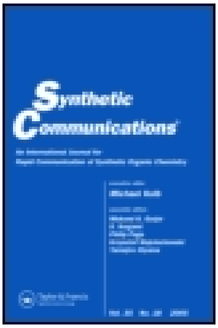

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Imidazole-Catalyzed Henry Reactions in Aqueous Medium

Mridula Phukan [a], Kalyan Jyoti Borah [a] & Ruli Borah [a]

[a] Chemical Sciences Department, Tezpur University, Napaam, Tezpur, Assam, India

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Imidazole-Catalyzed Henry Reactions in Aqueous Medium

Mridula Phukan, Kalyan Jyoti Borah, and Ruli Borah
Chemical Sciences Department, Tezpur University, Napaam,
Tezpur, Assam, India

Abstract: 2-Nitroalkanols can be efficiently synthesized using imidazole as a mild Lewis basic catalyst in aqueous medium as well as in organic solvents. The products have been found in good yields without purification ($>95\%$ purity by ^{1}H NMR) for aromatic aldehydes. Additionally, the very mild reaction conditions prevent the particular side reactions such as aldol condensation, Cannizzaro reaction, or dehydration of the 2-nitro alcohols into nitro alkenes even if aromatic aldehydes are used. This report satisfies the criteria for green synthesis in terms of reaction medium and recycling of the catalyst (imidazole).

Keywords: Aqueous medium, Henry reaction, imidazole, nitroalkane

INTRODUCTION

β-Nitroalkanols are considered useful intermediates in organic synthesis for various transformations,[1–3] especially for the synthesis of nitroalkenes, 2-amino alcohols, and 2-nitro-ketones. Moreover, they are also important as fungicides.[4] The nitroaldol reaction (Henry reaction) involves base-catalyzed addition of nitroalkanes to a carbonyl compound.[5,6] Several catalysts such as alkali metal hydroxides, alkaline earth oxides, carbonates, bicarbonates, alkoxides, and quaternary ammonium salts have been used for the nitroaldol reactions. However, nitroaldol reactions are associated with various competitive reactions[7,8] such as aldol condensation, Cannizzaro reaction, Tishchenko reaction,

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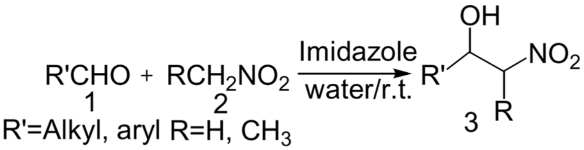
Address correspondence to Ruli Borah, Senior Lecturer, Department of Chemical Sciences, Tezpur University, Napaam, Tezpur 784028, Assam, India. E-mail: ruli@tezu.ernet.in



Scheme 1. Imidazole-catalyzed Henry reaction.

and Nef-type reaction. In addition, base-catalyzed elimination of water can lead to nitro-olefin, which polymerizes readily.[9] Recently, many new catalysts[10,11] have been developed for the Henry reaction such as rhodium complex, KG-60-NEt$_2$, 2:1 Mg–Al hydrotalcite, phosphine, guanidines, proazaphosphatranes, and ionic liquids. The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing attention to the use of less toxic and environmentally compatible materials in the design of new green methodologies.[12] Therefore, the development of new methodologies for the preparation of 2-nitroalkanols is very attractive in terms of greener reaction condition. Ballini and Bosica[13] reported an environmentally benign synthesis protocol for nitroaldol reaction in aqueous medium using cetyltrimethyl–ammonium chloride as catalyst. In addition, Ballini et al.[14] published another aqueous-phase Henry reaction in the presence of eco-friendly catalyst cetyltrimethylammonium hydroxide (CTAOH) at room temperature. In this communication, a new green synthetic method of nitroaldol reaction (Scheme 1) is reported using imidazole as catalyst in aqueous medium.

RESULTS AND DISCUSSION

In connection with our research interest in the development of green syntheses,[15] initially we decided to evaluate the effect of solvent on the imidazole-catalyzed Henry reaction in different organic solvents as well as in an aqueous medium. For this study, the reaction between p-nitrobenzaldehyde and nitromethane was chosen as a model. The reaction proceeds smoothly at room temperature in water (Table 1, entry 4) with 98% yield of β-nitroalcohol in 30 min. The reaction was carried out at room temperature in organic solvents such as dichloromethane, 1,4-dioxane, chloroform, tetrahydrofuran, acetonitrile, and methanol (Table 1). In the case of solvents such as dichloromethane, 1,4-dioxane, and chloroform (Table 1, entries 1–3) the conversions were quite similar to aqueous medium. Interestingly, the use of polar aprotic and protic organic solvents such as tetrahydrofuran, acetonitrile, and methanol

Table 1. Effect of solvent on the imidazole-catalyzed reactions of p-nitrobenzaldehyde with nitromethane

Entry	Solvent	Nitroalkane	Time (min)	Nitroalcohol[a,b] yield (%)
1	Dichloromethane	CH_3NO_2	35	94
2	1,4-Dioxane	CH_3NO_2	25	93
3	Chloroform	CH_3NO_2	30	92
4	Water	CH_3NO_2	30	98
5	Tetrahydrofuran	CH_3NO_2	5	95
6	Acetonitrile	CH_3NO_2	5	95
7	Methanol	CH_3NO_2	5	94
8	Tetrahydrofuran–water (1:1)	CH_3NO_2	5	92
9	Acetonitrile–water (1:1)	CH_3NO_2	5	95
10	Methanol–water (1:1)	CH_3NO_2	5	91
11	Dichloromethane–water (1:1)	CH_3NO_2	35	92
12	Chloroform–water (1:1)	CH_3NO_2	35	90

[a] Reactions were carried out on a 0.5-mmol scale (2 ml of solvent) in the molar ratio of aldehyde/nitromethane/catalyst = 1:3:0.25.

[b] Isolated yields of pure products.

(Table 1, entries 5–7) gave excellent conversion to the nitroaldol product within 5 min. This can be explained in terms of a homogeneous solution of reaction mixture with the catalyst imidazole in polar organic solvent, which possesses a slight amount of miscible water. Again, the reactants are in a different phase with the catalyst imidazole in a less polar organic solvent. Similarly, for an aqueous medium, the reactants are in different phases with the water-soluble catalyst imidazole. Thus, the aqueous medium reaction took a similar reaction period to less polar organic solvents. Carrying out the same reaction in a 1:1 mixture of various organic solvents and water medium (Table 1, entries 8–12) can indirectly prove this explanation. It was observed that the reaction completed within 35 min in a heterogeneous 1:1 mixture of less polar organic and aqueous solvent systems (Table 1, entries 11 and 12). Similarly, a homogeneous 1:1 mixture of polar organic and aqueous solvent systems showed comparable results with the polar organic solvent (Table 1, entries 8–10).

We next examined the extent and feasibility of the imidazole-catalyzed aqueous Henry reaction of nitroalkane with various aldehydes (Table 2). For aryl aldehydes bearing electron-withdrawing groups, the reaction took place smoothly to afford the desired nitroaldol products in good to excellent yields (Table 2, entries 3–7). However, for arylaldehydes bearing electron-donating groups such as p-tolualdehyde, anisaldehyde (Table 2, entries 8–12), and aliphatic aldehyde (Table 2, entries 13

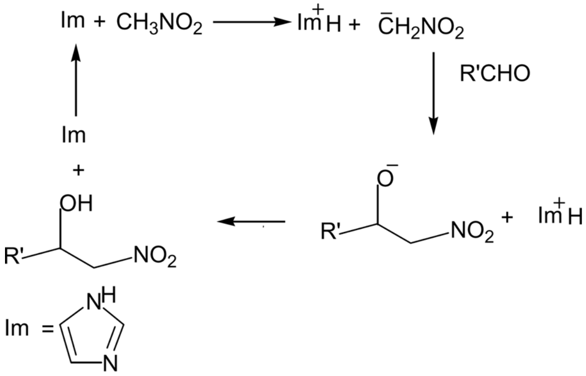
Table 2. Henry reaction in aqueous medium

Entry	R′ (1)	Nitroalkane (2)	Time	[a,b]Product (3) yield (%)
1	C_6H_5	CH_3NO_2	15 min	90
2	C_6H_5	$CH_3CH_2NO_2$	30 min	88
3	4-O_2N-C_6H_4	CH_3NO_2	30 min	98
4	2-O_2N-C_6H_4	CH_3NO_2	15 min	97
5	3-O_2N-C_6H_4	CH_3NO_2	15 min	90
6	4-O_2N-C_6H_4	$CH_3CH_2NO_2$	15 min	85
7	3-O_2N-C_6H_4	$CH_3CH_2NO_2$	15 min	94
8	4-MeC_6H_4	CH_3NO_2	45 min	96
9	4-$OMeC_6H_4$	$CH_3CH_2NO_2$	2 h	87
10	2-OHC_6H_4	CH_3NO_2	90 min	97
11	4-ClC_6H_4	CH_3NO_2	3 h	95
12	4-MeC_6H_4	$CH_3CH_2NO_2$	1 h	96
13	Pentanal	$CH_3CH_2NO_2$	12 h	60
14	Pentanal	CH_3NO_2	12 h	55
15	Furyl	$CH_3CH_2NO_2$	4 h	65

[a] All products were characterized by FT-IR, ^{1}H NMR, CHN analyzer and also their comparison with authentic sample.

[b] Isolated yields.

and 14), the reactions were slow. Similarly, the reaction of furaldehyde (Table 2, entry 15) with nitroethane was slow, resulting in 65% of the corresponding nitroalcohol after 4 h. The role of the imidazole catalyst appears to be that of a base that deprotonates the nitromethane, facilitating



Scheme 2. Possible reaction mechanism.

the nitroaldol reaction (Scheme 2). In addition, the imidazole-containing aqueous phase (after extraction of the product) was recycled (Table 2, entry 4) three times using a similar amount of 2-nitrobenzaldehyde (1 mmol).

EXPERIMENTAL

General Method for Henry Reaction in Aqueous Medium

A mixture of 2-nitrobenzaldehyde (1 mmol), nitromethane (3 mmol), and imidazole (0.25 mmol) was charged with 2 ml of distilled water. The heterogeneous reaction mixture was stirred at ambient temperature and monitored by thin-layer chromatography (TLC). After completion of the reaction, the product was extracted with 10 ml of diethyl ether. The organic layer was dried over anhydrous sodium sulfate and filtered. The organic filtrate was evaporated under reduced pressure and dried under vacuum to give the crude product, which is reasonably pure ($>95\%$ purity by ^{1}H NMR) for aromatic aldehydes. However, the residue was further purified by preparative TLC on silica gel to give the desired analytically pure products.

CONCLUSION

In summary, we have developed a new environmentally benign Henry reaction condition in aqueous media using imidazole as catalyst. The catalyst can be reused several times without appreciable loss of activity.

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