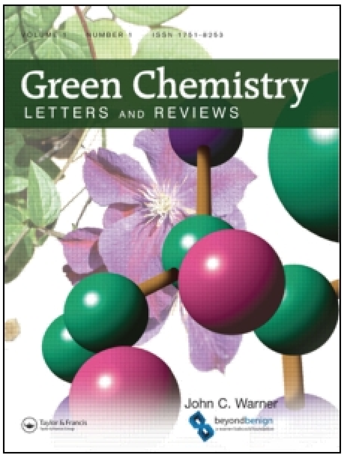

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RESEARCH ARTICLE

Henry reaction in environmentally benign methods using imidazole as catalyst

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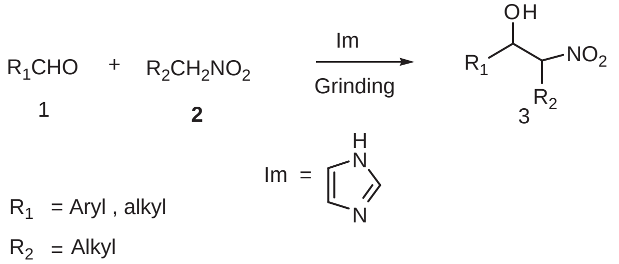
Imidazole has been found to be an efficient Lewis base catalyst for the synthesis of 2-nitroalkanols from nitro-aldol reaction in aqueous medium as well as using solvent-free grinding methods. In both cases, the products have been found in good to moderate yields without formation of any side product. Recycling of the catalyst is also possible with imidazole containing aqueous phase reaction medium (after extraction of product).



Keywords: imidazole; solid state; grinding; Henry reaction

Introduction

The principle of green chemistry (*1,2*) itself demands the use of less toxic chemicals and solvents in chemical processes. Many conventional chemical processes have been developed simply to maximize product yields, neglecting the environmental aspects of waste and toxic by-products formed during the process. The waste not only causes pollution but also requires expenditure for clean up. In recent years, design of green synthetic methodologies (*3–5*) to reduce energy consumption, use of toxic solvents and waste products has gained prime importance. The efficient use of non-toxic and more selective catalyst in solvent-free conditions is very desirable in the context of clean synthesis. Similarly, the use of water as a safe alternative (*6,7*) to volatile organic solvent is another attractive technique. Moreover, development of convenient and rapid synthetic procedures with high energy efficiency becomes significant.

The Henry reaction is one of the fundamental carbon–carbon bond (*8–10*) forming reactions in organic synthesis and has been one of the most useful methods for the preparation of β-nitroalkanols, which are considered as useful, intermediates in organic synthesis (*11–14*), for their easy transformation into useful derivatives such as nitroalkenes, 2-amino alcohols, and 2-nitro-ketones. β-Nitroalkanols are also important because of their properties as fungicides (*15*). The nitro-aldol reaction (Henry reaction) involves the base-catalyzed addition of nitroalkanes to a carbonyl compound. Several catalysts such as alkali metal hydroxides, alkaline earth oxides, carbonates, bicarbonates, alkoxides, alkaline earth hydroxides, and quaternary ammonium salts have been used for the nitro-aldol reaction. However, any base-catalyzed nitro-aldol reactions are associated with various competitive reactions (*16–20*) such as Aldol condensation, Cannizzaro reaction, Tishchenko reaction, and Nef-type reaction. In addition, the base-catalyzed elimination of water can lead to the formation of nitro-olefin, which polymerizes readily (*16–20*). Recently, many new catalysts (*21–26*) have been developed for the Henry reaction such as rhodium complex, KG-60-NEt_2, 2:1 Mg:Al hydrotalcite, phosphine, proazaphosphatranes, and ionic liquids. Thus it becomes necessary to adopt experimental conditions which suppress these competitive reactions and to have a careful control of the basicity

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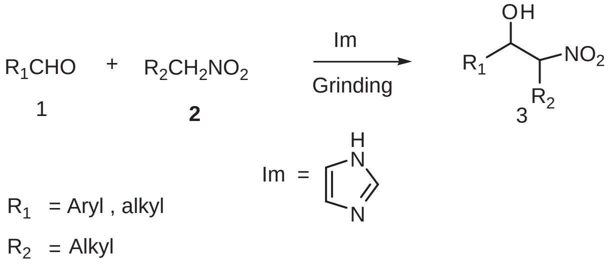
of the reaction medium to obtain a better yield of 2-nitro alcohols.

In the present scenario, solid-state chemistry is a fast-growing science. The pioneering work of Toda and his group (*27–29*) have shown that many reactions such as the Grignard reaction, Reformatsky reaction, and Aldol condensation can be conducted in high yield by simply grinding solids together using a mortar and pestle. Furthermore, these solid-state grinding reactions (or solvent-free reaction) have several advantages: more eco-friendly, low costs, higher yields and simplicity in process, and handling which are mainly important from the point of view of industrial manufacturing. These considerations serve as motivation for our efforts in developing new methodologies for the Henry reaction using a solvent-free grinding technique for the first time along with aqueous phase reaction using imidazole as a mild Lewis base catalyst.

In continuation of our research interest in the development of environmentally benign syntheses, recently, we have reported imidazole, a suitable base for catalyzing the Henry reaction in aqueous medium (*30*) and organic solvent which prevents side reactions. The catalyst in aqueous medium was recyclable several times without lost of catalytic activity. As such no reported work has been found regarding introduction of solid-state grinding to the Henry reaction this report describes the achievement of synthesizing 2-nitroalkanols **3** (Scheme 1) by hand grinding the aldehyde **1**, nitroalkane **2**, and catalytic amounst of imidazole (1:5:0.35) together using mortar and pestle. The addition of sand has given very satisfactory result in promoting the reaction between liquid–liquid and solid–liquid reagents pairs by grinding method by enhancing friction (*31*). The reaction proceeds by itself after initiation with a small amount of energy transfer through friction to the reactant molecule due to the exothermic nature of the Henry reaction. This approach to the reaction is more efficient in terms of energy consumption, rapid synthesis at ambient temperature, with moderate to good yields, no side product in solvent-free grinding condition.



Scheme 1. Imidazole catalyzed Henry reaction.

Results and discussion

In order to generalize the reaction procedure, two test experiments (Table 1, entry 1–2) were conducted by grinding together different molar ratios of (1:5:0.25 and 1:5:0.35, respectively) benzaldehyde, nitromethane, and imidazole as mild Lewis base catalyst. We found that the reaction shows the best result (entry 2) with molar ratios of 1:5:0.35 of benzaldehyde, nitromethane, and imidazole. With 0.25 mmol of imidazole, it yielded only 60% of 2-nitroalkanol within 5 minutes (entry 1) as monitored by TLC. Interestingly, 0.25 mmol of imidazole is however found to be sufficient to complete most of the reaction of the aromatic aldehyde within a short period of time in the aqueous phase as we have reported recently (*30*). Most probably, in solid state this amount of catalyst is not sufficient to catalyze the Henry reaction. Similarly, if we reduced the amount of nitromethane to 3 mmol in the solid state using 0.35 mmol of catalyst, it resulted in an incomplete of reaction (entry 3). We then examined the extent and feasibility of the imidazole catalyzed Henry reaction of nitroalkane with various aldehydes (Table 1) by solid-state grinding with a molar ratio 1:5:0.35 of aldehyde, nitroalkane, and imidazole. Under this novel condition, the reaction time was significantly shortened from hours by the classical method to minutes (entry 2) with improved yields (94%). Further investigations on the electronic effects of the substituted groups on the benzene ring of the aromatic aldehydes were done. For aryl aldehydes bearing electron-withdrawing groups, the reaction took place smoothly to afford the desired nitro-aldol products in good to excellent yields (entry 5–11). However, for arylaldehydes bearing electron-donating groups such as p-tolualdehyde, anisaldehyde (entry 12–19) the reactions were slow. With increasing chain length of nitroalkane, the reaction showed longer reaction time (entry 4, 7, 17, and 19). For aliphatic aldehyde (entry 22) the results are satisfactory on increasing the amount of catalyst from 0.35 to 0.5 mmol of imidazole. In a similar way, anisaldehyde showed 40–45% conversion with 0.5 mmol of catalyst (entry 16 and 17) as compared to 15% (entry 15) conversion with 0.35 mmol of catalyst in 3 hours. Furthermore, the addition of sand as a friction-enhancing solid has accelerated the rate of the Henry reaction tremendously (Table 2) for solid/liquid and liquid/liquid reagent pairs with 0.35 mmol of imidazole as catalyst. It was found that for pentanal in presence of sand the yield of 2-nitroalkanol increases from 60 (Table 1, entry 23) to 95% (Table 2, entry 13) within 45 min. Similarly, the reaction of furaldehyde (Table 2, entry 12) with nitromethane was also fast

Table 1. Imidazole catalyzed nitro-aldol condensation using solvent-free grinding method.

Entry	Aldehyde **1**	Nitroalkane **2**	Time (min)	Yield (%)[a] **3**
1	C_6H_5	CH_3NO_2	5	60[b]
2	C_6H_5	CH_3NO_2	5	94
3	C_6H_5	CH_3NO_2	5	50
4	C_6H_5	$CH_3CH_2NO_2$	20	95
5	4-$NO_2C_6H_4$	CH_3NO_2	70	75
6	4-$NO_2C_6H_4$	CH_3NO_2	15	95[c]
7	4-$NO_2C_6H_4$	$CH_3CH_2NO_2$	90	70
8	2-$NO_2C_6H_4$	CH_3NO_2	10	90
9	2-$NO_2C_6H_4$	$CH_3CH_2NO_2$	20	95
10	3-$NO_2C_6H_4$	CH_3NO_2	10	84
11	3-$NO_2C_6H_4$	$CH_3CH_2NO_2$	25	85
12	4-MeC_6H_4	CH_3NO_2	60	95
13	2-OHC_6H_4	CH_3NO_2	60	87
14	2-OHC_6H_4	$CH_3CH_2NO_2$	120	60
15	4-MeO-C_6H_4	CH_3NO_2	180	15
16	4-MeO-C_6H_4	CH_3NO_2	180	45[c]
17	4-MeO-C_6H_4	$CH_3CH_2NO_2$	210	40[c]
18	4-Cl-C_6H_4	CH_3NO_2	36	97
19	4-Cl-C_6H_4	$CH_3CH_2NO_2$	180	98
20	Furyl	CH_3NO_2	20	55
21	Furyl	$CH_3CH_2NO_2$	60	45
22	Pentanal	CH_3NO_2	90	90[c]
23	Pentanal	CH_3NO_2	45	60
24	Pentanal	$CH_3CH_2NO_2$	90	92[c]

[a] Isolated yields. All products were characterized by FT-IR, ^1H NMR, CHN analyzer, and also their comparison with authentic sample.
[b] These reactions was carried out in 1 mmol scale with molar ratio 1:5:0.25 of aldehyde/nitromethane/catalyst.
[c] Reactions were carried out in 1 mmol scale with molar ratio 1:5:0.50 of aldehyde/nitroalkane/catalyst.

resulting in 50% of the corresponding nitroalcohol after 12 min. The role of the imidazole catalyst appears to be that of a base which deprotonates the nitromethane, facilitating the nitro-aldol reaction.

In this report we have developed the first solid-state grinding method for the Henry reaction without formation of any side product using imidazole as a catalyst. The catalyst used is readily available, cost-effective and safe to handle.

Experimental

All chemicals are commercially available and were used without further purification. The products were

Table 2. Improved results of selected Henry reactions in presence of sand using solvent-free grinding method.

Entry	Aldehyde **1**	Nitroalkane **2**	Time (min)	Yield (%)[a] **3**
1	C_6H_5	$CH_3CH_2NO_2$	15	95
2	4-$NO_2C_6H_4$	$CH_3CH_2NO_2$	25	90
3	2-$NO_2C_6H_4$	$CH_3CH_2NO_2$	12	95
4	3-$NO_2C_6H_4$	$CH_3CH_2NO_2$	20	85
5	2-OHC_6H_4	$CH_3CH_2NO_2$	35	65
6	4-MeO-C_6H_4	$CH_3CH_2NO_2$	120	42
7	Furyl	$CH_3CH_2NO_2$	45	62
8	Pentanal	$CH_3CH_2NO_2$	75	94
9	4-MeC_6H_4	CH_3NO_2	15	95
10	2-OHC_6H_4	CH_3NO_2	25	88
11	4-MeO-C_6H_4	CH_3NO_2	90	60
12	Furyl	CH_3NO_2	13	50
13	Pentanal	CH_3NO_2	45	95

[a] Reactions were carried out in 1 mmol scale with molar ratio 1:5:0.35 of aldehyde/nitroalkane/catalyst in presence of 80 mg of sand.

identified by comparison of their FT-IR, ^{1}H NMR spectroscopic data and CHN analyzer data with those of authentic compounds (prepared by known method) and literature reported data (*32–34*).

General procedure for Henry reaction in solid-state grinding method

A mixture of aldehyde **1** (1 mmol), nitroalkane **2** (5 mmol), and imidazole (0.35 mmol) was gently ground by hand using a mortar and pestle of an appropriate size. The progress of the reaction was monitored by TLC (1:5 ethyl acetate and *n*-hexane) and indicates the formation of a single product along with an unreacted starting compound. The mixture becomes a sticky paste during the course of reaction. Finally, it was diluted with 10 ml of distilled water and the organic mixture was extracted with 15 ml of diethyl ether. The organic layer was dried over anhydrous sodium sulfate and filtered. The dried organic layer was evaporated under reduced pressure to give the crude reaction mixture. The crude mixture was further purified by column chromatography using different ratio of ethyl acetate and *n*-hexane as effluent to get the desired analytically pure products.

In this method, the above reaction mixture was ground for the appropriate amount of time by adding 80 mg of sand. The progress of the reaction was monitored by TLC (1:5 ethyl acetate and *n*-hexane) indicates the formation of a single product along with a small amount of starting compound. The sticky reaction mixture was diluted with 15 ml of diethyl ether and then filtered. The filtrate was again washed with 10 ml of distilled water for removal of water soluble catalyst from the reaction mixture. After that the ether layer was dried over anhydrous sodium sulfate and decanted. The ether extract was evaporated under reduced pressure to give the crude mixture which is again purified by column chromatography using different ratios of ethyl acetate and *n*-hexane as effluent to get the desired analytically pure products.

Spectral data of selected compounds

1-(4-methylphenyl)-2-nitroethan-1-ol (Table 1, entry 12): IR (film, cm^{-1}) 3437, 2925, and 1556. ^{1}H NMR ($CDCl_3$, δ ppm): 2.365 (s, 3H), 2.031–2.074 (br, 1H), 4.742–4.759 (m, 1H), 4.764–4.781 (m, 1H), 4.982–5.00 (m, 1H), 7.26 (d, 2H, $J = 8$ Hz), 7.34 (d, 2H, $J = 8$ Hz) CHN found: C, 59.3%; H, 6.1%; N, 7.5%, calculated for $C_9H_{11}NO_3$: C, 59.66%; H, 6.07%; N, 7.73%

2-Nitro-heptane-3-ol (Table 1, entry 24): IR (film, cm^{-1}) 3445 and 1553. ^{1}H NMR ($CDCl_3$, δ ppm): 0.824–.882 (6H, m), 1.1–1.3 (6H, m), 2.5 (br, 1H), 3.48–4.133 (m, 1H), 4.44–4.5 (m, 1H) CHN found: C, 52%; H, 9.1%; N, 8.5%, calculated for $C_7H_{15}NO_3$: C, 52.3%; H, 9.3%; N, 8.69%.

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