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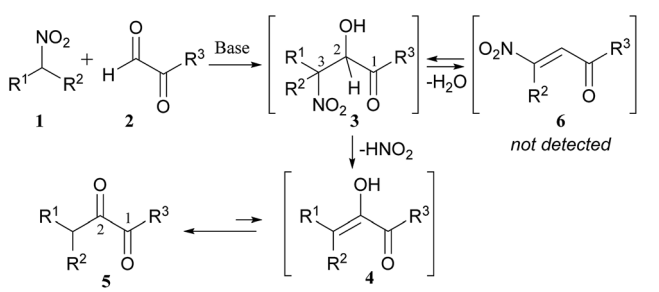
The nitroaldol (Henry) reaction of 2-oxoaldehydes with a variety of nitroalkanes, under basic heterogeneous conditions and microwave irradiation, affords 1,2-diketones in a one-pot way. The key step of the process involves the nitrous acid elimination from the nitroalkanol intermediates instead of the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

1,2-Diketones are a powerful class of molecules widely used as key building blocks in organic synthesis[1] for the preparation of a large variety of heterocyclic targets,[2] and present in several biologically active compounds.[3] 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,[4] (ii) oxidation of alkenes,[5] (iii) oxidation of aryl ketones,[6] (iv) rearrangement of α,β-epoxy ketones,[7] (v) nucleophilic acylation of esters,[8] (vi) reductive cross-coupling reactions of imines with nitriles,[9] (vii) carbonation-diketonization of terminal aromatic alkenes with nitroalkanes,[10] and (viii) reaction of α-oxo acid chlorides with organostannanes.[11] 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,[8a,b] inert atmosphere,[8a,b] usage of toxic reagents,[8a,10,11] and autoclave.[11] 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.[12]

Since its discovery, the nitroaldol (Henry) reaction has become one of the most valuable methods for the generation of C–C bonds[13] and as key starting synthetic step for the preparation of important fine chemicals, often with important ecological advantages.[14] 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 **5**, we focused our attention to the α-oxoaldehydes **2** as strategic partners of nitroalkanes **1** in the Henry reaction. Our idea was the formation of the 3-nitro-2-alkanols **3** in which the elimination of nitrous acid *vs.* the conventional water elimination is favoured (during experiments, no trace of the dehydrated specie **6**, R^1 = H, 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 HNO_2 affording the enolic form **4**, which acts as the spontaneous precursor of the 1,2-diketones **5**.

In this context, to the best of our knowledge, only a sporadic example of Henry reaction involving nitrous acid elimination was reported in literature,[15] 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 Our synthetic approach.

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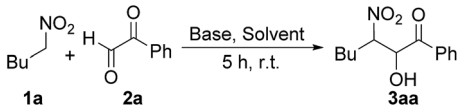
Table 1 Optimization of the Henry reaction



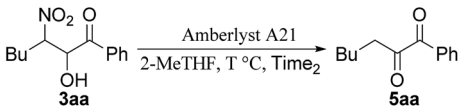
Entry	Base (g mmol^{-1})	Solvent	Yield[a] (%)
a[b]	TBD on polymer (0.3)	2-MeTHF	38
b[b]	Carbonate on polymer (0.3)	2-MeTHF	37
c[b]	KF/Al_2O_3 (0.3)	2-MeTHF	32
d[b]	Amberlyst A21 (0.3)	2-MeTHF	46
e[b]	Amberlyst A21 (0.4)	2-MeTHF	51
f[b]	Amberlyst A21 (0.5)	2-MeTHF	55
g[b]	Amberlyst A21 (0.6)	2-MeTHF	54
h[c]	Amberlyst A21 (0.5)	2-MeTHF	58
i[d]	Amberlyst A21 (0.5)	2-MeTHF	76
j[e]	Amberlyst A21 (0.5)	2-MeTHF	71
k[d]	Amberlyst A21 (0.5)	EtOAc	69
l[d]	Amberlyst A21 (0.5)	MeCN	51
m[d]	Amberlyst A21 (0.5)	DCM	49

[a] Yield of pure isolated product. [b] Scale: **1a** = 0.5 mmol and **2a** = 0.5 mmol. [c] Scale: **1a** = 0.5 mmol and **2a** = 0.65 mmol. [d] Scale: **1a** = 0.65 mmol and **2a** = 0.5 mmol. [e] Scale: **1a** = 0.75 mmol and **2a** = 0.5 mmol.

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).

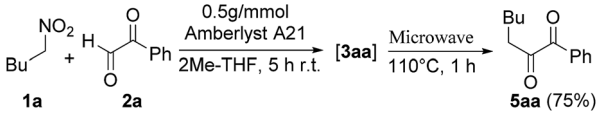
The best result (entry i, yield = 76%) was obtained using Amberlyst A21 (0.5 g mmol^{-1}), 2-MeTHF (as green solvent)[16] at room temperature (5 hours) and in presence of a slight excess of nitroalkane (1.3 equivalents). Once optimized the first step, we explored the reaction conditions for converting the nitro alcohol **3aa** into the diketone **5aa**, using Amberlyst A21 and 2-MeTHF (Table 2).

Table 2 Investigation on the conversion of **3aa** into **5aa**

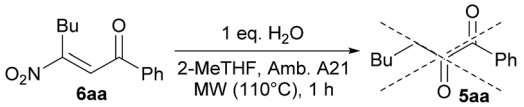


Entry	Amb. A21 (g mmol^{-1})	T (°C)	Time$_2$ (h)	Yield[a] (%)
a	0.3	Reflux[b]	4	63
b	0.4	Reflux[b]	4	71
c	0.5	Reflux[b]	4	72
d	1.0	Reflux[b]	4	51
e	0.5	100[c]	1	78
f	0.5	110[c]	1	85
g	0.4	110[c]	1	83
h	0.5	120[c]	1	72

[a] Yield of pure isolated product. [b] 80 °C (b.p. 2-MeTHF) heated by conventional oil bath. [c] Heated under microwave irradiation.



Scheme 2 One-pot process.



Scheme 3 Further mechanism investigations.

The conversion works efficiently both with 0.4 and 0.5 g mmol^{-1} of Amberlyst A21, and the best results were obtained under microwave irradiation at 110 °C after 1 hour (83% and 85% respectively).

Then, we combined the two steps to achieve the one-pot protocol and, applying the best reaction conditions, we isolated the diketone **5aa** in 75% of overall yields (Scheme 2).

Successively, with the aim to clarify the reaction mechanism, and in particular concerning a possible equilibrium between **3** and **6**, we investigated the reaction of the β-nitroenones **6a** in presence of water (Scheme 3). Under the optimized reaction conditions, the formation of the diketone **5aa** was not observed, demonstrating that the specie **6** is not involved in the mechanism and that the elimination of nitrous acid is the actual synthetic pathway.

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, 42–76%), 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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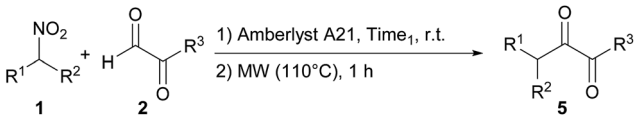
Table 3 Synthesis of 1,2-diketones **5**



	R^1	R^2		R^3	$Time_1$ (h)		Yield[a] (%)
1a	Bu	H	**2a**	Ph	5	**5aa**	75
1b	*n*-Pr	H	**2a**	Ph	5	**5ba**	72
1c	$CH_3(OCH_2CH_2O)CCH_2$	H	**2a**	Ph	4	**5ca**	70
1d	$Ph(CH_2)_2$	H	**2a**	Ph	5	**5da**	76
1d	$Ph(CH_2)_2$	H	**2b**	2-F-C_6H_4	5	**5db**	68
1e	$CH_3(CH_2)_8$	H	**2c**	4-MeO-C_6H_4	6	**5ec**	62
1f	$Cl(CH_2)_3$	H	**2c**	4-MeO-C_6H_4	6	**5fc**	52
1g	$NC(CH_2)_4$	H	**2d**	2-Napthyl	6	**5gd**	74
1h	$CH_3(CH_2)_4$	H	**2d**	2-Napthyl	6	**5hd**	71
1i	$MeOOC(CH_2)_4$	H	**2a**	Ph	5	**5ia**	70
1j	Me	Me	**2e**	4-NO_2-C_6H_4	12	**5je**	42
1k	$-(CH_2)_4-$		**2a**	Ph	15	**5ka**	51

[a] Yield of pure isolated product.

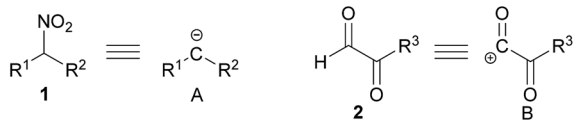


Fig. 1 Synthetic equivalents.

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