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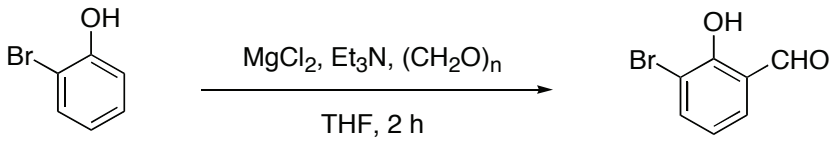
*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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# *ORTHO*-FORMYLATION OF PHENOLS; PREPARATION OF 3-BROMOSALICYLALDEHYDE

**(**3-Bromo-2-hydroxybenzaldehyde)




Submitted by Trond Vidar Hansen[1] and Lars Skattebøl.[2]
Checked by David Guthrie and Dennis P. Curran.

## 1. Procedure

A dry 500-mL, three-necked round-bottomed flask equipped with a stirring bar, reflux condenser and rubber septa is purged with argon gas. Anhydrous magnesium dichloride (Notes 1 and 2) (9.52 g, 100 mmol) and solid paraformaldehyde (Notes 3 and 4) (4.50 g, 150 mmol) are added, while a slight positive pressure of argon is maintained. Dry tetrahydrofuran (Note 5) (250 mL) is added by syringe. Triethylamine (Notes 6 and 7) (10.12 g, 100 mmol) is added dropwise by syringe and the mixture is stirred for 10 min. 2-Bromophenol (Note 8) (8.65 g, 50 mmol) is added dropwise by syringe, resulting in an opaque, light pink mixture. This mixture is immersed in an oil bath at about 75 °C (bath temperature) and soon turns a bright orange-yellow color. Heating at gentle reflux is maintained for 4 hr (Note 9).

The reaction mixture is cooled to room temperature and 100 mL of ether is added. The resulting organic phase is transferred to a 1-L separatory funnel and washed successively with 1N HCl (3 x 100 mL) (*Caution! gas evolves*) and water (3 x 100 mL) (Note 10), dried over anhydrous magnesium sulfate ($MgSO_4$), and filtered. The solvent is removed by rotatory evaporation leaving a pale yellow oil that solidifies on further vacuum drying at 1-2 mmHg. The resulting yellow solid (8.09-8.11 g, 80-81%) consisting mainly (≥95 %) of 3-bromosalicylaldehyde (Note 11) is sufficiently pure for further synthetic use. Recrystallization from hexane (50 mL) gives 6.80-6.94 g (68-69%, Note 12) of pure aldehyde as pale yellow needles (Note 13).

## 2. Notes

1. Magnesium dichloride, anhydrous beads, –10 mesh, 99.9% was purchased from the Aldrich Chemical Company, Inc. The submitters dried the beads over phosphorus pentoxide under reduced pressure for 24 hr prior to use. The checkers purchased the beads in ampules with less than 100 ppm water and used these directly. The use of anhydrous beads is crucial; the checkers observed little or no reaction when using anhydrous magnesium chloride powder dried over phosphorous pentoxide.

2. The submitters report that the reaction proceeds at a slower rate with less than two equivalents of magnesium dichloride and gives a lower yield of aldehyde.

3. Paraformaldehyde powder was purchased from Aldrich Chemical Company, Inc. and dried over phosphorus pentoxide under reduced pressure for 24 hr prior to use.

4. The reaction requires two equivalents of paraformaldehyde; however, the submitters report that an excess of this reagent results in a faster reaction and higher yield of aldehyde.

5. Tetrahydrofuran was purchased from Aldrich Chemical Company, Inc. The submitters emphasize the use of dry solvent in this reaction and the THF was distilled from sodium benzophenone ketyl prior to use. The checkers passed the THF through a column of dry, activated aluminum oxide.

6. Triethylamine was purchased from Aldrich Chemical Company, Inc., distilled from calcium hydride and stored over 4Å molecular sieves prior to use.

7. Equimolar amounts of triethylamine and magnesium dichloride are required.

8. 2-Bromophenol was purchased from Aldrich Chemical Company, Inc. and used as received.

9. Progress of the reaction was followed by thin layer chromatography using Merck silica gel 60 F254 aluminum-backed plates, eluting with hexane/EtOAc (10:1) and visualizing with a 254 nm UV lamp: 2-bromophenol R$f$ ≈ 0.58; 3-bromsalicylaldehyde R$f$ ≈ 0.45.

10. Vigorous shaking of the separatory funnel should be avoided since emulsions can result. The mixture is swirled and tilted back and forth

gently for 3-4 min per washing. This results in rapid separation of the layers on standing.

11. The main impurity is the starting bromophenol. The product can be analyzed by GLC on a Varian GC 3300 instrument equipped with a 25 m SP2100 capillary column or by $^{1}$H NMR spectroscopy.

12. The submitters obtained 9.05 g (90 %) of the recrystallized product.

13. 3-Bromosalicylaldehyde exhibited the following physical and spectral properties: mp (uncorr.) 52-53 °C (lit.[3] 52 °C); $^{1}$H NMR (300 MHz, $CDCl_3$) δ: 6.94 (t, $J$ = 7.8 Hz), 7.55 (dd, $J$ = 1.3 Hz, 7.7 Hz), 7.75 (dd, $J$ = 1.3 Hz, 7.7 Hz), 9.85 (s, 1H), 11.60 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 111.0, 120.7, 121.2, 132.9, 139.9, 157.9, 196.0; FTIR spectrum ($CHCl_3$) $cm^{-1}$: 3152, 2852, 1662, 906; LRMS (EI), *m/z* 202/200 ($M^+$), 159, 149, 117, 115, 71, 57, 55; HRMS, Calcd. for $C_7H_5BrO_2$: 199.9473; Found: 199.9475.

## Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

Surprisingly few substituted salicylaldehydes are commercially available even though they are important intermediates in organic synthesis for the preparation of a variety of oxygen-containing heterocyclic compounds and as a source for salen ligands.[5] Salicylaldehydes are accessible from the corresponding phenols by several classical formylation reactions;[4] however, the yields are often moderate and the lack of regioselectivity is problematic.

The present procedure is a simple, efficient and regioselective method for the preparation of substituted salicylaldehydes that is based on the work reported by Hofsløkken and Skattebøl.[6] It is applicable for large-scale preparations; on a 0.25 molar scale, 3-bromosalicylaldehyde was obtained in 90% yield. The method gives exclusively *ortho*-formylation of phenols and naphthols; no bis-formylation has been observed. Tetrahydrofuran may be replaced by acetonitrile with a negligible effect on yields. Reactions usually

require 2-4 hours for completion. Electron releasing substituents enhance the reaction rate while the opposite effect is observed for electron withdrawing substituents. Prolonged reaction times increase the amounts of byproducts, particularly formation of the corresponding 2-methoxymethylphenol derivatives.[6]

Some representative examples of salicylaldehydes prepared by this method are compiled in the Table, and a recent reference presents further examples.[9]

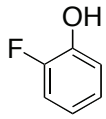
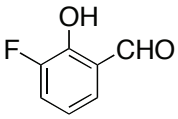
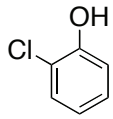
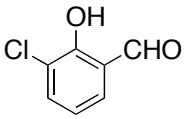
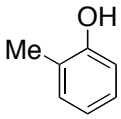
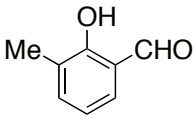
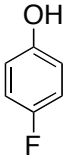
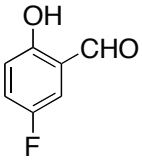
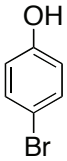
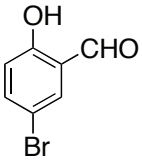
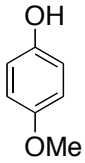
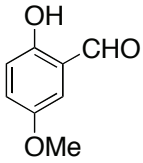
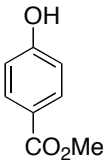
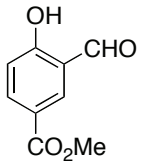
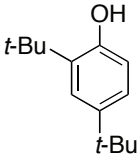
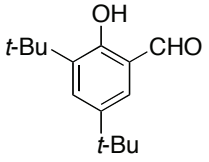
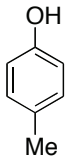
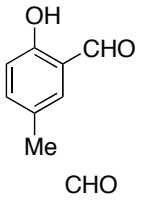

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**8.** Hansen, T. V.; Skattebøl, L. *Tetrahedron Lett.* **2005**, *46*, 3829.
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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Triethylamine: Ethanamine, *N,N*-diethyl- (9); (121-44-8)
Paraformaldehyde (9); (30525-89-4)
2-Bromophenol: benzene, 2-bromo-1-hydroxy- (9); (95-56-7)
Magnesium chloride (8); (7786-30-3)
3-Bromosalicylaldehyde: benzaldehyde, 2-hydroxy-3-bromo- (9); (1829-34-1)

**TABLE**

**ORTHO FORMYLATION OF PHENOLS AND NAPHTHOLS WITH $MgCl_2$/PARAFORMALDEHYDE**

| Phenol | Salicylaldehyde | Yield[Ref] |
|---|---|---|
|  |  | 80%[7] |
|  |  | 87%[6] |
|  |  | 99%[6] |
|  |  | 85%[7] |
|  |  | 91%[7] |
|  |  | 87%[6] |
|  |  | 88%[6] |
|  |  | 84%[8] |
|  |  | 90%[6] |