

0040-4039(95)00592-7

Highly Regioselective ortho-Chlorination of Phenol With Sulfuryl Chloride in the Presence of Amines

Jallal M. Gnaim¹ and Roger A. Sheldon*,2

¹ The Institutes for Applied Research, Ben-Gurion University of the Negev, POB 653,

Beer-Sheva 84105, Israel

² Department of Organic Chemistry and Catalysis, Delft University of Technology,

Julianalaan 136, 2628 BL, Delft, The Netherlands

Abstract: Chlorination of phenol with sulfuryl chloride catalyzed by amines in non-polar solvents is fast, and specific for monochlorination and highly regioselective for *ortho*-substitution. Under optimal conditions, phenol was chlorinated with an equimolar quantity of sulfuryl chloride in the presence of di-s-butylamine (0.8 mole% relative to phenol) to give after 1 h of reaction at 70°C a 90.1% yield of *ortho*-chlorophenol with an *ortho/para* ratio of 22.0.

The commercial significance of isomerically pure *ortho*- and *para*-chlorophenols as intermediates for the manufacture of dyestuffs, preservatives and disinfectants,¹ has led to the investigation of a wide variety of reagents and conditions for the chlorination of phenols.² Such reactions are subject to problems of both chemo- and regio-selectivity, generally giving mixtures of mono-, di-, and tri-chlorinated products.³⁻⁵ Sulfuryl chloride is widely used as a reagent for efficient *para*-chlorination of phenol and other activated aromatic compounds.⁶⁻⁷ The high *para*-selectivities observed in these reactions are a consequence of the bulky nature of the reagent.⁸⁻¹⁰

In this communication, we wish to report a simple and convenient procedure for the regioselective *ortho*-chlorination of phenol with SO₂Cl₂ in the presence of amines.

The chlorination results of phenol with SO_2Cl_2 in the presence of a variety of amine catalysts are summarized in Table 1. Data for a control reaction are also included for comparison. As shown in Table 1, phenol is slowly monochlorinated with SO_2Cl_2 in toluene at 70°C (Run 1). The addition of a catalytic amount of amine (8 mole% relative to phenol) increased the conversion of phenol from 7.2 to 97.5%, and the reaction was completed in as little as 1 h. The reaction was highly specific for monochlorination, with small amounts of polychlorophenols being produced. The observed selectivities for *ortho*-chlorophenol (2)



Table 1. Chlorination of Phenol with Sulfuryl Chloride in the Presence of Amine Catalysts*

Run no.	Amine catalyst	Amount of amine mole%**	Amount of SO2Cl2 mole%**	Time h	1	Yield 2	wt%	4+5+6	o/p ratio
1	None	-	100	2	92.8	3.8	3.4	traces	1.1
2	2-Aminopyridine	7.9	100	1	5.0	32.3	60.3	2.9	0.5
3	Triethylamine	7.9	100	1	4.8	52.7	39.4	3.1	1.3
4	Pyridine	7.9	100	1	2.5	55.1	37.9	4.5	1.5
5	Tri-n-propylamine	7.9	100	1	4.7	61.0	31.5	2.8	1.9
6	s-Butylamine	7.9	100	1.5	5.7	73.4	18.0	2.9	4.1
7	Diethylamine	7.9	100	1	3.6	83.3	10.5	2.6	7.9
8	Di-n-propylamine	7.9	100	1	6.5	82.3	9.0	2.2	9.1
9	2-Aminopentane	7.9	100	1	4.2	84.6	8.8	2.4	9.6
10	t-Butylamine	7.9	100	1	8.4	84.2	7.4	traces	11.4
11	Di-iso-butylamine	7.9	100	1	3.6	87.0	6.4	3.0	13.6
12	Benzylmethylamine	7.9	100	1	5.1	87.1	6.0	1.9	14.0
13	Di-iso-butylamine	0.8	100	1	3.0	91.0	4.1	1.9	22.2
14	Di-iso-butylamine	79.4	100	1	9.9	67.8	8.2	14.0	8.3
15	Di-iso-butylamine	7.9	115	1	0.3	82.5	2.6	14.6	30.6
16	Di-iso-butylamine	7.9	125	1	0.0	79.1	1.2	17.7	65.9

For details of the experimental procedure, see note 11.
** Relative to phenol.

and *para*-chlorophenol (3) were in the range of 95.4-100%, while the corresponding values for di- and trichlorophenols (4-6) were less than 4.6% (Runs 2-12).

The type of amine catalyst used in the reaction had a pronounced effect on the distribution of isomers observed in the chlorination. Tertiary amines were found to give relatively low *ortho/para* ratios (i.e. < 1.9, Runs 2-5), while in the presence of primary or secondary amines the reactions were substantially regioselective for *ortho*-chlorination (i.e. *ortho/para*> 4.1, Runs 6-12). The most *ortho*-selective of the amines studied were N-methylbenzylamine, di-*iso*-butylamine, and *t*-butylamine which provided *ortho/para* ratios of 14.0, 13.6, and 11.4, respectively (Runs 10-12). These observations suggest that primary or secondary amines having bulky substituents are efficient as *ortho*-selective catalysts.

The amine catalytic system was applied in a detailed study in which the effects of solvent, concentration of reactants, and reaction temperature on orientation in the chlorination of phenol were investigated. The results clearly indicated that high temperature (e.g., $50-70^{\circ}$ C) and high dilution chlorinations (< 10 w/w% of phenol) in non-polar solvents (e.g., toluene, pentane, carbon tetrachloride, etc.) afforded the highest yield of **2** as well as the highest *ortho/para* ratio.

In an attempt to optimize the catalytic process, experiments were carried out with different amounts of di-*iso*-butylamine catalyst and SO₂Cl₂ reagent. The results in Runs 13 and 14 showed that by decreasing the amount of the catalyst from 79.4 to 0.8 mole% (based on phenol) the *ortholpara* ratio was increased from 8.3 to 22.2 and the yield of **2** was improved from 67.8 to 91.0%. Furthermore, the use of excess SO₂Cl₂ not only removed most of the phenol from the reaction mixture but also gave a significant improvement in the *ortholpara* ratio, e.g., addition of 15 and 25 mole% excesses of SO₂Cl₂ afforded *ortholpara* ratios of 30.6 and 65.9, respectively (Runs 15 and 16). The dramatic changes in the *ortholpara* ratio during the final stages of the reaction were due to different reaction rates of **2** and **3** with excess SO₂Cl₂. This was confirmed by competitive chlorination of a mixture of **2** and **3** (1:1 molar ratio) under comparable reaction conditions. The reaction profile indicated that **3** reacted with SO₂Cl₂ about five times faster than **2**. From a practical point of view, the removal of phenol from the reaction mixture simplifies the isolation of **2**.¹²

When 2 equivalents of SO₂Cl₂ were used for the amine-catalyzed chlorination of phenol, 2,6-dichlorophenol (4) was obtained as the major product in an 81.0% yield. The latter compound was also formed by starting from 2 and using 1 equivalent of SO₂Cl₂, affording 4 with an 89.6% yield. These data confirmed that the selectivity for *ortho*-chlorination was significantly improved under the amine-catalyzed SO₂Cl₂ conditions and suggested that this method could be applicable to other phenolic compounds.

Based on our evidence and that from analogous systems,¹³⁻¹⁸ we believe that the high regioselectivity is a consequence of the *in situ* formation of N-chloroamine intermediates, which attack the *ortho* position of phenol via intermolecular hydrogen bonding. A detailed discussion of the mechanism of such chlorinations will be presented in a subsequent paper.

Acknowledgement: We thank Coalite Chemicals for financial support for this work.

References and Notes

- Freiter, E. R. Kirk-Othmer Encyclopedia of Chemical Technology: 3rd Edition, Vol. 5; John Wiley & Sons, New York, Inc.: 1979; pp. 864-872.
- de la Mare, P. B. D. *Electophilic Halogenation*: Cambridge University Press: Cambridge, 1976.
- 3. Harvey, D. R.; Norman, R. O. C. J. Chem. Soc. 1961, 3604-3616.
- 4. Campbell, A.; Shields, D. J. Tetrahedron 1965, 21, 211-216.
- 5. Watson, W. D. J. Org. Chem. 1974, 39(8), 1160-1164.
- a) Bolton, R. J. Chem Soc. (B) 1968, 712-717.
 b) Bolton, R. J. Chem Soc. (B) 1970, 1770-1772.
- 7. Delaude, L.; Laszlo, P. J. Org. Chem. 1990, 50, 5260-5269.
- 8. Watson, W. D. J. Org. Chem. 1985, 55, 2145-2148.
- 9. Masilamani, D.; Rogic, M. M. J. Org. Chem. 1981, 46, 4486-4489.
- 10. Watson, W. D. Tetrahedron Lett. 1976, 30, 2591-2594.
- Typical procedure: to a mixture of phenol (12.6 mmole), amine (1.0 mmole) and toluene (87.0 g), sulfuryl chloride (12.6 mmole) was added at 70°C. Samples were taken periodically, and volatile solvents were removed under vacuum before analysis by GLC. The GLC analyses were performed with a Hewlett Packard instrument equipped with F.I.D. coupled to a Perkin Elmer GP100 recorder. A glass column (50 m, 0.53 mm i.d.) was packed with CP sil 5 CB (2.0 μm). Yields, given in weight percent, determined with 1,2-dichlorobenzene as an internal standard.
- 12. The boiling points of 1 and 2 are 175 and 182°C, respectively, while those of 3, 4, 5, and 6 are 220, 219, 210, and 246°C, respectively.
- 13. Pearson, D. E.; Buehler, C. A. Synthesis 1971, 9, 455-477.
- Eguchi, H.; Tokumoto, K.; Fujisaki, S.; Nishida, A. 2nd International Symposium on Chemistry of Brominated Compounds and their Uses: Jerusalem, Israel, June 27-July 2, 1993; pp. 35.
- 15. Neale, R. S.; Schepers, R. G.; Walsh, M. R. J. Org. Chem. 1964, 29, 3390-3393.
- Ogata, Y.; Takag, K.; Kondo, Y.; Hsin, S. C.; Woo, W. I.; Chen, F. C. J. Chinese Chem. Soc 1983, 30, 261-266.
- a) Smith, K.; Butters, M. Tetrahedron Lett. 1988, 29(11), 1319-1322.
 b) Butters, M.; Nay, B.; Smith, K. GB Patent Appl. 2 165 244A, 1986; US SN 34747, 1987.
- 18. Leblac, J. C. Eur. Pat. Appl. EP 196,260, 1986.

(Received in UK 13 March 1995; accepted 31 March 1995)