

Microwave-assisted organocatalytic cross-aldol condensation of aldehydes†

Cite this: DOI: 10.1039/c3ra00114h

Received 9th January 2013,
Accepted 29th January 2013

DOI: 10.1039/c3ra00114h

www.rsc.org/advances

Dimitris Limnios and Christoforos G. Kokotos*

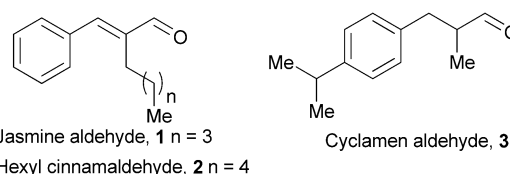
An environmentally benign organocatalytic cross-aldol condensation of aldehydes under microwave irradiation in the absence of solvent is described. Using pyrrolidine as a catalyst, an efficient and sustainable atom economic method was developed for the cross-aldol condensation of various aldehydes with excellent results. Among the products, jasmine aldehyde, α -hexyl cinnamaldehyde and cyclamen aldehyde, three compounds of great industrial demand, were synthesised.

Introduction

Today, more than ever, there is a high demand for the development of novel environmentally-friendly procedures for well known organic transformations that will deal efficiently with energy and waste concerns.¹ A process that combines stoichiometric amount of reagents, minimal or no by-product formation and solvent-free reaction conditions to minimize waste, as well as a low-weight organic catalyst that is cheap, will be a highly desirable concept both for academia and industry. The aldol reaction is one of the most powerful tools for the construction of C–C bonds.² With the advent of organocatalysis, a variety of elegant catalytic systems have appeared for the efficient asymmetric synthesis of aldol products.³ However, the corresponding aldol condensation of carbonyl compounds leading to α,β -unsaturated carbonyl compounds has received less attention. Although there is a handful of reports utilizing metal- or solid supported catalytic systems,⁴ the field of organocatalysis has “neglected” aldol condensation, with the exemption of Pihko and coworkers.⁵ They reported the aldol condensation of various aldehydes with formaldehyde leading to α -substituted acroleins using pyrrolidine as the catalyst.^{5b,c} The use of formaldehyde eliminated the danger for cross-aldol condensation and the possibility of obtaining complicated reaction mixtures and no other aldehydes were employed. Moreover, the simple self-condensation reaction of

aldehydes^{5c,6} and ketones⁷ is a well known process. However, the cross aldol condensation of aldehydes is less studied since it suffers from the propensity of aldehydes either to react with themselves (self-condensation) or polymerise, thus leading to a number of undesired by-products. Usually a large excess of one reagent is used to ensure high yields and the reaction is typically carried out using the ketone substrate as the solvent and an inorganic base, usually KOH or NaOH.⁸ Among the various products of cross-aldol condensations, we became interested in aldehydes used in the fragrance industry such as jasmine aldehyde (α -*n*-amylcinnamaldehyde) **1**, which is a traditional perfumery product with a violet scent and can be obtained by the aldol condensation of heptanal with benzaldehyde (Scheme 1).^{4b,9} A variety of catalysts have been utilized for its synthesis. However in almost all cases, the yield of the desired product is not high due to by-product formation. Cyclamen aldehyde **3** is another interesting perfumery adduct that can be synthesized in a few steps from the cross-aldol product of cuminaldehyde with propanal (Scheme 1).^{9a}

During the last few years, researchers have turned their attention to alternative methods to perform reactions. Microwave irradiation is becoming an increasingly popular method. It offers a clean, cheap and convenient way of heating, which often results in higher yields and shorter reaction times.¹⁰ Taking into consideration the high value of the transformations mentioned above and the great utility of the products for the synthesis of pharmaceuticals and fine chemicals, we present here our studies for a green approach towards a microwave-assisted process for the cross-aldol condensation of carbonyl compounds.



Scheme 1 Important aldehydes in the perfume industry.

Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis 15771, Athens, Greece. E-mail: ckokotos@chem.uoa.gr; Fax: +30 210 7274761; Tel: +30 210 7274281

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra00114h

Results and discussion

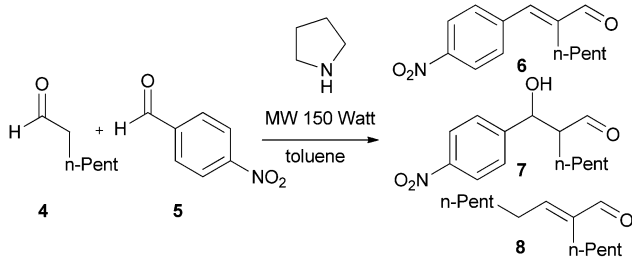
The majority of the methods reported for the cross-aldol condensation of aldehydes employ the use of ionic liquids in excess in combination with a base,¹¹ the use of Lewis acids^{4a} and solid base catalysts.^{4b,e,g,h} Usually, a large excess of one reagent is used in order to ensure high yields and to avoid undesired by-products. Initially, an optimization was carried out for the cross-aldol condensation between heptanal and 4-nitro-benzaldehyde. Bearing in mind the tendency of secondary cyclic amines to easily form enamines and the concept of atom economy,¹² which supports the green chemistry philosophy, we decided to use pyrrolidine as our organocatalyst. Using 40 mol% pyrrolidine as a catalyst and toluene as the solvent under microwave irradiation (120 °C, 150 W initial power) for 30 min, the desired product was isolated in high yield (Table 1, entry 1). Further investigation showed that reducing the catalyst loading to 30 mol% or 25 mol% did not cause considerable changes to yield, whereas 10 mol% catalyst loading led to a significantly lower yield (Table 1, entries 2–4). Moreover, neither reducing the reaction time to half nor lowering the ratio between heptanal and 4-NO₂-benzaldehyde to 1.2 : 1 affected the yield (Table 1, entries 5–7). Increasing the temperature to 140 °C or reducing it to 100 °C led to a minor decrease in the yield (Table 1, entries 8 and 9). When the reaction time was reduced (10 min), a lower yield was observed and consequently a higher percentage of the aldol product was produced (Table 1, entry 10). That proved that the ideal reaction time would be 15 min in order for the aldol product to condensate. Bearing in mind the results mentioned above and our intention to embrace a more green approach in our study, we performed the reaction in the absence of solvent using 1.1 equiv.

heptanal, which led to an almost quantitative yield (Table 1, entry 11).

Having established the optimum conditions for our reaction, a series of aromatic aldehydes were tested for aldol condensation with heptanal (Table 2). *o*-Nitro and *m*-nitro benzaldehyde gave the corresponding products in high yields (Table 2, entries 2 and 3). Unfortunately, the more sterically hindered *o*-nitro benzaldehyde provided a mixture of *E/Z* isomers (Table 2, entry 3). In addition, *p*-CF₃ and *p*-Br benzaldehydes worked equally well (Table 2, entries 4 and 5). However, electron-rich aromatic aldehydes, containing substituents like *p*-methoxy or *p*-isopropyl, led to relatively lower but satisfactory yields (Table 2, entries 6 and 7). The main reason for the lower yields is that the reaction did not reach completion and starting material was recovered. When benzaldehyde was utilized, the natural fragrance of jasmine aldehyde **1** was isolated in very high yield (Table 2, entry 8). The product can be isolated by column chromatography with prior silica deactivation with Et₃N. Other efforts for the synthesis of jasmine aldehyde involve the use of amorphous aluminophosphates or magnesium silicates,^{4b,g} and metal-organic frameworks (MOFs).^{9c} Moreover, the reaction of heptanal with cinnamaldehyde afforded the product in a reasonable yield, whereas an α -containing proton aldehyde like α -Cl-3-phenylpropanal led to a lower but noteworthy yield due to the kinetically faster self-aldol condensation of heptanal (Table 2, entries 9–10).

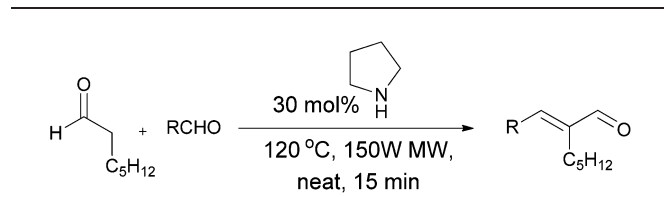
In order to shed more light on our study and to expand the potential of the substrate scope of the reaction, we turned our attention to the cross-aldol condensation of 4-nitro-benzaldehyde with a variety of aldehydes. Various simple aliphatic aldehydes such as propanal, butanal and isovaleraldehyde provided the products in very high yields (92–95%) (Table 3, entries 1–3). Also, 3-phenylpropanal and 5-phenyl-pentanal afforded excellent

Table 1 Microwave-assisted aldol condensation between heptanal and 4-nitro-benzaldehyde using pyrrolidine as a catalyst



Entry	Pyrrolidine Loading (%)	Time (min)	Temp. (°C)	Product 6 (%) ^a	Aldol 7 (%)	Self-aldol 8 (%)
1 ^b	40	30	120	88	9	3
2 ^b	30	30	120	87	9	4
3 ^b	25	30	120	84	10	5
4 ^b	10	30	120	58	13	29
5 ^c	40	15	120	84	8	8
6 ^c	30	15	120	86	7	7
7 ^c	25	15	120	85	8	7
8 ^c	30	15	100	81	10	9
9 ^c	30	15	140	83	7	10
10 ^c	30	10	120	74	19	7
11 ^d	30	15	120	98	0	2

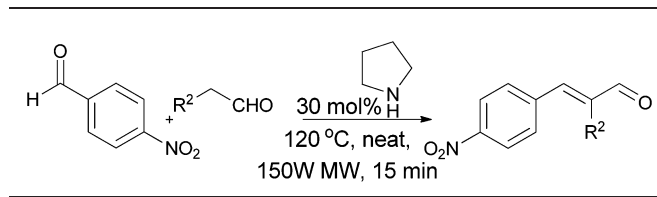
^a Isolated yield. ^b Heptanal (2 equiv.). ^c Heptanal (1.2 equiv.). ^d Reaction performed neat using 1.1 equiv. heptanal.

Table 2 Microwave-assisted cross-aldol condensation between heptanal and aldehydes using pyrrolidine as a catalyst

Entry	RCHO	Yield (%) ^a	E/Z
1		98	>98 : 2
2		96	>98 : 2
3		95	85 : 15
4		98	>98 : 2
5		94	>98 : 2
6		65	>98 : 2
7		63	>98 : 2
8		93	>98 : 2
9		72	>98 : 2
10		52	>98 : 2

^a Yield of isolated product.

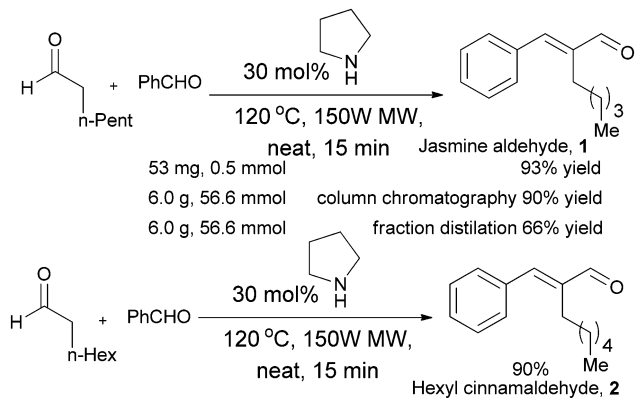
results, indicating that aryl moieties are well tolerated (Table 3, entries 4 and 5). When the naturally occurring aldehydes *rac*-citronellal and geranial were utilized, the products were isolated in very high yields, showing that the method can be applied even to more complex substrates containing unsaturated functionalities (Table 3, entries 6 and 7). Furthermore, nitrogen-protected and

Table 3 Microwave-assisted cross-aldol condensation between 4-NO₂-benzaldehyde and various aldehydes using pyrrolidine as a catalyst

Entry	R ¹ CHO	Yield (%) ^a	E/Z
1		94	80 : 20
2		95	>98 : 2
3		92	>98 : 2
4		97	95 : 5
5		95	>98 : 2
6		94	>98 : 2
7		95	92 : 8
8		88	76 : 24
9		95	93 : 7
10		88 ^b	>98 : 2

^a Yield of isolated product. ^b Cyclohexanone (2 equiv.).

oxygen-containing aldehydes were successfully used to provide the corresponding products in very high yields. Finally, this methodology can be extended to the use of ketones instead of aldehydes and a high yield was observed (Table 3, entry 10). As it was mentioned earlier, our inspiration for performing this investigation was the desire to produce a high-yielding but at the same time environmentally-friendly methodology for the synthesis of aldehydes that are utilised extensively in the fragrance industry. Thus, in Scheme 2, a fast one-step high-yielding green process for the synthesis of **1** and **2** is described from cheap, commercially available materials. In order to highlight the utility of our methodology, the reaction was also performed on a larger scale (6.0 g, 56.6 mmol, benzaldehyde). Utilizing standard reaction conditions and column chromatography for the purification, the reaction product was obtained in a similar yield. In order to minimize the use of solvents in the purification step, fractional distillation can be employed for purification of the product, however the yield of the product is lower (66% yield). Also, utilizing fractional distillation, a percentage of the catalyst, pyrrolidine, can be recovered (around 30%) and thus be reused.



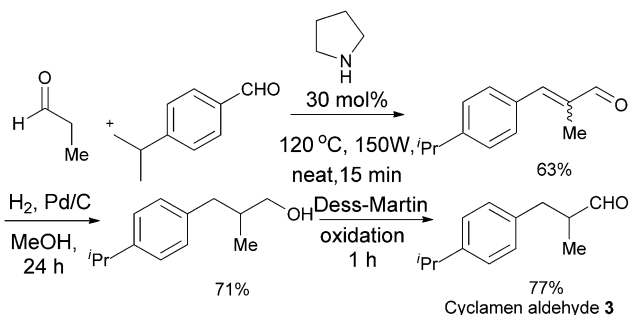
Scheme 2 One-step synthesis of jasmine aldehyde **1** and hexyl cinnamaldehyde **2**.

Furthermore, hexyl cinnamaldehyde **2** is a jasminaldehyde-related compound that has been identified in rice. It is commonly used in flower compositions and in soap perfumes.^{9a}

For the case of cyclamen aldehyde **3**, a number of steps had to follow our initial cross-aldol condensation (Scheme 3). All of our efforts for selective hydrogenation of the double bond in the presence of the carbonyl moiety were met with failure. Among the methods utilised, transition-metal catalysed hydrogenation and Hantzsch ester-mediated organocatalytic hydrogenation failed to deliver the desired product in high yield. Thus, a two-step hydrogenation–oxidation had to be employed, affording cyclamen aldehyde **3** in just three steps from commercially available materials in 34% overall yield.

Conclusions

A fast, atom-economic, high-yielding process for the cross-aldol condensation of aldehydes is described under microwave irradiation. A variety of aldehydes can be utilised and the products are obtained in good to excellent yields and high to excellent regiocontrol. Quick and high-yielding access is provided to three aldehydes: jasminaldehyde **1**, hexyl cinnamate **2** and cyclamen aldehyde **3**, which are materials of high significance in the fragrance industry, *via* this methodology.



Scheme 3 Synthesis of cyclamen aldehyde **3**.

References

- (a) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; (b) R. Mestres, *Green Chem.*, 2004, **6**, 583–603; (c) C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927–934; (d) R. A. Sheldon, *Chem. Commun.*, 2008, 3352–3365; (e) R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437–1451.
- (a) R. Mahrwald, *Modern Aldol Reactions*, Wiley-VCH, Weinheim, 2004, vol. 1 and 2; (b) B. M. Trost and C. S. Brindle, *Chem. Soc. Rev.*, 2010, **39**, 1600–1632.
- (a) A. B. Northup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798–6799; (b) Y. Chi, S. T. Scroggins, E. Boz and J. M. Frechet, *J. Am. Chem. Soc.*, 2008, **130**, 17287–17289; (c) T. Kano, H. Sugimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2011, **133**, 18130–18133.
- (a) N. Iranpoor and F. Kazemi, *Tetrahedron*, 1998, **54**, 9475–9480; (b) M. J. Climent, A. Corma, V. Fornes, R. Guill-Lopez and S. Iborra, *Adv. Synth. Catal.*, 2002, **344**, 1090–1096; (c) A. A. Esmaeli, M. S. Tabas, M. A. Nasser and F. Kazemi, *Monatsh. Chem.*, 2005, **136**, 571–576; (d) N. Lahmar, J. Aatar, T. B. Ayed, H. Amri and M. Bellassoued, *J. Organomet. Chem.*, 2006, **691**, 3018–3026; (e) L.-T. An, J.-P. Zou and L.-L. Zhang, *Catal. Commun.*, 2008, **9**, 349–354; (f) A. E. Kadib, K. Molvinger, M. Bousmina and D. Brunel, *Org. Lett.*, 2010, **12**, 948–951; (g) A. Alireza, J. K. Roozbeh and Z. Farzad, *Chin. J. Chem.*, 2010, **28**, 2074–2082; (h) R. Resaie, M. Heidary, M. N. Soltani Rad and S. Behrouz, *Chin. J. Chem.*, 2011, **29**, 1221–1226.
- (a) For a review on non-asymmetric organocatalysis, see: P. Renzi and M. Bella, *Chem. Commun.*, 2012, **48**, 6881–6896 and references therein; (b) A. Erkkila and P.M. Pihko, *J. Org. Chem.*, 2006, **71**, 2538–2541; (c) A. Erkkila and P.M. Pihko, *Eur. J. Org. Chem.*, 2007, 4205–4216.
- Y. Watanabe, K. Sawada and M. Hayashi, *Green Chem.*, 2010, **12**, 384–386 and references therein.
- L. K. Sharma, K. B. Kim and G. I. Elliot, *Green Chem.*, 2011, **13**, 1546–1549 and references therein.
- (a) P. S. Gradeff, *US Patent*, 1974, 3,840,601; (b) P. W. D. Mitchell, *US Patent*, 1989, 4,874,900.
- (a) H. Surburg and J. Panten, *Common Fragrance and Flavor Materials: Preparation, Properties and Uses*, Wiley-VCH, Weinheim, 2006; (b) D. Abenheim, C. P. Ngog Son, A. Loupy and N. Ba Hiep, *Synth. Commun.*, 1994, **24**, 1199–1205; (c) F. Vermoortele, R. Ameloot, A. Vimont, C. Serre and D. DeVos, *Chem. Commun.*, 2011, **47**, 1521–1523.
- (a) A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; (b) G. L. Kad, K. P. Kaur, V. Singh and J. Singh, *Synth. Commun.*, 1999, **29**, 2583–2586.
- (a) S. Abello, F. Medina, X. Rodriguez, Y. Cesteros, P. Salagre, J. E. Sueiras, D. Tichit and B. Coq, *Chem. Commun.*, 2004, 1096–1097; (b) G. V. Kryshnal, G. M. Zhdankina and S. G. Zlotin, *Eur. J. Org. Chem.*, 2005, 2822–2827.
- B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281.