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Facile synthesis of Mikanecicacid diesters from Baylis-Hillman adducts, alkyl-3-hydroxy-2-methylenepropanoates

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Abstract: An efficient method for the synthesis of Mikanecic acid diesters from Baylis-Hillman adducts, (alkyl-3-hydroxy-2-methylenepropanoates) obtained by treatment with various aldehydes with suitable acrylates catalyzed by 1,4-diazabicyclo[2.2.2]octane (**DABCO**) which on treatment with 4-Dimethylaminopyridine (**DMAP**) led directly to the formation of Mikanecic acid diesters, through Diels-Alder type self-dimerization of 1,3-butadiene-2-carboxylate is reported. The product is obtained in good yield. This method offers an alternative route for the novel synthesis of mikanecic acid diesters in reasonable yields making the process more economic than other conventional methods.

Key Words: Mikanecic acid, Baylis-Hillman adducts, DMAP, Diels-Alder reaction.

Introduction

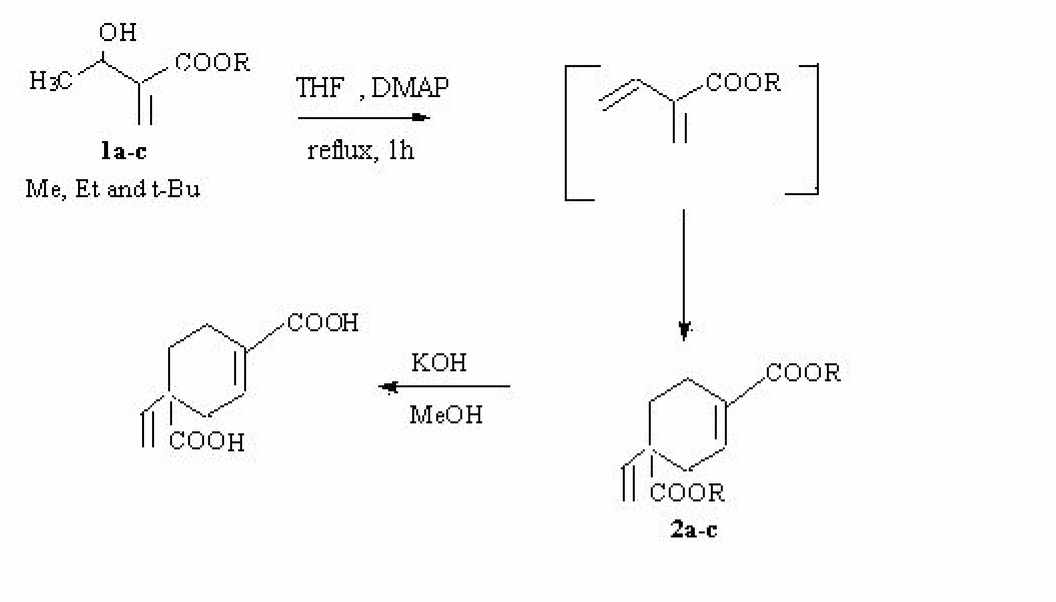
Synthetic organic chemistry is one of the most developing, expanding and successful branches of science. During the last fifteen years, synthetic organic chemistry has seen enormous growth[1-4], not only in terms of development of new methodologies for construction of carbon-carbon and carbon-hetero atom bonds but also in terms of development of new reagents, catalysts, strategies, transformations and technologies often involving the concepts of atom economy.

Construction of quaternary carbon center has been one of the challenging and attractive areas in synthetic areas in synthetic organic chemistry, because a number of biologically active natural products contain such structural sub-units[5-8].

4-vinyl-1-cyclohexene-1,4-dicarboxylic acid (**Mikanecic acid**) is a terpenoid dicarboxylic acid, has attracted our attention owing to its special feature of having vinylic quaternary carbon center in a functionalized six membered cyclic system. Mikanecic acid was isolated in 1936 by Manske[9] from the products of alkaline hydrolysis of the alkaloid Mikanoidine obtained from *Senecio mikakioides otto*. Many works have appeared regarding the history[10], characterization and synthesis of racemic Mikanecic acid[11].

DMAP catalyzed[12] organic reactions are gaining importance owing to their inexpensive nature and special catalytic attributes in heterogeneous reactions. In view of this and in continuation of our ongoing program to develop environmentally benign protocols, we, herein, report DMAP catalyzed synthesis of Mikanecic acid diesters in fairly good yields.

The reaction of acetaldehyde with suitable acrylates in the presence of DABCO afforded Baylis-Hillman adducts[13-28] (**1a-1c**) which on treatment with DMAP (0.2 equiv.) led directly to the formation of Mikanecic acid diesters (**2a-2c**), through Diels-Alder type self-dimerization of 1,3-butadiene-2-carboxylate (**Scheme 1, Table 1, Fig. 1**) which on hydrolysis gave Mikanecic acid.



Scheme 1: Synthesis of Mikanecic acid diesters

Table 1 . Synthesis of Mikanecic acid diesters[a,b]

substrate	Reaction time	product	Yield[c] (%)
1a	1h	**2a**	59
1b	1h	**2b**	55
1c	1h	**2c**	67

[a] All reactions were carried out in 10 mm scale of Baylis-Hillman adduct in 5 ml THF with DMAP (0.2 equiv.) and the reaction mixture refluxed for 1 hr.
[b] Satisfactory spectral data are obtained.
[c] Isolated yield after column chromatography (hexane/ether, 5:1).

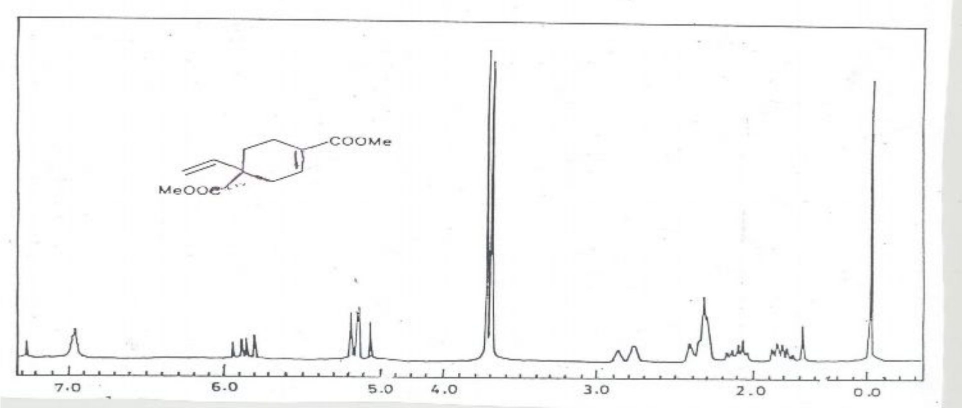


Fig. 1 : ^1H –NMR spectrum of compound 2a

Experimental

Melting points were determined in an open capillary tube with a Buchi melting point apparatus and are uncorrected. Elemental analyses were carried out using Perkin-Elmer 240C CHN-analyzer. IR spectra were recorded on a Perkin Elmer IR spectrophotometer. ^{1}H- NMR spectra was run in ($CDCl_3$) solvent at 200 MHz on a NMR spectrophotometer (chemical shifts in δ ppm). ^{13}C-NMR spectra was run in ($CDCl_3$) solvent at 50 MHz on a NMR spectrophotometer (chemical shifts in δ ppm).

General Procedure for the Synthesis of Mikanecic Acid:

The experimental procedure is very simple and straight forward. As shown in Scheme 1, the reaction can be carried out with 0.01 mole scale of Baylis-Hillman adduct in THF in the presence of DMAP (0.2 equiv.) were refluxed for 1 hr. After completion of the reaction (monitored by TLC), usual workup and column chromatographic purification (hexane/ether, 5:1) gave products, which were characterized by IR, NMR spectral data. The results obtained are very much consistent with literature report.

The spectral and analytical data of the compound **2a**: IR (neat): 1712, 1640 cm^{-1}; ^{1}H-NMR (200 MHz, CDCl3): δ 1.71-1.90 (1H, m), 2.08-2.16 (1H, m), 2.28-2.44 (3H, m),2.72-2.92 (1H, m),3.69 (3H, s), 3.73 (3H, s), 5.12-5.20 (2H, m), 5.78-5.98 (1H, m), 6.97 (1H, m) ; Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.28; H, 7.14 %. Found: C, 63.34; H, 6.92%.

Spectral data for Mikanecic acid: IR (KBr): 1690, 1640 cm^{-1}; ^{1}H-NMR (200 MHz, CDCl3): δ 1.67-2.82 (6H, m), 5.02-5.29 (1H, m), 5.75-6.04 (1H, m), 6.85 (1H, m), 12.42 (2H, s, br); ^{13}C-NMR (50 MHz, CDCl3): δ 21.58, 29.09, 31.70, 46.53, 114.55, 129.31, 136.78, 140.29, 167.66, 175.21; EI-MS: *m/z* 196 (M·) ; *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12 %. Found: C, 57.48; H, 6.50 %.

Conclusions

As a conclusion, this paper described a facile synthesis of Mikanecic acid diesters from Baylis-Hillman adducts, (alkyl-3-hydroxy-2-methylene propanoates) which on treatment with DMAP led directly to the formation of Mikanecic acid diesters, through Diels-Alder type self-dimerization of 1,3-butadiene-2-carboxylate. The method represented here is an indirect way of performing the Diels-Alder type reaction involving the same molecule can act as diene and dienophile thus utilizing the synthetic potentiality of Baylis-Hillman adducts.

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