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A facile synthesis of 1,7-dicarbonyl compounds via three-component Michael addition reactions

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Abstract—A convenient one-pot synthesis of 1,7-dicarbonyl compounds has been accomplished by a three-component Michael addition reaction of nitromethane with two unsymmetric α,β-unsaturated carbonyl compounds in the presence of a base.

Multi-component reactions (MCR) are an important field of research in combinatorial chemistry.[1] Being one-pot reactions, multi-component reactions can afford good yields and are different from two-component reactions in several respects.[2] In the last decade, there has been tremendous development in three- and four-component reactions involving Passerini,[3] Ugi[4] and Mannich reactions,[5] which has led to the renaissance of MCRs. However, in spite of the enormous scope of MCRs, only 3-CRs with isocyanides have been developed into popular organic reactions. Nevertheless, great efforts have been and still are being made to find and develop new MCRs.[6]

1,7-Dicarbonyl compounds are initial starting materials for the synthesis of enantiomerically pure alcohols that are useful building blocks for natural product synthesis.[7] Whereas many ring-closing reactions of 1,7-dicarbonyl compounds to form five- and six-membered carbocycles have been reported in the literature,[8] less work has been focussed on their synthesis. Among convenient methods reported for the two-component preparation of 1,7-dicarbonyl compounds are the mercury(II) catalysed hydration of monosubstituted alkynes,[9] the addition of alkyl cadmiums to acetyl chloride,[10] palladium catalysed oxidation of monosubstituted olefins,[11] oxidative cleavage of 2-methylcycloheptanone[12] and condensation of bromo ketals with methyl acetoacetate.[8a] However, these methodologies have disadvantages such as less accessible substrates as starting materials and multi-step synthesis or stringent reaction conditions. Although the Michael addition of α,β-unsaturated ketones can provide efficient strategies for the two-component preparation of 1,5-diketones,[13] to the best of our knowledge, such attempts are rare in the case of 1,7-dicarbonyl compounds. Recently, we demonstrated the convenience of a Michael addition reaction for a one-pot synthesis of 1,6-dicarbonyl compounds utilising a three-component reaction.[14] In continuation of our interest, we report herein a facile base-catalysed three-component synthesis of 1,7-dicarbonyl compounds using a Michael addition reaction of nitromethane with two unsymmetric α,β-unsaturated carbonyl compounds.

When a mixture of benzylidene acetophenone (**1a**, 1 mmol), nitromethane (1 mmol) and ethyl acrylate (**2a**, 1 mmol) was treated with sodium ethoxide (3 mmol) in ethanol (30 mL) under reflux for 2 h, the product ethyl 6-benzoyl-4-nitro-5-phenyl caproate **3a** was obtained as a mixture of two diastereomers in 85% yield.[15] Product **3a** was characterised by spectroscopic and analytical analysis.[15] From the ^{1}H and ^{13}C NMR spectra a *syn*/*anti* ratio of 65:35 was determined. Similarly, the three-component reactions of **1a** and nitromethane with methyl vinyl ketone **2b** and methyl acrylate **2c** afforded diastereomeric mixtures of the 1,7-dicarbonyl products **3b–c** in good yields (Table 1). In order to broaden the scope of the reaction, α,β-unsaturated ketones **1b–d** and 16-dehydropregnenolone acetate **1e** were reacted with **2a–c** in presence of nitromethane, which also led to the 1,7-dicarbonyl products **3d–o** as diastereomeric mixtures (entries 4–15).

Keywords: 1,7-Dicarbonyl; Three-component; Michael addition; Nitromethane; α,β-Unsaturated carbonyl compounds.

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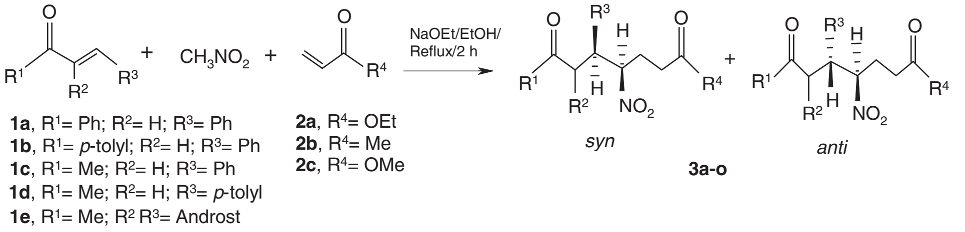
Table 1. Preparation of 1,7-dicarbonyl compounds **3a–o** by a 3-CR[a]



Entry	Product[b]	R^1	R^2	R^3	R^4	Reaction time (h)	Yield[c] (%)	*syn/anti* Ratio[d]
1	**3a**	Ph	H	Ph	OEt	2	85	65:35
2	**3b**	Ph	H	Ph	Me	2.5	80	60:40
3	**3c**	Ph	H	Ph	OMe	4	81	55:45
4	**3d**	*p*-Tolyl	H	Ph	OEt	2	85	62:38
5	**3e**	*p*-Tolyl	H	Ph	Me	2.5	80	64:36
6	**3f**	*p*-Tolyl	H	Ph	OMe	4	81	55:45
7	**3g**	Me	H	Ph	OEt	5	75	62:38
8	**3h**	Me	H	Ph	Me	4	73	61:39
9	**3i**	Me	H	Ph	OMe	4	70	58:42
10	**3j**	Me	H	*p*-Tolyl	OEt	5	75	62:38
11	**3k**	Me	H	*p*-Tolyl	Me	4	77	59:41
12	**3l**	Me	H	*p*-Tolyl	OMe	4	70	57:43
13	**3m**	Me	Androst		OEt	3	84	70:30
14	**3n**	Me	Androst		Me	3.5	82	66:44
15	**3o**	Me	Androst		OMe	3	80	67:33

[a] Carried out in the manner described in the experimental.

[b] Spectral data are in agreement with the structures.

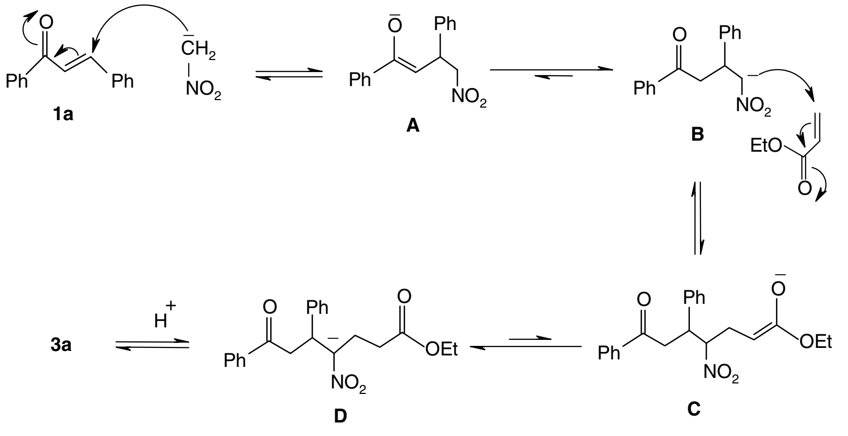
[c] Isolated yields.

[d] *syn/anti* Ratios were determined from ^1H NMR and ^{13}C NMR spectra of the diastereomers.

The 3-CR reaction is expected to proceed via a reaction pathway involving sequential Michael additions driven by the acidity of the hydrogen atoms attached to the carbon α to the nitro group. Under the influence of base, initial deprotonation of the nitromethane followed by conjugate addition to the α,β-unsaturated ketone **1a** gives an intermediate **A**, which equilibrates with anion **B** (presumably the major species at equilibrium). The intermediate **B** will then add to the unsaturated ester, again to give an enolate **C**, which equilibrates with the major species **D**, followed by protonation to afford the three-component product **3a**. An attempt to induce the base (NaOH) catalysed intramolecular aldol reaction of **3a** however failed, rather it afforded 1-nitro-2,4-diphenyl-4-butanone and acrylic acid as the sole products. The fragmentation of **3a** could be explained by the reversal of the second conjugate addition (intermediate **B–C**), accompanied by simple ester hydrolysis.

In conclusion, we report the one-pot synthesis of 1,7-dicarbonyl compounds using a three-component Michael reaction of nitromethane with two unsymmetric conjugated carbonyl compounds.

Mechanism of the 3-component Michael reaction



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15. Typical procedure for the three-component reaction: preparation of ethyl 6-benzoyl-4-nitro-5-phenyl caproate **3a**: To a 50 mL round bottom flask, equipped with a reflux condenser, was added benzylidene acetophenone (**1a**, 500 mg, 2.4 mmol), nitromethane (0.13 mL, 2.4 mmol) and ethyl acrylate (**2a**, 0.48 g, 4.8 mmol) in ethanol (30 mL). To the reaction mixture was added freshly prepared sodium ethoxide (0.34 g, 5 mmol) in small portions and the mixture refluxed for 2 h. On completion of the reaction (vide TLC), the solvent was removed from the reaction mixture under reduced pressure. The residue was stirred with 50 mL water, neutralised with dilute HCl and extracted with CH_2Cl_2 (2 × 25 mL), washed with water and dried over Na_2SO_4 (anhydrous). Removal of solvent afforded **3a** in 85% yield, mp 91 °C (MeOH); $R_f = 0.4$ (EtOAc/hexane = 1/9). IR (KBr): ν_{max}, = 1732, 1686, 1551, 1443, 1376 cm^{-1}. MS ESI $m/z = 392$ (M^++23). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N,3.79. Found: C, 67.97; H, 6.19; N, 4.11. ^1H NMR (300 MHz, $CDCl_3$) *syn*: $\delta = 7.91$–6.90 (10H, m), 4.81 (1H, m), 4.48 (1H, m), 4.15 (2H, q, $J = 7.14$ Hz), 3.44 (2H, d, $J = 4.63$ Hz), 2.47–2.40 (4H, m), 1.25 (3H, t, $J = 7.13$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) *syn*: $\delta = 197.3$, 172.74, 139.65, 136.77, 133.95, 129.41, 129.13, 129.02, 128.70 (2C) 128.40, 128.20, 127.89, 127.26, 74.76, 61.23, 41.91, 39.67, 30.87, 22.98, 14.54. ^1H NMR (300 MHz, $CDCl^3$) *anti*: $\delta = 7.91$–6.90 (10H, m), 4.67 (1H, m), 4.21 (1H, m), 4.14 (2H, q, $J = 7.13$ Hz), 3.42 (2H, d, $J = 4.68$ Hz), 2.33–2.25 (4H, m), 1.24 (3H, t, $J = 7.11$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) *anti*: 196.84, 172.28, 138.64, 136.03, 133.20, 129.41, 129.13, 129.02, 128.75 (2C), 128.50, 128.40, 127.84, 127.20, 73.98, 61.10, 41.55, 39.21, 30.59, 22.76, 14.33.