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A chemoselective method for the reductive *N*-formylation of aryl azides under catalytic transfer hydrogenation conditions

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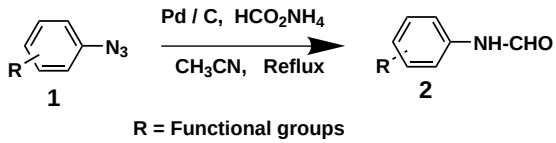
Abstract—A highly facile and chemoselective method for the reductive *N*-formylation of aryl azides under catalytic transfer hydrogenation conditions is described.

Catalytic transfer hydrogenation (CTH) is an important synthetic methodology by which compounds such as cyclohexadiene,[1] formic acid,[2] hydrazine[3] and phosphinic acid[4] act as in situ hydrogen donors. With the advent of ammonium formate as a source of hydrogen,[5] catalytic transfer hydrogenation has become a versatile synthetic tool to achieve the hydrogenation/hydrogenolysis of several functional groups.[6] Unlike conventional hydrogenation techniques, CTH reactions do not require any elaborate experimental set up or high-pressure reactors. The ammonium formate–Pd/C reagent system has been used for the facile reduction of azides to amines,[7a] dehalogenation of mono- and polychlorinated aryl compounds,[7b] the conversion of aryl cyano to arylmethyl derivatives,[7c] the reduction of aryl ketones to aryl alcohols,[7d] the reduction of aryl oximes to amines,[7e] the stereoselective reduction of nitro alcohols to 1,2-amino alcohols,[7f] the reductive cyclization of β-nitro styrenes to indoles,[7g] the deoxygenation of heteroaromatic *N*-oxides,[7h] the regioselective hydrogenolysis of benzyl glycosides,[7i] the hydrogenolysis of dibenzyl uracils[7j] and the selective reduction of α,β-unsaturated ketones.[7k]

Catalytic transfer hydrogenation reactions are usually carried out in protic solvents such as methanol.[6] Although CTH reactions are very facile in methanol, they are non-selective and almost all labile functional groups undergo reduction under these conditions. Chemoselective reduction of a functional group in the presence of other sensitive functional groups is much sought after, but difficult to achieve under CTH conditions. During the course of our study to moderate the reactivity of CTH, we made the interesting observation that ammonium formate in aprotic solvents such as acetonitrile can function as a formylating agent as well as being a source of hydrogen.[8] Herein we report a novel and chemoselective method which makes it possible to convert aryl azides directly into the corresponding *N*-formanilides in the presence of several reducible functional groups under CTH conditions (Scheme 1). To the best of our knowledge, this is the first example of a one-step, reductive, *N*-formylation of aryl azides under mild conditions.

Given the synthetic utility of *N*-formanilides as key intermediates for the synthesis of biologically active compounds[9] such as *N*,*N*-diaryl ureas,[10] cancer chemotherapeutic agents[11] and quinolone antibacterials,[12] we feel that this one-pot transformation will be of great use to synthetic chemists.

The aryl azide **1** on treatment with Pd/C and ammonium formate at reflux temperature was smoothly converted to the corresponding *N*-formanilide **2** in good yields. In a typical experiment, the aryl azide **1** in acetonitrile was stirred under reflux with a suspension of 10% Pd/C and ammonium formate for several hours until the completion of reaction as indicated by TLC. The usual work up and evaporation of the solvent



Scheme 1.

Keywords: chemoselective; aryl azide; formanilide; CTH.

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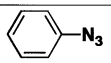
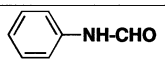
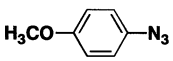
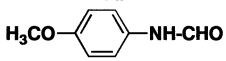
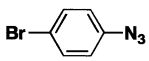
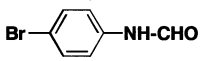
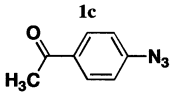
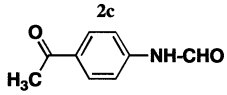
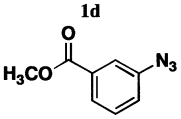
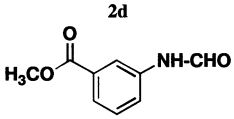
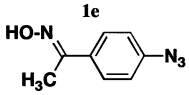
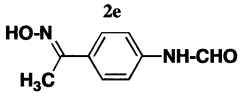
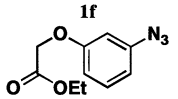
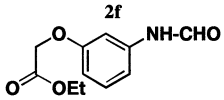
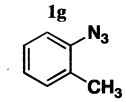
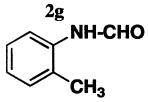
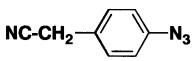
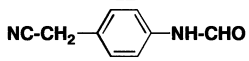
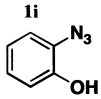
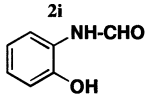
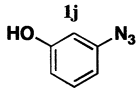
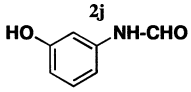
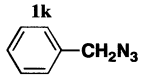
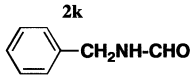
followed by purification by column chromatography furnished the pure *N*-formanilide **2** as a mixture of rotamers.[13] In general, 10% by weight of Pd/C and 5 equiv. of ammonium formate were found to give the best results. A wide range of chemically sensitive aryl azides has been subjected to these CTH conditions to provide the corresponding *N*-formylated anilines, chemoselectively, in good yields. Selected examples of this one-step transformation are shown in Table 1, which summarizes some important findings.

The unique ability of the ammonium formate mediated CTH reaction in acetonitrile is apparent from the chemoselective reductive *N*-formylation of aryl azides in the presence of other reducible functional groups such as aryl halides, oximes, aryl ketones, nitriles and ethers. The dehalogenation of aryl halides under CTH conditions is a facile and well studied transformation,[7b] however, under our reaction conditions, 4-bromophenyl azide (entry 3) afforded 4-bromoformanilide **2c** in good yield as the only product. Although aryl ketones are known to undergo Leuckart-reductive amination in the presence of ammonium formate,[14] 4-acetylphenyl azide **1d** (entry 4) was smoothly converted to 4-acetyl formanilide **2d** with the keto group intact. Similarly, carboxylic esters (entries 5 and 7) and aryl alkyl ethers (entries 2 and 7) were also found to be stable under the reaction conditions. Interestingly, hydroxy phenyl azides (entries 10 and 11) were chemoselectively converted to the corresponding formanilides in excellent yields. It is worth mentioning that aryl azides having oxime and cyano functional groups (entries 6 and 9) were also found to be compatible with the reaction conditions and provided the corresponding *N*-formyl derivatives, respectively, in excellent yields. Aliphatic azides, however, gave the corresponding alkyl ammonium salts with benzyl azide (entry 12) being an excep-

Table 1. Reductive *N*-formylation of aryl azides under CTH conditions

Entry	Substrate	Time (in hours)	Product[a]	% Yield[b]
1	 **1a**	11	 **2a**	79
2	 **1b**	7.5	 **2b**	87
3	 **1c**	12	 **2c**	85
4	 **1d**	10	 **2d**	58[c]
5	 **1e**	10	 **2e**	95
6	 **1f**	14	 **2f**	89
7	 **1g**	20	 **2g**	75
8	 **1h**	11	 **2h**	83
9	 **1i**	15	 **2i**	90
10	 **1j**	12	 **2j**	92
11	 **1k**	9	 **2k**	93
12	 **1l**	9	 **2l**	89

[a] Mixture of rotamers.[b] Isolated yields. [c] Intermediate aniline was isolated in 27 % yield.

tion as it gave the expected *N*-benzyl formamide **2l** in good yield.

Although a detailed investigation of the mechanism of this novel transformation is yet to be carried out, a plausible mechanism is given in Eqs. (1–4). In the presence of Pd/C, ammonium formate can undergo decomposition to generate hydrogen along with carbon dioxide and ammonia (Eq. (1)).[6] Reduction of the aryl azide to the aniline takes place in the presence of Pd/C and hydrogen (Eq. (2)).[7a] It is known that under thermal conditions, ammonium formate can decompose to generate formamide[14] (Eq. (3)) which in turn can react with aniline to furnish *N*-formanilide (Eq. (4)).[15]

$$HCO_2NH_4 \xrightarrow{Pd/C} H_2+CO_2+NH_3 \quad (1)$$

$$Ar\text{–}N_3 \xrightarrow{Pd/CH_2} Ar\text{–}NH_2 \quad (2)$$

$$HCO_2NH_4 \overset{\Delta}{\rightleftharpoons} NH_2\text{–}CHO+H_2O \quad (3)$$

$$Ar\text{–}NH_2+NH_2\text{–}CHO \rightarrow Ar\text{–}NH\text{–}CHO+NH_3\uparrow \quad (4)$$

In conclusion, we have developed an unusually novel and chemoselective method for the direct conversion of aryl azides to *N*-formanilides under catalytic transfer hydrogenation reaction conditions. We are confident that this one-pot, reductive, *N*-formylation method will allow us to construct biologically important heterocyclic ring systems in a more efficient manner.

1. Experimental

1.1. Representative procedure[16]

Synthesis of ethyl 3-(*N*-formylamino)phenoxy acetate (2 g): To a stirred solution of ethyl 3-azidophenoxy acetate **1g** (130 mg, 0.59 mmol) in dry acetonitrile (5 mL) was added 10% palladium on carbon (26 mg) and anhydrous ammonium formate (185 mg, 2.94 mmol). The resulting mixture was stirred for 20 h at reflux temperature under a nitrogen atmosphere. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue obtained was diluted with ethyl acetate (20 mL), washed with water (2×10 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure to afford the pure title compound **2g** as a mixture of rotamers (98 mg, 75% yield): mp = 62–64°C; ^{1}H NMR (400 MHz) δ = 8.68 and 8.34 (two d, J = 11.3 Hz and 2.0 Hz, 1H), 8.05 (bd) and 7.50 (bs, 1H), 7.31–7.21 (m, 2H), 7.09–7.07 and 6.73–6.67 (two m, 2H), 4.63 (s, 2H), 4.28 and 4.27 (two q, J = 7.3 Hz, 2H), 1.31 and 1.30 (two t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz) δ = 14.1, 61.4, 61.5, 65.3, 105.8, 106.6, 110.4, 110.7, 111.8, 113.1, 129.8, 130.6, 138.1, 138.3, 158.1, 158.7, 159.3, 162.5, 168.6, 168.9; IR (KBr): 3335, 1745, 1704 cm^{-1}; MS (EI, 70 eV) m/z (rel. intensity) 223 (M^+, 49), 65 (100). Anal. calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 58.97; H, 5.65; N, 6.15.

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16. For published data on the formanilides in Table 1, see: (a) formanilide and 2-methylformanilide are commercially available from Aldrich; (b) (4-methoxyformanilide and 4-bromoformanilide) Carter, R. E. *Acta Chem. Scand.* **1968**, *22*, 2643; (c) (4-acetyl formanilide) Passerini, M.; Banti, G. *Gazz. Chim. Ital.* **1929**, *58*, 640; (c) (*N*-benzylformanilide) Buehler, C. A.; Mackenzie, C. A. *J. Am. Chem. Soc.* **1937**, *59*, 421; (d) (4-(*N*-formylamino) benzyl cyanide) Maron, D.; Kontorowitsch, M.; Bloch, J.-J. *Ber.* **1914**, *47*, 1347; (e) (2-hydroxyformanilide) Farley, T. M.; Strong, R. M.; Bydalek, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3501; (f) (3-hydroxyformanilide) Fierz-David, H. E.; Meister, H. *Helv. Chim. Acta* **1939**, *22*, 579; (g) (methyl 3-(*N*-formylamino)-benzoate) *Inorg. Chim. Acta* **1997**, *264*, 161.