Synthesis of *N*,*O*-Diacetylated *N*-Arylhydroxylamines by Reduction of Nitroaromatics with Zinc and Acetic Anhydride†

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Reduction of nitroaromatic compounds with zinc and acetic anhydride in dichloromethane gave *N*,*O*-diacetylated *N*-arylhydroxylamines in good yields under mild conditions.

Esters of *N*-hydroxy-*N*-arylacetamides, such as ArN(OR)-COMe (**1a**; R = COMe, **1b**; R = SO_3^-), are considered to be the reactive metabolites of mutagenic and carcinogenic aromatic amides.[1] In spite of their biological interest, useful preparative methods for **1** were not well-established. While the direct chemical reductive diacetylation of nitroarene was not successful,[2,3] the electrochemical reduction of both aliphatic and aromatic nitro or nitroso compounds in aprotic media with Ac_2O produced *N*,*O*-diacetylated hydroxylamines in yields from 40 to 80%.[4] We now wish to report on the study of an efficient chemical method for the one-pot *N*,*O*-diacetylation of nitroaromatics by using zinc dust and Ac_2O in an aprotic solvent under mild conditions.

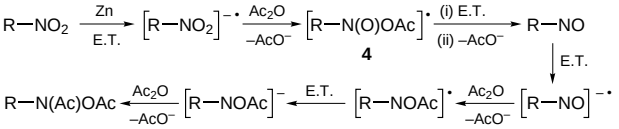
Nitrobenzene (1 mmol), when treated with acetic anhydride (4 mmol) and Zn (5 mmol) in CH_2Cl_2 at room temperature for 50 min, gave *N*,*O*-diacetylated *N*-phenylhydroxylamine, PhN(OAc)Ac, in 87% yield along with 5% of acetanilide (Table 1, entry 1). Surprisingly, reduction to aniline was barely observed on GLC. In protic solvents such as methanol, the acetylation reaction was completed within 25 min at 0 °C to give PhN(OAc)Ac in 71% yield and acetanilide in 7%. For the desired *N*,*O*-diacetylated *N*-phenylhydroxylamine, the aprotic solvent dichloromethane showed better yield than the protic methanol medium in all cases even though it proceeded more slowly at relatively higher reaction temperatures.

The formation of nitrosobenzene was observed by GC-MS analysis during the reductive acetylation of nitrobenzene. To verify the intermediate step of the reaction, we carried out the same reaction with nitrosobenzene in place of nitrobenzene, and diacetylated product **2a** was obtained in 95% yield and a trace amount of monoacetylated product **3a** was detected on GLC (Table 1, entry 2). Therefore acetylations of nitroaromatics to **2** and **3** seem to proceed through nitrosoaromatic intermediates.

We have extended the acetylation reaction to a variety of nitroaromatics and the results are summarized in Table 1. In most cases, diacetylations of nitroaromatics were successful with fair to excellent yields. It is worth mentioning that in the case of halo-substituted nitroarene the corresponding diacetylated product was obtained in high yield without giving any dehalogenated products (Table 1, entries 6, 8), which are frqeuently encountered problems in electrochemical methods. Not only for nitroarene derivatives but also for nitropyridine, the diacetylation product was obtained in high yield (Table 1, entry 8).

Upon reductive acetylation of 4-nitrophenol in the presence of Ac_2O (4 equiv.)/Zn (5 equiv.) in dichloromethane at room temperature (45 min), additional acetylation on the hydroxy group occurred to produce *p*-$AcOC_6H_4N$-(Ac)OAc (56%) and *p*-$AcOC_6H_4NHOAc$ (43%).

To manifest the direction of electron transfer from zinc to nitro functionality, the cyclic voltammetric behaviour of nitrobenzene and acetic anhydride was examined. In case of nitrobenzene the reductive wave was observed at −0.92 V (Pt cathode, 0.1 M TBAP/CH_2Cl_2, Ag/AgCl, 20 mV s^{-1}), which indicated that nitrobenzene could be a good electron acceptor. However, under the same cyclic voltammetric condi-



Scheme 1

Table 1 Reductive acetylation of nitroarenes or nitrosoarene in the presence of Ac_2O (4 equiv.)/Zn (5 equiv.) in CH_2Cl_2 at room temperature

$$R\text{–}NO_x + Ac_2O \longrightarrow \underset{\mathbf{2}}{R\text{–}N(Ac)OAc} + \underset{\mathbf{3}}{R\text{–}NHAc}$$

Entry	Substrate	Time (*t*/min)	Product (% yield)[a]	
1	Nitrobenzene	50	**2a** (87)	**3a** (5)
2	Nitrosobenzene	50	**2a** (95)	**3a** (tr)
3	2-Nitrotoluene	120	**2b** (73)	**3b** (27)
4	3-Nitrotoluene	50	**2c** (78)	**3c** (20)
5	4-Nitrotoluene	50	**2d** (85)[b]	**3d** (13)[b]
6	1-Bromo-3-nitrobenzene	50	**2e** (91)	**3e** (7)
7	2-Nitrofluorene	50	**2f** (83)[b]	**3f** (5)[b]
8	2-Chloro-5-nitropyridine	50	**2g** (93)	—

[a]GLC yield with an internal standard; [b]isolated yield.

ditions acetic anhydride did not exhibit any observable reduction wave. Thus, the reaction would be initialized as nitrobenzene accepts an electron. The possible reaction path is shown in Scheme 1. The radical anion of nitrobenzene gener-

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ated by the electron transfer from zinc to nitrobenzene may react rapidly as a nucleophile toward the acetic anhydride electrophile to form an intermediate, **4**. Following electron transfer, loss of the acetate anion could produce the nitroso intermediate. Through similar continuous electron transfer and acetylation, the nitroso intermediate may be transformed to an *N*,*O*-diacetylated *N*-arylhydroxylamine.

In conclusion, we have now established a mild and novel reaction route for *N*,*O*-diacetylated hydroxylamines by using $Ac_2O/Zn/CH_2Cl_2$, which would be a useful chemical method for the reductive diacetylation of nitroaromatics. As far as dehalogenation is concerned, our chemical method is superior to the electrochemical one.

Experimental

Most of the chemical reagents were purchased from Aldrich and used without further purification in most cases. Acetic anhydride was purchased from Duksan P. and purified by a standard method. Zinc powder was purchased from Junsei Chemical Co. and was used without further purification. Solvents were purchased and dried by the usual laboratory techniques. Solvents were deoxygenated before use by bubbling argon through them.

Analytical GC was performed on a Donam 6200 gas chromatograph equipped with a DB-1 column and Hitachi D-2500 integrator. ^{1}H NMR spectra were recorded on a 300 MHz Bruker instrument and ^{13}C NMR spectra were recorded on a 125 MHz Bruker instrument. Chemical shifts are in ppm from tetramethylsilane (TMS). High-resolution mass spectra (EI) were recorded on a Jeol JMS-DX 303 mass spectrometer. Infrared spectra (IR) were recorded on a Nicolet 205 FT-IR.

Most products were isolated by flash column chromatography on silica gel (70–230 mesh ATSM, Merck) with eluents of mixed solvents (hexane and ethyl acetate). GC yields were determined by using an internal standard (toluene) and were corrected with predetermined response factors.

General Procedure for the Diacetylation of Nitro- or Nitroso-aromatics.—Zinc powder (327 mg, 5 mmol) and CH_2Cl_2 (3 ml) were placed in a 20 ml vial equipped with a rubber septum. Acetic anhydride (0.38 ml, 4 mmol) was added to the reaction mixture followed by nitrobenzene (0.10 ml, 1 mmol). The mixture was stirred under nitrogen or argon at room temperature. It was then quenched with 10% NH_4Cl and extracted with CH_2Cl_2 (3×20 ml). The combined CH_2Cl_2 extract was dried over $MgSO_4$ and the solvent evaporated. The GC yield was determined with an internal standard and, if necessary, the products were isolated by flash column chromatography with ethyl acetate–hexane co-solvent. In general, δ_C (125 MHz, $CDCl_3$) for $OCOCH_3$ and $NCOCH_3$ of the following compounds were 167–168 and 165–166, respectively.

N-(*Acetyloxy*)-N-*phenylacetamide* (**2a**).—The compound was obtained as a liquid. The yield was 87% when nitrobenzene was starting substrate, and 95% with nitrosobenzene. TLC (30% ethyl acetate–hexane) R_f 0.37; δ_H (300 MHz, $CDCl_3$) 7.48–7.40 (5 H, m), 2.20 (3 H, s), 2.07 (3 H, s); ν_{max}/cm^{-1} (Nujol) 3059, 2993, 1803, 1694, 1600, 1496 (Found: *m*/*z*, 193.0754. $C_{10}H_{11}NO_3$ requires M_r, 193.0739).

N-(*Acetyloxy*)-N-(2-*methylphenyl*)*acetamide* (**2b**). Yield: 73% (liquid); TLC (30% ethyl acetate–hexane) R_f 0.38; δ_H (300 MHz, $CDCl_3$) 7.51–7.27 (4 H, m), 2.38 (3 H, s), 2.17 (3 H, s), 1.92 (3 H, s); ν_{max}/cm^{-1} (Nujol) 3057, 2993, 1799, 1694, 1430, 1185 (Found: *m*/*z*, 207.0895. $C_{11}H_{13}NO_3$ requires M_r, 207.0895).

N-(*Acetyloxy*)-N-(3-*methylphenyl*)*acetamide* (**2c**). Yield: 78% (liquid); TLC (30% ethyl acetate–hexane) R_f 0.39; δ_H (300 MHz, $CDCl_3$) 7.35–7.21 (4 H, m), 2.38 (3 H, s), 2.19 (3 H, s), 2.06 (3 H, s); ν_{max}/cm^{-1} (Nujol) 3057, 2993, 1799, 1688, 1378 (Found: *m*/*z*, 207.0899. $C_{11}H_{13}NO_3$ requires M_r, 207.0895).

N-(*Acetyloxy*)-N-(4-*methylphenyl*)*acetamide* (**2d**). Yield: 85% (liquid); TLC (30% ethyl acetate–hexane) R_f 0.39; δ_H (300 MHz, $CDCl_3$) 7.35 (2 H, d, *J* 8.4 Hz), 7.25 (2 H, d, *J* 8.4 Hz), 2.38 (3 H, s), 2.18 (3 H, s), 2.03 (3 H, s); ν_{max}/cm^{-1} (Nujol) 3064, 2992, 1799, 1688, 1428, 1284 (Found: *m*/*z*, 207.0888. $C_{11}H_{13}NO_3$ requires M_r, 207.0895).

N-(*Acetyloxy*)-N-(3-*bromophenyl*)*acetamide* (**2e**). Yield: 91% (liquid); TLC (30% ethyl acetate–hexane) R_f 0.39; δ_H (300 MHz, $CDCl_3$) 7.65 (1 H, t, *J* 1.9 Hz), 7.44–7.41 (2 H, m), 7.31–7.29 (1 H, m), 2.23 (3 H, s), 2.10 (3 H, s); ν_{max}/cm^{-1} (Nujol) 3057, 2989, 1805, 1703, 1589, 1425, 1272 (Found: *m*/*z*, 270.9856. $C_{10}H_{10}BrNO_3$ requires M_r, 270.9844).

N-(*Acetyloxy*)-N-(9H-*fluoren*-2-*yl*)*acetamide* (**2f**). Yield: 83% (liquid); TLC (30% ethyl acetate–hexane) R_f 0.34; δ_H (300 MHz, $CDCl_3$) 7.74–7.72 (2 H, m), 7.61 (1 H, s), 7.50–7.42 (2 H, m), 7.37–7.26 (2 H, m), 3.82 (2 H, s), 2.17 (3 H, s), 2.07 (3 H, s); ν_{max}/cm^{-1} (Nujol) 3057, 2988, 1799, 1691, 1425, 1272, 1187 (Found: *m*/*z*, 281.1046. $C_{17}H_{15}NO_3$ requires M_r, 281.1052).

N-(*Acetyloxy*)-N-(2-*chloropyridin*-5-*yl*)*acetamide* (**2g**). Yield: 93% (liquid); TLC (30% ethyl acetate–hexane) R_f 0.32; δ_H (300 MHz, $CDCl_3$) 8.49 (1 H, d, *J* 2.6 Hz), 7.85 (1 H, dd, *J* 2.6 and 8.5 Hz), 7.39 (1 H, d, *J* 8.5 Hz), 2.26 (3 H, s), 2.16 (3 H, s); ν_{max}/cm^{-1} (Nujol) 3063, 2983, 1810, 1703, 1612, 1425, 1266 (Found: *m*/*z*, 228.0286. $C_9H_9ClN_2O_3$ requires M_r, 228.0301).

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