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Henry reaction in WELAN: A green approach

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Using natural feedstock extract we have successfully accomplished the Henry reaction at room temperature. Herein, we have used a very simple and highly abundant waste material to prepare natural base such as 'Water Extract of Leaf Ash of Neem' (WELAN). It is remarkable that the catalytic system does not require activation or any toxic ligand, additive/promoter, base, organic solvent and so on. A range of substituted aldehydes have been screened to investigate the scope of this protocol.

Keywords: Nitro-aldol reaction, Water Extract of Leaf Ash of Neem (WELAN), Nitromethane, Arylaldehydes

Among carbon-carbon bond-forming reactions, the synthesis of β-nitro alcohols by using Henry or nitro aldol reaction is one of the most widely studied methods in organic synthesis and has been the subject of continuous effort to improve better synthetic protocols over the years[1]. Basically, this reaction describes the coupling of an electrophilic aldehyde or ketone with a nucleophilic nitro alkane to produce a highly synthetically useful β-nitro alcohol because hydroxyl and nitro groups are in a vicinal relationship that provides a template for acquiring valued chemical entities including pharmaceuticals[2]. The conventional nitroaldol reaction is performed, as routine procedure, in presence of a base such as sodium methoxide, sodium hydroxide, sodium carbonate, barium hydroxide, tetrabutylamonium hydroxide, triethylamine, LDA, and butyl lithium in an organic solvent. At the present time, the significant aspect which is receiving growing attention is the use of alternative reaction media that avoid the problems associated with many of the traditional bases and volatile organic solvents[3]. To date, a lot of efforts have been made by researchers to carry out organic reactions in neat water[4]. Among those developed transformations, the Henry reaction is an unique example, which is one of the most versatile and powerful tools for the construction of nitro alcohols. Our interest is in using highly abundant natural feedstock extract to replace organic solvents in Henry reaction because feedstock extract provides the reaction with green and safe properties.

Literature report reveals that there are several methodologies of Henry reactions. But the practical applications of those methods was limited owing to the relatively stringent reaction conditions such as the use of hazardous organic solvents, longer reaction time, high temperature, use of expensive, less abundant catalysis and limited substrate scope[5].

Results and Discussion

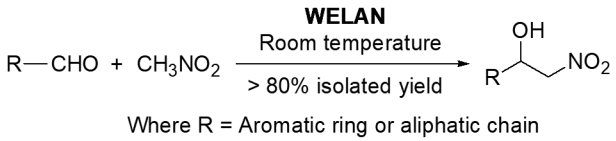
Herein, we present a highly novel protocol with broad applicability regarding the range of substrates and functional group tolerance for Henry reactions. In this communication, Water Extract of Leaf Ash of Neem (WELAN) was chosen as reaction media without using any external promoters, external base and organic co-solvents or biphasic media. Here, we have prepared the Water Extract of Leaf Ash of Neem (WELAN) (Scientific Name: *Azadirachta indica*; Family: Meliaceae) by first drying the neem leafs followed by burning to ash. Water was added to the ash, mixed well and then filtered. The filtered extract is termed as WELAN here. This system exhibits high thermal, air and moisture stability and shows superior catalytic activity in comparison to a variety of reported catalyst systems. There is no doubt that WELAN has very great potential in green chemical processes from the economic and environmental points of view in the near future.

In view of the potential of Henry reaction and the necessity to make industrial processes more environmentally friendly, we develop this catalytic concept to describe the first Henry reaction of various aliphatic/aromatic aldehydes on the use of novel basic aqueous extract WELAN. To the best of our

knowledge this is the first communication of the Henry reaction in neat Water Extract of Leaf Ash of Neem (WELAN) at RT without using any external base, toxic or hazardous reagent, additives/promoters and organic co-solvents (Scheme 1). It is highly significant to note that we have prepared our catalyst system from waste product. Consequently, we strongly believed that our catalyst system WELAN is the best and highly green catalyst ever reported. Therefore, the present synthetic method would be extremely beneficial and more efficient to synthetic chemistry community in the near future.

Our initial efforts focused on identifying the optimal reaction conditions for our proposed reaction and are shown in Table 1. At first we have explored the process by doing a typical reaction between 4-methoxybenzaldehyde and nitromethane by applying these truly nontoxic conditions using the natural feedstock WELAN as a neat reaction media at RT by using equivalent amount of the respective reactant. Under this reaction conditions the yield was relatively poor and therefore, we studied the effect of nitromethane equivalent on both the reaction yield and reaction time and it was observed that increasing the equivalent of CH_3NO_2 increased the product yield with somewhat increased in reaction time (Table 1, entries 1–3).

Based on our optimized results, several aromatic and aliphatic aldehydes were taken and examined their relevant possibility of Henry reaction as shown in Table 2. We were quite satisfied to see that our reaction could proceed for a wide range of aromatic aldehydes having electron-donating and electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions and up to 80% products were isolated after a reaction time of 2-3 h (Table 2, entries 1–5 and 7–13). Unusually, electron-withdrawing substituents such as fluoro, cyano and nitro on the phenyl ring of aromatic aldehydes somewhat enhanced the reaction (Table 2, entries 2–5). An excellent yield of the desired Henry products has been observed for aliphatic aldehydes, such as pentanal and octanal (Table 2, entries 16 and 17). Michael acceptor cinnamaldehyde gives both the Henry and Michael products under same reaction condition with equal yields (Table 2, entry 21). This feature would allow the present process to make a wide variety of nitroalcohols. In view of the results presented in this communication, we also believe that this is one of the best and greenest procedures ever reported for the title reaction and opens a new avenue to the Henry reaction. Therefore, the present synthetic method would be extremely beneficial and more efficient to the synthetic chemistry community.



Scheme 1 — Henry reaction in Natural Feedstock Extract at RT

Experimental Section

5 g of Leaf Ash of Neem (Scientific Name: *Azadirachta indica*; Family: Meliaceae) was taken in a 250 mL beaker and add 100 mL of distilled water and mixed well for 10 min. The mixture was then filtered through sintered glass crucible and the filtrate was used as WELAN.

General experimental procedure for Henry reaction

A mixture of arylaldehydes (1 mmol), nitromethane (3 mmol) in WELAN (3 mL) was stirred for the indicated time at RT. Afterwards, the reaction solution was extracted four times with diethyl ether (4 × 10 mL). The products were purified by column chromatography over silica gel using *n*-hexane–ethyl acetate (9:1 v/v) to obtain the desired coupling products. The products were characterized using IR, ^{1}H NMR and GC-MS.

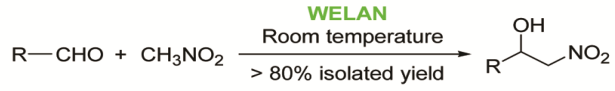
1-(4-Methoxy-phenyl)-2-nitro-ethanol, 1a: Yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.93 (1H, s),

Table 1 — Effects of the nitromethane equivalent and time in the Henry reaction in neat WELAN at RT [a]

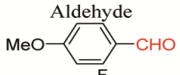
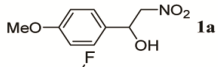
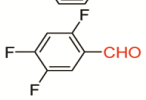
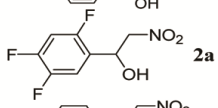
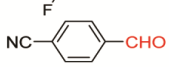
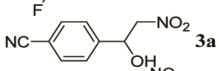
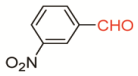
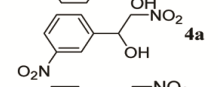
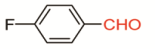
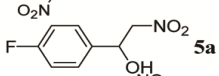
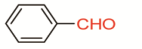
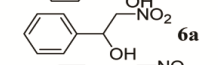
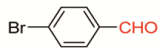
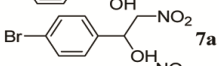
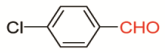
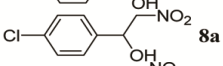
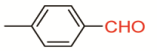
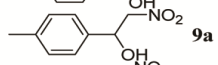
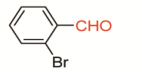
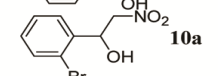
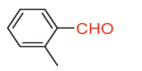
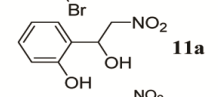
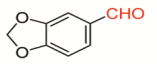
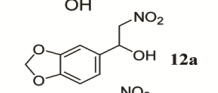
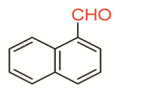
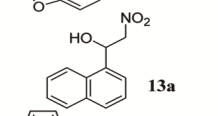
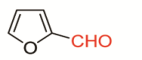
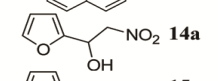
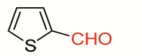
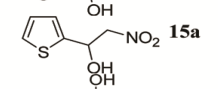
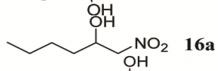
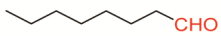
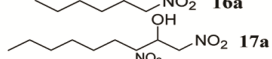
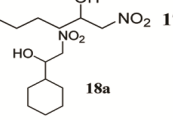
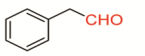
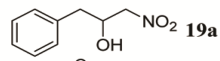
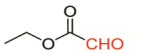
Entry	CH_3NO_2 (equiv.)	Time (h)	Yield [b] (%)
1	1	1	40
2	1.5	2	50
3	3	2	85

[a] Reaction conditions: 4-Methoxybenzaldehyde (1 mmol), nitromethane (3 mmol) in WELAN at RT.
[b] Yield refers to isolated yields

Table 2 — Formation of nitroalcohols from aryl/alkylaldehydes in neat WELAN at RT [a]



Where R = Aromatic ring or aliphatic chain

S. No.	Aldehyde	Product	Time (h)	Yield [b] (%)
1		 **1a**	2	82
2		 **2a**	2	92
3		 **3a**	3	86
4		 **4a**	3	82
5		 **5a**	2	88
6		 **6a**	3	85
7		 **7a**	3	88
8		 **8a**	2	90
9		 **9a**	2	88
10		 **10a**	2	93
11		 **11a**	2	87
12		 **12a**	3	78
13		 **13a**	3	78
14		 **14a**	3	92
15		 **15a**	3	85
16		 **16a**	2	90
17		 **17a**	2	91
18		 **18a**	3	92
19		 **19a**	3	80
20		**20a**	3	81
21		**21a** Nitro Aldol **21b** Michael and Nitro Aldol	3 3	44 41

[a] Reaction conditions: Arylaldehydes (1 mmol), nitromethane (3 mmol) in WELAN (3 mL) at RT.
[b] Yields refer to isolated yields.

3.81 (3H, s), 4.44 (1H, d, *J*=12.4 Hz), 4.56 (1H, t, *J*=10 Hz), 5.39 (1H, d, *J*=8 Hz), 6.9 (2H, d, *J*= 7.6 Hz), 7.31 (2H, d, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.45, 70.61, 80.26, 114.30, 127.0, 128.61, 130.50, 159.91; IR (KBr): 3378, 3083, 2943, 2896, 2780, 1612, 1536, 1425, 1182, 1050, 790, 663 cm^{-1}.

2-Nitro-1-(3-nitrophenyl)ethanol, 4a: Yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (1H, s), 4.46-4.77 (2H, m), 5.62-5.67 (1H, m), 7.65 (1H, t, *J*=8 Hz), 7.73 (1H, d, *J*=8 Hz), 8.15 (1H, d, *J*=8 Hz), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 69.81, 80.81, 121.19, 123.67, 130.27, 132.32, 140.34, 148.44; IR (KBr): 3304, 3075, 2956, 2870, 1612, 1545, 1511, 1437, 1368, 1329, 1095, 1058, 775, 668 cm^{-1}.

1-(4-Chlorophenyl)-2-nitroethan-1-ol, 8a: Colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.51 (1H, s), 4.52 (1H, d, *J*= 3.6Hz), 4.76 (1H, t, *J*= 7.2 Hz), 5.41-5.48 (1H, m), 7.21 (2H, d, *J*=8.4 Hz), 7.37 (1H, d, *J*=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 70.22, 127.31, 129.20, 128.87, 132.71, 138.29; IR (KBr): 3408, 3035, 2979, 2989, 2756, 1536, 1428, 1389, 1326, 1275, 1185, 1115, 840, 756 cm^{-1}.

1-Nitro-hexan-2-ol, 16a: Light yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92-0.97 (3H, m), 1.31-1.39 (4H, m), 2.11 (3H, d, *J*=4.4), 2.61 (1H, s), 3.89-3.91 (1H, m), 4.21-4.24 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.68, 16.21, 18.31, 34.87, 71.3, 86.35; IR (KBr): 3306, 2946, 2830, 1608, 1536, 1206, 1148, 1035, 838, 755 cm^{-1}.

2-Nitro-1-phenylethanol, 18a: Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (s, 1H), 4.58-4.34 (m, 2H), 5.38-5.20 (m, 1H), 7.47-7.20 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.14, 77.67, 113.49, 117.59, 127.16, 135.18; IR (KBr): 3429, 3018, 2408, 1553, 1433, 1221, 1035, 963, 777, 677 cm^{-1}.

Conclusion

In conclusion, we have reported a very environment-friendly procedure for Henry reaction using abundant natural waste at RT with high substrate variety. No use of mineral base, organic solvents or other additives/promoters and method gives the excellent yields of the desired Henry products. Our protocol not only establishes a new methodology to synthesize β-nitro alcohols, but also gives a very efficient green catalyst system for the nitro aldol reactions of some challenging aliphatic aldehydes. In terms of both economic and environmental considerations, we believe that this protocol holds potential value in the laboratory and industry in the near future. All these advantages make WELAN a competitive catalyst and thus can be a clean and suitable alternative for other industrially important reactions. Further work is in progress to exploit this natural extract (WELAN) in different valuable organic transformations.

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