

Improved Selectivity in the Chloromethylation of Alkylbenzenes in the Presence of Quaternary Ammonium Salts

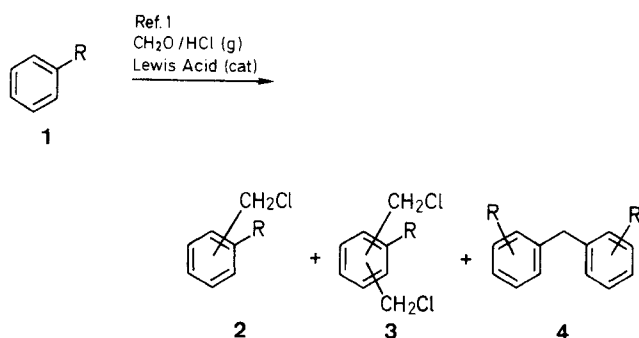
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Improved yield and selectivity in the chloromethylation of aromatic hydrocarbons in the presence of several phase transfer catalysts are reported. The best yield (98%) and selectivity (*p/o* ratio = 8.2) were obtained in the chloromethylation of cumene in the presence of a classical micellar catalyst.

Reaction of aromatic compounds **1** with formaldehyde in the presence of gaseous hydrogen chloride and a Lewis acid as catalyst, usually zinc chloride, affords chloromethylated derivatives **2**. Other Lewis acids such as boron trifluoride, tin tetrachloride, iron trichloride etc have also been used. Acetic acid is often the solvent of choice.¹

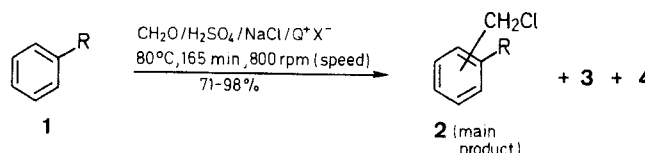


Yield of the chloromethylation product is controlled by the consecutive formation of the *polychloromethylation* byproducts **3** and the formation of diphenylmethane derivatives **4**, because of the Friedel–Crafts alkylation catalyzed by the same Lewis acid.

Regioselectivity is not high and cannot be easily controlled. Noticeably, *para/ortho* (*p/o*) isomer ratio varies within wide ranges, according to the steric hindrance of the alkyl side chain. Reaction of toluene with formaldehyde, hydrochloric acid and zinc chloride gives *p/o* = 1.1. Under the same conditions no *ortho* isomer was detected in the chloromethylation of *tert*-butylbenzene.² The *p/o* ratio depends on the reaction conditions; best result in *para*-selectivity was achieved when the reaction is carried out under a biphasic system (aqueous/organic layer) with fast stirring (> 1000 rpm) and with an external flow of gaseous hydrogen chloride. Toluene yields 97% of conversion with a selectivity of 92.2% in *mono*-chloromethyl derivative.³ More recently good results were claimed operating with concentrated hydrochloric acid, a Lewis acid catalyst and phosphoryl chloride. No gaseous hydrogen chloride was used.⁴

We report here that operating under milder conditions in a two-phase system and in the presence of a catalytic amount of quaternary onium salts (Scheme) high conversion, high selectivities in the *mono*-chloromethyl derivatives and negligible diphenylmethane derivatives were obtained. The *p/o* isomers ratio was in accordance with

most of the results already reported. Aromatics considered here for the chloromethylation are toluene (**1a**), ethylbenzene (**1b**), cumene (**1c**) and isobutylbenzene (**1d**).



1-4	a	b	c	d
R	Me	Et	<i>i</i> -Pr	<i>i</i> -Bu

Scheme

Table 1 illustrates the results obtained without using a catalyst and also under liquid–liquid phase-transfer catalysis (LL-PTC) conditions with tetraethylammonium bromide as a catalyst. Higher conversion are reached operating in the presence of a quaternary onium salt; the difference between catalyzed and uncatalyzed reactions increases with the steric hindrance of the alkyl group.

Operating at more moderate stirring (500 rpm) a lower conversion was achieved; however, it applied in both cases that the less reactive the substrate, the higher the difference in the observed conversion between the catalyzed and the uncatalyzed reaction. Table 1 shows that double chloromethylation and Friedel–Crafts alkylation byproducts are affected by reaction conditions as well: by employing tetraethylammonium bromide as a catalyst, selectivity in *mono*-chloromethylation is improved.

The nature of the phase-transfer catalyst also influences the reaction. Table 2 reports the results obtained on the chloromethylation of cumene with different phase-transfer catalysts. In particular, better results in both conversion and selectivity were obtained with hexadecyltrimethylammonium bromide: at 89% conversion, selectivity was 99%.

It is known that amphiphilic surfactants like hexadecyltrimethylammonium bromide having a very polar head do not provide high catalytic activity in phase-transfer catalysis reaction; *vice versa* they are good micellar catalysts,^{5,6} as they form emulsions in the two-phase system. In our case this provides a high surface area between the two phases, which might improve the selectivity for *mono*-chloromethylation, as already observed under fast stirring conditions.³

Also in other electrophilic aromatic substitutions like bromination of α -substituted alkylbenzenes, the nature of

Table 1. Chloromethylation of Aromatics in Two-Phase System in the Presence of $\text{Et}_4\text{N}^+\text{Br}^-$ and in Its Absence (shown in parenthesis)^a

Aromatic Substrate	Conversion (%)					Products					Stirring speed (rpm)	
1a	99.5	(96.8)	2a	71.3	(70.8)	3a	24.9	(27.0)	4a	3.9	(3.4)	800
1b	91.2	(76.2)	2b	89.2	(79.0)	3b	7.6	(17.1)	4b	3.3	(4.3)	800
1c	73.7	(42.5)	2c	95.7	(87.0)	3c	3.3	(8.2)	4c	0.9	(4.9)	800
1d	37.0	(15.1)	2d	97.8	(93.4)	3d	1.1	(5.3)	4d	1.1	(1.3)	800
1a	46.0	(45.3)	2a	48.7	(48.6)	3a	48.5	(46.6)	4a	2.8	(4.8)	500
1b	41.0	(27.3)	2b	65.8	(57.5)	3b	32.4	(38.8)	4b	1.7	(3.7)	500
1c	7.5	(3.8)	2c	81.3	(78.9)	3c	18.7	(21.0)	4c	< 1.3	(–)	500

^a T = 80°C; reaction time = 165 min; by GC analysis on a Varian 3400 Gaschromatograph.

Table 2. Influence on the Selectivity of Quaternary Onium Salt in the Chloromethylation of Cumene (**1c**)^a

Onium salt	Conversion (%)	Products		
		2c	3c	4c
$\text{Et}_4\text{N}^+\text{Br}^-$	73.7	95.7	3.3	0.9
$\text{Bu}_4\text{N}^+\text{HSO}_4^-$	75.7	95.4	2.8	1.5
$\text{Et}_3\text{N}^+\text{CH}_3\text{MeOSO}_3^-$	32.3	96.0	4.0	-
$\text{C}_{16}\text{H}_{35}\text{N}^+\text{Me}_3\text{Br}^-$	88.8	99.2	0.4	-

^a T = 80°C; reaction time = 165 min; *p/o* ratio ranges between 90–92%, being little affected by the nature of PT catalysts.

the phase-transfer catalysts showed peculiar influences in the reactions selectivities.⁷

Chloromethylation of cumene (**1c**) was also performed in a preparative scale (see experimental section) with hexadecylpyridinium bromide yielding after 4 hours 97.5% of conversion with 90.0% selectivity in *mono*-chloromethyl isopropylbenzene (*p/o* ratio = 8.2).

All the reagents employed were commercial samples (ACS grade) and used without further purifications.

Preparation of Methyl Methyltriethylammonium Sulphate:

Dimethyl sulphate (10 mL, 0.1 mol) is carefully added, under stirring, to NEt_3 (17.5 mL, 0.12 mol) at 0°C during a period of 0.5 h. After standing 12 h at r.t. the excess of NEt_3 is removed under vacuum. Methyl methyltriethylammonium sulphate is a low melting compound and is not further characterized.

¹H-NMR (CDCl_3): δ = 1.43 (t, 9H, $J_{\text{t,9H}}$ = 9 Hz, CH_2CH_3), 3.16 (s, 3H, CH_3), 3.60 (q, 6H, $J_{\text{q,6H}}$ = 8.7 Hz, CH_2CH_3), 3.77 (s, 3H, CH_3).

Chloromethylation of Arenes **1**; General Procedure:

To a cold solution of water (6 mL) and conc. H_2SO_4 (12 mL), are added alkylbenzene (0.050 mol), phase-transfer catalyst

(0.00476 mol), paraformaldehyde (2.65 g, 0.0882 mol) and NaCl (10.0 g, 0.1711 mol). The mixture is kept in an oil bath at 80°C and mixed by magnetic stirring for 165 min. The organic layer is analyzed with GC.

Chloromethylation of Cumene (**1c**); Preparative Procedure:

To a mixture of conc. H_2SO_4 (66 mL) and water (33 mL), are added cumene (30 g, 0.25 mol), hexadecylpyridinium bromide (6.5 g, 0.017 mol), formaldehyde (10.0 g, 0.333 mol) and NaCl (40.0 g, 0.6845 mol). The mixture is kept in an oil bath at 80°C and mixed by conventional mechanical stirring for 4 h; conversion by GC = 97.5%. At the end of the experiment the organic layer is separated and the aqueous phase is extracted with pentane (3×200 mL). The solvent is removed and the residue distilled; yield: 37.1 g (88%); bp 60–62°C/0.15 Torr; *p/o* ratio = 8.2.

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