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One-pot conversion of alkyl aldehydes into substituted propanoic acids via Knoevenagel condensation with Meldrum's acid

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ABSTRACT

Reaction of a range of alkyl aldehydes and Meldrum's acid in triethylammonium formate (TEAF) at 100 °C generates substituted propanoic acids in a single step.

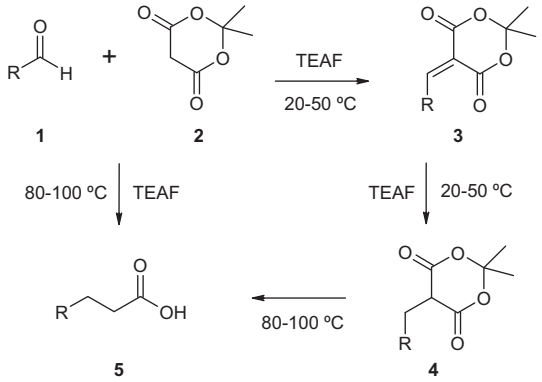
The Knoevenagel condensation of Meldrum's acid with aromatic aldehydes to produce arylidene derivatives is a well-documented reaction.[1] Arylidene Meldrum's acids are useful reactive intermediates, being susceptible to 1,4-addition,[2] acting as activated dienophiles in Diels–Alder reactions[3] and being used for the preparation of heterocyclic molecules such as coumarins,[4] benzofurans and indoles.[5] When the condensation of aromatic aldehydes (**1**) and Meldrum's acid (**2**) is carried out in triethylammonium formate (TEAF) at temperatures between 20 °C and 50 °C, a transfer hydrogenation of the arylidene Meldrum's acid occurs.[6] The double bond in the intermediate **3** is reduced to give **4**, which can be isolated or converted into the corresponding 3-arylpropanoic acid **5** by heating to 80–100 °C (Scheme 1). If the reaction is carried out at 80–100 °C, direct conversion of aryl aldehyde **1** into 3-arylpropanoic acid **5** is generally completed within 3 h.

This facile method of generating 3-arylpropanoic acids from the corresponding benzaldehydes has also been extended to include heteroaromatic aldehydes.[7] In contrast, the corresponding reaction of aliphatic aldehydes with Meldrum's acid has received little attention. Tóth and Köver reported that the reaction of straight-chain aldehydes with Meldrum's acid in TEAF gave Michael adducts rather than the corresponding substituted propanoic acids.[6]

Typically, when alkyl-substituted Meldrum's acids have been isolated (**4**, where R = alkyl), reductive alkylation conditions have been employed.[8] In order to obtain substituted propanoic acids, the isolated alkyl-substituted Meldrum's acid is subsequently decarboxylated; a one-pot conversion is yet to be reported.[9]

Recently, we required 3-(tetrahydro-2*H*-pyran-4-yl)propanoic acid (**5a**) as a versatile intermediate in an ongoing medicinal chemistry programme. This material is not readily available from commercial sources and the only documented route for its preparation involves a three-step synthesis from 4-(bromomethyl)tetrahydro-2*H*-pyran.[10] Having previously prepared 3-(4-cyanophenyl)propanoic acid from 4-formylbenzonitrile via the method reported by Tóth and Köver, we decided to investigate the reaction of tetrahydro-2*H*-pyran-4-carbaldehyde (**1a**) with Meldrum's acid. We were gratified to obtain 3-(tetrahydro-2*H*-pyran-4-yl)propanoic acid (**5a**) as the exclusive product in 87% yield.[11]

This result encouraged us to further explore the scope of this reaction, as summarised in Table 1. Starting with close analogues of tetrahydro-2*H*-pyran-4-carbaldehyde, 3-cyclohexylpropanoic acid (**5b**) and 3-(1-{[(phenylmethyl)oxy]carbonyl}-4-piperidinyl)propanoic acid (**5c**) were obtained in good yields from cyclohexanecarbaldehyde (**1b**) and phenylmethyl 4-formyl-1-piperidinecarboxylate (**1c**), respectively. In five-membered ring systems, 3-cyclopentylpropanoic acid (**5d**) was obtained in an excellent yield from cyclopentanecarbaldehyde (**1d**), but 3-(*N*-Boc-2-pyrrolidinyl)propanoic acid (**5e**) was only isolated in 26% yield from *N*-Boc-L-prolinal (**1e**). In this case a small amount of a second product, believed to be 7-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-4-oxoheptanoic acid, formed via ring-opening, was also obtained. Interestingly, a similar reaction using *N*-Boc-2-formylpiperidine (**1f**) did not show any signs of ring-open-



Scheme 1. Stepwise route for conversion of aldehydes to substituted propanoic acids.

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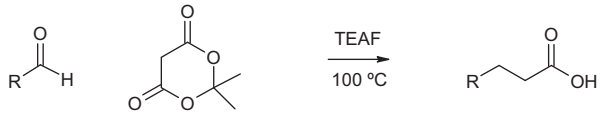
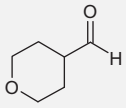
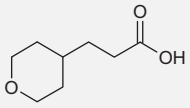
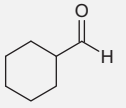
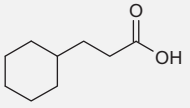
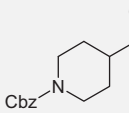
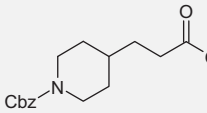
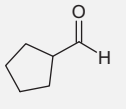
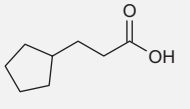
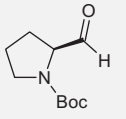
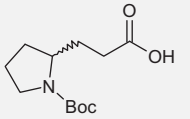
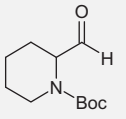
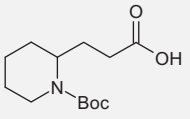
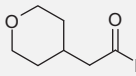
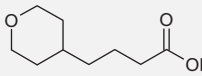
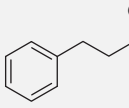
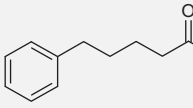
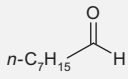
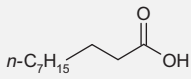
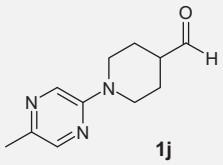
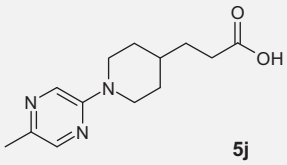
Table 1
Synthesis of substituted propanoic acids[11]



Entry	Aldehyde	Product	Yield (%)
1	 **1a**	 **5a**	87
2	 **1b**	 **5b**	78
3	 **1c**	 **5c**	90
4	 **1d**	 **5d**	89
5	 **1e**	 **5e**	26[a]
6	 **1f**	 **5f**	41[b]
7	 **1g**	 **5g**	87
8	 **1h**	 **5h**	89
9	 **1i**	 **5i**	93
10	 **1j**	 **5j**	93

[a] Another product, believed, but not confirmed to be 7-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-4-oxoheptanoic acid was isolated along with **5e**.
[b] Required additional purification by flash column chromatography, recovery lower than expected based on the crude yield.

ing, 3-(*N*-Boc-2-piperidinyl)propanoic acid (**5f**) being obtained in 41% yield.

Other *N*-Boc-protected amino aldehydes such as Boc-L-alaninal and *N*-Boc-D-phenylalaninal were not tolerated and complex mixtures of products were obtained. Similarly, a reaction using (*S*)-perillaldehyde failed, suggesting that sensitive substrates are not suitable when using these conditions.

We also investigated the chain length as a factor in this reaction. Tetrahydro-2*H*-pyran-4-ylacetaldehyde (**1g**) and 3-phenylpropanal (**1h**) gave 4-(tetrahydro-2*H*-pyran-4-yl)butanoic acid (**5g**) and 5-phenylpentanoic acid (**5h**), respectively. We were delighted to find that *n*-octanal (**1i**) gave decanoic acid (**5i**) in 93% yield, with no Michael addition products observed.

The reaction using 1-(5-methyl-2-pyrazinyl)-4-piperidinecarbaldehyde (**1j**) gave 3-[1-(5-methyl-2-pyrazinyl)-4-piperidinyl]propanoic acid (**5j**) in 93% yield.[12] This product was previously unreported and represents a novel drug-like template for further medicinal chemistry exploration.

In conclusion, we have reported the efficient one-pot conversion of a range of alkyl aldehydes into substituted propanoic acids via Knoevenagel condensation with Meldrum's acid in TEAF. The reaction works well for straight-chain and branched aldehydes. *N*-Cbz protection is well tolerated. *N*-Boc-protected aldehydes gave much lower yields but it is inconclusive whether the protecting group was responsible for this outcome.

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11. *General method for the preparation of substituted propanoic acids: 3-(tetrahydro-2H-pyran-4-yl)propanoic acid* (**5a**). Et_3N (3.36 mL, 24.11 mmol) was added dropwise to formic acid and (2.26 mL, 58.9 mmol) cooled in an ice bath to give triethylammonium formate. This was added to tetrahydro-2*H*-pyran-4-carbaldehyde (**1a**) (250 mg, 2.190 mmol) and Meldrum's acid (316 mg, 2.190 mmol), and the mixture was heated at 100 °C for 5 h. The reaction mixture was treated with 2 M NaOH (40 ml), and the aqueous layer extracted with Et_2O (3 × 40 ml). The combined organic layer was then acidified to pH 4 with 5 M aq HCl and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 ml). The combined organics were dried ($MgSO_4$), filtered and evaporated to give the title compound **5a**, as a white solid (301 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (m, 2H), 1.52 (m, 1H), 1.60 (m, 4H), 2.39 (m, 2H), 3.37 (dt, 2H, J = 11.8, 2.0 Hz), 3.97 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 30.7, 31.4, 32.3, 33.8, 66.9, 174.5.
12. *3-[1-(5-Methyl-2-pyrazinyl)-4-piperidinyl] propanoic acid* **(5j).** Prepared via the above method. Obtained as a pale yellow solid (296 mg, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06 (m, 2H), 1.46 (m, 3H), 1.72 (m, 2H), 2.25 (m, 5H), 2.77 (dt, 2H, J = 12.7, 2.4 Hz), 4.32 (m, 2H), 7.66 (s, 1H), 8.08 (s, 1H), 12.06 (br s, 1H). LC/MS $[M+H]^+$ = 250.