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Stereocontrol in the Michael Reaction of Dimethyl Malonate with Alkyl 2-(1-Hydroxyalkyl)propenoates

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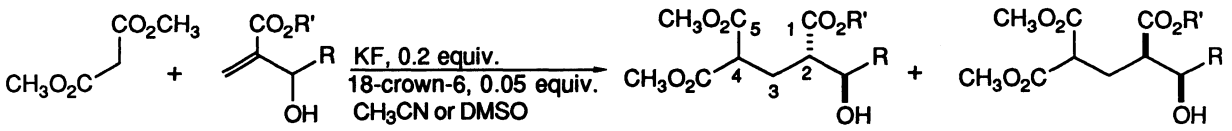
In this paper we show that the stabilized carbanion dimethyl malonate adds to alkyl 2-(1-hydroxyalkyl)propenoates under basic conditions. Side reactions, such as lactonization or elimination, may be reduced and/or completely avoided by the use of phase transfer catalysis. The high stereoselectivity associated with the additions discussed here was found to be under thermodynamic control.

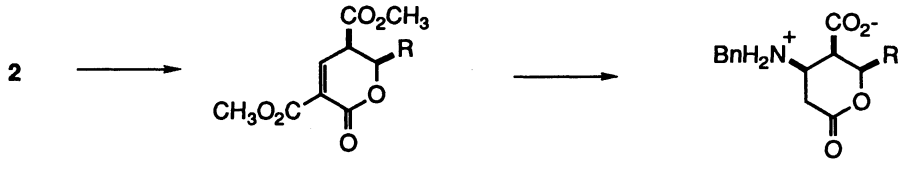
There has been considerable interest in the development of stereoselective versions of the Michael reaction.[1] Recently, we showed that amines add in a conjugate fashion to 2-(1-hydroxyalkyl)propenoates with good kinetic stereoselectivity.[2,3] We now report that these conjugate acceptors, which bear a carbon-based stereogenic centre attached to C2, undergo stereoselective Michael reactions with dimethyl malonate (Scheme 1).



1a-f **2a-f** **3a-f**

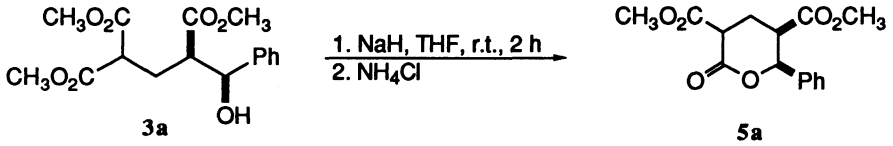
Scheme 1.

These products are of interest as they serve as valuable intermediates in our synthesis of carbapenems.[4] For example, diastereomer **2** can be converted into the unsaturated lactone **6** which, upon treatment with benzylamine, gives a conjugate adduct. Hydrolysis of this adduct then provides a simple approach to the carbapenem intermediate, **7**.



6 **7**

As is evident from Table 1, reasonable yields of 1,4-adducts may be obtained using phase-transfer catalysis (PTC).[5] In addition, useful levels of stereoselectivity were obtained, especially for reactions carried out in acetonitrile. In one case the relative stereochemistry of the adducts was determined by treating the major diastereomer **3a** with sodium hydride in tetrahydrofuran. This resulted in efficient cyclisation, yielding only the *syn* lactone **5a** (Scheme 2). The stereochemical assignment of the products of the other conjugate additions follows from analysis of their ^{1}H n.m.r. spectra. In all cases (except **3e**), the major diastereomer displayed a resonance at δ 4.8 ppm whereas the minor diastereomer displayed a resonance at δ 5.0 ppm. For **3e**, the trend was the same although a downfield shift of ~0.8 ppm was observed.



3a 5a

Scheme 2.

Table 1. Phase-transfer catalyzed Michael reactions with 2-(1-hydroxyalkyl)propenoates

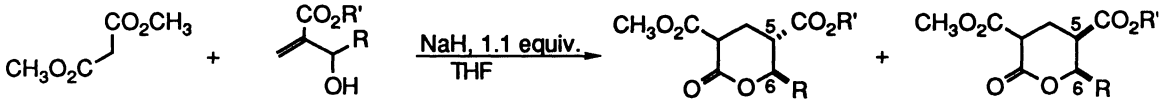
Cpd	R	R'	T /°C	t /h	Method	Solvent	Yield /%[a]	3 : 2 [b]
1a	Ph	CH_3	80	0.6	B	DMSO	60 (69)	7 : 1
1a	Ph	CH_3	40	168	A	CH_3CN	49 (76)	15 : 1
1a	Ph	CH_3	81	1.5	A	CH_3CN	46	15 : 1
1b	Ph	$PhCH_2$	80	0.6	B	DMSO	54 (62)	5 : 1
1b	Ph	$PhCH_2$	81	1.5	A	CH_3CN	37 (53)	>10 : 1
1c	β-pyridyl	CH_3	60	1.5	B	DMSO	54 (55)	6 : 1
1c	β-pyridyl	CH_3	81	1.5	A	CH_3CN	31	20 : 1
1d	α-furyl	CH_3	60	1.5	B	DMSO	56 (60)	4 : 1
1d	α-furyl	CH_3	81	1.5	A	CH_3CN	64	17 : 1
1e	α-naph	CH_3	80	0.6	B	DMSO	68	20 : 1
1f	*p*-nitrophenyl	CH_3	81	1.5	A	CH_3CN	44	17 : 1

a) Values refer to yields of products isolated after chromatography on silica gel. Values in parentheses refer to crude yields estimated by ^{1}H NMR spectroscopy. b) Determined by 200 MHz ^{1}H NMR spectroscopy.

That the *syn* diastereomer is the thermodynamic product was established by following the progress of the reaction using ^{1}H NMR spectroscopy at 20 °C in CD_3CN. The chemical shift of the proton alpha to the hydroxyl group for each of the isomeric products is sufficiently different (0.2 ppm) to allow their direct observation. Over the course of 168 hours the ratio of **3** to **2** was observed to change significantly. After 2 hours' reaction time, the ratio was ≈2:1. However after 168 hours the ratio had changed to 15:1. Thus **2** isomerises under the reaction conditions to **3**. At this stage it has not proven possible to determine the exact

kinetic ratio of products. Unlike the conjugate addition of primary amines[2] or organic free radicals[3] to these acceptors, any allylic control[6] associated with the additions described here is obscured by the rapid isomerisation of the *anti* adduct to the more stable *syn* isomer.

We have also found that by employing other sets of reaction conditions the nature of the products could be varied. For example, using sodium hydride as the base, rather than potassium fluoride/18-crown-6, only small amounts of **2** and **3** were obtained. Instead, the lactones **4** and **5** were the major products (see Scheme 3, Table 2). Evidence of relative stereochemistry came from $J_{5,6}$. For **4** this was ≈9 Hz, and for **5** ≈4 Hz.[7]



4 **5**

Scheme 3.

Table 2. Direct lactone synthesis from Michael reactions

Cpd	R	R'	T/°C	t/h	Solvent	Yield /%[a]	4 : 5 [b]
1 a	Ph	CH_3	25	2	THF	66	2 : 3
1 c	β-pyridyl	CH_3	25	22	THF	31	1 : 1
1 d	α-furyl	CH_3	25	3	THF	30	1 : 1
1 g	CH_3	CH_3	25	2	THF	46	7 : 3

a) Isolated yield. b) Determined by 200 MHz ^{1}H NMR spectroscopy.

Typical procedures for the phase-transfer catalyzed Michael reaction are described below.
Method A: To a stirred solution of 18-crown-6 (40 mg, 0.17 mmol) in dry acetonitrile (10 mL) was added anhydrous potassium fluoride (40 mg, 0.68 mmol), dimethyl malonate (0.39 mL, 3.4 mmol) and methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**) (1.0 g, 3.4 mmol) in acetonitrile (10 mL). The mixture was then refluxed for 1.5 h after which, the acetonitrile was evaporated *in vacuo*. Ethyl acetate (25 mL) was then added and the whole was washed with 3 M HCl (2x10 mL), saturated aqueous NaCl solution (2x10 mL) then dried (Na_2SO_4) and the solvent removed *in vacuo*. The diastereomeric ratio was estimated by ^{1}H NMR to be ≈15:1 (*syn/anti*). Preparative TLC (silica gel; diethyl ether/light petroleum, 3:1) of the crude product yielded the *syn* diastereomer of dimethyl 2-[(1-hydroxy)- phenylmethyl]-4-(methoxycarbonyl)-1,5-pentanedioate (**3a**) as a colourless oil (0.51 g, 46%). (Found: C, 59.5; H, 6.0%. Calcd for $C_{16}H_{20}O_7$: C, 59.3; H, 6.2%). ν_{max} (Film): 3465br, 1730vs, 1435s, 1205s, 1165s, 1030m, 775m, 705s cm^{-1}. ^{1}H NMR (200MHz): δ 1.98, ddd, *J* 14.2, 9.6, 4.7Hz, 1H, CH(H)CHCO2Me; 2.16, ddd, *J* 14.1, 10.1, 5.7 Hz, 1H, CH(H)CHCO2Me; 2.58, bs, 1H, OH; 2.87, ddd, *J* 10.1, 7.5, 4.6Hz, 1H, CHCO2Me; 3.33, dd, *J* 9.5, 5.6Hz, 1H, CH(CO2Me)2; 3.68, s, 9H, OCH3; 4.82, d, *J* 7.5Hz, 1H, CHOH; 7.29-7.40, m, 5H, ArH. Mass spectrum: *m/z* 324 ($M^{+\cdot}$, 1%), 292 (1), 264 (10), 218 (10), 178 (12), 158 (25), 132 (100), 77 (30). The minor diastereomer could not be isolated pure.

Method B: To a stirred solution of 18-crown-6 (20 mg, 8.5×10^{-5} mol) in dry dimethyl sulfoxide (5 mL) was added anhydrous potassium fluoride (20 mg, 0.34 mmol), dimethyl malonate (0.15mL, 1.3 mmol) and methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**) (250 mg, 1.3 mmol) in dry dimethyl sulfoxide (5 mL). The mixture was then heated at 80 °C for 40 min after which it was poured into 3 M HCl (25 mL). Ethyl acetate (25 mL) was then added. The organic layer was washed with saturated aqueous NaCl solution (3x10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The diastereomeric ratio was estimated by ^1H NMR to be ≈7:1 (*syn/anti*). Column chromatography (silica gel; diethyl ether/light petroleum, 2:1) of the crude product afforded the *syn* diastereomer of dimethyl 2-[(1-hydroxy)phenylmethyl]-4-(methoxycarbonyl)-1,5-pentanedioate (**3a**) as a colourless oil (250 mg, 60%). Attempts to isolate the *anti* diastereomer using both preparative TLC and column chromatography were unsuccessful, with the *anti* readily isomerising to the *syn* diastereomer.

At this stage there is no simple explanation for the apparent stability of the *syn* isomers. Preliminary calculations indicate that there is little difference in energy between the lowest energy conformation of each diastereomer.[8] We are currently carrying out more detailed calculations in order to probe further this question.

In conclusion, the stereoselectivity associated with the Michael reaction of dimethyl malonate with 2-(1-hydroxyalkyl)propenoates is under thermodynamic control, producing the *syn* isomer in each case.

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References

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