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A SIMPLE ONE-POT PREPARATION OF MIKANECIC ACID DERIVATIVES *VIA* ALLYLIC CARBAMATES.

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Abstract: Mikanecic acid derivatives can be prepared in high yield from α-hydroxyalkyl acrylates *via* an allylic carbamate intermediate.

Mikanecic acid was first prepared in 1901 by the alkali treatment of ethyl 2-methyl-3,3-di-(phenylsulfonyl)-butanoate[1] and was isolated from *Senecio mikanioides* Otto in 1961[2]. The allylic alcohol products of the Baylis-Hillman reaction[3] have been found to be versatile intermediates and were first used by Hoffmann in his preparation of mikanecic acid derivatives[4]. Hoffmann prepared the mikanecic acid derivatives by a mesylation/elimination procedure using 1,4-diazabicyclo[2,2,2]octane (DABCO) as a base, methanesulfonyl chloride and a catalytic amount of 4-dimethylamino-pyridine (DMAP). Recently Basavaiah has

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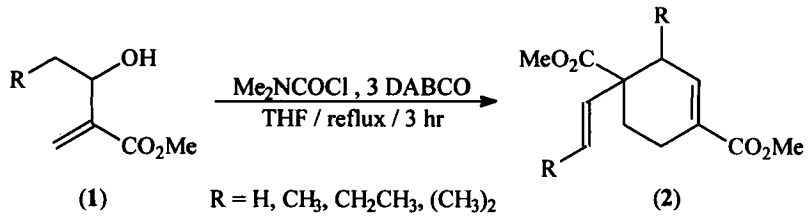
reported the asymmetric synthesis of mikanecic acid derivatives using chiral acrylates by a similar method, using triethylamine as the base[5]. Recent studies by ourselves has shown that allylic carbamates can be readily substituted *via* an S_N2' mechanism[6] and on elimination of the carbamate group one generates the corresponding dialkylamide, which is a strong base[7]. We have also found that DABCO is a particularly good nucleophile for the S_N2' elimination of allylic acetates[8]. Based on these observations we felt that mikanecic acid derivatives could be prepared *via* allylic carbamates.

Optimal conditions were found to be refluxing the allylic alcohol with 1.1 equivalents of dimethylcarbamoyl chloride and 3 equivalents of DABCO in THF for 3 hours (Scheme 1, Table). The reaction can be also carried out using diethylcarbamoyl chloride, but reaction times are slightly longer and the yield slightly lower. Pyridine may also be used as the solvent/base, with comparable yields.



(1) R = H, CH_3, CH_2CH_3, $(CH_3)_2$ (2)

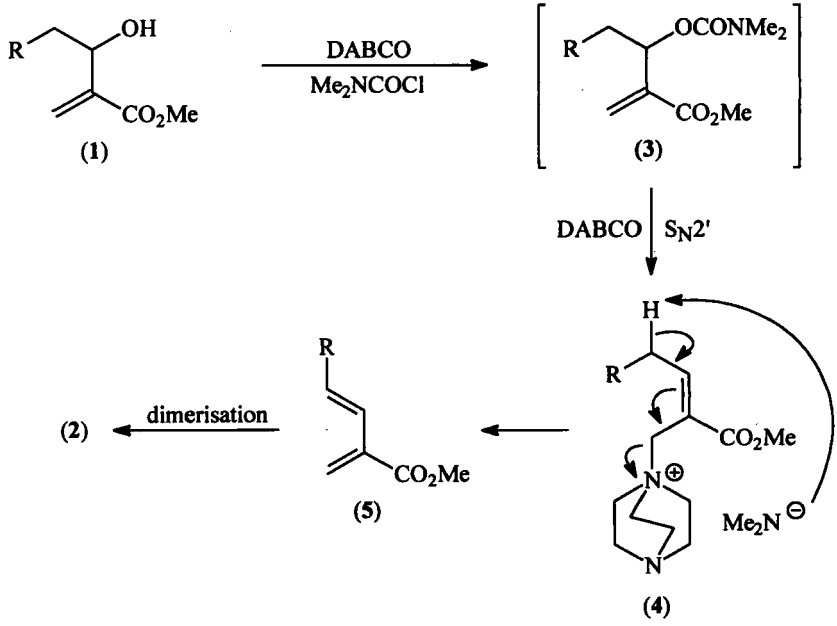
Scheme 1

Table: Yields of mikanecic acid derivatives (**2**) from allylic alcohols (**1**).

Allylic Alcohol (1)	R	% Yield of (2)[a]
a	H	98
b	CH_3	95
c	CH_2CH_3	91
d	$(CH_3)_2$	0[b]

a) Isolated yield. b) No reaction.

Yields are good in all cases except for when R is $(CH_3)_2$, where no reaction occurs, most likely for steric reasons. In the case of products (**2b**) and (**2c**), d.e.'s of 60 % were obtained. The reaction is thought to proceed according to the mechanism shown in Scheme 2, which is essentially that proposed by Hoffmann.



Scheme 2

We feel that the dimethylamide anion may play a role in deprotonating intermediate (**4**). The existence of the diene (**5**) hasn't been proven, and may in fact be unlikely since adding a large excess of another dienophile does not result in any cross products, as Hoffmann also observed. The allylic carbamates (**3**) have not been isolated, but the DABCO salt (**4a**), where R = H, has been isolated when the reaction is carried out in chloroform. Allylic alcohols derived from aromatic aldehydes do not react, since they do not have a proton β to the hydroxy group.

The preparation described is a useful alternative for the preparation of mikanecic acid derivatives and highlights the usefulness of the carbamate functionality as a synthetic intermediate. Further studies are underway.

Experimental:

Preparation of mikanecic acid derivatives: Method 1.

Allylic alcohol (**1**) (6.0 mmol), N,N-dimethylcarbamoyl chloride (6.1 mmol) and DABCO (18.0 mmol) were dissolved in dry THF (50 ml) and refluxed for 3 hours. The reaction was quenched with 2N HCl (50 ml), diluted with diethyl ether (100ml) and the organic layer dried over anhydrous $MgSO_4$. The solvent was removed and the residue purified by column chromatography (silica; ether/hexane,

1 : 9) to give (**2**). All products are known[4,5] and gave the expected spectroscopic data.

Preparation of mikanecic acid derivatives: Method 2.

Allylic alcohol (**1**) (6.0 mmol), N,N-dimethylcarbamoyl chloride (6.1 mmol) and DABCO (18.0 mmol) were dissolved in pyridine (50 ml) and refluxed for 3 hours. The reaction mixture was diluted with diethyl ether (100 ml) and washed with 2N HCl (2x 25 ml) and the organic phase dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica; ether/hexane, 1 : 9) to give (**2**).

Preparation of DABCO Salt (**4a**).

To a solution of methyl 3-hydroxy-2-methylenebutanoate (**1a**) (1.00 g, 7.75 mmol) in dry chloroform (20 ml) under an atmosphere of nitrogen was added DABCO (2.60 g, 22.3 mmol). N,N-Dimethylcarbamoyl chloride (1.07 g, 10.0 mmol) in chloroform (10 ml) was added dropwise and the mixture stirred at room temperature for 1 hour. The white precipitate was filtered off, washed with chloroform and dried under reduced pressure to afford (**4a**) (0.98 g, 52 %) as a mixture of E- and Z-isomers (10 : 1). All manipulations were carried out in the absence of moisture. ^{1}H NMR (200 MHz, CD_3OD) δ 2.13 (3H, d, $CHCH_3$), 3.16 - 3.26 (6H, m, $(CH_2)_3N^+$), 3.25 (6H, s, $DN(CH_3)_2$), 3.32 - 3.86 (6H, m, $(CH_2)_3N$),

3.85 (3H, s, CO_2CH_3), 4.30 (2H, s, C=CCH_2), 7.70 (1H, q, C=C*H*). *Anal.* Calcd for $C_{12}H_{27}N_3O_2$: C, 58.74; H, 11.09; N, 17.12; Found: C, 58.52; H, 10.81; N, 17.61. Note: The dimethylamide anion is deuterated in CD_3OD.

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