Nitroaldol (Henry) reaction of 2-oxoaldehydes with nitroalkanes as a strategic step for a useful, one-pot synthesis of 1,2-diketones†

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The nitroaldol (Henry) reaction of 2-oxoaldehydes with a variety of nitroalkanes, under basic heterogeneous conditions and microwave irradiation, affords 1,2-diketones in a one-pot way. The key step of the process involves the nitrous acid elimination from the nitroalkanol intermediates instead of the standard water elimination.

1,2-Diketones are a powerful class of molecules widely used as key building blocks in organic synthesis† for the preparation of a large variety of heterocyclic targets, and present in several biologically active compounds. Given their great importance, over the years a number of procedures have been proposed in the literature for their preparation. The most valuable ones are: via (i) oxidation of alkynes, (ii) oxidation of alkenes, (iii) oxidation of ary ketones, (iv) rearrangement of α,β-epoxy ketones, (v) nucleophilic acylation of esters, (vi) reductive cross-coupling reactions of imines with nitriles, (vii) carbonation-diketonization of terminal aromatic alkenes with nitroalkanes, and (viii) reaction of α-oxo acid chlorides with organostannanes. In summary, they could be classified in two distinct approaches: (a) transformation of substrates maintaining the same carbon backbone (e.g. i–iv) and, (b) ex-novo structure construction, by new C–C bonds generation, through a reaction between specific nucleophiles and electrophiles (e.g. v–viii).

Although the first approach requires the preparation of precise substrates, the approach (b) seems to be more flexible but presents important limitations such as the need of very low temperature, inert atmosphere, usage of toxic reagents, and autoclave. Furthermore, all the reported procedures involve an articulate work-up, with evident disadvantages from ecological point of view. In this context, the sustainability of a chemical process is one of the main aspect that, nowadays, must be considered, and the implementation of new simple, mild and greener methodologies is of dramatic importance.

Since its discovery, the nitroaldol (Henry) reaction has become one of the most valuable methods for the generation of C–C bonds† and as key starting synthetic step for the preparation of important fine chemicals, often with important ecological advantages. Thus, following our studies on the nitroaldol reactions, and with the aim to discover a more efficient and general method for the production of the title compounds, we focused our attention to the α-oxoaldehydes as strategic partners of nitroalkanes in the Henry reaction.

Our idea was the formation of the 3-nitro-2-alkanols in which the elimination of nitric acid vs. the conventional water elimination is favoured (during experiments, no trace of the dehydrated specie was detected, Scheme 1). The driving force of the reaction can be rationalized with the increased acidity of the proton in 2-position, due to the geminal presence of carbonyl moiety, which leads to the irreversible elimination of HNO2 affording the enolic form, which acts as the spontaneous precursor of the 1,2-diketones.

In this context, to the best of our knowledge, only a sporadic example of Henry reaction involving nitric acid elimination was reported in literature, which anyway, seems to work in moderate yields just with 2-quinolinecarboxaldehyde and in the presence of a large excess of simple nitroalkanes (3 equivalents).

![Scheme 1](image_url)
Initially, with the aim to optimized our approach, we studied the process as two distinct separate steps: (i) the Henry reaction between 1a and 2a, and (ii) the conversion of 3aa into 5aa. Concerning the Henry reaction, we did a deep screening in terms of base type, stoichiometry and solvents (Table 1).

The best result (entry i, yield = 76%) was obtained using Amberlyst A21 (0.5 g mmol⁻¹) at room temperature (5 hours) at in presence of a slight excess of conventional oil bath. In conclusion we have found a new, general, efficient strategy to provide an easy, sustainable synthesis of 1,2-dicarbonyl derivatives, in fact the title compounds can be prepared in a one-pot way, in good overall yields, and avoiding any elaborate and wasteful work-up. In addition, our report expands the extraordinary synthetic potential of the nitroaldol (Henry) reaction.

Finally, we extended our study to a variety of nitroalkanes and α-oxoaldehydes obtaining in all cases from moderate to good overall yields (Table 3), thus demonstrating the generality of our protocol. In addition, thanks to the mildness of the reaction conditions, several functionalities such as chlorine, fluorine, nitro, ketal, cyano and ester, can be preserved. Furthermore, thanks to the use of Amberlyst A21, as solid supported base, the work-up can be minimized to an easy filtration saving resources and time and thus reducing the waste generation. It is important to point out that the overall transformation (1 + 2 to 5) makes the nitroalkane 1 as a synthetic equivalent of the carbanionic A, while the aldehyde 2 acts as the synthetic equivalent of the acyl cation synthon B (Fig. 1).

**Conclusions**

In conclusion we have found a new, general, efficient strategy to provide an easy, sustainable synthesis of 1,2-dicarbonyl derivatives, in fact the title compounds can be prepared in a one-pot way, in good overall yields, and avoiding any elaborate and wasteful work-up. In addition, our report expands the extraordinary synthetic potential of the nitroaldol (Henry) reaction.

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Table 3  Synthesis of 1,2-diketones 5

| R¹       | R²       | R³       | Time¹ (h) | Yield² (%) |
|----------|----------|----------|-----------|------------|
| 1a Bu    | H        | 2a Ph    | 5         | 5aa 75     |
| 1b n-Pr  | H        | 2a Ph    | 5         | 5ba 72     |
| 1c CH₃(OCH₂CH₂O)₄CH₃ | H     | 2a Ph    | 4         | 5ca 70     |
| 1d Ph₂(C₆H₄)₂ | H  | 2a Ph    | 5         | 5da 76     |
| 1e Ph₂(C₆H₄)₂ | H  | 2b 2-F-C₆H₄ | 5    | 5db 68     |
| 1f Cl₂(C₆H₄)₂ | H  | 2c 4-MeO-C₆H₄ | 6   | 5ec 62     |
| 1g NC(CH₃)₄ | H  | 2d 2-Naphthyl | 6   | 5fd 74     |
| 1h CH₃(CH₂)₄ | H  | 2d 2-Naphthyl | 6   | 5hd 71     |
| 1i MeOOC(CH₂)₄ | H  | 2a Ph    | 5         | 5ia 70     |
| 1j Me     | Me       | 2e 4-NO₂-C₆H₄ | 12  | 5je 42     |
| 1k -(CH₂)₄- | 2a       | Ph       | 15        | 5ka 51     |

¹ Yield of pure isolated product.

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