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Preparation of 2′-aminoacetophenones: a one-pot hydration and reduction of 1-ethynyl-2-nitrobenzenes

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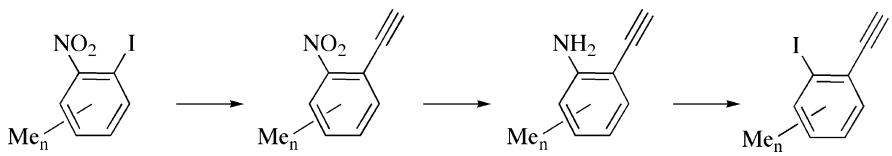
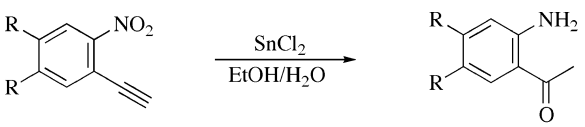
Abstract—The reductive hydration of 1-ethynyl-2-nitrobenzenes to the corresponding 2′-aminoacetophenones with a range of common reducing agents is described.

Nitroarenes are versatile synthons in organic synthesis. They are readily prepared and serve as indirect precursors to a wide variety of other functionalized aromatics.[1] An extremely useful reaction sequence involves reduction to the corresponding amine[2] followed by aryl diazonium chemistry.[3] As part of our program aimed at the synthesis of metal acetylide based metallocycles,[4] we were interested in reducing a series of 1-ethynyl-2-nitrobenzenes to the corresponding 2-ethynylanilines. Our goal was to synthesize 2-iodophenylacetylenes as outlined in Eq. (1).



(1)

The 1-ethynyl-2-nitrobenzenes were prepared from the corresponding 1-iodo-2-nitrobenzenes using Sonogashira coupling with trimethylsilylacetylene followed by basic deprotection.[5] We first attempted to reduce the nitro group of the parent compound 1-ethynyl-2-nitrobenzene, **1**, with stannous chloride as the reductant[6] and were surprised to note that the only product isolated was 2′-aminoacetophenone, **2**, as shown in Eq. (2). This resulted from reduction of the nitro group with concomitant hydration of the alkyne.



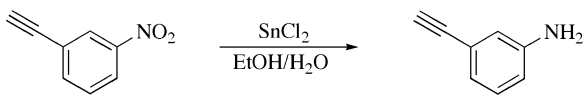
1 (R=H)
3 (R=CH_3)

2 (R=H)
4 (R=CH_3)

(2)

Similar results were obtained with a variety of other reducing agents including iron,[7] nickel boride[8] and zinc.[9] The reaction of 1-ethynyl-4,5-dimethyl-2-nitrobenzene, **3**, with the same series of reductants yielded the corresponding aminoacetophenone **4**, as shown in Table 1.[10]

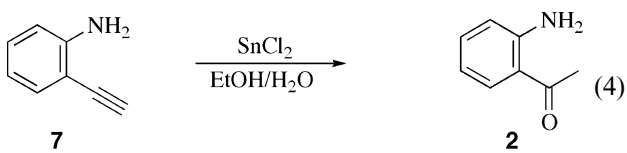
This is in stark contrast to the reaction of 1-ethynyl-3-nitrobenzene with stannous chloride that yielded quantitative reduction of the nitro group to yield 3-ethynylaniline as the only organic product (Eq. (3)).[11]



5 **6**

(3)

We have not completed our mechanistic studies of this reaction, however, we have noted that 2-ethynylaniline is hydrated under similar reducing conditions (Eq. (4)).



7 **2**

(4)

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Table 1. Preparation of 2′-aminoacetophenones

Substrate	Conditions	Product	Yield
1	Ni_2B	**2**	73
1	Fe/HCl	**2**	66
1	Zn/HCl	**2**	63
1	$SnCl_2$	**2**	71
3	Fe/HCl	**4**	64
3	Ni_2B	**4**	68
3	$SnCl_2$	**4**	75

Acknowledgements

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10. Compound **1**: ^{1}H NMR ($CDCl_3$) δ 3.52 (s, 1H), 7.51 (dt, $J=1.8$, 8.0 Hz, 1H), 6.60 (dt, $J=1.4$, 7.6 Hz, 1H), 7.71 (dd, $J=1.8$, 7.6 Hz, 1H), 8.06 (dd, $J=1.4$, 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 78.53, 85.14, 117.47, 124.61, 129.37, 132.84, 135.54, 150.36. Anal. calcd for $C_8H_5NO_2$: C, 65.31; H, 3.43. Found C, 65.29; H, 3.41. Compound **2**. ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 6.27 (br s, 2H), 6.64 (m, 2H), 7.25 (dt, $J=2.2$, 7.3 Hz, 1H), 7.71 (dd, $J=1.6$, 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 27.77, 115.65, 117.12, 118.16, 131.96, 134.30, 150.21, 200.69. Compound **3**: ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.34 (s, 3H), 3.44 (s, 1H), 7.44 (s, 1H), 7.86 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.43, 19.58, 78.94, 83.59, 114.50, 125.33, 136.08, 138.92, 143.00, 147.54. Anal. calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.16. Found C, 68.40; H, 5.31. Compound **4**. ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.19 (s, 3H), 2.54 (s, 3H), 6.08 (br s, 2H), 6.46 (s, 1H), 7.44 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.73, 20.04, 27.67, 114.47, 117.95, 123.92, 132.09, 144.31, 148.59, 200.02. Anal. calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found C, 73.36; H, 8.11. Compound **6**. ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 1H), 3.69 (br s, 2H), 6.62 (ddd, $J=1.0$, 2.2, 8.0 Hz, 1H), 6.83 (t, 1H, $J=2.2$ Hz, 1H), 6.92 (td, $J=1.2$, 8.0 Hz, 1H), 7.11 (t, $J=8.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 76.5, 83.8, 115.7, 118.1, 122.2, 122.5, 129.1, 146.2.
11. The reduction of 3-ethynylnitrobenzene with iron/ammonium chloride in acetic acid to yield 3-ethynylaniline has been reported in a Japanese patent. Yamakawa, K.; Sato, T. JP 10036325 [CA 128:167247].