

**HIGH *ortho*-SELECTIVITY IN THE CHLORINATION OF PHENOLS WITH  
*N*-CHLORODIALKYLAMINES IN THE PRESENCE OF SILICA.**

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**SUMMARY:** Phenols are readily chlorinated by *N*-chlorodialkylamines in the presence of silica. Furthermore, this approach allows greater selectivity for *mono:di* and *ortho:para* chlorination than is possible with many other approaches.

We have recently reported a novel method for chlorination of moderately active aromatic compounds which involves the use of an organic chlorinating agent such as *tert*-butyl hypochlorite in the presence of silica<sup>1</sup> or a proton-exchanged zeolite.<sup>2</sup> In a similar way, the use of *N*-bromosuccinimide together with silica allows clean bromination of certain heterocyclic compounds.<sup>3</sup> Unfortunately, the reagent systems developed for the chlorination reaction are of little advantage for chlorination of phenols which react readily with the particular chlorinating agents even in the absence of a solid support. Thus, we have investigated other types of chlorinating agents for the chlorination of phenols. We now report that *N*-chlorodialkylamines readily chlorinate phenols in the presence of silica. Furthermore, the *ortho:para* and *mono:di* chlorination ratios are unusually favourable.

The commercial significance of the products has led to the investigation of a wide variety of reagents and conditions for chlorination of phenols.<sup>4</sup> Such reactions are not very amenable to selective control, generally giving mixtures containing substantial amounts of *di*- and/or *poly*-chloro products as well as the products of substitution at positions both *ortho* and *para* to the phenolic hydroxyl group.<sup>5</sup> Some control over the regioselectivity of chlorination of phenol can be achieved by use of isomeric hexachlorocyclohexadienones as the chlorinating agents, but high regioselective ratios (e.g. *o:p* > 4) are obtained only under conditions which produce low yields (< 25%).<sup>6</sup> Similarly, substantial *ortho*-selectivity has been achieved in only low yield by use of a detergent-based chlorinating agent.<sup>7</sup>

Recently, successful *para*-selectivity has been achieved using reagent systems which may give rise to bulky active species such as the chlorodiphenylsulphonium ion<sup>8</sup> or a chlorodi- or chlorotri-alkylammonium ion.<sup>9</sup> For example, chlorination of phenol with *N*-chloropiperidine in trifluoroacetic acid gives *para*-chlorophenol and *ortho*-chlorophenol in proportions of 97:3.<sup>9</sup>

In view of the above it was of interest to investigate the chlorination of phenol with *N*-chloroamines in the presence of an acidic silica. Thus, standard reactions were set up in which phenol (2.5 mmol) was stirred with silica (3 g, BDH chromatography grade, 60-120 mesh) and an *N*-chloroamine (2.5 mmol) in tetrachloromethane (10 ml), at 25°C, overnight. All reactions appeared to be complete well within this time, and gave mixtures containing six components (1-6, eq.1). The reaction solutions were filtered, the silica was washed with methanol, and the combined filtrates were analysed by GC. The results are presented in Table 1.

As can be seen from Table 1 all of the reactions are *ortho*-selective, which was surprising to us in view of the high *para*-selectivity of *N*-chloropiperidine in trifluoroacetic acid.<sup>9</sup> A possible explanation is that the silica surface binds the OH group of the phenol in close proximity to the site of protonation of the *N*-chloroamine thereby encouraging *ortho*-attack. Alternatively, it is possible that phenyl hypochlorite is generated as an intermediate. In an attempt to gain some insight into this question, an attempt was made to chlorinate anisole with one of the reagent systems. However, very little chlorination occurred under comparable reaction conditions.

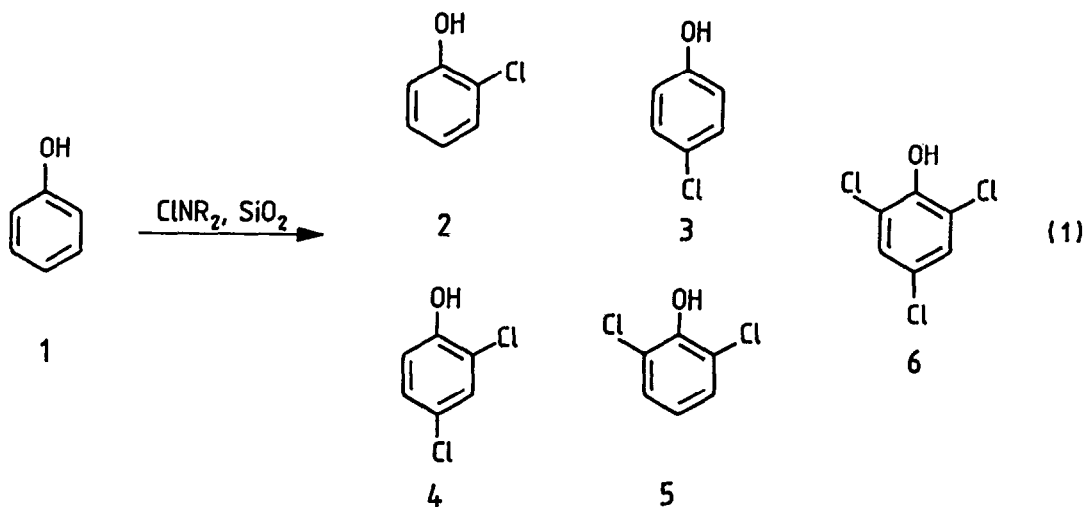

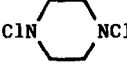
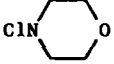


Table 1 Chlorination of phenol with *N*-chloroamines and SiO<sub>2</sub>

ClNR <sup>a</sup>	Total chlorination yield (%) <sup>b</sup>	Extent of chlorination <sup>c</sup> (1 : 2 + 3 : 4 + 5 + 6)	<i>ortho:para</i> ratio of monochlorophenols <sup>d</sup> (2 : 3)
ClNPr <sub>2</sub> <sup>i</sup>	70	50 : 35 : 15	5.0
	70	50 : 35 : 15	5.0
	88 <sup>e</sup>	36 : 43 : 21	2.6
	83	40 : 42 : 18	5.0
ClN(CH <sub>2</sub> CH <sub>2</sub> OMe) <sub>2</sub>	82	40 : 39 : 21	12.0
ClN(CH <sub>2</sub> CH <sub>2</sub> Cl) <sub>2</sub>	83	34 : 50 : 16	15.8

a) Prepared from HNR<sub>2</sub> and NaOCl, the product being extracted into CCl<sub>4</sub>; concentration estimated by iodimetry.

b) Based on the maximum possible yield if all ClNR<sub>2</sub> were used in the chlorination of phenol.

c) Ratio of unchlorinated phenol : monochlorinated phenols : polychlorinated phenols.

d) The ratio is somewhat dependent on the extent of reaction, being a composite of the rates of appearance and further reaction of monochlorophenols.

e) Only 1.25 mmol of reagent used in this case because of the availability of two N-Cl groups.

The most selective of the reagents tried is *N*-chlorobis(2-chloroethyl)amine, which gives both exceptional *ortho*-selectivity and a favourable mono : polychlorination ratio. As a result, this reagent system was applied to several simple phenols (eq.2). The results are given in Table 2.

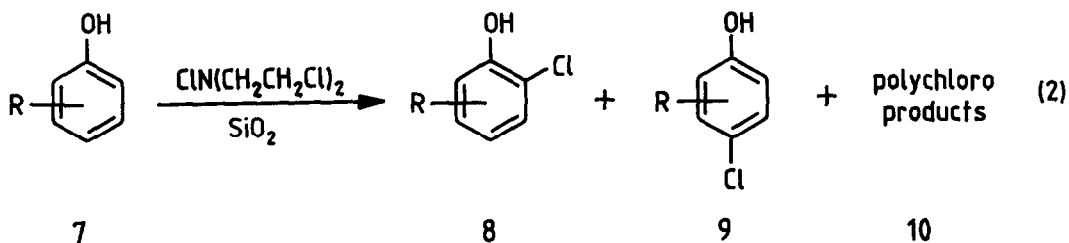





Table 2 Chlorination of phenols with  $\text{ClN}(\text{CH}_2\text{CH}_2\text{Cl})_2$  and  $\text{SiO}_2$ 

Phenol <sup>a</sup>	Total chlorination yield (%) <sup>b</sup>	Extent of chlorination <sup>c</sup> (7 : 8 + 9 : 10)	<i>ortho:para</i> ratio (8 : 9) <sup>d</sup>
	100	6 : 86.5 : 7.5	8.2
	74	38 : 50 : 12	4.7
	87	29 : 55 : 16	-

a) Reactions were carried out on a 5 mmol scale, but otherwise as described for the reaction with phenol.

b, c, d) See the corresponding footnotes to Table 1.

The results are very encouraging. Both *ortho*-chlorophenol and *ortho*-cresol show mono : dichlorination ratios and *ortho* : *para* ratios which are substantially better than those obtained with traditional reagent systems. No attempt has been made to optimise individual reactions, but it is clear that use of excess reagent will bring about the removal of the initial phenol from any given reaction mixture, whereas use of a deficiency of reagent will result in higher mono : di chlorination ratios. The reactions also possess practical advantages over traditional chlorination methods. Thus, the combination of an *N*-chlorodialkylamine and silica is recommended as a convenient reagent system for selective *ortho*-chlorination of phenols.<sup>10</sup>

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