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AN EFFICIENT, SIMPLE SYNTHESIS OF 4-AZIDOBENZALDEHYDE

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ABSTRACT. A three-pot synthesis of 4-azidobenzaldehyde from 4-nitrobenzaldehyde in overall yield of 71% is described. The new synthesis is superior in its ease of reproducibility and reduction of waste side products.

In the course of work involving the synthesis of a variety of aziodoarenes, we had occasion to require considerable quantities of 4-azidobenzaldehyde, (**1**). Although this has been accomplished by other workers, we found standard synthetic techniques to be not only fairly tedious and time consuming, but productive of considerable amounts of waste side products. We therefore set out to devise a synthesis of 4-azidobenzaldehyde that is convenient to run and gives high yields. The synthetic procedure described below fulfills these criteria.

One published synthesis for (**1**) involves reduction of 4-aminobenzoic acid to 4-aminobenzyl alcohol, diazotization/azidification, and finally reoxidation of the alcohol to yield the desired product.[1] The reported yields of these steps from the acid are 61%, 71%, and 63%, for an overall yield of 27%. The final product (**1**) may then purified by column chromatography.

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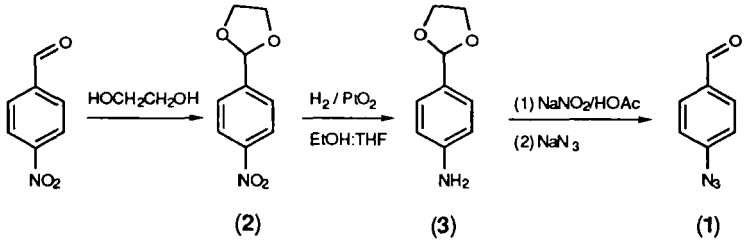
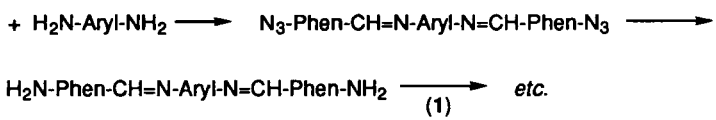


FIG. 1
Synthesis of 4-azidobenzaldehyde.

A more common route to synthesis of (1) has been via Sandmeyer azidification of 4-aminobenzaldehyde,[2] which is available by a one-pot conversion from 4-nitrotoluene described by Campaigne, Budde, and Schaefer.[3] It is possible by this route to make multigram amounts of aminobenzaldehyde, but the reaction is often plagued by considerable amounts of polymer formation, even with the best of care. The reaction is fairly messy in the workup, given that the yield of 4-amino-benzaldehyde is 40-50% based on the starting material and "contains some impurities".[3] Thus, although the overall process from 4-nitrotoluene to 4-azidobenzaldehyde involves cheap staring materials, we hoped to identify a more convenient and high yield route.

Our synthesis of (1) is summarized in Figure 1. Commercially available 4-nitrobenzaldehyde is protected as the ethylene acetal, catalytically reduced to the amine, then diazotized/azidified/deprotected in a single, final step to give the product. The overall yield is 71% from 4-nitrobenzaldehyde. The final product has excellent purity by ^{1}H-NMR and IR spectroscopy. We do not distill it in order to avoid possible explosion hazards, but have found it quite pure enough to use in a variety of reactions even without chromatography. In addition, this synthesis allows easy differentiation of the amino and aldehyde moieties of 4-amino-

benzaldehyde. The azide is an amine synthon which is readily converted by reduction with lithium aluminum hydride[5] or by reaction with triphenylphosphine followed by hydrolysis.[6] For example, one could achieve synthesis of polyhydrazones with controlled degree of oligomerization by use of (**1**) as an



effective amino-aldehyde synthon. We have already found (**1**) to be useful for chemical strategies related to this. Alternatively, the amino acetal intermediate (**3**) could be used to carry out amine coupling reactions prior to release of the aldeyhde by deprotection. Such chemistry would require some caution, since (**3**) is rather sensitive to trace amounts of acid, in the presence of which it gives polymeric materials presumably derived from self-condensation of deprotected 4-aminobenzaldehyde.

Overall, the procedure summarized in Fig. 1 and described in the experimental section is a convenient, high-yield method to make 4-azidobenzaldehyde, a useful intermediate for synthesis of organic azides and a good amino-aldehyde synthon. Multigram quantities of product are readily made from commercially available 4-nitrobenzaldehyde in a short time with a considerable reduction in the waste stream that is attendant on previous methods of making (**1**).

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Experimental Procedures. 4-Nitrobenzaldehyde was obtained from Aldrich Chemical Company. Other solvents and reagents were commercially obtained and used without further purification.

2-(4-Nitrophenyl)-<1,3>dioxolane (2). 4-nitrobenzaldehyde (15.1 g, 0.1 mol) and 150 mL of benzene were placed in a 250 mL round-bottomed flask fitted with a reflux condenser and Dean-Stark trap, then heated with mechanical stirring to dissolve the aldehyde. A small amount (0.5 g) of *p*-toluenesulfonic acid monohydrate plus 55.8 mL of ethylene glycol were added to the flask. Heat was continued at reflux for 3 h. After cooling, the reaction was extracted with a saturated solution of $NaHCO_3$, treated with decolorizing charcoal, dried over anhydrous sodium sulfate, and the organic layer contentrated on a rotary evaporator.

The product is 18.2 g of a white powder (93%). This material is sufficiently pure for use in the subsequent step. Further purification may be performed by heating this product in pentane, adding hot ethyl acetate to finish dissolving the sample, and cooling to yield white needles of (2) with a melting point of 90-91 °C (lit mp 90.5°C).[4] ^{1}HNMR($CDCl_3$, 200 MHz): δ 8.2 (AB d, J = 8.7 Hz, 2H, Ar-H ortho to NO_2), 7.6 (AB d, J = 8.7 Hz, 2H, Ar-H ortho to acetal), δ 5.9 (s, 1H, acetal O-CH-O), δ 4.1 (s, 4H, O-CH_2).

4-<1,3>dioxolan-2-yl-benzeneamine (3). Compound (2) (18.2 g, 93.4 mmol) was dissolved in 200 mL of a 1:1 mixture of ethanol:tetrahydrofuran and placed in a Parr pressure bottle. More tetrahydrofuran may be added as needed to dissolve all of the compound. Platinum (IV) oxide (ca. 200 mg) was added, and the Parr bottle was sealed and shaken under 50 psi of hydrogen gas for 5 h. The reaction dried over anhydrous sodium sulfate, filtered through Celite, and the filtrate concentrated using a rotary evaporator. The crude product (3) is a yellow oil (15.7 g, 95%). This material is sufficiently pure to use in the subsequent step, and has spectral data in agreement with those in the literature.[7] It is best to proceed as soon as possible to the next step, else polymerization of the product occurs through apparent slow deprotection of the acetal. ^{1}H NMR ($CDCl_3$, 80 MHz): δ 7.3 (AB

d, J = 8.4 Hz, 2H, Ar-H ortho to acetal), 6.7 (AB d, J = 8.5 Hz, 2H, Ar-H ortho to NH_2), 5.7 (s, 1H, O-CH-O), 4.0 (m, 4H, O-CH_2), 3.7 (br, 2H, NH_2).

4-Azidobenzaldehyde (1). Compound (3) (15.7 g, 95 mmol) was added to 50 mL of cooled glacial acetic acid containing 5 mL of concentrated sulfuric acid, yielding a black, tarry solid. Keeping the reaction mixture below 10°C, a solution of sodium nitrite (6.5 g, 94 mmol) in a minimum amount of cold water was then added dropwise with stirring to yield a yellow solution. After 10 min., a solution of sodium azide (6.5 g, 100 mmol) in a minimum amount of cold water was added dropwise, during which copious frothing occurred. The reaction was allowed to warm to room temperature and diluted with 50 mL of water to deprotect aldehyde. The reaction was extracted with ether and the combined ether layers washed with saturated aq. $NaHCO_3$. The organic layer was dried over anhydrous sodium sulfate and concentrated in minimal laboratory light using a rotary evaporator at less than 40°C to yield (1) as a dark orange oil (10.4 g, 84%). The product may be stored in the dark at ≤10°C for many weeks without appreciable decomposition based upon ^{1}H-NMR and IR spectral analysis. All spectral characterization is in accord with information listed in the literature for this compound.[8] For this product without further purification, Anal. Calcd for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 59.15; H, 4.21; N, 26.84. Greater purity with limited loss of sample mass may be realized through simple column chromatography (chloroform on silica gel, then 1:1 chloroform:hexane on silica gel) to give Anal. Found: C, 57.56; H, 3.67; N, 27.81. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.9 (s, 1H, CH=O), 7.9 (AB d, J = 8.6 Hz, 2H, Ar-H ortho to CH=O), 7.1 (AB d, J = 8.6 Hz, 2H, Ar-H ortho to N_3). IR (neat): 2100 cm^{-1} (N_3). The phenylanilino derivative Ph-N=CH-*p*-C_6H_4-N_3 has mp 60-62 °C (lit.[9] mp 52-55 °C); Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 69.99; H, 4.33; N, 25.09.

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