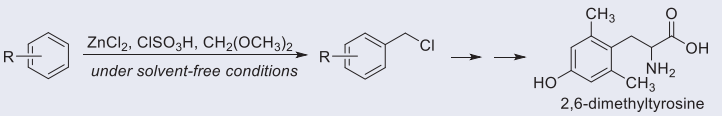
ABSTRACT

Chloromethylation of various aromatic hydrocarbons and substituted phenolic derivatives with dimethoxymethane and chlorosulfonic acid was carried out in the presence of 10 mol% of $ZnCl_2$ in a mild and efficient manner under solvent-free conditions. In addition, 2,6-dimethyltyrosine was synthesized in high yield via this protocol.

GRAPHICAL ABSTRACT



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KEYWORDS
Aromatic compounds; chloromethylation; chlorosulfonic acid; zinc chloride

Introduction

Chloromethyl substituted aromatic compounds are promising key intermediates for a variety of fine or special chemicals, polymers, and pharmaceuticals. The chloromethylation of aromatic compounds has been well documented,[1–8] including the chloromethylation of aromatic hydrocarbons with hydrochloric acid and trioxane or paraformaldehyde in the absence of a catalyst.[6–8] However, the reaction is very slow and insufficient for practical chemical processes. Later Lewis acids such as zinc chloride, stannic chloride, aluminum chloride, and boron trifluoride have been employed as catalysts for the reaction.[9–11] These catalysts, in general, suffer from the inherent problems of corrosiveness, high susceptibility to water, environmental hazards, waste control after the reaction, etc.[12–14] Zinc chloride is one of the most effective catalysts. However, normally a stoichiometric amount of zinc chloride is required, making the workup procedure tedious. Recently, rare-earth metal triflates were reported as active catalysts for this reaction, but these catalysts are expensive and not suitable to be used in industry.[15,16] The use of ionic liquids[17–21] and surfactant micelles[22,23] as catalysts for the chloromethylation of aromatic hydrocarbons were also reported. However, these ionic liquids are inevitably associated with one or more disadvantages, such as high cost or difficulty of synthesis. Therefore, it is important to replace these highly corrosive,

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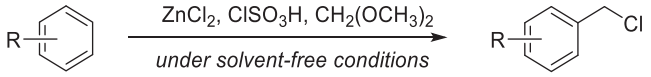
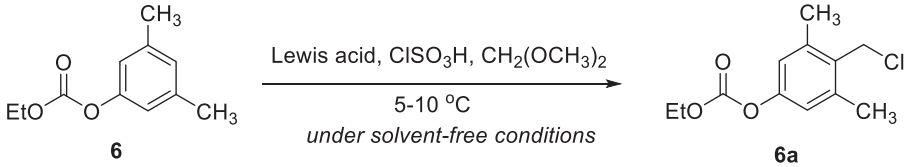


Scheme 1. Chloromethylation of aromatic compounds.

Table 1. Optimization of reaction conditions for Lewis acid-catalyzed chloromethylation reaction under solvent-free conditions[a].



Entry	Lewis acid	Amounts of catalyst (mol%)[b]	Time (h)	Yields (%)[c]
1	None	None	7.0	30
2	$AlCl_3$	50	5.0	25
3	$CaCl_2$	50	20.0	26
4	$SnCl_4$	50	2.0	35
5	LiCl	50	20.0	34
6	$FeCl_3$	50	2.0	50
7	$TiCl_4$	50	2.5	60
8	$ZnCl_2$	15	2.0	86
9	$ZnCl_2$	10	2.0	88
10	$ZnCl_2$	5	12.0	68
11	$ZnCl_2$	1	12.0	56
12	$Zn(OAc)_2$	10	2.0	68
13	ZnO	10	2.0	66
14	$Zn(OTf)_2$	10	2.0	55
15	$ZnSO_4$	10	2.5	36

[a]The reaction was carried out by the mixture of chlorosulfonic acid (31 mmol), dimethoxymethane (31 mmol) and *O*-carbethoxy-3,5-dimethylphenol (26 mmol) in the presence of Lewis acid at 5–10 °C under solvent-free condition.
[b]Relative to the amount of *O*-carbethoxy-3,5-dimethylphenol.
[c]Isolated yield by silica gel flash chromatography.

hazards and polluting acid catalysts with eco-conscious catalysts which are active under mild conditions.

Herein, we wish to report an efficient and convenient method for the chloromethylation of aromatic compounds with dimethoxymethane as a formaldehyde precursor and chlorosulfonic acid catalyzed by $ZnCl_2$ under solvent-free conditions (Scheme 1).

Results and discussion

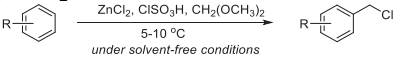
Initially, we chose *O*-carbethoxy-3,5-dimethylphenol **6** as the model substrate for surveying the reaction parameters. The results are shown in Table 1. The reaction was carried out sluggishly without a catalyst under the solvent-free condition and the yield was only 30% (Table 1, entry 1). By screening various Lewis acid catalysts we have found that low yields were given using 50 mol% of $AlCl_3$, $CaCl_2$, $SnCl_4$, LiCl as promoters, respectively (Table 1, entries 2–5). $FeCl_3$ and $TiCl_4$ could give moderate yields (Table 1, entries 6–7). Gratifyingly, the chloromethylation of *O*-carbethoxy-3,5-dimethylphenol was proceeded effectively in a short time catalyzed by 10 mol% of $ZnCl_2$ and gave exclusively *O*-carbethoxy-3,5-dimethyl-4-chloromethylphenol product in 88% yields (Table 1, entry 9).

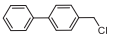
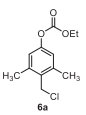
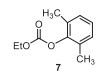
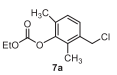
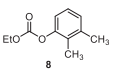
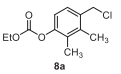
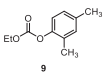
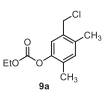
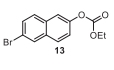
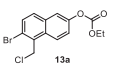
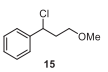
To examine the anion effect, a variety of zinc salts such as $Zn(OAc)_2$, ZnO, $Zn(OTf)_2$, and $ZnSO_4$ were compared under similar conditions, respectively. Moderate yields were given in the presence of $Zn(OAc)_2$ and ZnO (Table 1, entries 12 and 13). $Zn(OTf)_2$ and $ZnSO_4$ were less effective in terms of substrate conversion (Table 1, entries 14 and 15).

With these optimal conditions in hand, we further explored the scope and limitation of this simple process by reaction of electronically, sterically and functionally diverse aromatic compounds under the optimized conditions (Table 2). The reaction proceeded smoothly under solvent-free conditions and provided mono-chloromethyl substituted aromatic compounds in moderate to good yields, which was attributed to the deactivating effect of a $-CH_2Cl$ group. The aromatic compounds such as ethylbenzene, cumene, and *tert*-butylbenzene gave mono-chloromethylated products in better yields (Table 2, entries 3-5) than that of benzene, phenyl benzene (Table 2, entries 1 and 2), which are attributed to the electron-donating effect of the alkyl group. In addition, we have found that the chloromethylation of 3,5-dimethyl phenol failed due to its coordination of hydroxyl group with $ZnCl_2$. When the hydroxyl group of 3,5-dimethyl phenol was protected by ethyl chloroformate, the chloromethylation could be carried out smoothly and provided the desired products in good yield (Table 2, entry 6). The chloromethylation of various substituted *O*-carbethoxy phenol was also carried out smoothly in a short time and afforded good yields, respectively (Table 2, entries 7–10). The chloromethylation of *O*-carbethoxy phenol bearing electron-withdrawing group (i.e. –Cl, $–NO_2$) on benzene ring was inert under the parallel condition. The chloromethylation of *O*-carbethoxy-1-naphthol exclusively provided *O*-carbethoxy- 8-chloromethyl-1-naphthol **11a** at 5–10 °C (Table 2, entry 11). As well, the chloromethylation of 1-chloronaphthalene afforded 8-chloromethylated product **12a** (Table 2, entry 12), while no reaction was observed in the case of chlorobenzene at 5–10 °C. The chloromethylation of *O*-carbethoxy-6-bromo-2-naphthol **13** exclusively afforded the desired 5-chloromethyl product in moderate yield at 40 °C (Table 2, entry 13). It is worthy to be noted that no double chloromethylation products are observed by this protocol. In addition, to our surprise, no chloromethylation of styrene was observed on the benzene ring under this catalysis system, which was replaced by addition of double bond and afforded 1-phenyl-1-chloro-3-methoxypropane **15** (Table 2, entry 14).

A plausible mechanism for this catalysis is shown as Scheme 2. Firstly, treatment of dimethoxymethane with chlorosulfonic acid *in situ* produces methyl chloromethyl ether, followed by excretion of methanol and SO_3. Then, methyl chloromethyl ether reacts with $ZnCl_2$ to yield chloromethyl cation ($ClCH_2^+$) and methoxylated zinc chloride anion ($[CH_3OZnCl_2]^-$). Electrophilic addition occurred by a subsequent attack of the $[ClCH_2]^+$ on the benzene ring of the aromatic compounds to give chloromethylated aromatic carbonium ion, which very rapidly gave the desired products via aromatization. Finally, methoxylated zinc chloride anion ($[CH_3OZnCl_2]^-$) was protonated to produce methanol and led to the regeneration of $ZnCl_2$. In this process, the catalyst $ZnCl_2$ plays a vital role in the activation of methyl chloromethyl ether to form chloromethyl cation and methoxylated zinc chloride anion ($[CH_3OZnCl_2]$). As a control experiment, the chloromethylation of benzene using CH_3OCH_2Cl as chloromethylation reagent[10] was furnished in the presence of $ZnCl_2$ under solvent-free conditions in 65% yield.

Table 2. Chloromethylation of aromatic compounds catalyzed by $ZnCl_2$ under solvent-free conditions[a].

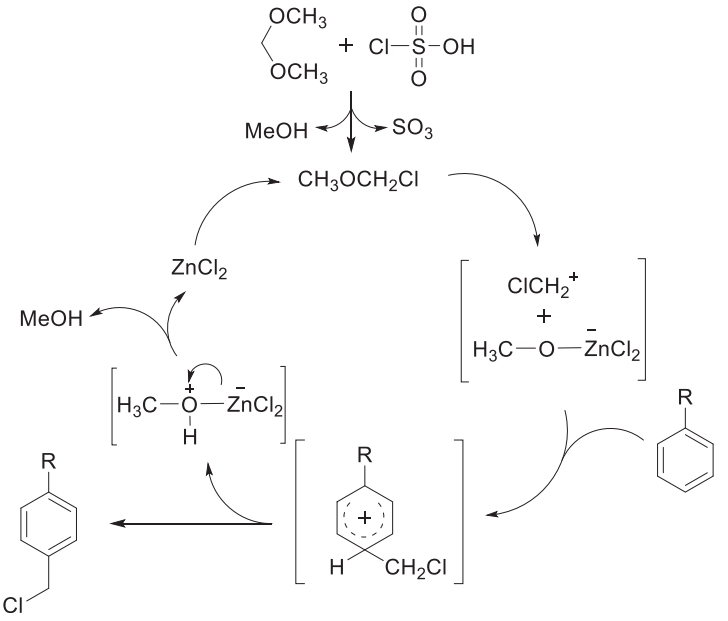


Entry	Substrate	t (h)	Product	Yield (%)[b]
1		4.0		67
2		4.0.		66
3		3.0		77
4		1.0		75
5		1.0		76
6		2.0		88
7		2.0		84
8		2.0		87
9		2.0		85
10		2.0		82
11		4.0		82
12		5.0		65
13[c]		2.0		68
14		2.0		90

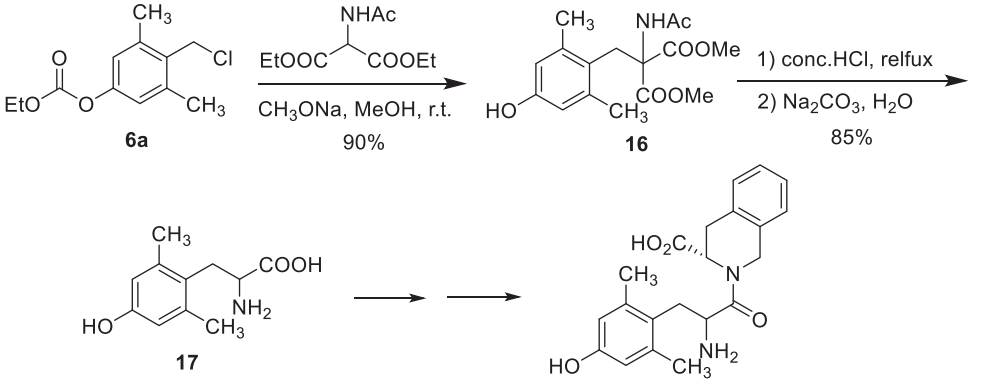
[a]Reaction conditions: The reaction mixture of aromatic compounds (26 mmol), chlorosulfonic acid (31 mmol) and dimethoxymethane (31 mmol) was carried out in the presence of 10 mol% of $ZnCl_2$.

[b]Isolated yield by silica gel flash chromatography.

[c]The reaction was carried out at 40 °C.



Scheme 2. Plausible mechanism of chloromethylation catalyzed by $ZnCl_2$.



Scheme 3. Synthesis of dimethyltyrosine.

To demonstrate the applicability of this protocol we employed it for the synthesis of 2,6-dimethltyrosine (Scheme 3), which is the key intermediate of δ-opioid receptor antagonist H-Dmt-Tic-OH[24]. The condensation of chloromethylated compound **6a** with diethyl 2-acetamidomalonate in the presence of sodium methoxide afforded dimethyl acetamido-(2,6-dimethyl-4-hydroxybenzyl) malonate **16** in 90% yield, which was subjected to decarboxylation in concentrated hydrochloric acid under reflux to give the desired product 2,6-dimethyltyrosine.

Conclusion

In conclusion, an efficient and practical chloromethylation protocol with $ZnCl_2$ as a catalyst in combination with chlorosulfonic acid and dimethoxymethane has been developed, which is capable of converting aromatic compounds into the corresponding

chloromethyl substituted aromatic compounds in moderate to good yields under solvent-free conditions. This methodology has some advantages such as simple operation, mild condition, and easy product purification. We expect this method will find wide application in organic synthesis and pharmaceutical industry.

Experimental

***General procedure for $ZnCl_2$-catalyzed chloromethylation of aromatic compounds*:** A three-necked flask was charged with $ZnCl_2$ (2.6 mmol), chlorosulfonic acid (31 mmol), followed by dropwise addition of dimethoxymethane (31 mmol) at −10 °C. After stirring for 30 minutes, aromatic compound (26 mmol) was slowly added into the reaction mixture. The resulting mixture continued to be stirred at 5–10 °C for several hours. The reaction was monitored by TLC analysis. After completion, the reaction was quenched by the addition of water in an ice bath. After extraction with CH_2Cl_2, the organic phase was washed with 5% sodium carbonate solution, water and brine, then evaporated to dryness in vacuo. The residue was purified by flash column chromatography on a silica gel to give the desired product.

Dimethyl Acetamido-(2,6-dimethyl-4-hydroxybenzyl)malonate (**16**)[25]: A three-necked flask was charged with 500 mL absolute methanol and diethyl 2-acetamidomalonate (98.5 g, 453 mmol), followed by addition of 28% sodium methoxide solution (95.5 g 494.5 mmol). Then **6a** (100 g, 412 mmol) was slowly added dropwise. The reaction mixture was stirred at room temperature for 4 hours. 150 mL of water was added and then concentrated in vacuo. The reaction residue was filtered and dried at 60 °C to give 120 g of **16** as white solid. m.p. 155–156 °C (lit.[25]156–157 °C); R_f = 0.50 (Petroleum ether: EtOAc = 1:1); 1 H NMR (500 MHz, DMSO) δ 8.33 (s, 1H), 6.38 (s, 2H), 3.57 (s, 6H), 3.49 (s, 2H), 2.09 (s, 6H), 1.89 (s, 3H) ppm. ^{13}C NMR (125 MHz, DMSO) δ 169.4, 168.2, 155.3, 139.2, 122.7, 114.8, 66.8, 52.7, 32.3, 22.1, 20.1. ppm.

***2,6-Dimethyltyrosine*(17)**[25]: A mixture of **16** (50.0 g 154.8 mmol) and 200 mL of conc. HCl was refluxed for 3.5 hours. The reaction mixture was cooled, and the crystalline product was collected, washed with cooled water, and dried to give 32.5 g of 2,6-dimethyltyrosine hydrochloride. The dimethyltyrosine hydrochloride was dissolved in 300 mL of warm water and neutralized to pH 6.5 with saturated aqueous sodium carbonate. The reaction mixture was cooled to room temperature. The crystalline amino acid was collected and washed with acetone to give 24.3 g of **17** as light yellow solid. m.p. 232–233 °C (lit.[25] 230–231 °C); R_f = 0.20 (MeOH: EtOAc = 1:1); ^{1}H NMR (500 MHz, D_2O) δ 6.45 (s, 2H), 3.93 (t, J = 8.2 Hz, 1H), 3.10 (dd, J = 14.7, 8.5 Hz, 1H), 2.95 (dd, J = 14.7, 7.8 Hz, 1H), 2.08 (s, 6H) ppm. ^{13}C NMR (125 MHz, D_2O) δ 171.9, 154.3, 139.5, 123.4, 115.1, 52.6, 29.7, 19.2. ppm.

Funding

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