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CHIRAL ACRYLATES AS SUBSTRATES IN BAYLIS-HILLMAN REACTION

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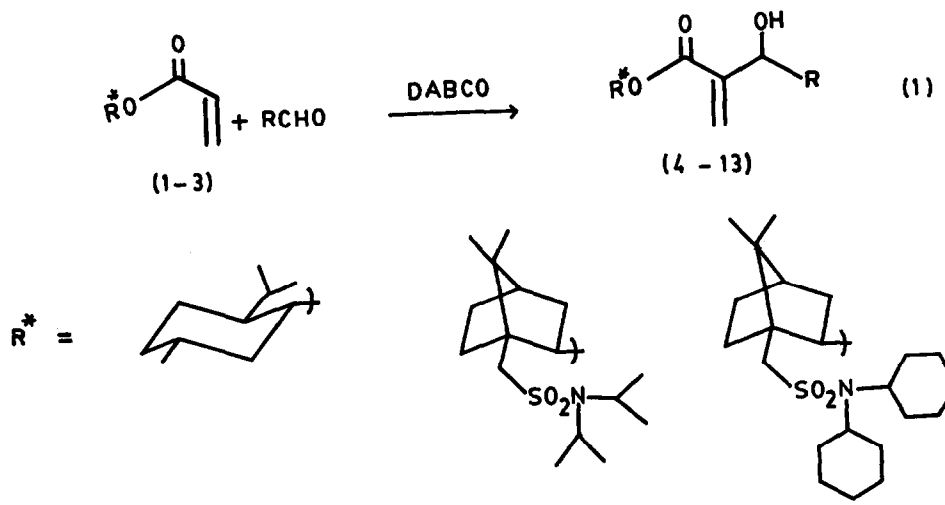
Summary: DABCO induces diastereoselective (7-70%) coupling of chiral acrylates (**1-3**) with aldehydes to produce the corresponding 2-(1-hydroxyalkyl)acrylates.

Chiral auxiliary mediated reactions that manifest high levels of diastereoselection represent a valuable source for preparation of enantiomerically enriched synthetic intermediates.[1,2] In continuation of our interest[3-8] in multifunctional molecules, we herein report our studies towards 1,4-diazabicyclo-(2.2.2)octane (DABCO) induced diastereoselective (7-70%) coupling of three selected chiral acrylates (1-3) with aldehydes to produce 2-(1-hydroxyalkyl)acrylates.

In recent years there has been increasing interest in Baylis-Hillman coupling reactions i.e. DABCO induced or catalyzed carbon-carbon bond forming reactions leading to multifunctional molecules.[3-15] It has been well documented that methyl acrylate couples with aldehydes,[9,10] and α-keto esters[6] under the influence of catalytic amount of DABCO to provide the corresponding multifunctional molecules. It occurred to us that chiral acrylates would be applicable to the synthesis of optically active 2-(1-hydroxyalkyl)acrylates. Accordingly, we have first investigated the possible applicability of easily accessible (-)-menthyl acrylate (1). We have examined the coupling reaction of (-)-menthyl acrylate with propionaldehyde under the influence of DABCO. We have found that the coupling reaction is faster and the yield of the product **5** is very high when DABCO is used in 100 mole% (i.e. in molar ratio). The diastereoselectivity is found to be 16% as determined by ^{1}H NMR analysis of corresponding acetate using $Eu(hfc)_3$ shift reagent. This is also confirmed by capillary GC (methyl silicone column) analysis of the acetate. A variety of aldehydes (Table 1) have been coupled with (-)-menthyl acrylate under the influence of DABCO (eq. 1) and the diastereoselectivities are found to be in the range of 7-20% (Table 1).

With a view to achieving high diastereoselectivities in Baylis-Hillman C-C bond forming reaction, we have selected the chiral acrylates **2** and **3** for our studies. These acrylates **2** and **3** are easily obtained from the chiral alcohols (Oppolzer's chiral auxiliaries),[16,17] (1S, 2R, 4R)-1-(diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol and (1S, 2R, 4R)-1-(dicyclohexylaminosulfonyl)-methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol, respectively.[18]

Coupling reaction of the acrylate **2**[19] with acetaldehyde using 100 mole% of DABCO was found to be reasonably fast taking two days for completion thus providing the desired product **9**.[20] The diastereomeric excess was determined by ^{1}H NMR spectrum analysis of the corresponding acetate in the presence of Eu(hfc)$_3$ and found to be 30%. Propionaldehyde and benzaldehyde are the other two aldehydes selected for coupling reaction with this acrylate and the corresponding coupled products are obtained in 42% and 15% diastereoselectivities respectively.



Similar Baylis-Hillman coupling reactions of the chiral acrylate **3**[19] with propionaldehyde and benzaldehyde were carried out to provide the desired multifunctional molecules **12** and **13** in 70% and 25% diastereoselectivities respectively (Table 1). The coupling products (**8-13**) are nice solids and fractional crystallization cleanly provides the corresponding products with 100% diastereomeric excess (pure single diastereomers).

Studies to establish the absolute stereochemistry of these pure crystallized products and studies towards the utilization of these products in organic synthesis are now underway in our laboratory. Our efforts now are also directed towards fabrication of a suitable chiral acrylate for 100% diastereoselective Baylis-Hillman coupling reaction.

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Table 1: Preparation of chiral 2-(1-hydroxyalkyl)acrylates from chiral acrylates (1-3) and aldehydes.[a,b,c]

Acrylate	Aldehyde	Product	Yield(%)[d]	Time(days)	$[\alpha]_D^{20}$	de(%)
1	CH_3CHO	4[21]	83	7	-73.4°(c1.6, MeOH)	11[e,f]
1	CH_3CH_2CHO	5	78	7	-75.4°(c2.5, Acetone)	16[e,f]
1	$(CH_3)_2CHCHO$	6	77	14	-50.0°(c1.2, Acetone)	7[f]
1	Furfural	7	85	0.75	-63.1°(c1.5, Acetone)	20[e]
1	C_6H_5CHO	8[h]	89	7	-51.7°(c0.73, Acetone)	15[e]
2	CH_3CHO	9[h]	70	2	-60.0°(c0.8, Acetone)	30[e]
2	CH_3CH_2CHO	10[h]	70	7	-52.5°(c0.4, Acetone)	42[e]
2	C_6H_5CHO	11[h]	84	10	-36.6°(c0.3, Acetone)	15[e]
3	CH_3CH_2CHO	12[h]	45	10	-37.5°(c0.48, Acetone)	70[g]
3	C_6H_5CHO	13[h]	80	15	-30.4°(c0.3, Acetone)	25[g]

(a) All the products were characterised by IR, ^1H NMR, ^{13}C NMR spectroscopy and elemental analysis.

(b) All reactions with acrylate 1 were carried out on 5 mmol scale using 5 mmol DABCO.

(c) All reactions with acrylates 2 and 3 were carried out on 2 mmol scale using 2 mmol DABCO.

(d) Yields of the column chromatography purified products. The products (4-7) are obtained as liquids and (8-13) are obtained as solids.

(e) Determined by the integration of methyl ($COCH_3$) signals in the ^1H NMR spectra of acetates with $Eu(hfc)_3$.

(f) Capillary GC analysis (methyl silicone column) of the corresponding acetates indicate that the products 4,5,6 are obtained in 12%, 15%, 7% de respectively.

(g) In the ^1H NMR spectrum of the acetate of 12 the olefinic proton cis to ester functionality appears as two singlets arising from two diastereomers. Diastereomeric excess was determined by integration of these signals. Similarly, ^1H NMR spectrum of the acetate of 13 shows two singlets for the olefinic proton trans to the ester functionality and de is determined by the integration of these two singlets.

(h) Crystallization affords selectively one diastereomer (100% de).

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18. We prepared these chiral alcohols, (1S, 2R, 4R)-1-(diisopropylaminosulfonyl)methyl-7,7-dimethylbicylco(2.2.1)heptan-2-ol and (1S, 2R, 4R)-1-(dicyclohexylaminosulfonyl)methyl-7,7-dimethylbicyclo-(2.2.1)heptan-2-ol *via* the opening of the sultone [obtained from (+)-camphor-10-sulfonic acid] with bromomagnesium diisopropylamide (6 equivalents) and bromomagnesium dicyclohexylamide (8 equivalents) respectively.
19. The acrylates **2** and **3** are obtained by the action of the corresponding bromomagnesium salts of the alcohols on acryloyl chloride.
20. Representative experimental procedure (Preparation of the product **9**): Acetaldehyde (1 mL, excess aldehyde was added to dissolve DABCO and acrylate) acrylate **2** (0.74 g, 2 mM) and DABCO (0.224 g, 2 mM) were mixed and allowed to react at room temperature. The reaction was monitored by TLC. Reaction is complete in 2 days. Direct column chromatography of the reaction mixture (10% ethyl acetate in hexane) provides 70% (0.58 g) of the pure compound **9**. The structure of the product is confirmed by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectral data.
21. During the homogeneous hydrogenation studies Brown and coworkers have prepared the same compound **4** in 16% de by the action of (-)-menthyl acrylate with acetaldehyde under the influence of DABCO. J.M. Brown, I. Cutting, P.L. Evans and P.J. Maddox, Tetrahedron Lett., **1986**, 27, 3307.

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