A Novel Proline-Catalyzed Three-Component Reaction of Ketones, Aldehydes, and Meldrum's Acid

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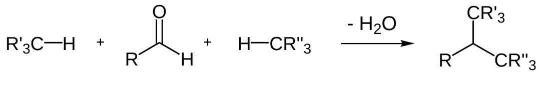
Abstract: We describe a novel proline-catalyzed three-component domino reaction between ketones, aldehydes and Meldrum's acid. Two new carbon–carbon σ-bonds from three different components are formed in this efficient transformation.

Key words: multicomponent reactions, organocatalysis, C–C coupling, combinatorial chemistry, domino reactions

The diversity generating potential of multicomponent reactions (MCR's) has been recognized and their utility in preparing libraries to screen for functional molecules is well appreciated. Consequently, the design of novel MCR's is an important field of research.[1–3] We have recently developed an asymmetric aminocatalytic variant of the three-component Mannich reaction.[4] Based on our experience with this efficient transformation, we decided to explore a related MCR, in which two C–H-bond-containing compounds condense with an aldehyde as shown in Scheme 1.[5]



Scheme 1

Symmetrical variants of this process include reactions of either two molecules of Knoevenagel nucleophiles or arenes with one molecule of aldehyde to furnish products of type **A** or **B**, respectively (Figure 1).[6]

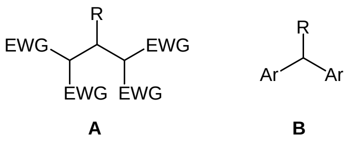


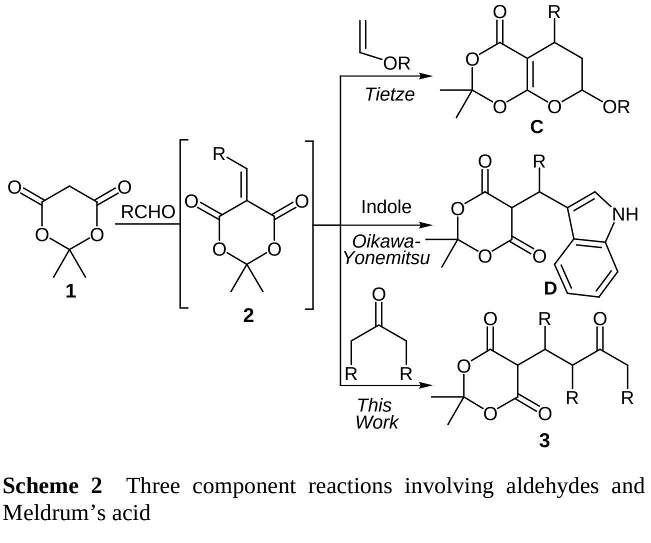
Figure 1

Unsymmetrical variants, in which two *different* C–H-bond containing compounds combine with an aldehyde are much less studied but useful for the creation of tertiary stereogenic centers.[1,7,8] Herein we describe a novel proline-catalyzed three-component reaction of unmodified ketones with aldehydes and Meldrum's acid. In this efficient and highly diastereoselective process a tertiary stereogenic center is created under concomitant formation of two new carbon–carbon σ-bonds.

Our reaction design was inspired by elegant three-component reactions introduced by Tietze et al. and Oikawa and Yonemitsu et al. that utilize aldehydes, Meldrum's acid (**1**), and enol ethers or indoles to furnish products of type **C** and **D**, respectively (Scheme 2).[1,7,8] These transformations are catalyzed by ammonium salts or proline and follow a domino Knoevenagel–hetero-Diels–Alder mechanism via intermediate alkylidene Meldrum's acids **2**. Furthermore, silyl enol ethers and enamines are known to react with activated olefins (e.g. **2**), to give Michael-products (e.g. **3**).[9,10] We reasoned that alkylidene derivatives **2** and enamines could be generated *in situ* from ketones, aldehydes and Meldrum's acid (**1**) by using a catalytic amount of proline. Consequently, this reaction mixture would directly furnish keto esters **3**.

It was gratifying to find that mixing *p*-nitrobenzaldehyde (1 equiv), Meldrum's acid (1 equiv) and acetone (excess) with a catalytic amount of L-proline in chloroform at room temperature readily furnished crystalline keto ester **3a** in 78% yield (Table 1, entry 1).

Moreover we found that other aldehydes including α-branched (entry 4) and unbranched (entries 2,3) and cyclic aldehydes (entry 5) can readily be used to give the expected products in good yields (Table 1).



Scheme 2 Three component reactions involving aldehydes and Meldrum's acid

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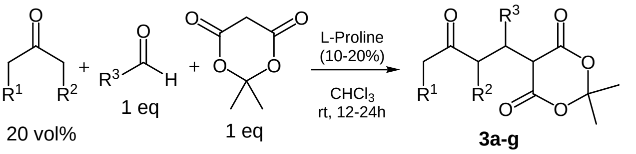
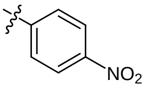
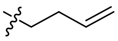
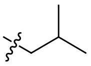
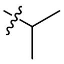
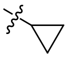
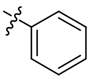
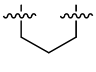
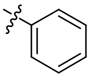
Table 1 Proline-Catalyzed Three-Component Reaction of Aldehydes with Ketones and Meldrum's Acid.



Entry	Product	R^1	R^2	R^3	Yield	dr^a
1	**3a**	H	H		78%	
2	**3b**	H	H		83%	
3	**3c**	H	H		79%	
4	**3d**	H	H		51%	
5	**3e**	H	H		65%	
6	**3f**				69%	>95%
7	**3g**				75%	>95%

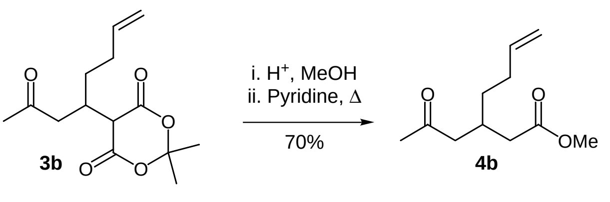
[a] Determined from HPLC and NMR analyses.

Cyclic ketones may be used as well and the corresponding products (**3f**, **3g**) are obtained as single diastereomers (entries 6,7). The enantioselectivity of this new reaction is generally low and keto esters **3** were typically obtained in ee's under 5%. This result is consistent with our earlier experiments on proline-catalyzed Michael additions of ketones to nitro-olefins, which showed low enantioselectivities.[11] Presumably both proline-catalyzed transformations, Michael reaction and the present three-component reaction, have similar mechanisms, which differ from the highly enantioselective proline-catalyzed aldol- and Mannich reactions.[12–15,4]

We propose that this new three-component reaction involves the domino Knoevenagel–hetero-Diels–Alder sequence postulated for the Tietze-three-component reaction (Scheme 3).[1,7] In this sequence, proline utilizes both iminium- and enamine-catalysis.[11] Accordingly, the initial Knoevenagel condensation (a–c) proceeds via iminium ion **7** and ammonium ion **8** to give olefin **2**. The role of proline in the hetero-Diels–Alder step (d–f) is to generate the dienophile, enamine **9**, which reacts with hetero diene **2** furnishing cyclo-adduct **10** and upon hydrolysis the final product (**5**) while regenerating the catalyst.

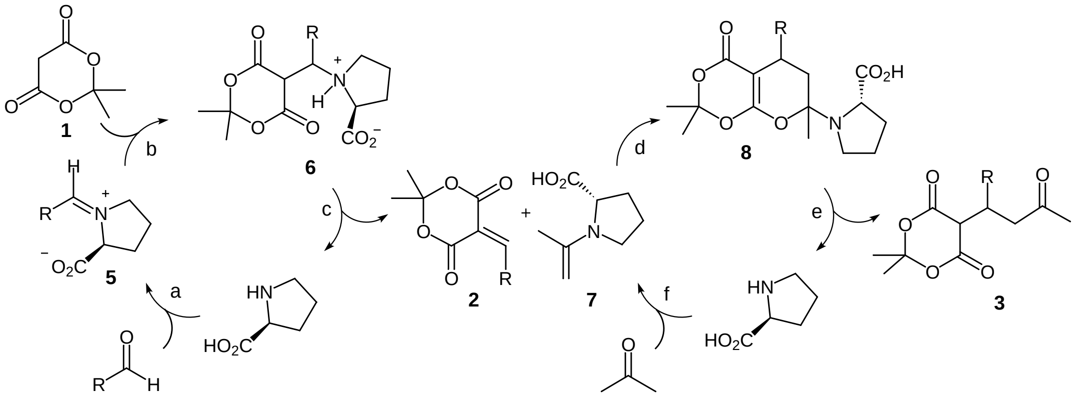
Although proline's α-chirality is not utilized for asymmetric induction, the carboxylate functionality seems essential for catalysis as indicated by the fact that pyrrolidine is ineffective.

Meldrum's acid derivatives **3** are valuable precursors of diversified 1,5-dicarbonyl compounds.[8,9] This was demonstrated by methanolysis and in situ decarboxylation of compound **3b** to give keto ester **4b** in good yield (Scheme 4).



Scheme 4

In summary we have developed a novel proline-catalyzed three-component reaction of aldehydes, ketones and Meldrum's acid. The reaction allows the rapid construction of complex carbon-scaffolds with two new C–C σ-bonds from three different commercially available components. From our initial experiments the scope of this new transformation appears to be broad since all aldehydes tested and various small and inexpensive cyclic and acyclic ketones could be used. Operational simplicity, mild reaction



Scheme 3 Proposed mechanism

conditions, and the inexpensive and non-toxic catalyst proline all contribute to the overall usefulness of the process.

Our new reaction adds to an increasing number of efficient organocatalytic transformations that are catalyzed by small-molecule amines and amino acids.[16] Future studies include the search for novel *enantioselective* aminocatalysts for this three-component reaction and the utilization of resin-bound Meldrum's acid. We are also pursuing the question whether additional substrates may be used to extend this novel MCR[17] beyond three components.

Acknowledgement

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(5) A transformation of this class formally represents a *bis-alkyl(or aryl)-de-oxo-bisubstitution* reaction. As this reaction has close similarities to the acetalization, which is a bis-alkoxy-de-oxo-bisubstitution reaction, we refer to this process as *carba-acetalization*.

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(17) The synthesis of **3b** illustrates the general experimental procedure: 4-Pentenal (1.66 mL, 17 mmol), Meldrum's acid (2.16 g, 15 mmol), acetone (30 mL) and L-proline (3 mmol, 20 mol%) were stirred in $CHCl_3$ (120 mL) at r.t. for 12 h. The mixture was washed with sat. aq NH_4Cl solution and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Chromatography on SiO_2 with hexanes–ethyl acetate (gradient 4:1 →1:2) furnished product **3b** (3.33 g, 83%). ^{1}HNMR (250 MHz, $CHCl_3$): δ = 1.50 (m, 2 H), 1.71 (s, 3 H), 1.72 (s, 3 H), 2.05 (m, 2 H), 2.21 (s, 3 H), 2.75 (dd, 1 H, *J* = 3.3, 12.3 Hz), 2.88, (m, 1 H), 2.97 (dd, 1 H, *J* = 9.9, 12.3 Hz), 4.12 (d, 1 H, *J* = 2.2), 4.96 (m, 2 H), 5.72 (m, 1 H). ^{13}CNMR (75 MHz, $CHCl_3$): δ = 26.7, 28.2, 30.4, 31.5, 32.2, 43.7, 47.7, 104.8, 115.3, 137.5, 165.0, 165.1, 209.0. FT-IR(neat): 2924, 1746, 1301, 1206. HRMS (MALDI-FTMS): calcd for $[M-H]^-$ 267.1238, found 267.1231.