



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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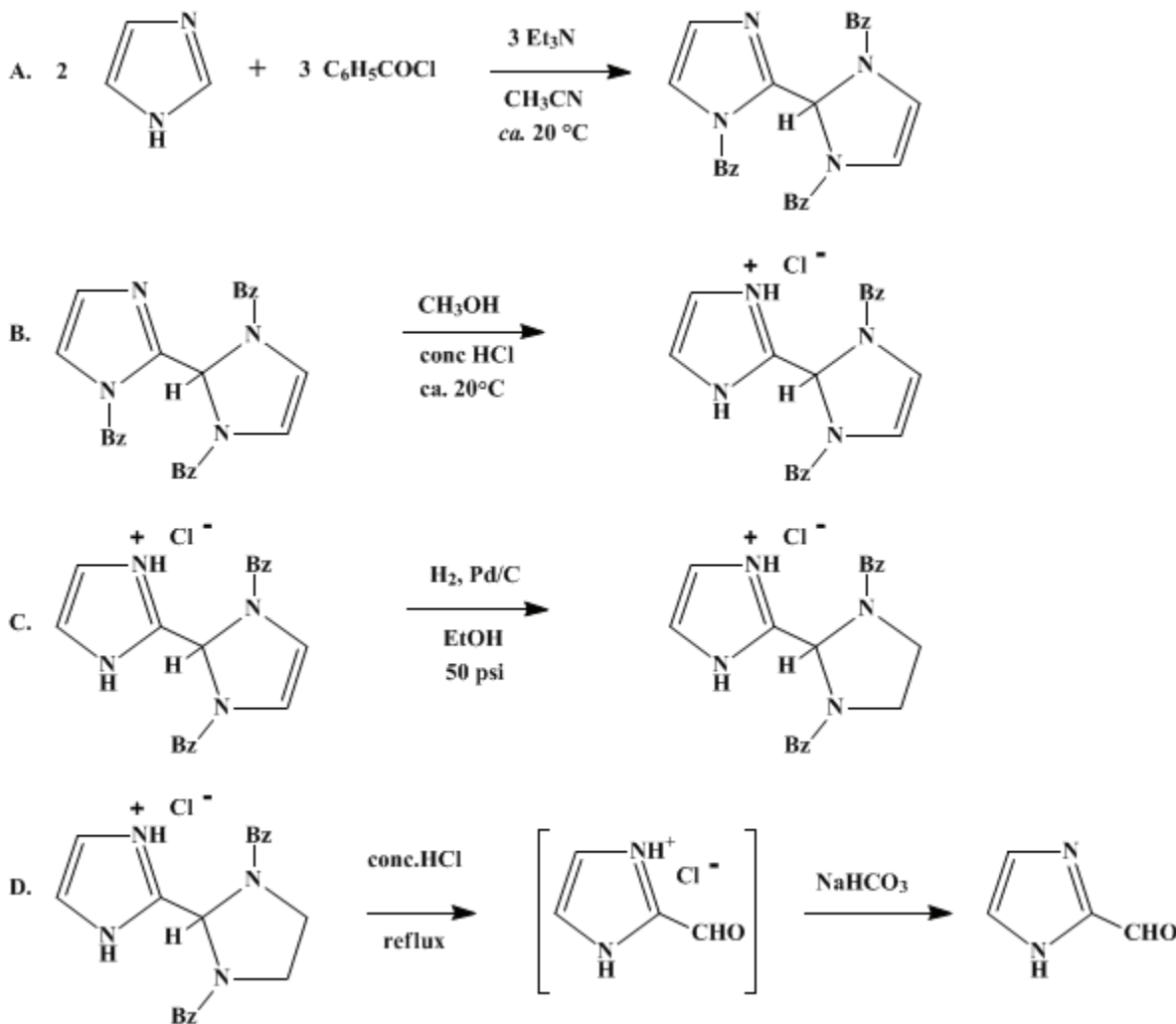
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 7, p.287 (1990); Vol. 60, p.72 (1981).

IMIDAZOLE-2-CARBOXALDEHYDE

[1*H*-Imidazole-2-carboxaldehyde]



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1. Procedure

A. *1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolyl)imidazole*.² A 12-L, wide-mouthed, round-bottomed vessel fitted with an efficient air-driven stirrer and thermometer is charged with 68 g (1.0 mol) of imidazole (Note 1), 202 g (2 mol) of triethylamine (Note 2), and 1000 mL of acetonitrile (Note 3). To the mixture is added dropwise over a 1-hr period and with external cooling 281 g (2.0 mol) of benzoyl chloride (Note 2), the temperature is maintained at 15–25°C. After addition is complete, stirring is continued for another hour at ambient temperature. With continued stirring 1 L of ether and 5 L of water are introduced, whereupon the temperature is brought to 5°C. The crystalline product is removed by filtration and is sucked dry with the aid of a rubber dam. Rinsing of the filtercake with, successively, water, acetone, and ether gives, on air-drying, 181–190 g (80–85%) of product, mp 197–198°C (Note 4). This product (5 g), taken up in 50 mL of boiling 90% dimethylformamide diluted while hot with water to the cloud point, gives, on cooling, 4.5 g of analytically pure stout prisms, mp 202–203°C (Note 5).

B. *2-(1,3-Dibenzoyl-4-imidazolin-2-yl)imidazole hydrochloride*.³ Into a 3-L beaker equipped with an air-driven stirrer are successively introduced 150 g (0.335 mol) of dry, unrecrystallized *1-benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole*, 500 mL of technical-grade *methyl alcohol*, and 30 mL of concentrated *hydrochloric acid*. The mixture is stirred as the solids gradually dissolve. After 1 hr a clear yellow solution results, which is allowed to stand for another 5 hr, during which time white solid product begins to precipitate. Technical *diethyl ether* (1500 mL) is next added, and the mixture is allowed to stand overnight. Filtration and rinsing of the crystals with fresh *ether* and ultimate air drying furnish 114–119 g (89–93%) of product, mp 238–239° C (Note 6). Analytically pure material, obtained on recrystallizing a small sample from *methyl alcohol-ether*, has mp 240–241° C

C. *2-(1,3-Dibenzoylimidazolidin-2-yl)imidazole hydrochloride*.³ A 1000-mL Parr hydrogenation bottle is charged with 38.0 g (0.10 mol) of dry, unrecrystallized *2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole hydrochloride* suspended in 300 mL of 95% reagent-grade *ethyl alcohol*. Then 2 g of 10% *palladium on carbon* (Note 7) is cautiously added (Note 8). The reaction vessel is now attached to the Parr hydrogenator and, after alternate evacuation and flushing with *hydrogen* gas, is shaken under a 50-psi atmosphere of *hydrogen*. Gas uptake ceases after absorption of 1 mol-equiv per mole of substrate; this requires ca. 2 hr. The catalyst is removed by vacuum filtration through Hyflow, the filtercake is rinsed with three portions of 95% *ethyl alcohol* (Note 9), and the filtrate is stripped to leave solid, impure product. This is triturated with 200 mL of ice-cold *acetone*; filtration and rinsing of the solids with fresh *acetone* and ultimately with *ether* yield 33.2–35.8 g (87–94%) of air-dried material, mp 225–226° C (Note 10). An analytically pure sample from *isopropyl alcohol-ether* melts at 225–226° C.

D. *Imidazole-2-carboxaldehyde*.³ A solution of 19.1 g (0.05 mol) of dry, unrecrystallized *2-(1,3-dibenzoylimidazolidin-2-yl)imidazole hydrochloride* in 200 mL of concentrated *hydrochloric acid* is refluxed for 22 hr (Note 11). The mixture is then chilled on ice, causing deposition of *benzoic acid*, which is removed by filtration (Note 11). The filtrate, on evaporation, leaves a residue that is first digested with 100 mL of 95% *ethyl alcohol* and then cooled on ice. The remaining solids are essentially pure *ethylenediamine dihydrochloride* and are filtered off (Note 12). Filtrate solvent is again removed under reduced pressure to leave solid residue. This is dissolved in 40 mL of water. Addition of solid *sodium bicarbonate* until foaming ceases causes *imidazole-2-carboxaldehyde* to crystallize. The mixture is chilled on ice, and the product is filtered and washed with ice-water to give, after thorough drying, 3.2–3.7 g (67–77%) of beige crystals, mp 206–207° C. Analytical material, prepared from water, has mp 206–207° C (Note 13).

2. Notes

1. *Imidazole* is a bulk chemical available from the Badische Anilin- & Sodafabrik AG, 6700 Ludwigshafen/Rhein, West-Germany. The checkers used Aldrich *imidazole*, 99%, from Aldrich Chemical Company, Inc.
2. *Triethylamine* and *benzoyl chloride*, both 99.5% pure, were purchased from Fluka. The checkers used material from Aldrich Chemical Company, Inc.
3. *Acetonitrile*, 99%, was obtained from Aldrich-Europe, B-2340 Beerse, Belgium.
4. Observing the theoretical stoichiometry, i.e., 2 equiv of *imidazole* and 3 equiv each of *benzoyl chloride* and *triethylamine*, resulted in significantly lower product yields.
5. The ¹H NMR spectrum (CDCl₃) corresponded to that in the literature²: δ 6.43 (s, 2, vinyl protons), 7.07 (t, 2, imidazole protons), 8.05 (s, 1, methine proton). Analysis calculated for C₂₇H₂₀N₄O₃: C, 72.31; H, 4.49; N, 12.49. Found: C, 72.27; H, 4.54; N, 12.53.
6. The checkers obtained variable melting points that were accompanied by decomposition and depended on the rate of heating. ¹H NMR (CD₃OD) δ: 6.57 (s, 2), 7.50 (m, 13, aromatic protons). Analysis calculated for C₂₀H₁₆N₄O₂ · HCl: C, 63.07; H, 4.56; N, 14.71. Found: C, 63.02; H, 4.60; N, 14.79.
7. Merck-Schuchardt "Hydrierkatalisator," purchased from E. Merck, Darmstadt. The checkers used Pd/C from Alfa Products, Morton Thiokol Inc.
8. Direct introduction of a dry hydrogenation catalyst into an alcoholic system has been known to bring about spontaneous ignition. This risk may be obviated by addition of a slurry of 2.0 g of catalyst in 15 mL of water to the substrate in 285 mL of absolute *ethyl alcohol*.
9. Filtercakes of fresh, spent hydrogenation catalysts are known to be pyrophoric and should not be

sucked completely dry.

10. The checkers obtained an oily foam that remained oily on adding cold [acetone](#). The oily material became solid on adding and evaporating [benzene](#) (2 × 100 mL). The checkers obtained variable melting points accompanied by decomposition. ¹H NMR (CD₃OD) included an *AA' BB'* system centered around δ 4.17 (4, CH₂CH₂). Analysis calculated for C₂₀H₁₈N₄O₂·HCl: C, 62.74; H, 5.00; N, 14.64. Found: C, 62.96; H, 4.98; N, 14.42.

11. [Benzoic acid](#) sublimes into the condenser and will plug a small-bore condenser.

12. The [benzoic acid](#) and [ethylenediamine dihydrochloride](#) isolated after the cited reaction time amount to ca. 90%.

13. [Imidazole-2-carboxaldehyde](#) has been reported to melt at 204°C,⁴ 195–205°C,⁵ 195°C,⁶ 202°C,⁷ and 190–196°C.⁸ The material prepared has an ¹H NMR spectrum corresponding to that of the literature⁸: δ 7.43 (s, 2, imidazole protons), 9.67 (s, 1, CHO). Analysis calculated for C₄H₄N₂O: C, 49.99; H, 4.19; N, 29.16. Found: C, 50.05; H, 4.26; N, 28.96.

3. Discussion

Synthesis of [imidazole-2-carboxaldehyde](#) has previously been reported by [manganese dioxide](#) oxidation of the corresponding carbinol,⁴ by acid-promoted cyclization of *N*-(2,2-diethoxyethyl)-2,2-diethoxyacetamide,⁵ and by methods centering around formylation of appropriately protected 2-imidazolelithium reagents.^{6,7} The present method constitutes an optimization of the route recently reported from our laboratories.³ Inexpensive, commercially available bulk chemicals are utilized to give [imidazole-2-carboxaldehyde](#) via high-yield processes mostly in open vessels and at ambient temperatures. All products are isolated directly from the reaction mixtures in a high state of purity without resorting to extractions, distillations, or recrystallizations. The by-products, [benzoic acid](#) and [ethylenediamine dihydrochloride](#), are recovered in nearly quantitative yields. Waste and environmental pollution are kept to a minimum.

References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

[ethyl alcohol](#) (64-17-5)

[hydrochloric acid](#),
[HCl](#) (7647-01-0)

[Benzene](#) (71-43-2)

[methyl alcohol](#) (67-56-1)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

Benzoic acid (65-85-0)

acetone (67-64-1)

carbon (7782-42-5)

benzoyl chloride (98-88-4)

isopropyl alcohol (67-63-0)

palladium (7440-05-3)

manganese dioxide (1313-13-9)

dimethylformamide (68-12-2)

Imidazole (288-32-4)

triethylamine (121-44-8)

Imidazole-2-carboxaldehyde,
1H-Imidazole-2-carboxaldehyde (10111-08-7)

1-benzoyl-2-(1,3-dibenzoyl-4-imidazolyl) imidazole,
1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolyl)imidazole (62457-77-6)

2-(1,3-dibenzoyl-4-imidazolyl)imidazole hydrochloride (65276-00-8)

2-(1,3-dibenzoylimidazolylidyl) imidazole hydrochloride,
2-(1,3-Dibenzoylimidazolylidyl)imidazole hydrochloride (65276-01-9)

ethylenediamine dihydrochloride (333-18-6)

2-imidazolelithium

N-(2,2-diethoxyethyl)-2,2-diethoxyacetamide