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AROMATIC FLUORINE CHEMISTRY. PART 3. PREPARATION OF FLUOROPHENOLS VIA HYDROLYSIS OF CHLOROFLUOROBENZENES

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SUMMARY

The 1,2-, 1,3-, and 1,4-fluorophenols have been prepared by a copper (e.g. CuO, $CuSO_4$) catalyzed hydrolysis of chlorofluorobenzenes under conditions of controlled pH.

INTRODUCTION

Fluorophenols are valuable intermediates for the preparation of bioactive compounds [1]. The preparation of fluorophenols via hydrolysis of the corresponding bromofluorobenzenes is well documented in the literature. A process for making fluorophenols from the bromofluoro derivatives was described by Britton and Dietzler [2] utilizing either copper or a copper containing catalyst. During the same period, Boudakian and coworkers [3] reported a detailed study on the hydrolysis of p-bromofluorobenzene and presented evidence to suggest a nonrearranging SN2-type mechanism. The absence of m-fluorophenol suggested a nonbenzyne mechanism. The reaction conditions for the Boudakian study were temperatures in the 225-310°C range with resulting reaction pressures of 325-2000 psi. The catalysts investigated were cuprous oxide, copper naphthenate and cupric oxide in the presence of calcium hydroxide.

An extension of this work was reported by Riemenschneider who employed barium compounds as the acid acceptors and utilized quaternary compounds as cocatalysts [4]. Yakobson and coworkers [5], who have also reported on the hydrolysis of bromofluorobenzenes, appear to have the only report on the liquid phase hydrolysis

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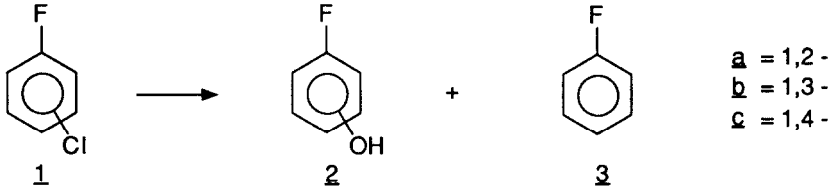
of chlorofluorobenzenes [6]. In the reaction of m-chlorofluorobenzene with caustic potash in the presence of cuprous oxide (300°C for 6 hours), approximately 89-90% of the fluorine and chlorine were lost from the starting material. The resulting mixture of phenols consisted of at least nine components of which phenol, m-fluorophenol, m-chlorophenol and resorcinol were identified. Copper promoted hydroxyapatites have been found to be useful catalysts for the vapor phase hydrolysis of chlorobenzene to phenol [7]. This approach to fluorophenols was unsuccessful [8]. A biologically mediated synthetic route to o-fluorophenol has also been investigated [9]. Commercially, fluorophenols are prepared from the corresponding fluoroanilines via Balz-Schiemann (diazotization) reaction [10]. We now describe the preparation of fluorophenols from the corresponding chlorofluorobenzenes by a copper catalyzed hydrolysis under 'controlled pH.'

RESULTS AND DISCUSSION

The results for the preparation of fluorophenols by hydrolysis of chlorofluorobenzenes are summarized in Table 1. Preliminary experiments utilizing reaction



conditions comparable to those for the successful hydrolysis of the 2-bromofluorobenzene utilizing calcium or barium hydroxide as the acid acceptor gave very low yields of 2a. Byproducts identified by GC:MS analysis, phenol, 2-chlorophenol, and catechol as well as coupled products, were consistent with derivatives of diphenyl oxide. When the aqueous calcium hydroxide reaction media was replaced with a 1 M K_2HPO_4 solution with additional amounts of K_2HPO_4 added as the acid acceptor, yields of 2a were improved to the 60-70% range with mass balances above 80%. Yields appear rather independent of catalyst, temperature and reaction time. Conversions, as expected, increase with temperature, but are somewhat lower with either the copper sulfate or cuprous oxide catalyst compared to the cupric oxide. Similar observations were observed for 1b, the meta isomer. Further work under 'controlled pH conditions' is required to study reaction variables and yield optimization.

TABLE 1

Preparation of Fluorophenols

Run	Temp. (°C)	Time (Hr)	1 Mol.	Catalyst g	Reaction Medium ml	Base Mol.	pH Before (After)	Reaction Composition (Mol.) 2	1	3	MB	Percent Conv.	Yield
1	250	20	1a (0.10)	CuO (0.10)	135[c]	$Ca(OH)_2$ (0.10)	--	trace	0.090	--	90	--	--
2	250	24	1a (0.25)	CuO (2.55)	270[c]	$Ca(OH)_2$ (0.25)	--	0.014	0.098	0.007	48[a]	61	9
3	230	6	1a (0.125)	$CuSO_4$ (5.30)	135	$Ba(OH)_2$ (0.10)	--	--	--	--	--[b]	-	-
4	250	12	1a (0.25)	CuO (2.55)	270	K^2HPO_4 (0.25)	7.8 (6.0)	0.050	0.015	0.016	81	59	56
5	250	24	1a (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.4 (4.2)	0.081	0.100	0.013	85	60	67
6	250	12	1a (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.8 (4.8)	0.100	0.114	0.012	85	54	64
7	250	6	1a (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.5 (5.4)	0.087	0.153	0.009	90	39	64
8	235	12	1a (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.5 (5.4)	0.062	0.189	0.002	89	24	54
9	250	12	1a (0.25)	$CuSO_4$ (5.30)	270	K_2HPO_4 (0.13)	6.6 (4.4)	0.082	0.159	0.003	90	36	69
10	270	24	1a (0.25)	Cu_2O (2.55)	270	K_2HPO_4 (0.13)	--	0.014	0.050	0.043	71	80	42
11	250	12	1b (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.5 (5.6)	0.062	6.155	0.002	80	38	65
12	250	12	1b (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.5 (5.5)	0.046	0.185	0.001	93	26	71
13	270	12	1b (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.5 (4.8)	0.102	0.108	0.002	85	57	72
14	270	12	1b (0.25)	$CuSO_4$ (5.30)	270	K_2HPO_4 (0.13)	6.5 (4.1)	0.082	0.137	0.002	88	45	73
15	270	12	1c (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.6 (3.8)	0.120	0.080	0.004	82	68	71
16	270	12	1c (0.25)	CuO (2.55)	270	K_2HPO_4 (0.13)	6.7 (4.1)	0.110	0.084	--	78	69	66

[a] Reaction mixture also contained phenol, 2-chlorophenol and catechol in amounts comparable to 2-fluorophenol.

[b] Main products were chlorophenol and catechol.

[c] $Ca(OH)_2$ and $Ba(OH)_2$ runs (1-3) were in H_2O. Runs 4-16 were in IM K_2HPO_4 buffer solution.

EXPERIMENTAL

Procedure for the Hydrolysis of Chlorofluorobenzenes

The reactions were carried out in either a 300 ml or 600 ml Hastelloy C Parr reactor. The chlorofluorobenzene, catalyst, buffer solutions, and base were charged to the reactor which was then sealed and pressure tested. After the reaction was complete, the reactor was cooled and vented. The solids (catalyst) were removed by filtration. The reaction mixture was extracted twice with dichloromethane (200 ml) and the organic extract dried over $MgSO_4$. The organic extract was analyzed by GC analysis using toluene as an internal standard. The aqueous phase was acidified with concentrated HCl and the extraction repeated. The second organic extract was dried over $MgSO_4$ and analyzed by GC analysis using toluene as an internal standard. GC analyses were performed on either a Hewlett-Packard 5700A-GC with OV-17 packed column using thermal conductivity detection or a Hewlett-Packard 5730A with a HP-Ultra-2 crosslinked 5% Bh Mesilicone (25 m x 0.2 mm x .033 µml) flame ionization. GC-MS analyses were carried out on a Hewlett-Packard 5995 gas chromatographic mass spectrometer equipped with an identical capillary column.

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