A facile synthesis of *N*-formylbenzamides by oxidative decarboxylation of *N*-aroylglycine induced by $Ag^+/S_2O_8^{2-}$

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A facile method is described for the synthesis of *N*-formylbenzamides by oxidative decarboxylation of *N*-aroylglycine using catalytic silver(I) and 2 equivalents of ammonium persulfate as an oxidant in a biphasic system ($CHCl_3$/water).

Keywords: decarboxylation, persulfate, *N*-aroylglycine, *N*-formylbenzamide, silver

N-Formylbenzamides have been prepared by reactions of benzamides with dimethylformamide dimethyl acetal,[1] by condensation of *N,N*-bis(trimethylsilyl)formamide with acyl chlorides,[2] by dibenzoylation of formamide followed by decomposition of the resulting *N*-formyldibenzamide,[3] or by hydroxymethylation of benzamide, followed by oxidation of the resulting *N*-hydroxymethylbenzamide.[4] These methods are either difficult or require anhydrous conditions. Our strategy is based on oxidative decarboxylation of *N*-aroylglycine. It has been reported that the oxidative decarboxylation of *N*-aroylglycines using stoichiometric lead(IV) acetate gave *N*-formylbenzamides in low yields.[5] The oxidative decarboxylation of *N*-aroylglycine has also been employed in the Minisci radical alkylation, where the resulting 1-amidomethyl radical was trapped by a heterocyclic compound.[6] The reaction is catalysed by silver(I) using persulfate as a stoichiometric oxidant in aqueous solution ($Ag^+/S_2O_8^{2-}$). In the absence of a heterocyclic compound, the amidomethyl radical **3** formed would be oxidised to **4**, which would give *N*-formylbenzamides after hydrolysis and further oxidation by persulfate (see Scheme).

N-Aroylglycine was prepared by classic Schotten–Baumann techniques by addition of the aroyl choride and 2 M sodium hydroxide simultaneously to the amino acid in aqueous sodium hydroxide solution at 0°C with vigorous stirring, acidification and collection of the *N*-aroyl amino acid by filtration followed by recrystallisation from water or aqueous ethanol. Initially we used hippuric acid as a substrate to optimise the usage of persulfate. The best yield (71%) of *N*-formylbenzamide was obtained when 2.0 equivalents of ammonium persulfate were used. Reducing the amount of persulfate to 1.5 equivalents resulted in a poor yield (30%) while increasing to 2.5 equivalents gave a slightly lower yield (68%).

As shown in Table 1, 4-bromo- and 4-chloro-hippuric acid gave the corresponding *N*-formyl products in 67% and 59% yields, respectively. 4-Methylhippuric acid gave **2d** in 43% yield possibly due to oxidation of the methyl group. 2-Methoxyhippuric acid gave **2e** in 20% yield, indicating that a strong electron-donating substituent at 2- or 4-position is unfavourable for the reaction. For 4-nitrohippuric acid, no *N*-formyl product was obtained but the 3-nitro derivative gave the product **2f** in 68% yield, indicating that the reaction was strongly affected by a strongly electron-withdrawing group at 4- or 2-position. An attempt to synthesise *N*-acetylbenzamide by using *N*-benzoylalanine was unsuccessful.

Table 1 Synthesis of *N*-formylbenzamides

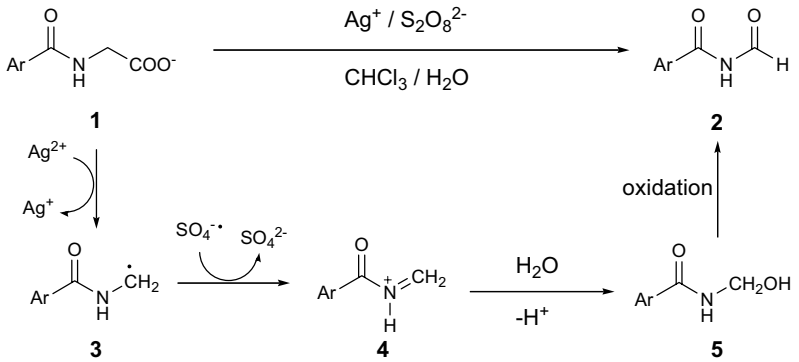
Entry	1	Ar	$S_2O_8^{2-}$/equiv	Yield[a] of **2**/%
1	**1a**	Ph	1.5	30
2	**1a**	Ph	2.0	71
3	**1a**	Ph	2.5	68
4	**1b**	4-ClC_6H_4	2.0	59
5	**1c**	4-BrC_6H_4	2.0	67
6	**1d**	4-MeC_6H_4	2.0	43
7	**1e**	2-$MeOC_6H_4$	2.0	20
8	**1f**	3-$O_2NC_6H_4$	2.0	68
9	**1g**	4-$O_2NC_6H_4$	2.0	–

[a]Isolated yields by preparative TLC.

In summary, we demonstrate a synthesis of *N*-formylbenzamide by oxidative decarboxylation of *N*-aroylglycine using catalytic silver and inexpensive reagents in reasonable yields.

Experimental

All the products except **2e** were confirmed by comparison with known compounds (IR, TLC and NMR). All melting points were measured on a melting apparatus with microscope and hot stage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 or a MercurPlus 400 NMR spectrometer. IR spectra were recorded on a Thermo Nicolet Avatar 360 IR spectrometer. Electrospray ionisation mass spectra were obtained on an LCQ Advantage MAX (Finnigan) instrument operating in positive ion mode. Elemental analyses were performed on a Heraeus Vanio-EL CHN analyser. All reactions were carried out under nitrogen.



Scheme

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General procedure for the synthesis of N-formylbenzamides: To a reaction tube with a condenser, *N*-aroylglycine (1.0 mmol), silver nitrate (0.01 mmol), chloroform (8 ml) and water (7.5 ml) were added. Ammonium persulfate (2.0 mmol) was added to a short glass tube with pinholes covered with glass wool at the bottom, which was hung in the condenser in order to let condensing solvents wash the persulfate into the reaction mixture. After the reaction mixture was degassed by sparging nitrogen, the reaction tube was placed in a water bath preheated to 60°C. After the persulfate was completely washed out (*ca* 30–40 min), the reaction mixture was stirred for 1 h, and then evaporated to remove all solvents. The residue was extracted with acetone (2 × 15 ml), and the product was isolated from the extracts by preparative TLC (MeOH/$CHCl_3$: 1/20, v/v).

N-Formylbenzamide (**2a**): A white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.56 (m, 2 H, *m*-ArH), 7.63–7.68 (m, 1 H, *p*-ArH), 7.92–7.98 (*m*, 2 H, *o*-ArH), 9.39 (d, *J* = 10 Hz, 1 H, CHO), 9.72 (br, 1 H, NH); IR (KBr) 1724, 1670 cm^{-1}; m.p. 109–110°C (lit.[5] 109–110°C).

4-Chloro-N-formylbenzamide (**2b**): A white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ7.60–7.63 (m, 2 H, 3,5-ArH), 8.00–8.03 (m, 2 H, 2,6-ArH), 9.23 (s, 1 H, CHO), 11.78 (br, 1 H, NH); IR (KBr) 3266, 1737, 1693 cm^{-1}; m.p. 158–160°C (lit.[5] 163–165°C).

4-Bromo-N-formylbenzamide (**2c**): A white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73–7.76 (m, 2 H, 3,5-ArH), 7.90–7.94 (m, 2 H, 2,6-ArH), 9.22 (s, 1 H, CHO), 11.78 (brs, 1 H, NH); IR (KBr) 3270, 1740, 1694 cm^{-1}; m.p. 209–210°C (lit.[1] 210–212°C).

N-Formyl-4-methylbenzamide (**2d**): A white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3 H, CH_3), 7.31–7.34 (m, 2 H, 3, 5-ArH), 7.84–7.87 (m, 2 H, 2,6-ArH), 9.37 (d, *J* = 9.6 Hz, 1 H, CHO), 9.76 (br, 1 H, NH); IR (KBr) 3287, 1719, 1674 cm^{-1}; m.p. 131–132°C (lit.[5] 104°C).

N-Formyl-2-methoxybenzamide (**2e**): A white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 3 H, CH3), 7.02–7.05 (m, 1 H, 3-ArH), 7.11–7.15 (m, 1 H, 4-ArH), 7.57–7.60 (m, 1 H, 5-ArH), 8.19–8.22 (m, 1 H, 6-ArH), 9.40 (d, *J* = 10 Hz, 1 H, CHO), 10.17 (br, 1 H, NH); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 56.0, 57.0, 112.2, 113.3, 120.6, 121.7, 122.0, 130.2, 131.3, 133.9, 135.0,157.8, 163.2, 164.6, 167.7; IR (KBr) 3340, 1731, 1668 cm^{-1}; ESI-MS *m/z* 242 (30), 237 (10), 202 (32), 196 (100), 180 (47) $(M + H)^+$, 152 (15), 64 (8), 60 (6); m.p. 98–99°C. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.1; H, 5.5; N, 7.45.

N-Formyl-3-nitrobenzamide (**2f**)[7]: A white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (br, 1 H, NH), 7.73–7.77 (m, 1 H, 5-ArH), 8.29 (d, *J* = 7.6 Hz, 1 H, CHO), 8.32–8.37 (m, 2 H, 4, 6-ArH), 8.67 (s, 1 H, 2-ArH); IR (KBr) 3448, 1715, 1683, 1623 cm^{-1}; m.p. 139–140°C.

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