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Microwave-Assisted Henry Reaction: Solventless Synthesis of Conjugated Nitroalkenes[§]

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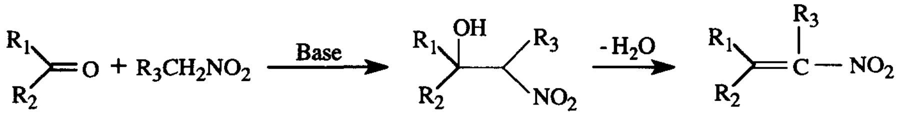
Henry reaction; Microwave irradiation

Abstract: In a solventless system and under microwave irradiation, nitroalkanes react with arylaldehydes in the presence of a catalytic amount of ammonium acetate to afford, in one step, conjugated nitroalkenes without the isolation of intermediary β-nitro alcohols.

Nitroalkenes are abundantly utilized for the preparation of a variety of organic compounds[1] and possess significant biological activities such as insecticidal[2,3] fungicidal,[3-6] bactericidal,[7,8] rodent-repellent[9] and antitumor agents.[10] The utility of nitroalkenes in organic synthesis is largely due to their ease of conversion into a variety of functionalities. They are strong dienophiles in Diels-Alder reactions and alternatively, these electrophilic alkenes readily undergo addition reactions with various nucleophiles thus providing an array of valuable products.

The most versatile synthesis of nitroalkenes involves the Henry condensation reaction of a carbonyl compound **1** with nitroalkane **2** to give β-nitro alcohol **3** which undergoes dehydration affording conjugated nitroalkene **4** (**Eqn.**).[11] This condensation reaction is usually accomplished under mildly basic conditions.



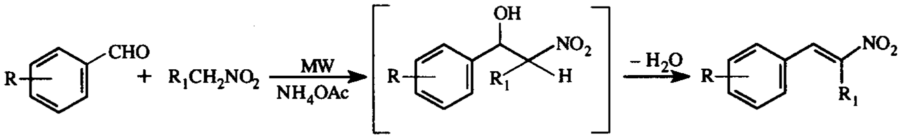
(**Eqn.**)

1 **2** **3** **4**

Several reagents such as phthalic anhydride,[12,13] methanesulfonyl chloride,[14] dicyclohexylcarbodiimide (DCC),[15] pivaloyl chloride,[16,17] ammonium acetate-acetic acid[18,19] and amines[7,19] have been used for the dehydration of the ensuing β-nitro alcohols. However, some of these reactions require elevated temperature and may not be amenable to the dehydration of functionalized nitroalcohol intermediates.

The significance of nitroalkenes in organic synthesis[1] and our continued interest in the development of environmentally benign synthetic protocols using microwave (MW) irradiation under solvent-free 'dry' conditions,[20] prompted us to investigate the Henry reaction that involves the excessive use of nitrohydrocarbons. We wish to report herein a solventless synthesis of conjugated nitroalkenes using microwaves in the presence of catalytic amount of ammonium acetate. The method reduces longer reaction times and requirement of large quantities of nitrohydrocarbons that normally play the dual role of a solvent as well as a reactant in the conventional solution phase chemistry. Microwave heating has been used for a wide variety of applications including the rapid synthesis of organic compounds.[21-24] The useful solution phase chemistry utilizing microwaves[22] is finding numerous applications under solventless 'dry' conditions where the MW effect is more pronounced.[20,23-24] The environmentally benign aspect of the approach is obvious in view of the elimination or reduction of solvents which are normally employed in large amounts.

The condensation of aldehydes with nitroalkanes using a catalytic amount of ammonium acetate (0.25 mmol/mmol of carbonyl compound used) coupled with the pulsed microwave irradiation is found to be an ideal condition that affords high yields of the conjugated nitroalkenes directly without the isolation of the intermediary β-nitroalcohols. That the effect is not purely *thermal*[25] is supported by the fact that using an alternate heating mode (oil bath) at the same temperature of 90 °C, the reaction (α-naphthaldehyde, entry **8j**) could be completed in 18 hours.



5 **6** **7** **8**

Table: Microwave-assisted synthesis of conjugated nitroalkenes.[a]

Entry	R	R_1	Time (min)	Yield (%)[b]	m.p. (Lit) (°C)
8a	H	H	8.0	80	58 (58-9)[19]
8b	4-OH	H	4.0	88	165 (168-9)[19]
8c	3-MeO-4-OH	H	3.0	89	166 (167-8)[19]
8d	3,4-$(MeO)_2$	H	2.5	90	139 (141-2)[19]
8e	H	CH_3	7.0	83	64 (64-5)[19]
8f	4-OH	CH_3	3.5	89	124 (124-5)[19]
8g	3-MeO-4-OH	CH_3	3.0	91	100 (100-1)[19]
8h	3,4-$(MeO)_2$	CH_3	3.0	92	66 (67-8)[19]
8i	4-MeO	CH_3	4.0	90	44 (44-5)[19]
8j	1-Naphthyl	H	8.0	80	76 (72-74)[26]
8k	2-Naphthyl	H	7.5	83	121 (121-2)[27]

[a] Although we have not used any special safety equipment because of adequate air ventilation of the microwave cavity but prudent care is recommended in view of the flammable and irritant nature of the nitrocompounds.

[b] Unoptimized yields of the products that exhibited physical and spectral characteristics in accord with the assigned structures.

In a typical synthetic procedure, a mixture of benzaldehyde **5a** (0.106 g, 1 mmol) and nitromethane **6a** (0.061 g, 1 mmol) is placed in a glass tube containing ammonium acetate (0.019 g, 0.25 mmol) and is exposed to pulsed microwave irradiation[28] in an alumina bath for 2 min using an unmodified microwave oven operating at its 40% power.[25] The reaction mixture is cooled to room temperature (~ 1 min) and is irradiated again for 2 min. After two such successive irradiations (2 min) and cooling (~ 1 min) sequences, another 1 mmol of nitromethane is added to the reaction mixture that is further irradiated for two similar successions. After completion of the reaction (followed by TLC), the reaction mixture is passed through a short silica gel column using hexane:AcOEt (9:1,v/v) as an eluent. The evaporation of the solvent on a rotary evaporator affords β-nitrostyrene (**8a**). Other nitroalkenes prepared following this general procedure are summarized in the **Table**.

In conclusion, we have developed an environmentally benign method for the rapid synthesis of conjugated nitroalkenes that avoids the use of excessive nitrohydrocarbons and proceeds in high yields.

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[§] A part of this work was presented in *First World Congress on Microwave Processing*, Abstr. # XIV-3, Lake Buena Vista, Florida, 5-9 January, 1997; For commentary on this congress proceedings see: Dagani, D. *Chem. Eng. News* February 10, **1997**, 26.

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