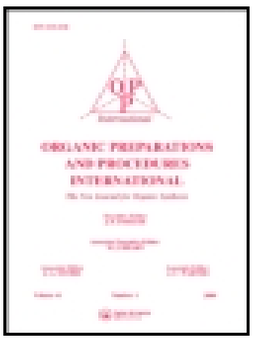

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MODIFIED SYNTHETIC ROUTE TO 2-HYDROXYIMINO-N-ARYLACETAMIDES

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(10/15/03)

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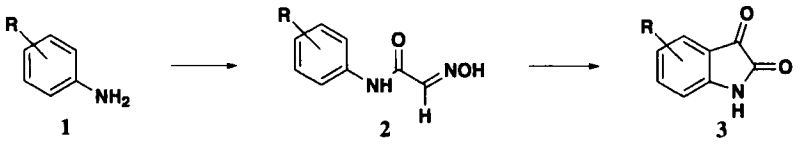
During the course of another investigation, we required several 2-hydroxyimino-N-arylacetamides **2** (isonitrosoacetanilides) as intermediates leading to substituted isatins **2** (indole-2,3-diones). The venerable two-step Sandmeyer reaction is most frequently utilized for the preparation of isatins.[1-7]



The standard preparation of aryl 2-hydroxyimino-N-arylacetamides **2** involves treatment of the corresponding substituted anilines **1** with chloral hydrate in the presence of hydroxylamine hydrochloride. Acid treatment of **2** leads to the isatins **3**. The problem in the first step is the availability of chloral hydrate, which is a Drug Enforcement Agency controlled substance (DEA Schedule 4).[8-10] To circumvent this problem, we report the use of the commercially available 2,2,2-trichloro-1-ethoxyethanol (ethyl hemiacetal of chloral)[11] instead of chloral hydrate.

Treatment of the hydrochlorides of *o-, m- and p*-toluidines **1** with 2,2,2-trichloro-1-ethoxyethanol in water in the presence of sodium sulfate and hydroxylamine hydrochloride led to good yields of the desired 2-hydroxyiminoacetamides **2** in 50%, 62% and 64% yields, respectively.

This procedure may be adaptable to the synthesis of other substituted 2-hydroxyiminoacetamides and future studies will expand on this finding.

EXPERIMENTAL SECTION

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker ARX-500 pulsed spectrometer with tetramethylsilane as an internal standard.

Preparation of 2-Hydroxyimino-N-*m*-tolylacetamide. Typical Procedure.- Sodium sulfate (57 g) was added to a stirred solution of 2,2,2-trichloro-1-ethoxyethanol (10.5 g, 54.4 mmol) in 120 mL of water and 1 mL of concd. HCl. After complete dissolution of the sodium sulfate, a solution obtained by adding *m*-toluidine (4.50 g, 42.0 mmol) to 30 mL of water and 5.5 mL of

conc HCl was added. To the brown turbid mixture, a solution of $NH_2OH{\cdot}HCl$ (11.0 g, 158.3 mmol) in 50 mL of water was added. After addition of 10 mL of EtOH, the solution was heated at 80°C with stirring for 3 h. The brown solid which separated was collected by filtration of the hot mixture. The filtrate on cooling afforded 1.95 g of white plates. The brown residue was heated with water/EtOH and the insoluble material removed by filtration. The filtrate on cooling yielded 2.70 g of slightly beige crystals (total yield 4.65 g, 62%); mp 152-154°C , *lit.*[1] 146° C.

^{1}H-NMR (DMSO-d_6): δ 12.10 (s, 1H), 10.01 (s, 1H), 7.65 (s, 1H), 7.51 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 2.29 (s, 3H).

^{13}C-NMR (DMSO-d_6): δ 160.0, 149.9, 138.2, 137.8, 128.4, 124.4, 120.3, 116.9, 21.0.

2-hydroxyimino-N-*o*-tolylacetamide: mp 126-128°C, *lit.*[1] 121°C, 50% yield.

^{1}H-NMR (DMSO-d_6): δ 12.16 (s, 1H), 9.47 (s, 1H), 7.69 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H), 2.21 (s, 3H).

^{13}C-NMR (DMSO-d_6): δ 160.3, 143.8, 135.5, 131.8, 130.2, 125.9, 125.5, 124.8, 17.6.

2-hydroxyimino-N-*p*-tolylacetamide: mp 149-151°C, *lit.*[1] 162°C, 64% yield.

^{1}H-NMR ($CDCl_3$): δ 8.17 (br s, 1H), 7.85 (s, 1H), 7.58 (s, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 2.33 (s, 3H).

^{13}C-NMR (DMSO-d_6): δ 159.9, 144.0, 135.8, 132.8, 129.0, 119.8, 20.4.

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A VERSATILE AND CONVENIENT SYNTHESIS OF ALKYL NITROAROMATIC ETHERS BY NUCLEOPHILIC AROMATIC SUBSTITUTION

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One of our current projects required a series of allyl 2-nitroaromatic ethers as substrates for a new synthesis of benzoxazines.[1] During the preparation of several of these substrates, we found that conversion of the required allylic alcohol to the bromide and *O*-alkylation of 2-nitrophenol under basic conditions gave low yields of the desired products. We, therefore, sought a more direct approach involving nucleophilic substitution of an allylic alkoxide on 2-fluoro-1-nitrobenzene. Nucleophilic aromatic substitution of alkoxides and phenoxides on fluoronitroaromatics has recently found wide use in the synthesis of both natural[2] and unnatural[3] products. A number of the protocols that can be used for this transformation, however, have limitations with respect to the alcohols that will react[2,3a-d] or the cost of reagents.[3e] Typical conditions include CsF in DMSO (for phenols[2a-d]), KOH in PhOH (for phenol itself[3a-b]), K_2CO_3 in DMF (for 1° allylic, propargylic and benzylic alcohols[3c-d] as well as phenols[2]), potassium hexamethyldisilazide (KHMDS) in THF (for 3°, and presumably 1° and 2° alcohols[3e]), and NaH in DMF (for 1° alcohols[4a-c] and phenols[4d]). Of these five procedures, the last two appear to be the most versatile, though KHMDS is considerably more expensive than NaH. To date, no single set of conditions has been used to promote substitutions of all types of alcohols. Thus, in addition to our own target molecules, we wished to explore the possibility of optimizing one protocol applicable to the synthesis of a variety of alkyl nitroaromatic ethers. We report here a general procedure using NaH in DMF that permits the substitution of primary, secondary and tertiary alcohols as well as phenols to 2- and 4-fluoronitrobenzenes.