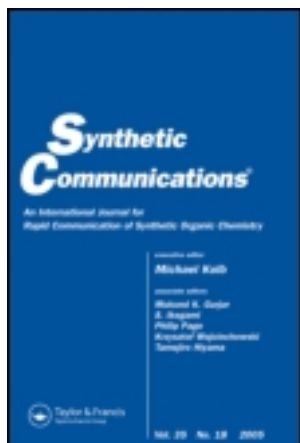


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## Potassium Phosphate Catalyzed Nitroaldol Reaction

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### ABSTRACT

Potassium phosphate was found to catalyze condensation of nitroalkanes with various aliphatic and aromatic aldehydes to form nitroaldols in excellent yields in acetonitrile medium at room temperature.

*Key Words:* Potassium phosphate; Catalysis; Nitroaldol; Nitroalkanol.

The reaction of a nitrostabilized carbanion with aldehydes and ketones leading to the formation of nitroalkanols was discovered by Henry.<sup>[1]</sup> It is an important C–C bond forming reaction and the resultant nitroalkanols are useful intermediates in organic synthesis.<sup>[2]</sup> The  $\beta$ -nitroalkanols are used as

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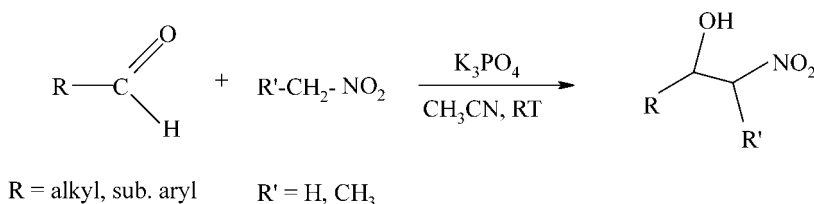
fungicides and are also useful in the synthesis of amino sugars and certain antibiotics like ezomycines, tunicamycin as well as alkaloids.<sup>[3]</sup>

Henry reaction is routinely performed in an organic solvent in the presence of a catalytic amount of base. Several basic catalysts like alkali and alkaline earth metal hydroxides, carbonates, alkoxides, TBAF etc., are normally used.<sup>[4,5]</sup> Various heterogeneous catalysts like alumina,<sup>[6]</sup> alumina supported KF,<sup>[7]</sup> SiO<sub>2</sub>,<sup>[8]</sup> Amberlyst A-21,<sup>[9]</sup> Mg-Al hydrotalcite,<sup>[10]</sup> layered zirconium phosphate,<sup>[11]</sup> benzyl trimethyl ammonium hydroxide,<sup>[12]</sup> and most recently N,N-diethylpropylamine supported on amorphous silica (KG-60-NEt<sub>2</sub>)<sup>[13]</sup> have also been used. The other procedures employing trialkylsilyl chloride,<sup>[14]</sup> rhodium complex,<sup>[15]</sup> tetramethyl guanidine,<sup>[16]</sup> NaOH-cetyltrimethyl ammonium chloride<sup>[17]</sup> and LiAlH<sub>4</sub><sup>[18]</sup> are also reported which are somewhat laborious and need the use of nitroalkanes in excess.

In the base catalyzed Henry reaction, aldol condensation and Cannizzaro reaction are the other competitive reactions, which need to be suppressed by adopting proper experimental conditions. The control of basicity is also essential to prevent the base catalyzed dehydration of the intermediate nitroalkanol to nitroalkenes, which is a bit difficult when aromatic aldehydes are used. Thus, to perform Henry reaction of aromatic aldehydes in the presence of a base but not allowing the formation of nitroalkene is of interest.

Potassium phosphate is a mild base and has recently been used as an effective catalyst in Knoevenagel condensation<sup>[19]</sup> and in the synthesis of hexasubstituted cyclotriphosphazenes<sup>[20]</sup> as well as dithiocarbamates<sup>[21]</sup> while the hydrated potassium phosphate is most recently used in the synthesis of aromatic ketones.<sup>[22]</sup> In view of our interest in the synthesis of natural products utilizing a nitroalkanol intermediate, we became interested in exploring the usefulness of potassium phosphate to effect nitroaldol condensation and we herein wish to report our findings obtained during the study.

As a case study, when a solution of *m*-nitrobenzaldehyde (1.51 g, 10 mmol) was stirred with nitroethane (0.83 g, 11 mmol) in the presence of catalytic amount of potassium phosphate (0.1 g, 0.46 mmol) desired nitroalkanol was obtained in almost quantitative yield (Sch. 1). To study the effect of solvent on the rate as well as yield of reaction, reactions were also



*Scheme 1.*



carried out in ethanol, water, acetonitrile and tetrahydrofuran medium and the results obtained (Table 1) clearly reveal that acetonitrile is the solvent of choice. In order to prove generality of the method, various aliphatic as well as aromatic aldehydes were condensed with nitroalkanes and the results obtained are summarized in Table 2. As expected, the rate of the reaction was found to be higher for aldehydes with electron withdrawing groups (entries 1 to 10) than for those having electron donating groups (entries 11 to 14). Especially with *p*-tolualdehyde and *p*-anisaldehyde (entries 11 to 14) the reaction did not go to completion even after modifying the reaction conditions such as the use of larger amount of catalyst, higher reaction temperature and higher proportion of nitroalkanes.

In conclusion, potassium phosphate was found to be an efficient base catalyst to effect nitroaldol reaction in excellent yields. The method affords a diastereomeric mixture of nitroalkanols but the interesting feature of this catalyst is that it does not bring about the dehydration of the resultant nitroalkanols even when used in excess.

## EXPERIMENTAL

General procedure: 1-(3-Nitrophenyl)-2-nitropropan-1-ol (2): To a stirred solution of nitroethane (0.83 g, 11 mmol) in acetonitrile (15 mL) was added anhydrous potassium phosphate (0.10 g, 0.46 mmol) followed by *m*-nitrobenzaldehyde (1.51 g, 10 mmol) and stirring continued. On completion of reaction (TLC monitoring) water (30 mL) was added to it and the reaction mixture was extracted with diethyl ether (50 mL). The ether extract was washed with water (3 × 20 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent gave a residue which was filtered through a short column of silica gel to afford 1-(3-nitrophenyl)-2-nitropropan-1-ol (2) (2.2 g, 93%) m.p. 74°C (Lit.<sup>10</sup> 74°C). IR (Nujol): 3510, 1520, 1352, 1210, 1050, 900, 816, 740 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.4 (d, *J* = 7.3 Hz, 3H), 1.5 (d, *J* = 5.8 Hz, 3H), 3.4 (d, *J* = 10.8 Hz, 1H), 4.7–4.85 (m, 1H), 5.2 (dd, *J* = 5.4 Hz each, 1H), 7.55–7.8 (m, 2H), 8.2 (m, 2H); <sup>13</sup>CNMR (50.3 MHz, CDCl<sub>3</sub>): δ 11.4, 15.8, 72.5, 86.5, 87.6, 120.8, 121.6, 123, 123.6, 129.5, 132, 133, 140, 147.9.

**Table 1.** Condensation of *m*-nitrobenzaldehyde with nitromethane.

Solvent	CH <sub>3</sub> CN	THF	EtOH	H <sub>2</sub> O
Time (min)	15	30	180	180
Yield (%)	95	93	60	30



**Table 2.** Potassium phosphate catalyzed preparation of nitroaldols.

Entry	R	R'	Time (min)	Yield (%) <sup>a,b</sup>
1	<i>m</i> -Nitrophenyl	CH <sub>3</sub>	15	95
2	<i>m</i> -Nitrophenyl	C <sub>2</sub> H <sub>5</sub>	20	93
3	<i>o</i> -Nitrophenyl	CH <sub>3</sub>	20	95
4	<i>o</i> -Nitrophenyl	C <sub>2</sub> H <sub>5</sub>	25	92
5	<i>p</i> -Chlorophenyl	CH <sub>3</sub>	35	93
6	<i>p</i> -Chlorophenyl	C <sub>2</sub> H <sub>5</sub>	45	89
7	<i>m</i> -Chlorophenyl	CH <sub>3</sub>	45	91
8	<i>m</i> -Chlorophenyl	C <sub>2</sub> H <sub>5</sub>	55	89
9	<i>o</i> -Chlorophenyl	CH <sub>3</sub>	50	95
10	<i>o</i> -Chlorophenyl	C <sub>2</sub> H <sub>5</sub>	55	90
11	<i>p</i> -Methylphenyl	CH <sub>3</sub>	180	45
12	<i>p</i> -Methylphenyl	C <sub>2</sub> H <sub>5</sub>	180	40
13	<i>p</i> -Methoxyphenyl	CH <sub>3</sub>	72 <sup>c</sup>	20
14	<i>p</i> -Methoxyphenyl	C <sub>2</sub> H <sub>5</sub>	72 <sup>c</sup>	10
15	Isopropyl	CH <sub>3</sub>	130	86
16	Isopropyl	C <sub>2</sub> H <sub>5</sub>	135	84
17	Ethyl	CH <sub>3</sub>	135	88
18	Ethyl	C <sub>2</sub> H <sub>5</sub>	135	81
19	<i>n</i> -Propyl	CH <sub>3</sub>	120	89
20	<i>n</i> -Propyl	C <sub>2</sub> H <sub>5</sub>	130	87

<sup>a</sup>All the compounds showed satisfactory spectroscopic data.

<sup>b</sup>Yields refer to pure isolated products.

<sup>c</sup>Time in hours.

The spectral data of all the other compounds synthesized were in agreement with those reported.<sup>[10]</sup>

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