



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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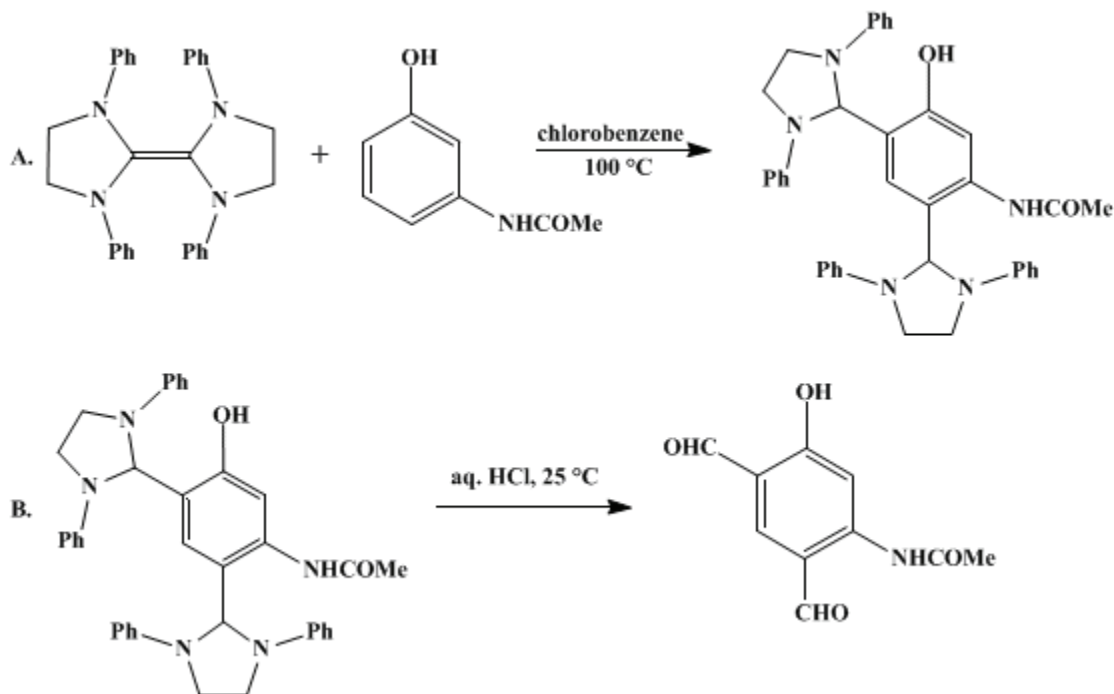
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 7, p.162 (1990); Vol. 60, p.49 (1981).

***N*-(2,4-DIFORMYL-5-HYDROXYPHENYL)ACETAMIDE**

[Acetamide, *N*-(2,4-diformyl-5-hydroxyphenyl)-]



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Checked by G. Saucy, Harvey Gurien, and Gerald Kaplan.

1. Procedure

A. *N*-[2,4-Bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide. A 500-mL, three-necked flask equipped with nitrogen inlet, mechanical stirrer, reflux condenser, and thermometer is charged with 88.8 g (0.2 mol) of 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene (Note 1) and 30.2 g (0.2 mol) of 3-acetamidophenol (Note 2). The system is flushed with and maintained under nitrogen, and 100 mL of chlorobenzene (Note 3) is added. The suspension is stirred at 100°C for 6 hr (Note 4). 2-Propanol (250 mL) is added to the hot mixture, which is then allowed to cool to room temperature. A pale-yellow solid precipitates which is filtered and washed with 200 mL of 2-propanol. Drying in vacuum affords 84.6–93.2 g (71–78%) of *N*-[2,4-bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide, mp 254–256°C (Note 5).

B. *N*-(2,4-Diformyl-5-hydroxyphenyl)acetamide. A suspension of 95 g of the phenol (prepared as described under Section A) (Note 6) in 1 L of aqueous 10% hydrochloric acid is stirred for 2 hr at room temperature. The colorless solid (Note 7) is filtered by suction and twice suspended in water at 40°C. Final filtration is followed with a water wash (1 L, 40°C), and the solid is sucked down on the filter. Crystallization from 800 mL of acetonitrile affords 21.8–22.3 g (66–67.5%) of *N*-(2,4-diformyl-5-hydroxyphenyl)acetamide, mp 215–217°C (Note 8).

2. Notes

1. This material was prepared by the procedure of H. W. Wanzlick, *Org. Synth., Coll. Vol. V* 1973, 115.
2. The checkers purchased 3-acetamidophenol from Aldrich Chemical Company, Inc.
3. The chlorobenzene was dried by azeotropic distillation.
4. The submitters checked the reaction progress by adding chloroform to an aliquot of the reaction

mixture and observing it under long-wavelength UV light (350 nm). A bright fluorescence indicated incomplete reaction. The checkers found that further heating did not eliminate the fluorescence or improve the yield. Adding 1-g quantities of the phenol resulted in quenching of the fluorescence but a lower yield.

5. The product showed the following spectroscopic properties: ^1H NMR (d_7 -DMF) δ : 1.92 (s, CH_3), 3.5–4.1 (m, 8 H, NCH_2), 6.05 (s, 1 H), 6.36 (s, 1 H), 6.5–7.5 (m, 23 H), 9.13 (s, 1 H).

6. The phenol should be ground in a mortar to eliminate lumps.

7. The checkers always obtained pale-yellow material.

8. The product had the following spectroscopic properties: IR (KBr) cm^{-1} : 1659, 1644, 1620; ^1H NMR (d_7 -DMF) δ : 2.24 (s, CH_3), 8.22 (s, 1 H), 8.24 (d, $J < 1$ Hz, 1 H), 9.87 (d, $J < 1$ Hz, 1 H), 10.16 (s, 1 H), 11.35, 12.05 (2s, OH, NH).

3. Discussion

The reaction of 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene with phenols illustrated in this procedure is a general method for the preparation of phenolaldehydes.² Table I gives the aldehydes that have been prepared by conditions similar to those described here.

Nitrogen-containing heterocyclic compounds such as indoles and imidazoles are also formylated by the electron-rich olefin. 3-Methylimidazole-5-carboxaldehyde can be prepared from 2-methylimidazole (yield 83%) and 2-phenylindole-3-carboxaldehyde from 2-phenylindole (yield 64%).

TABLE I
ALDEHYDES FROM PHENOLS AND 1,1',3,3'-TETRAPHENYL-2,2'-
BIIMIDAZOLIDINYLIDENE

Aldehyde	Yield (%)	
	Imidazolidin-2-yl-phenolHydrolysis	
4-Hydroxybenzaldehyde	55	88
4-Hydroxy-3,5-dimethylbenzaldehyde	58	80
3-Cyclohexyl-5-methylsalicylaldehyde	43	80
4-Dimethylamino-5-methylsalicylaldehyde	65	54
4-Dimethylaminosalicylaldehyde	52	90
Resorcinol-2,4,6-tricarboxaldehyde	43	96
4-Hydroxy-5-methoxyisophthalaldehyde	55	81
4-Hydroxy-6-methoxyisophthalaldehyde	57	87
Pyrogallol-4,6-dicarboxaldehyde	82	50
8-Hydroxyquinoline-7-carboxaldehyde	76	69

The formylation of phenols with the electron-rich olefin to give imidazolidin-2-yl-phenols is very selective and avoids mixtures of *o*- and *p*-isomers, which are frequently obtained by methods commonly employed for the synthesis of phenolaldehydes. Para substitution of the cyclic aminal group in the phenol is preferred. If the *p*-position is blocked or sterically hindered, the reaction proceeds via the *ortho*-aminals to salicylaldehydes. Incorporation of more than one aldehyde group in the benzene nucleus is often achieved with hydroxy- and aminophenols.

Reaction of phenols bearing strong electron-withdrawing substituents such as dichlorophenols and nitrophenols with 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene results in poor yields. Oxidation of the electron-rich olefin by nitro compounds is also possible.

References and Notes

1. Wissenschaftliches Hauptlaboratorium der BAYER AG, D-5090 Leverkusen-Bayerwerk, Germany.
 2. Hocker, J.; Merten, R. *Angew. Chem.* **1972**, *84*, 1022–1031; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 964–973; Hocker, J.; Giesecke, H.; Merten, R. *Angew. Chem.* **1976**, *88*, 151; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 169–170; Giesecke, G.; Hocker, J. *Justus Liebigs Ann. Chem.* **1978**, 345–361.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

indoles

imidazoles

3-Cyclohexyl-5-methylsalicylaldehyde

imidazolidin-2-yl-phenols

salicylaldehydes

dichlorophenols

nitrophenols

hydrochloric acid (7647-01-0)

acetonitrile (75-05-8)

chloroform (67-66-3)

phenol (108-95-2)

nitrogen (7727-37-9)

chlorobenzene (108-90-7)

2-propanol (67-63-0)

2-Phenylindole (948-65-2)

3-acetamidophenol (621-42-1)

3-Methylimidazole-5-carboxaldehyde

4-Hydroxybenzaldehyde (123-08-0)

4-Hydroxy-3,5-dimethylbenzaldehyde (2233-18-3)

4-Dimethylamino-5-methylsalicylaldehyde

4-Dimethylaminosalicylaldehyde

Resorcinol-2,4,6-tricarboxaldehyde

4-Hydroxy-5-methoxyisophthalaldehyde

4-Hydroxy-6-methoxyisophthalaldehyde

Pyrogallol-4,6-dicarboxaldehyde

8-Hydroxyquinoline-7-carboxaldehyde

2-methylimidazole (693-98-1)

2-phenylindole-3-carboxaldehyde (25365-71-3)

N-(2,4-Diformyl-5-hydroxyphenyl)acetamide,
Acetamide, N-(2,4-diformyl-5-hydroxyphenyl)- (67149-23-9)

N-[2,4-Bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide (67149-22-8)

1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene (2179-89-7)

Imidazolidin-2-yl-phenol