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# The Ultrasound Promoted Knoevenagel Condensation of Aromatic Aldehydes.

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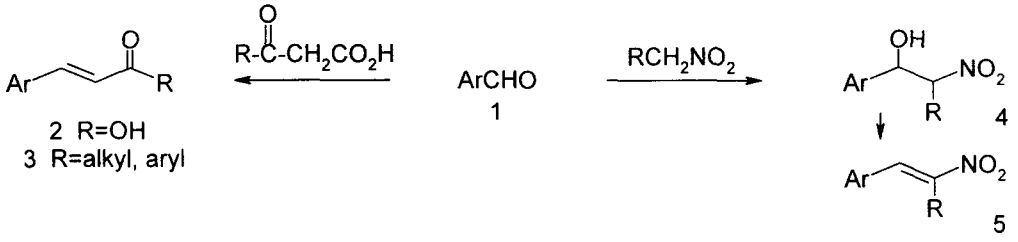
**Abstract:** Application of ultrasound has been found to greatly assist the Knoevenagel aldol condensation reaction of activated methylenes with aromatic aldehydes under mild conditions. The outcome of the ultrasound-promoted reaction depends upon the electronic nature of the aromatic aldehyde, the solvent employed and the addition of acids, bases or ammonium salts. 

***Keywords***: Aldol reactions; sonochemistry; alkenes; nitro compounds

The Knoevenagel condensation reaction of carbonyl-containing compounds with active methylenes is a classic general method for the preparation of valuable synthetic intermediates.[2] Examples include the condensation of aromatic aldehydes **1** with active methylenes such as malonic acid or ß-ketoacid derivatives, allowing access to cinnamic acid derivatives **2** and cinnamyl ketones **3**, while the use of nitroalkanes (Henry reaction) as the methylene component[3] leads to nitroaldol products **4** or nitroalkenes **5**, (Scheme 1). Our interest in this reaction stems from the value of the products **2-5** as substrates for asymmetric catalysis and as versatile reactive intermediates in the preparation of compounds of medicinal interest.[4]

Scheme 1




A multitude of promoters have been developed for these reactions including acids, bases and ammonium salts. Typical conditions to effect the condensation of nitroalkanes with aromatic aldehydes consist of heating an acetic acid solution of the aldehyde with the appropriate nitroalkane with ammonium acetate at 100 °C for a few hours.[5] In this way nitroalkenes **5** may be isolated in moderate to high (30-95%) yield depending on the aldehyde used. We have observed lower yields of nitroalkenes result from the condensation of electron rich aromatic aldehydes, a result that may be general.[6] For example, under these standard Henry conditions, 2,3-dimethoxybenzaldehyde **1a** condensed with nitromethane to give the nitroalkene **5a** in only 35% yield, the mother liquors being contaminated with a resinous non-crystalline material that we attributed to phenol-

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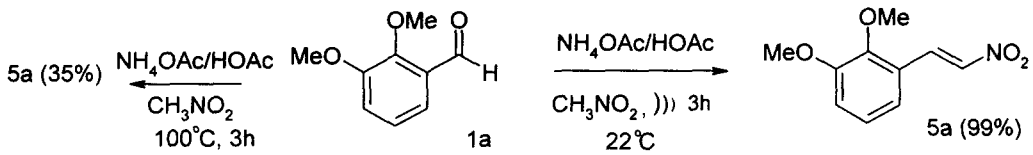
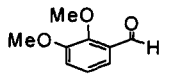
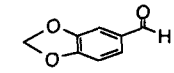
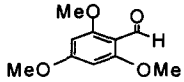
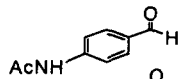
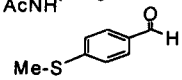
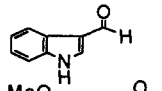
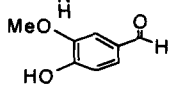
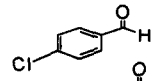
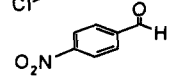
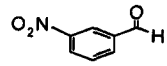
formaldehyde type polymerization. Recent reports concerning the ultrasound promoted elimination of HI from nitroalkanes to yield nitroalkenes[7] and ultrasound promoted carbonyl addition reactions[8,9] led us to consider the application of ultrasound as a low temperature promoter of the above Henry reaction. Repetition of the reaction of **1a** with the same reagents but at room temperature and application of ultrasound led to a rapid, clean condensation (complete in 3h) and subsequent isolation of the nitroalkene product **5a** in 99% yield, with no resinous side products being produced, (Scheme 2). This result prompted us to investigate the scope of the method further.[10]

Scheme 2




No reaction occurs under these conditions at room temperature until ultrasound is applied. In addition, attempts to conduct the ultrasound promoted reaction at room temperature without acetic acid, or without ammonium acetate, failed. Other studies using primary or secondary amines in place of ammonium acetate were not as successful. The ultrasound promoted reaction proved to be general (Table 1) for a variety of

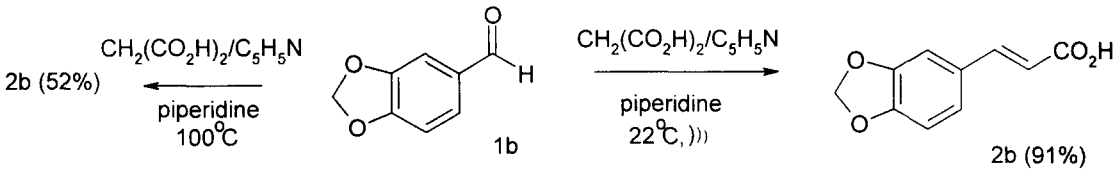
Table 1
Ultrasound Promoted Nitroaldol Reactions

| Entry | | Method[10] | Product | Yield |
|---|---|---|---|---|
|  | 1a | A | 5a | 99 |
|  | 1b | A | 5b | 99 |
|  | 1c | A | 5c | 85 |
|  | 1d | A | 5d | 95 |
|  | 1e | A | 5e | 96 |
|  | 1f | A | 5f | 93 |
|  | 1g | A | 5g | 89 |
|  | 1h | B | 4h | 70 |
|  | 1i | B | 4i | 61 |
|  | 1j | B | 4j | 51 |

electron rich aromatic aldehydes under these conditions.[10] High yields of nitroalkenes were isolated for all alkoxy-substituted aromatic aldehydes investigated. Thus, piperonal **1b** reacted to give nitroalkene **5b** (99%) while the 2,4,6-trimethoxy derivative **1c** gave nitroalkene **5c** (84%) demonstrating steric factors to be of little detriment. The hetero-substituted aldehydes **1d** and **1e** and indole-3-carboxaldehyde **1f** also produced the corresponding nitroalkenes efficiently, as did vanillin **1g** without protection of the phenolic hydroxyl, whereas the aromatic ketones acetophenone and benzophenone failed to react. Electron deficient aromatic aldehydes also reacted under our ultrasound promoted conditions but the major product proved to be the corresponding nitroaldols **4**, isolated in poor yield. Modification to the conditions by changing to base catalysis improved the yields to 50-70%. Sonication of a solution of 4-chlorobenzaldehyde **1h** according to method B[10] allowed for isolation of the nitroaldol **4h** in 70% yield. This method proved general for electron deficient aldehydes. Both 3-nitro and 4-nitrobenzaldehyde gave the corresponding nitroaldols **4i** and **4j** in good isolated yield.

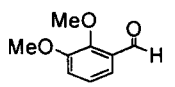
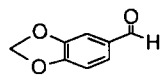
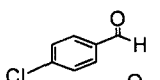
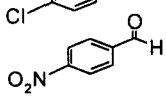
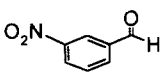
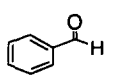
Extension of the ultrasound-promoted condensation to produce cinnamic acid derivatives proved less dependent upon the electronic nature of the starting aromatic aldehyde and much more efficient than classical reflux conditions. Classic Doebner modified condensation of piperonal **1b** (Scheme 3) with malonic acid in pyridine and piperidine (cat.)[3] under reflux for 3h gave cinnamic acid derivative **2b** in 52 % isolated yield.

Scheme 3




When the same reaction mixture was allowed to proceed at room temperature under sonication for 2-3h, the cinnamic acid derivative **2b** was isolated in 91% yield. Both reactions were worked up under identical

Table 2
Ultrasound Promoted Knoevenagel Reactions

| Entry | | Method[10] | Product | Yield |
|---|---|---|---|---|
|  | 1a | C | 2a | 75 |
|  | 1b | C | 2b | 91 |
|  | 1h | C | 2h | 99 |
|  | 1i | C | 2i | 87 |
|  | 1j | C | 2j | 61 |
|  | 1k | C | 2k | 99 |

conditions; precipitation into hydrochloric acid, filtration and recrystallization. The application of ultrasound is clearly superior to classical reflux conditions.[2,3] The same procedure (Table 2) applied to aldehyde **1a** gave the cinnamic acid derivative **2a** in good yield as did other alkoxy substituted aldehydes investigated. Further extension to the electron deficient aldehyde 4-chlorobenzaldehyde **1h**, under the same reaction conditions, furnished the corresponding 4-chlorocinnamic acid **2h** in an isolated yield of 99%. This result proved to be general for the other electron deficient aldehydes investigated. 4-Nitrobenzaldehyde **1i** and 3-nitrobenzaldehyde **1j** gave the cinnamic acid derivatives **2i** and **2j** in yields of 87 and 61% respectively, while benzaldehyde itself yielded cinnamic acid **2k** in near quantitative yield. As in the case of the Henry conditions, aromatic ketones such as benzophenone did not enter into reaction under these conditions.

Nitroalkene **5** and cinnamic acid **2** derivatives of simple electron rich aromatic aldehydes are highly valuable synthetic intermediates in the preparation of compounds of medicinal value.[4,6,11] In addition, they are valuable substrates for catalytic enantioselective reactions such as conjugate addition, cycloaddition, epoxidation, aziridination, etc.[12-14] The application of ultrasound in promoting the Knoevenagel condensation to produce these intermediates offers several advantages over classic refluxing methods. In addition to the general nature of the process described, the lower temperatures employed under ultrasound promotion allow for higher yields of isolated product due to less side reactions such as polymerization occurring. The reactions are also easily scaled-up to multi-gram levels.[10] The lower temperatures are also likely to allow selective condensation in cases involving acid or base labile substrates.

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10. General procedures. Nitromethane and pyridine (Aldrich) were freshly distilled. Ultrasound reactions were performed using a Branson 5510 ultrasound bath or a Crest Tru-Sweep ultrasonic cleaner with little difference. Method A: A mixture of aldehyde (20.0mmol), nitromethane (13.0mL), glacial acetic acid (3.3mL) and ammonium acetate (3.324g), sonicated at 22 °C for 3h. After removal of nitromethane, partition between dichloromethane and water then brine gave crude product which was recrystallized from aq. ethanol (except **5d**, AcOH). Method B: A solution of aldehyde (1.00mmol), nitromethane (1.0 mL), ammonium acetate (2.5 mmol) and diisopropylethylamine (0.1 mmol) was sonicated at 22 °C for 3-6h, according to tlc. After removal of solvents, work-up as above gave the crude product which was purified on silica gel. Method C: A solution of aldehyde (1.00 mmol), malonic acid (2.18 mmol) in pyridine (5.7 mmol) and piperidine (0.20 mmol) was sonicated at 22°C for 3h. Solution added to 5% aq. HCl, chilled and filtered by suction. The precipitate was recrystallized from aq. ethanol.
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