# Unusual Friedel-Crafts Reactions; 5[1]. Synthesis of Salicylanilides via *ortho*-Aminocarbonylation of Phenols with Phenyl Isocyanate

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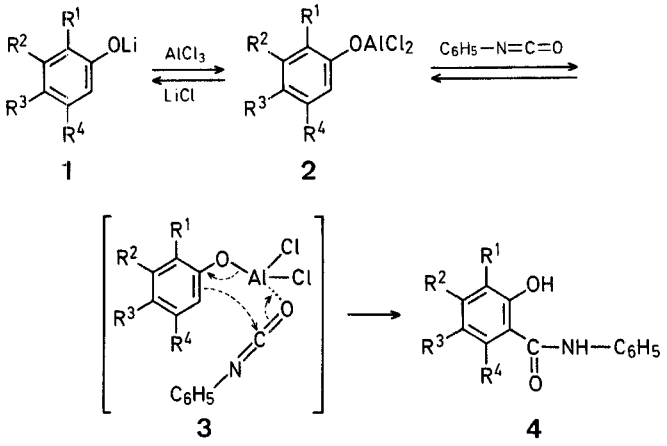
The use of isocyanates as aminocarbonylation agents of aromatic and heteroaromatic substrates under Friedel-Crafts conditions is well documented[2]. However, despite the intensive studies on phenylurethane production from phenols[3], only scant attention has been paid to the application of isocyanates to the synthesis of hydroxylated benzanilides[4].

Our current interest in the metal-driven *ortho*-specific alkylation of phenols[1,5], prompted us to investigate their reaction with phenyl isocyanate. This paper describes a generally applicable procedure for preparing salicylanilides **(4)** via aluminium trichloride-promoted *ortho*-specific aminocarbonylation of lithium phenolates **(1)** with phenyl isocyanate.

We propose the following mechanism in which aluminium phenolate, formed from lithium phenolate **(1)** and aluminium trichloride, attacks coordinated phenyl isocyanate to produce salicylanilides **(4)**.




Treatment of an equimolecular heterogenous mixture of **1** and aluminium trichloride in refluxing xylene with phenyl isocyanate (1.5 mol equiv) for 20 h followed by acidic quenching and purification by crystallization, afforded the salicylanilides **4a-h** in 15-36% yield (Table 1).

Strict adherence to specific reaction conditions is essential. Use of zirconium tetrachloride or tin tetrachloride instead of aluminium trichloride caused a marked drop of yield while use of phenol salts other than lithium phenolates such as sodium or potassium derivatives results in complex mixtures of

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**Table 1.** Salicylanilides **4a–h** prepared

| Product | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield[a] [%] | m.p. [°C] | Molecular formula[b] or Lit. m.p. [°C] |
|---|---|---|---|---|---|---|---|
| **4a** | H | H | H | H | 36 | 132–133° | 134–135° |
| **4b** | $CH_3$ | H | H | H | 30 | 119–120° | 123–124° |
| **4c** | H | H | $CH_3$ | H | 31 | 158–159° | 162–163° |
| **4d** | H | $OCH_3$ | H | H | 16 | 152–154° | $C_{14}H_{13}NO_3$ (243.3) |
| **4e** | H | H | $OCH_3$ | H | 15 | 158–160° | $C_{14}H_{13}NO_3$ (243.3) |
| **4f** | H | $CH_3$ | H | $CH_3$ | 24 | 143–145° | $C_{15}H_{15}NO_2$ (241.3) |
| **4g** | H | H | $-(CH=CH)_2-$ | | 29 | 170–171° | 171–172° |
| **4h** | H | OH | H | H | 27 | 129–132° | $C_{13}H_{11}NO_3$ (231.2) |

[a] Yield of isolated product based on the total amount of starting phenol.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.24; H, ±0.21; N, ±0.20. Analyses performed by Istituto di Chimica Farmaceutica dell'Università di Parma, Italy.

**Table 2.** Spectroscopic data of Compounds **4**

| Product | I.R. (film)[a] $\nu$ [$cm^{-1}$] | U.V. ($C_2H_5OH$)[b] $\lambda_{max}$ [nm] (log$\varepsilon$) | $^1$H-N.M.R. ($CDCl_3$/TMS)[c] $\delta$ [ppm] | M.S. $m/e$[d] (rel. int. %) |
|---|---|---|---|---|
| **4a** | 3300, 1625, 1460, 1240, 760 | 212 (4.33), 240 (4.02), 271 (4.08), 303 (3.87) | 6.5–7.6 (m, 9 $H_{arom}$); 8.25 (br. s, 1 H, NH); 11.85 (s, 1 H, OH) | 213 (18), 121 (27), 93 (100) |
| **4b** | 3420, 1608, 1448, 1254, 750, 700 | 210 (4.54), 245 (3.94), 270 (4.11), 314 (3.93) | 2.25 (s, 3 H, $CH_3$); 6.5–7.6 (m, 8 $H_{arom}$); 7.93 (br. s, 1 H, NH); 12.18 (s, 1 H, OH) | 227 (45), 135 (49), 93 (100), 77 (33) |
| **4c** | 3330, 1638, 1450, 1233, 830, 760, 695 | 213 (4.37), 244 (3.98), 272 (4.10), 311 (3.87) | 2.27 (s, 3 H, $CH_3$); 6.7–7.6 (m, 8 $H_{arom}$); 8.04 (br. s, 1 H, NH); 11.70 (s, 1 H, OH) | 227 (26), 135 (46), 107 (13), 93 (100), 77 (38) |
| **4d** | 3320, 1620, 1448, 1330, 1265, 1210, 848, 770, 695 | 211 (4.39), 269 (4.23), 275 (4.19), 301 (4.15) | 3.78 (s, 3 H, $OCH_3$); 6.2–7.6 (m, 8 $H_{arom}$); 7.75 (br. s, 1 H, NH); 12.30 (s, 1 H, OH) | 243 (41), 151 (100), 93 (83) |
| **4e** | 3320, 1640, 1460, 1218, 1044, 822, 768 | 212 (4.41), 237 (3.98), 271 (4.10), 328 (3.85) | 3.75 (s, 3 H, $OCH_3$); 6.8–7.7 (m, 8 $H_{arom}$); 7.95 (br. s, 1 H, NH); 11.25 (s, 1 H, OH) | 243 (60), 151 (51), 150 (60), 93 (100) |
| **4f** | 3320, 1632, 1540, 1453, 1318, 839, 752, 697 | 209 (4.40), 248 (4.19), 281 (3.84) | 2.25 (s, 3 H, 5-$CH_3$); 2.56 (s, 3 H, 3-$CH_3$); 6.4–7.7 (m, 7 $H_{arom}$); 7.63 (br. s, 1 H, NH); 10.30 (s, 1 H, OH) | 241 (35), 149 (100), 121 (6), 93 (99) |
| **4g** | 3365, 1640, 1545, 1445, 812, 742, 694 | 236 (4.48), 264 (4.19), 278 (4.12), 289 (4.05), 325 (3.71), 335 (3.76) | 6.9–8.3 (m, 11 $H_{arom}$ + NH); 10.95 (br. s, 1 H, OH) | 263 (42), 171 (84), 143 (20), 115 (78), 93 (100) |
| **4h** | 3330, 3180, 1635, 1260, 845, 750, 694 | 215 (4.19), 270 (4.19), 300 (4.16) | 6.2–6.5 (m, 2 $H_{arom}$); 6.9–8.0 (m, 6 $H_{arom}$); 9.40 (br. s, 1 H, NH); 12.43 (br. s, OH) | 229 (100), 137 (30), 93 (13) |

[a] Recorded on a Perkin-Elmer 298 instrument.

[b] Recorded on a Jasco UIDEC 505 instrument.

[c] Recorded on a Varian EM-360 instrument at 60 MHz.

[d] Recorded on a Varian CH-5 instrument at 70 eV.

products. The structures of compounds **4a–h** are confirmed by analytical and spectral data, namely, broad bands at about 3300 $cm^{-1}$ (NH) and peaks at about 1630 $cm^{-1}$ (CO) in the I.R. spectra and absorption bands at about $\delta = 11$–13 ppm (hydrogen-bonded OH) in chloroform-*d* in the N.M.R. spectra (Table 2). The purity was checked by T.L.C. on silica gel plates (eluent: hexane/ethyl acetate 8:2). Compounds **4** gave a single violet spot on spraying with an aqueous iron trichloride solution.

In conclusion, the present procedure has the advantage that *ortho*-hydroxybenzanilides **4** are obtained free from *para*-aminocarbonylated compounds in a one-step reaction[6] and that a wide variety of phenol substituents can be tolerated. A serious limitation of the present method is that it can only be applied to the synthesis of salicylanilides while the extension to alkyl isocyanates failed.

**2-Hydroxy-*N*-phenylbenzamide (Salicylanilide; 4a); Typical Procedure:**

To a suspension of lithium phenolate **(1a)**, prepared *in situ* from phenol (4.70 g, 50 mmol) and *n*-butyllithium (31.2 ml of 1.6 molar hexane solution) in anhydrous xylene (mixture of isomers, b.p. 140–142 °C; 150 ml), aluminium trichloride (8.0 g, 60 mmol) is added at room temperature. The resulting slurry is refluxed with stirring for 1 h under a stream of dry nitrogen. After cooling to room temperature, a solution of phenyl isocyanate (9.0 g, 75 mmol) in xylene (30 ml) is added dropwise. The heterogeneous mixture is heated under reflux with stirring for 20 h, then quenched with an excess of 10% hydrochloric acid. After extraction with ether (3 × 60 ml), the organic layer is extracted with 15% aqueous sodium hydroxide (3 × 50 ml). After washing with ether (25 ml), the aqueous solution is acidified to pH 1 with 37% hydrochloric acid. The product is crystallized and then suction filtered; yield: 3.83 g (36% on phenol); m.p. 132–133 °C.

Compounds **4b–h** are prepared similarly; preparative and significant spectroscopic data are collected in Tables 1 and 2.

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[1] Part 4, A. Arduini, F. Bigi, G. Casiraghi, G. Casnati, G. Sartori, *Synthesis* **1981**, 975.

[2] F. Effenberger, R. Gleiter, *Chem. Ber.* **97**, 472 (1964).
R. Richter, H. Ulrich, *Syntheses and Preparative applications of Isocyanates*, in *The Chemistry of Cyanates and their Derivatives*, S. Patai, Ed., Part 2, John Wiley & Sons, Inc., New York, 1977.
P. Krishnamurti, *J. Madras Univ.* **1928**, 4; *Chem. Zentralbl.* **1929** I, 2156.

[3] N. G. Graylord, J. J. O'Brien, *Recl. Trav. Chim. Pays-Bas* **74**, 218 (1955).
J. O. Weaver, E. J. Eisenbraun, *Chem. Ind. (London)* **1973**, 187.

[4] E. A. Shilov, M. N. Bogdanow, *Zh. Obshch. Khim.* **18**, 1060 (1948); *C. A.* **43**, 1351 (1949).

[5] F. Bigi, G. Casiraghi, G. Casnati, G. Sartori, *Synthesis* **1981**, 310.
F. Bigi, G. Casiraghi, G. Casnati, G. Sartori, *Synthesis* **1980**, 724.
F. Bigi, G. Casiraghi, G. Casnati, G. Sartori, *J. Heterocyclic Chem.* **18**, 1325 (1981).

[6] Using a similar strategy exclusive *ortho*-α-chloroacetylation of phenols was recently reported via aluminium trichloride-promoted reaction of phenoxydichloroboranes with chloroacetonitrile: T. Toyoda, K. Sasakura, T. Sugasawa, *J. Org. Chem.* **46**, 189 (1981).

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