Pergamon

Tetrahedron Letters 42 (2001) 5203–5205

TETRAHEDRON LETTERS

Clean synthesis in water. Part 2: Uncatalysed condensation reaction of Meldrum's acid and aldehydes

Franca Bigi,* Silvia Carloni, Leonetto Ferrari, Raimondo Maggi, Alessandro Mazzacani and Giovanni Sartori

Dipartimento di Chimica Organica e Industriale dell'Università, Parco Area delle Scienze 17/A, I-43100 Parma, Italy

Received 6 June 2001

Abstract—The environment-friendly condensation of Meldrum's acid and aromatic, heteroaromatic and hindered aliphatic aldehydes is performed carrying out the reaction in water at 75°C for 2 h, avoiding the addition of any catalyst.

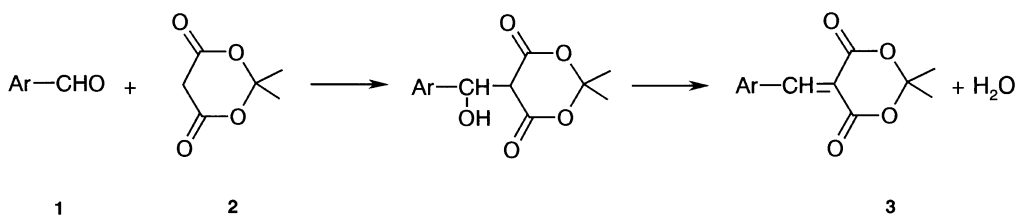
The use of water as a solvent in organic chemistry was rediscovered in the 1980s by Breslow,[1] who showed that hydrophobic effects can strongly enhance the rate of several organic reactions. Previously the scant solubility of the reactants was the main reason that ruled this solvent out from studies.

Further reasons that make water unique among solvents are that it is cheap, not inflammable, and more importantly, it is not toxic. Choice of solvent is one of the problems to face in order to perform eco-efficient processes. The reaction promoters also deserve to be reinvestigated, because large amounts of waste are produced in the fine-chemicals industry, mainly due to stoichiometric reactions and to organic and inorganic salt formation during the quenching procedure.[2]

As part of our research program concerning the use of water as an eco-compatible reaction solvent[3] and keeping in mind that 'the best catalyst is no catalyst',[4] we have investigated the condensation reaction of Meldrum's acid and aldehydes.

The reactivity of the Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione) as a methylene active compound was explored about 40 years after its preparation, when the structure was correctly attributed by Davidson and Bernhard[5] assigning the acidic proton to the central carbon, and its high acidity is still object of study.[6]

It is known that the Meldrum's acid undergoes standard Knoevenagel condensation with aromatic and heteroaromatic aldehydes furnishing the corresponding arylidene derivatives, which are versatile substrates for different kinds of reactions.[7] They are useful intermediates for cycloaddition reaction and for the synthesis of heterocyclic compounds with potential pharmacological activity.[8] The 1,4-addition of nucleophiles has been widely used synthetically, displaying some advantages over the acyclic malonate analogues, and the conju-



Scheme 1. Knoevenagel condensation of Meldrum's acid and aldehydes.

Keywords: Meldrum's acid; water; uncatalysed reaction; Knoevenagel condensation; arylidene Meldrum's acid; environmentally benign synthesis.
* Corresponding author. Tel.: +39-0521-905411; fax: +39-0521-905472; e-mail: bigi@unipr.it

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00978-9

gated reduction is the way most often used to prepare 5-monoalkyl Meldrum's acids, also applied to obtain deuterated carboxylic acids.[9]

The Knoevenagel condensation of aldehydes and Meldrum's acid is generally catalysed by bases, such as pyridine[5,10] or by piperidine/glacial acetic acid in benzene with water removal,[11] often using an excess of aldehyde to minimise the undesired formation of a bis adduct, due to the Michael addition with a second molecule of the methylene component.[7c] Uncatalysed reaction was reported in the literature using DMF or DMSO as solvent (solvents that are toxic, teratogenic and suspected carcinogens), giving mixtures of unsaturated and Michael addition products.[12] More recently anhydrous zinc chloride was reported to promote the reaction in absence of any solvent.[13]

Table 1. Solvent effect in the reaction between 4-chlorobenzaldehyde **1a** and Meldrum's acid **2**

Entry	Solvent	Yield (%)
1	Water	60
2	Toluene	38
3	Dioxane	23
4	Ethanol	30[a]

[a] Unselective reaction.

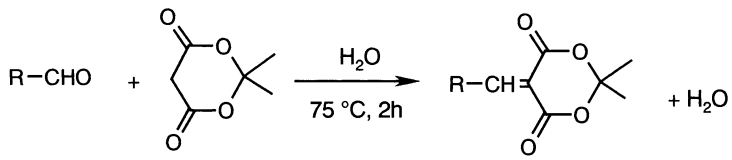
Our recent results on uncatalysed preparation of ylidenemalononitriles[3b] have prompted us to investigate the reaction of 2,2-dimethyl-1,3-dioxan-4,6-dione **2** and 4-chlorobenzaldehyde **1a** in water without adding any catalyst. As desired we succeeded in obtaining the unsaturated product **3a** in 60% yield carrying out the reaction at 75°C for 2 h without adding any catalyst (Scheme 1).

To investigate this reaction we first examined the solvent effect employing solvents with different properties, like polarity, proticity and dielectric constant.

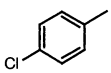
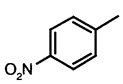
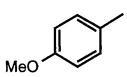
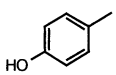
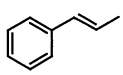
The data reported in Table 1 show that the reaction is favoured in water, although it involves the elimination of a molecule of water. Similar unusual solvent effects have been previously found by other authors[14] and by ourselves,[3] but usually in the presence of a catalyst.

It is interesting to observe the remarkable difference between the protic solvents water and ethanol. In ethanol the reaction was unselective, due to Michael addition and transesterification processes. We suggest that water is the best solvent because it favours the Meldrum's acid dissociation, due to its high ε value, that generates the nucleophilic species able to attack the aldehydic carbon. Although the reaction carried out without any solvent gave a similar result we selected water as the medium of choice because it offers some

Table 2. Uncatalysed condensation between Meldrum's acid and aldehydes



1 **2** **3**

Entry	R	Product **3**	Yield %	Selectivity %
1		**3a**	60	86
2		**3b**	84	90
3		**3c**	92	98
4		**3d**	95	98
5		**3e**	96	98
6		**3f**	94	97
7		**3g**	72[a]	95

[a]In a closed vessel.

advantages, in addition to its low cost and no inflammability. It also gives easy isolation of the product by Buckner filtration and the possibility of employing every kind of aldehyde, liquid as well as solid ones without any stirring problems.

This uncatalysed process was extended to different aldehydes, aromatic, heteroaromatic and hindered aliphatic ones (Table 2).[15]

The different reactivity of variously substituted aldehydes could be rationalised taking into account that the reaction occurs in two steps, i.e. the nucleophilic attack and the dehydration (Scheme 1). Electron-withdrawing substituents facilitate the first step, meanwhile electron-donor substituents facilitate the loss of water giving a conjugated stabilised olefin. Further, in these latter cases no trace of bis adduct was observed. This uncatalysed reaction could be extended to hindered aliphatic aldehyde **1g** furnishing the corresponding product **3g** in good yield.

It is noteworthy that all of the products **3** are easily isolated by simple Buchner filtration.

In order to check the reaction selectivity, detecting the possible formation of a bis adduct, we have examined the reaction crude mixture and products by ^{1}H NMR spectroscopy observing a dramatic solvent effect. It is necessary to use dilute solution in $CDCl_3$ as solvent, completely avoiding DMSO-d_6, in which the bis adduct converts in an equimolar mixture of olefin and Meldrum's acid. The same retro-addition process occurs when DMSO-d_6 is added to a sample in $CDCl_3$.

In conclusion we have shown that the condensation reaction of Meldrum's acid and aldehydes efficiently occurs in water without adding any catalyst, by heating at 75°C for 2 h, providing a convenient, salt-free and efficient synthesis of 5-arylidene and alkylidene Meldrum's acids.

Acknowledgements

We acknowledge the support of the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy, and the University of Parma (National Project 'Processi puliti per la Chimica Fine'). We are also grateful to the Centro Interfacoltà Misure (CIM) for the use of NMR and mass spectrometry instruments.

References

1. (a) Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817; (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164.
2. Sheldon, R. *Chem. Ind.* **1997**, 12–15.
3. (a) Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 1033–1035; (b) Bigi, F.; Conforti, M. L.; Maggi, R.; Piccinno, A.; Sartori, G. *Green Chem.* **2000**, *2*, 101–103.
4. This comment was written in *ChemWeb*, *The Alchemist* May **2000**, regarding our previous work on uncatalysed preparation of ylidenemalononitriles.
5. Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426–3428.
6. Byun, K.; Mo, Y.; Gao, J. *J. Am. Chem. Soc.* **2001**, *123*, 3974–3979.
7. For reviews see: (a) Chen, B.-C. *Heterocycles* **1991**, *32*, 529–597; (b) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358; (c) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp. 341–394.
8. Pita, B.; Sotelo, E.; Suarez, M.; Ravina, E.; Ochoa, E.; Verdecia, Y.; Novoa, H.; Blaton, N.; de Ranter, C.; Peeters, O. M. *Tetrahedron* **2000**, *56*, 2473–2479.
9. Kadam, A. J.; Desai, U. V.; Mane, R. B. *J. Labelled Comp. Radiopharm.* **1999**, *42*, 835–842.
10. Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897–5905.
11. (a) Kraus, G. A.; Krolski, M. E. *J. Org. Chem.* **1986**, *51*, 3347–3350; (b) Scuster, P.; Polansky, O. E.; Wessely, F. *Monatsch. Chem.* **1964**, *95*, 53–58.
12. Hedge, J. A.; Kruse, C. W.; Snyder, H. R. *J. Org. Chem.* **1961**, *26*, 3166–3170.
13. Rao, P. S.; Venkataratnam, R. V. *Indian J. Chem. B* **1993**, *32*, 484–486.
14. (a) Laszlo, P. *Acc. Chem. Res.* **1986**, *19*, 121–127; (b) Kloestra, K. R.; van Bekkum, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1005–1006; (c) Lednor, P. W.; de Ruiter, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1625–1626.
15. The general procedure for the synthesis of unsaturated compounds **3** is as follows: A mixture of Meldrum's acid (5.5 mmol) and the selected aldehyde (5 mmol) in water (10 ml) was stirred at 75°C for 2 h. After cooling to room temperature the solid product was filtered on Buchner and dried under vacuum. The purification from traces of starting aldehyde, when present, was performed by crystallisation. All products **3a–h** were characterised (^{1}H NMR, IR and MS) and their melting points compared with literature reported values.