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# A general and practical preparation of alkylidene Meldrum's acids

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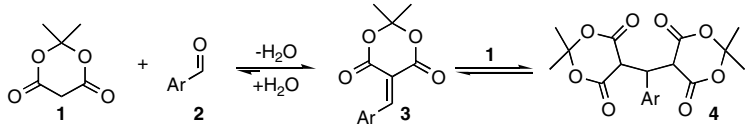
**Abstract**—Although many methods have been reported for the Knoevenagel condensation of aldehydes and Meldrum's acid, most are not general or use unconventional reagents and conditions. We have found that alkylidene Meldrum's acids form readily in benzene solution under mild pyrrolidinium acetate catalysis, and that this reaction is general, highly functional group compatible, and can be scaled-up easily.


5-Alkenyl-2,2-dimethyl-1,3-dioxane-4,6-diones (alkylidene Meldrum's acids, AMAs **3**) are highly reactive 1,1-diactivated alkenes that have been used extensively as acceptors in 1,4-addition of a variety of organometallic reagents,[1] as dienophile and diene in Diels–Alder and hetero-Diels–Alder reactions, respectively,[2] and as a versatile synthon in various other reactions.[3] In conjunction with ongoing research in our laboratories involving catalytic C–C bond forming reactions using AMAs,[4] we have prepared a large number of, especially, 5-(1-arylmethylidene) Meldrum's acids derived from benzaldehydes. For the preparation of mono-substituted AMAs, the most convenient method is the Knoevenagel condensation of Meldrum's acid **1** with an aldehyde **2**. This reaction has been studied extensively, and a wide range of conditions have been reported to carry out this seemingly simple transformation.[5]

However, as noted by Snyder as early as 1961, the condensation can be complicated by competing Michael addition of Meldrum's acid to AMA **3** to form products of type **4** (Scheme 1).[6] It has been our experience that certain alkylidenes are more prone to Michael addition than others depending on the condensation conditions used. Unfortunately we have been unable to predict which aldehydes will condense smoothly under which conditions, leading to a frustrating guessing game. Competing addition of **1** onto **3** can be circumvented by in situ addition of a nucleophile to the AMA, forming an adduct from which the AMA can be regenerated in a second step. Methoxide,[7] amines,[8] and thiols[9] have been successfully used in this manner, but this is an unsatisfactory solution in terms of atom and step economy. To further our own research, and to remove some of the difficulties involved with preparing AMAs, we therefore sought a Knoevenagel condensation that would be practical, general, and scaleable.

Qualitative observation of reactions in which significant amounts of **4** have formed led us to believe that the equilibrium between **3** and **4** was being shifted to the right by precipitation of the bis-Meldrum's acid adducts, which are generally poorly soluble in polar and non-polar solvents. We therefore reasoned that formation of **3** could be maximized by performing the reactions in dilute organic solvent (benzene[10]) to prevent precipitation of **4**. Since both the condensation of **1** and **2**, and reversion of **4** to **3** are known to be catalyzed by amino acids,[11]




**Scheme 1.**

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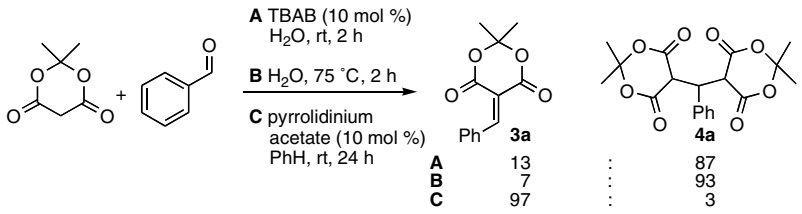
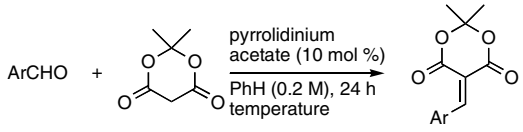



**Scheme 2.**

catalytic pyrrolidinium acetate was added to facilitate both reactions. This hypothesis was tested on the reaction of benzaldehyde and Meldrum's acid, which in our experience is the most problematic condensation (Scheme 2). For example, conditions reported by Ren et al. (Scheme 2, **A**) to give **3a** in 69% yield[5b] are irreproduceable, and in our hands gave a white powder consisting of a mixture of 13:87 **3a** and **4a**, along with 6% benzaldehyde. The conditions of Bigi et al.[5a] (Scheme 2, **B**), who did not report this exact reaction and which does work as reported for other benzaldehydes, gave a mixture of **3a** and **4a** in a 7:93 ratio. In contrast, reactions run in 0.2 M PhH with 10 mol % pyrrolidinium acetate (Scheme 2, **C**) yielded essentially pure **3a**.[12] From this, **3a** was isolated in 85% yield after a simple aqueous work-up. Previously we had prepared **3a** via condensation of Meldrum's acid with trimethyl orthoformate, followed by addition of PhMgBr to the resulting 5-(methoxymethylene) Meldrum's acid.[4a]

To demonstrate the utility and functional group compatibility of this method, benzaldehydes with various functionalities and substitution patterns were reacted under these conditions (Table 1).[13] It should be pointed out that under the conditions described, no formation of **4** was detected by $^1$H NMR analysis of the crude reaction mixture. While electron-rich methoxy-substituted benzaldehydes reacted easily at room temperature (entries 1–3), electron-withdrawing $CF_3$ substituents decreased conversion, likely due to slower elimination of water from the initially formed aldol product. This was easily overcome by performing the reactions at 50 °C; again, an EWG substitution at any position is handled well (entries 4–6). Alkyl substituents (Me) at any position can be used, with a higher reaction concentration to increase conversion (entries 7–9). Chlorine at all positions, and other halogens, are tolerated as well (entries 10–15). This was gratifying, as these benzaldehydes had often proven quite difficult to condense under other conditions.[14]

**Table 1.** Condensation of benzaldehydes with Meldrum's acid



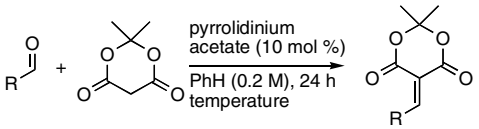

| Entry | Ar | Temperature (°C) | Yield (%) |
|---|---|---|---|
| 1 | 2-(OMe)$C_6H_4$ | rt | 84 |
| 2 | 3-(OMe)$C_6H_4$ | rt | 88 |
| 3 | 4-(OMe)$C_6H_4$ | rt | 88 |
| 4 | 2-($CF_3$)$C_6H_4$ | 50 | 83 |
| 5 | 3-($CF_3$)$C_6H_4$ | 50 | 82 |
| 6 | 4-($CF_3$)$C_6H_4$ | 50 | 71 |
| 7[a] | 2-Me$C_6H_4$ | 50 | 85 |
| 8[a] | 3-Me$C_6H_4$ | 50 | 80 |
| 9[a] | 4-Me$C_6H_4$ | 50 | 77 |
| 10 | 2-Cl$C_6H_4$ | 50 | 73 |
| 11 | 3-Cl$C_6H_4$ | 50 | 60 |
| 12 | 4-Cl$C_6H_4$ | 50 | 72 |
| 13 | 2,4-$(Cl)_2C_6H_4$ | 50 | 78 |
| 14 | 2-Br$C_6H_4$ | 50 | 76 |
| 15 | 2-F$C_6H_4$ | 50 | 84 |
| 16 | 4-($NO_2$)$C_6H_4$ | 50 | 81 |
| 17 | 4-(CN)$C_6H_4$ | 80 | 68 |
| 18[a] | 4-Ac$C_6H_4$ | 50 | 71 |
| 19 | 3-(OMe)-4-(OH)$C_6H_3$ | 50 | 79 |
| 20 | 3-(OMe)-4-(OAc)$C_6H_3$ | 50 | 76 |

[a] Concentration 0.5 M.

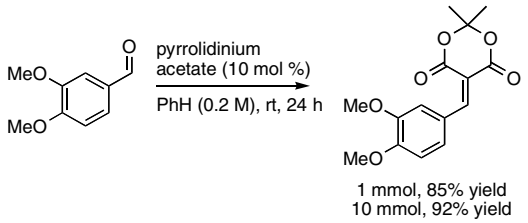
Functional group compatibility was shown by smooth condensation with nitro-, nitrile-, ketone-, ester-, and phenol-containing benzaldehydes (entries 16–20). At 50 °C, 4-cyanobenzaldehyde produced a roughly 1:1 mixture of **3** and **4**; increasing the temperature to 80 °C prevented precipitation of **4** and favored formation of **3**. The reaction proved to be highly chemoselective, as no condensation with the ketone was observed for 4-acetylbenzaldehyde. Vanillin and its acetate condensed cleanly without opening of Meldrum's acid by the phenol or cleavage of the labile ester.

Aldehydes other than simple benzaldehydes also condense smoothly under these conditions (Table 2). Naphthyl and furyl, as well as branched aliphatic, aldehydes are tolerated. Reaction with straight-chain aliphatic aldehydes (i.e. acetaldehyde) led to a complex mixture even when reacted at 0 °C. Cinnamaldehyde condensed cleanly without double bond isomerization.

**Table 2.** Condensation of naphthyl, furyl, and aliphatic aldehydes




| Entry | R | Temperature (°C) | Yield (%) |
|---|---|---|---|
| 1 | 1-Naphthyl | 50 | 92 |
| 2 | 2-Naphthyl | 50 | 89 |
| 3 | 2-Furyl | 50 | 79 |
| 4 | Isopropyl | rt | 78 |
| 5 | *trans*-Ph$(CH)_2$ | 50 | 84 |




**Scheme 3.**

Since we often need large quantities of AMAs for methodology development, the preparation of 5-[1-(3,4-dimethoxyphenyl)methylene]-Meldrum's acid was attempted on small and larger scale. As shown in Scheme 3, the reaction can be performed just as easily on 10 times the scale of the general procedure (yielding 2.6 g of AMA).

The above examples amply demonstrate the generality and usefulness of this condensation procedure for the synthesis of diverse AMAs. Problems associated with other methods are avoided, all the reagents are conventional and commercially available, and purification and isolation of the products is simple.

## Acknowledgments

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## References and notes

1. Enantioselective additions of organozinc reagents to AMAs derived from aldehydes: (a) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682–9683; (b) Watanabe, T.; Knöpfel, T. F.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4557–4558.
2. Fillion, E.; Dumas, A. M.; Hogg, S. A. *J. Org. Chem.* **2006**, *71*, 9899–9902, and references cited therein.
3. For reviews on Meldrum's acid in synthesis see: (a) Chen, B.-C. *Heterocycles* **1991**, *32*, 529–597; (b) Strozhev, M. F.; Lielbriedis, I. É.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1991**, 579–599; (c) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358.
4. (a) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316–1327; (b) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sitler, T. C. *J. Org. Chem.* **2006**, *71*, 409–412; (c) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775; (d) Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957–2959.
5. In water: (a) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203–5205; Using surfactants: (b) Ren, Z.; Cao, W.; Weiqi, T.; Jing, X. *Synth. Commun.* **2002**, *32*, 1947–1952; Using modified silica-gel catalyst: (c) Isobe, K.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Mol. Divers.* **2005**, *4*, 317–320; In ionic liquid: (d) Hu, Y.; Wei, P.; Huang, H.; Le, Z.-G.; Chen, Z.-C. *Synth. Commun.* **2005**, *35*, 2955–2960; (e) Darvatkar, N. B.; Deorukhkar, A. R.; Bhilare, S. V.; Salunkhe, M. M. *Synth. Commun.* **2006**, *36*, 3043–3051; By microwave irradiation: (f) Abdallah-El Ayoubi, S.; Texier-Boullet, F.; Hamelin, J. *Synthesis* **1994**, 258–260.
6. Hedge, J. A.; Kruse, C. W.; Snyder, H. R. *J. Org. Chem.* **1961**, *26*, 3166–3170.
7. Margaretha, P.; Polansky, O. E. *Tetrahedron Lett.* **1969**, *10*, 4983–4986.
8. Chhabra, B. R.; Bolte, M. L.; Crow, W. D. *Aust. J. Chem.* **1984**, *37*, 1795–1797.
9. Eberle, M.; Lawton, R. G. *Helv. Chim. Acta* **1988**, *71*, 1974–1982.
10. Reported as solvent for the preparation of 2- and 3-indolydene Meldrum's acids: Benzies, D. W. M.; Fresneda, P. M.; Jones, R. A.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1651–1654.
11. Buzinkai, J. F.; Hrubowchak, D. M.; Smith, F. X. *Tetrahedron Lett.* **1985**, *26*, 3195–3198.
12. Ratios determined by $^1$H NMR analysis of the crude reaction mixture. The following characteristic peaks were integrated to determine the ratios: benzaldehyde, $\delta \sim 10.0$ (s, 1H); **3a**, $\delta \sim 8.6$ (s, 1H); **4a**, $\delta \sim 4.68$–4.61 (m, 3H).
13. *General procedure*: Aldehyde (1.0 mmol, 1.0 equiv), Meldrum's acid (158 mg, 1.1 mmol, 1.1 equiv) and dry benzene (distilled from Na/benzophenone, 5.0 mL, 0.2 M) were added to a glass vial equipped with a magnetic stirbar. To this was added 200 μL of a 0.5 mM solution of pyrrolidinium acetate in benzene (prepared by dropwise addition of AcOH to pyrrolidine in benzene, 0.1 mmol, 10 mol %) at room temperature. The vial was capped tightly and stirred at the appropriate temperature (heated reactions performed in preheated oil-baths) for 24 h. Products can be purified either by diluting the reaction with EtOAc, washing the mixture with saturated $NaHCO_3$ solution, drying over $MgSO_4$, and concentrating dry or by removal of benzene by rotary evaporation and recrystallizing the resulting solid from MeOH.
14. For example, as reported by Bigi (Ref. 5a), the condensation of 4-chlorobenzaldehyde with Meldrum's acid in water gave an 86:14 mixture of **3**:**4**, from which the AMA was isolated in 60% yield.