



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

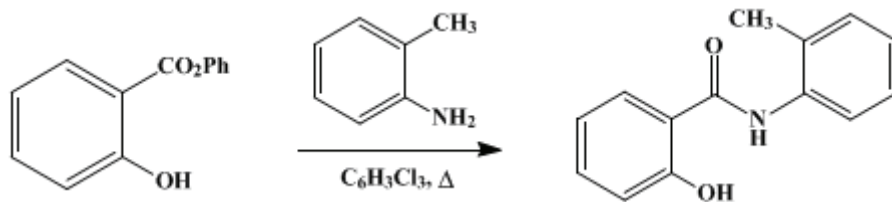
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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SALICYL-*o*-TOLUIDE

[*o*-Salicylotoluide]



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1. Procedure

In a 250-ml. flask attached to a Vigreux column 30 cm. in over-all length (Note 1), a mixture of 42.8 g. (0.2 mole) of phenyl salicylate ("Salol," m.p. 42–43°), 26.7 g. (0.25 mole) of *o*-toluidine, and 60 g. of 1,2,4-trichlorobenzene (m.p. 15–16°), is heated at the boiling point, so that the phenol formed slowly distils. The temperature rises from 183° to 187° during the first hour, and 22–23 g. of distillate is collected. Heating is continued until the temperature rises to 202° and a total of 45–46 g. of distillate has been collected (Note 2). The flask is then removed, and to it are added 3 g. of Norit and 10 ml. of trichlorobenzene. The mixture is heated to boiling and filtered hot by suction. The filtrate is allowed to stand in the ice chest overnight. The crystalline amide is filtered by suction, slurried with 75 ml. of ligroin (b.p. 90–120°) at 35–40°, and filtered. After being dried to constant weight, the salicyl-*o*-toluide, m.p. 143–144°, amounts to 33–35 g. (73–77%) (Note 3), (Note 4) and (Note 5).

2. Notes

1. These are measurements of standard ground-glass equipment.
2. The checkers preferred α -methyl-naphthalene (Eastman, practical) as the diluent. When it is used in the apparatus described the phenol does not distil, so that a reaction flask fitted with an air-cooled condenser is more convenient. The reactants in 60 g. of α -methyl-naphthalene are heated in an oil bath at 230° for 1.5–2 hours. Three grams of Norit and 20 g. more of α -methyl-naphthalene are then added, and the mixture is treated as described under Procedure. The yield and melting point of the product are identical with those described.
3. Since the pure material¹ melts at 144°, the product needs no further purification for ordinary purposes. It has a faint odor, which can be removed by recrystallization from aqueous ethanol (suitably by solution in 8–10 ml. of ethanol per gram of material and the addition of water just short of precipitation from the hot solution). The loss in recrystallization is only about 5%; the melting point is unchanged.
4. By working up the filtrate, only about 2 g. of material of poor quality can be secured.
5. Other anilides can be prepared by this procedure.

<i>Amine Used</i>	<i>M.p of Anilide Yield, %</i>	
Aniline	131–132°	70
2,5-Dichloroaniline	228°	89
β -Naphthylamine	188°	84
2-Aminopyridine	206°	86
1-Aminoanthraquinone	278–284°	79

When the boiling point of the amine is widely different from that of phenol, a diluent is unnecessary though it facilitates purification. In the absence of a diluent, the hot melt is poured into ethanol and

recrystallized, using a [decolorizing carbon](#); there is considerable tendency towards crystallization during the filtration from the charcoal.

[Salicylanilide](#) (m.p. 131–132°) is obtained by heating the mixture without a diluent for 3 hours at 180–200° with a short air condenser, pouring the melt into 100 ml. of [ethanol](#), and working up as above. The persistent pink color is not easily removed.

3. Discussion

[Salicyl-*o*-toluide](#) has been prepared only by the action of [phosphorus oxychloride](#) upon a mixture of [salicylic acid](#) and [*o*-toluidine](#). The useful methods of preparation of [salicylanilide](#) are by the interaction of [salicylic acid](#) and [aniline](#) in the presence of [phosphorus trichloride](#),^{2,3,4} by heating [phenyl salicylate](#) and [aniline](#),⁵ and from [*o*-hydroxybenzamide](#) and [bromobenzene](#) in the presence of small amounts of [sodium acetate](#) and metallic [copper](#).⁶ A number of these and other anilides have been described.⁷

References and Notes

1. Pictet and Hubert, *Ber.*, **29**, 1191 (1896).
 2. Wanstrat, *Ber.*, **6**, 336 (1873).
 3. Kupferberg, *J. prakt. Chem.*, [2] **16**, 442 (1877).
 4. Hubner and Mensching, *Ann.*, **210**, 342 (1881).
 5. Cohn, *J. prakt. Chem.*, [2], **61**, 547 (1900).
 6. Goldberg, *Ber.*, **39**, 1692 (1906).
 7. Fargher, Galloway, and Probert, *J. Textile Inst.*, **21**, 245T (1930) [*C. A.*, **24**, 6026 (1930)].
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

[ligroin](#)

[ethanol](#) (64-17-5)

[sodium acetate](#) (127-09-3)

[aniline](#) (62-53-3)

[phenol](#) (108-95-2)

[salicylic acid](#)

[copper](#) (7440-50-8)

[decolorizing carbon](#),
[Norit](#) (7782-42-5)

[Phosphorus Oxychloride](#) (21295-50-1)

[bromobenzene](#) (108-86-1)

[phosphorus trichloride](#) (7719-12-2)

2-aminopyridine (504-29-0)
phenyl salicylate (118-55-8)
1-aminoanthraquinone (82-45-1)
1,2,4-trichlorobenzene (120-82-1)
trichlorobenzene (87-61-6)
 α -methylnaphthalene (90-12-0)
2,5-Dichloroaniline (95-82-9)
Salicylanilide (87-17-2)
 β -naphthylamine (91-59-8)
o-toluidine (95-53-4)
Salicyl-o-toluide,
o-Salicylotoluide (7133-56-4)
o-hydroxybenzamide (65-45-2)