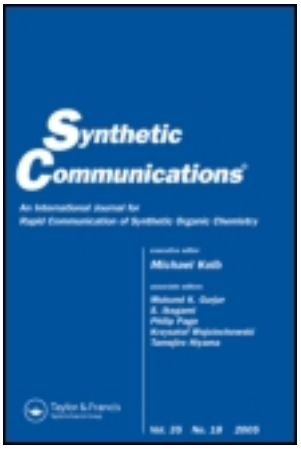

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Facile, Environmentally Friendly Synthesis of Benzaldehyde and Phenylacetaldehyde Analogs from Readily Available Toluene Derivatives

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FACILE, ENVIRONMENTALLY FRIENDLY SYNTHESIS OF BENZALDEHYDE AND PHENYLACETALDEHYDE ANALOGS FROM READILY AVAILABLE TOLUENE DERIVATIVES

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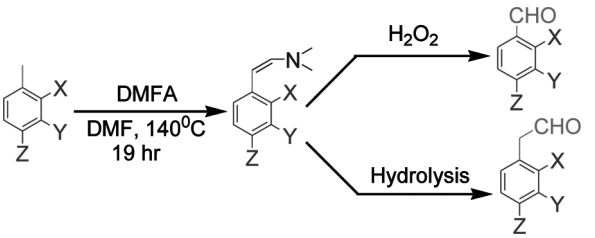
GRAPHICAL ABSTRACT



Abstract *A facile environmentally friendly synthesis of bezaldehyde and phenylacetaldehyde analogs from readily available toluene derivatives is described. Oxidation of the styrylamines by H_2O_2 affords benzaldehydes in moderate yields, while the hydrolysis of styrylamines afforded phenylacetaldehyde analogs in good yields.*

Keywords Bezaldehyde; hydrolysis; oxidation; phenylacetaldehyde

INTRODUCTION

Aromatic aldehydes constitute an important class of compounds with numerous applications in organic synthesis. They have been employed as building blocks for a wide variety of heterocyclic and pharmaceutical compounds and as intermediates for the synthesis of naturally occurring alkaloids. For example, 2-nitrobenzaldehyde is a precursor for the synthesis of enantiomerically pure α-amino acids,[1] and 2-aminobenzaldehyde[2] has been used as a key intermediate for preparation of α-methylamino acids.[3] 2-Nitro-4-chlorobenzaldehyde plays a very important role

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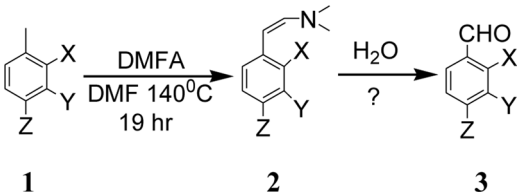
in the total synthesis of an anti-HIV agent siamenol.[4] 2-Chloro-4-nitrobenzaldehyde also serves as an essential intermediate in the preparation of another anti-HIV agent, orally active CCR5 antagonist.[5] 4-Nitrobenzaldehyde and 4-cyanobenzaldehyde are crucial materials for the production of diarylmethanols, important building blocks in the synthesis of natural products and pharmacologically active compounds.[6] Phenylacetaldehyde derivatives are extensively used in perfumery.

Traditional synthetic processes for manufacturing benzaldehyde and phenylacetaldehyde analogs with electron-withdrawing substituents often lead to serious contamination to the environment by releasing large amounts of pollutants to air and water. For example, the synthesis of 2-nitrobenzaldehyde from 2-nitrotoluene involved the bromination of 2-nitrotoluene to 2-nitrobenzylidenedibromide followed by the oxidation of 4-nitrosodimethylaniline to 2-nitrobenzaldehyde.[7] This procedure required the use of expensive bromine and carcinogenic 4-nitrosodimethylaniline. Another three-step sequence, consisting of the chlorination of 2- nitrotoluene, alkaline dimerization to 2,2′-dinitrostilbene, and ozonolysis, suffered from poor conversion rates and poor selectivity.[8] All approaches involving the intermediate 2-nitrobenzyl halides suffer from dangers of explosive decomposition of these compounds.[9] The synthesis of 2-nitrophenylacetaldehyde by the nitration of phenylacetaldehyde causes problems separating the other two isomers, 3-nitrophenylacetaldehyde and 4-nitrophenylacetaldehyde.[10] Diazotization of 2-nitroaniline to diazonium salt followed by the Meerwein arylation with an unsaturated acceptor afforded the desired product with a poor yield.[11] Although different methods are available for the synthesis of 2-nitrobenzaldehyde and 2-nitrophenylacetaldehyde, development of another facile, high-yielding, nonpolluting preparation is still of great importance.[12,13]

In 2007, Naffziger et al. reported an efficient pathway to the 2-nitro-4-chlorobenzaldehyde starting from 2-nitro-4-chlorotoluene.[4] In his article, the methyl group was oxidized by N,N-dimethylformamide dimethyl acetal (DMFA) in the presence of dimethylformamide (DMF) to the styrylamine, which was further oxidized by $NaIO_4$ to obtain 2-nitro-4-chlorobenzaldehyde in good yield. However, the high cost of the $NaIO_4$ and the production of inorganic halide waste impeded its application on a large scale. To facilitate the industrial manufacturing process, we turned our attention to other economic and environmentally friendly oxidants. Hydrogen peroxide finally became our choice (Scheme 1).

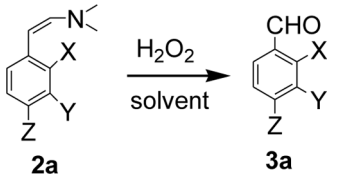
Initially, we set out to identify the optimal conditions for the new oxidation system. N,N-Dimethyl-2-(4-chloro-2-nitrophenyl)ethenamine **2a** was subjected to hydrogen peroxide–mediated oxidation in various solvents. Some representative results are given in Table 1. It was found that the oxidation in CH_3CN afforded a



1 **2** **3**

Scheme 1. Synthesis of benzaldehydes using H_2O_2 as the oxidant.

Table 1. Effect of solvents on oxidation of **2a** by H_2O_2[a]



2a **3a**

Entry	Solvent	Yield (%)[b]
1	CH_3CN	37
2	CH_3OH	27
3	DMF	nr[c]
4	$(CH_3)_2CHOH$	32
5	$(CH_3)_3COH$	34

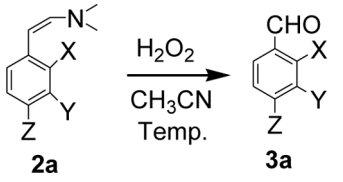
[a]Reaction conditions: styrylamine 4.4 mmol, H_2O_2 8.8 mmol, solvent 10 mL, T = rt, t = 5 h.
[b]Overall yield over two steps of isolated and purified product.
[c]nr, no reaction.

better yield (entry 1, Table 1). Two other solvents, isobutyl alcohol and tertbutyl alcohol, also gave comparable results (entries 4 and 5, Table 1).

Then we examined the oxidation of **2a** by H_2O_2 in the presence of CH_3CN at various temperatures (Table 2). The results in Table 2 showed that at 25 °C, a higher yield was obtained.

With the increased molar ratio of H_2O_2 to **2a** from 1:2 to 1:3, the yield of the aldehyde was increased to 45% (entry 1, Table 3). Other substrates also afforded the desired product as described in Table 3.

Table 2. Effect of temperatures on oxidation of 2a by H_2O_2[a]

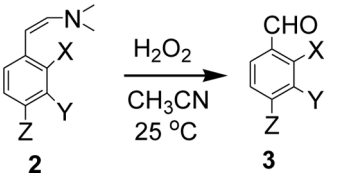


2a **3a**

Entry	Temperature (°C)	Yield (%)[b]
1	15	34
2	20	35
3	25	37
4	30	24
5	35	16

[a]Reaction conditions: styrylamine 4.4 mmol, H_2O_2 8.8 mmol, solvent, CH_3CN mL, t = 5 h.
[b]Overall yield over two steps of isolated and purified product.

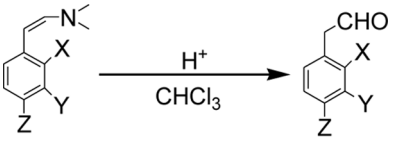
Table 3. Synthesis of benzaldehyde analogs using H_2O_2 as the oxidant[a]



2 **3**

Entry	X	Y	Z	Time (h)	Product	Yield (%)[b]
1	NO_2	H	Cl	5	**3a**	45
2	NO_2	H	H	4	**3b**	50
3	H	H	NO_2	6	**3c**	39
4	Cl	H	NO_2	12	**3d**	37
5	H	Cl	NO_2	7	**3e**	34
6	H	H	CN	3	**3f**	43

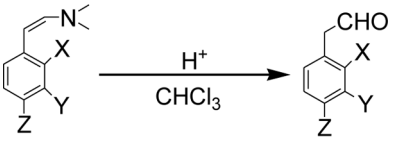
[a]Reaction conditions: styrylamine 1 g, molar ratio of H_2O_2 to styrylamine is 1:3, solvent CH_3CN 10 mL, T = 25°C.
[b]Overall yield over two steps of isolated and purified product.



2 **4**

Scheme 2. Synthesis of phenylacetaldehyde analogs by hydrolysis of the styrylamines.

Table 4. Synthesis of phenylacetaldehyde analogs by hydrolysis[a]



2 **4**

Entry	X	Y	Z	Product	Yield (%)[b]
1	NO_2	H	Cl	**4a**	85
2	NO_2	H	H	**4b**	77
3	H	H	NO_2	**4c**	68
4	Cl	H	NO_2	**4d**	65
5	H	Cl	NO_2	**4e**	60
6	H	H	CN	**4f**	70

[a]Reaction conditions: styrylamine 1 g, 30% (m/m) sulfuric acid 10 mL, $CHCl_3$ 10 mL, rt, t = 2 h.
[b]Overall yield over two steps.

The hydrolysis of the styrylamine would afford phenylacetaldehyde, which was also an important building block for organic synthesis. We then investigated the reaction of styrylamines in the presence of sulfuric acid in $CHCl_3$ (Scheme 2). Hydrolysis results are displayed in Table 4. In all the cases, moderate to good yields of phenylacetaldehyde were obtained.

In summary, we disclosed a facile, environmentally friendly synthesis of benzaldehydes and phenylacetaldehydes analogs from the readily available toluene derivatives. The mild reaction condition, low cost, and diversity make our methodology a valid contribitution to the existing process in the field of aromatic aldehyde sythesis.

CHARACTERIZATION DATA OF REPRESENTATIVE COMPOUNDS 3

2-Nitro-4-chlorobenzaldehyde (3a)

Yellow crystal, mp 64–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.39$ (s, 1 H), 8.11 (d, $J = 1.95$ Hz, 1 H), 7.95 (d, J = 8.25 Hz, 1 H), 7.77 (m, 1 H).

2-Nitrobenzaldehyde (3b)

Yellow crystal, mp 42–43 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.43$ (s, 1 H), 8.13 (m, 1 H), 7.96 (m, 1 H), 7.80 (m, 2 H).

4-Nitrobenzaldehyde (3c)

Yellow crystal, mp 101–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.17$ (s, 1 H), 8.41 (m, 2 H), 8.08 (m, 2 H).

2-Chloro-4-nitrobenzaldehyde (3d)

Orange crystal, mp 68–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.55$ (s, 1 H), 8.35 (d, $J = 2.10$ Hz, 1 H), 8.24 (m, 1 H), 8.11 (d, $J = 8.55$ Hz, 1 H).

3-Chloro-4-nitrobenzaldehyde (3d)

Orange crystal, mp 56–57 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.07$ (s, 1 H), 8.07 (d, $J = 1.60$ Hz, 1 H), 7.99 (d, $J = 8.25$ Hz, 1 H), 7.94 (m, 1 H).

4-Cyanobenzaldehyde (3f)

Yellow crystal, mp 96–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.10$ (s, 1 H), 8.01 (m, 2 H), 7.86 (m, 2 H).

CHARACTERIZATION DATA OF REPRESENTATIVE COMPOUNDS 4

2-Nitro-4-chlorophenylacetaldehyde (4a)

Yellow crystal, mp 65–66 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.81$ (s, 1 H), 8.12 (d, $J = 2.21$ Hz, 1 H), 7.59 (m, 1 H), 7.27 (d, $J = 8.20$ Hz, 1 H), 4.12 (s, 2 H).

2-Nitrophenylacetaldehyde (4b)

Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.80$ (s, 1 H), 8.08 (m, 1 H), 7.60 (m, 1 H), 7.48 (m, 1 H), 7.31 (m, 1 H), 4.11 (s, 2 H).

4-Nitrophenylacetaldehyde (4c)

Orange crystal, mp: 85–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.82$ (m, 1 H), 8.23 (m, 2 H), 7.40 (d, $J = 8.60$ Hz, 2 H), 3.87 (d, $J = 1.40$, 2 H).

2-Chloro-4-nitrophenylacetaldehyde (4d)

Yellow crystal, mp 67–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.80$ (d, $J = 1.05$ Hz, 1 H), 8.28 (d, $J = 2.30$ Hz, 1 H), 8.11 (m, 1 H), 7.44 (d, $J = 8.42$ Hz, 1 H), 4.02 (s, 2 H).

3-Chloro-4-nitrophenylacetaldehyde (4e)

Orange viscous liquid, ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.81$ (m, 1 H), 7.90 (d, $J = 8.30$, 1 H), 7.43 (d, $J = 1.59$ Hz, 1 H), 7.28 (d, $J = 3.29$ Hz, 1 H), 3.83 (s, 2 H).

4-Cyanophenylacetaldehyde (4f)

Yellow viscous liquid, ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.79$ (m, 1 H), 7.65 (d, $J = 8.20$ Hz, 2 H), 7.34 (d, $J = 8.16$ Hz, 2 H), 3.83 (d, $J = 1.41$ Hz, 2 H).

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