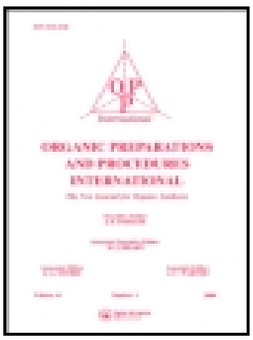

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L. Rajender Reddy & K. Rama Rao

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OPPI BRIEFS

RATE ACCELERATION OF THE BAYLIS-HILLMAN REACTION USING CRYSTALLINE CYCLODEXTRIN COMPLEXES†

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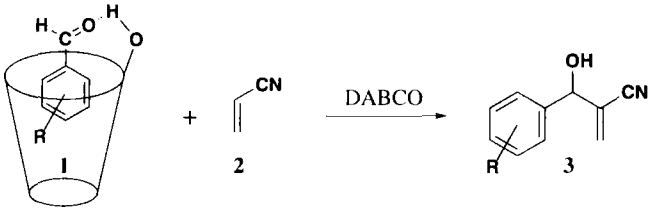
L. Rajender Reddy and K. Rama Rao*

Organic Chemistry-I
Indian Institute of Chemical Technology
Hyderabad-500007, INDIA.

The controlled formation of carbon-carbon bonds continues to be one of the challenging areas of organic synthesis. An emerging trend in this endeavour is the Baylis-Hillman reaction[1] involving the coupling of activated vinyl moiety such as acrylonitrile with a carbon electrophile (usually an aldehyde) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO).[2]



The Baylis-Hillman reaction produces a highly functionalized vinyl system useful for the elaboration of a variety of compounds including several natural products.[1-3] However, the major drawback is the rate at which this reaction occurs. Reaction times of one week or more are common, and even of one month have also been reported.[4] Aromatic aldehydes having wide application in the synthesis of multifunctional molecules,[5] could not be utilized as substrates under relatively mild conditions due to the diminished reactivity of carbonyl carbon.[6] This problem has been addressed to some extent by various means, such as the use of different substituted vinyl compounds, variation of catalyst or catalytic quantities.[5,7-10] More recently, there have been reports of improving the efficiency of this reaction by carrying it out at temperatures as low as 0° or by the use of co-catalysts.[11-13] Thus, there is need to further improve the efficiency of this versatile reaction.

At this juncture, we came across the interesting finding that the rate of the Baylis-Hillman coupling reaction can be enhanced by hydrogen bonding,[1] presumably by activation of the aldehyde as one of the factors. Our earlier expertise in the field cyclodextrins,[14-16] prompted us to attempt

Baylis-Hillman reaction involving cyclodextrin complexes of aromatic aldehydes due to the following reasons : i) cyclodextrins are cyclic oligosaccharides with hydrophobic cavities which selectively encapsulate aromatic guest molecules, ii) they form stable complexes with guests by hydrogen bonding wherever they contain functionalities capable of forming H-bonding and iii) they are chiral in nature and can induce asymmetric reactions. By involving cyclodextrin complexes of aldehydes in the Baylis-Hillman reaction, we not only expected the rate enhancement due to activation of aldehyde by hydrogen bonding with cyclodextrins but also the possibility of induced asymmetry.

Accordingly, the β-cyclodextrin complex of aldehydes **1**, described by us earlier[14-16] were treated in water with acrylonitrile **2** and DABCO at room temperature for 8 h. However, under these conditions no rate enhancement was observed and the yields were poor (20-25%). Since this might be due to mobility of the guest molecule in solution, we performed these reactions in the solid state where the movement of the guest molecule is restricted. Thus the ß-CD complex of the aldehyde **1**, acrylonitrile **2** and DABCO were ground by hand in a mill for the time shown in the Table. The Baylis-Hillman reaction under these solid state conditions has led to dramatic improvement in reaction rates (Table), though no asymmetric induction was observed.

Thus, this significant improvement in the efficiency of the Baylis-Hillman reaction makes it one of the most useful synthetic transformations. Further applications of this reaction are under study.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on Gemini-200 Spectrometer in $CDCl_3$ as the solvent with TMS as an internal standard. The mass spectra were obtained on CEC-21-100B Finnigan Mat-1210 Spectrometer. The silical gel (100-200 mesh) was used for column chromatography.

Table. Baylis-Hilman Reaction under Solid State Conditions

		Present work		*lit.*[9,17-19]	
Product	R	Time (min.)	Yield (%)[a,b]	Time	Yield (%)
3a	C_6H_5	60	70	40 hrs	70
3b	4-$MeOC_6H_4$	60	71	3 days	13
3c	4-ClC_6H_4	45	72	--	55
3d	3,4,5-$(MeO)_3C_6H_2$	60	65	3 days	80
3e	4-MeC_6H_4	60	72	3 days	32
3f	4-$NO_2C_6H_4$	45	74	3 days	45
3g	4-BrC_6H_4	45	70	3 days	54
3h	C_6H_5CH=CH	60	67	3 days	10
3i	1-Naphthyl	60	65	40 hrs.	57
3j	2-Naphthyl	60	71	3 days	55

a) Yields were based on the aldehyde. b) All the products were characterised by mass and ^{1}H NMR data

Inclusion Complexes. General Procedure.- The β-CD complexes were prepared by the addition of a solution of the aldehyde (10 mmol) in acetone (5 mL) to β-cyclodextrin (10 mmol) in water (200 mL) at 60°. The crystalline complexes obtained after cooling were collected and dried.

Baylis-Hilman Reaction under Solid State Conditions. General Procedure.- A mixture of cyclodextrin complex of **1** (10 mmol), acrylonitrile **2** (15-30 mmol, added intermittently during the course of the reaction) and DABCO (1.5 mmol) was ground by hand in a mill for the reaction times as shown in the table. The solid was extracted with diethyl ether (3 x 20 mL), washed with cold 2N HCl (2 x 15 mL) followed by water, dried over anhydrous sodium sulfate and the solvent was evaporated in a rotavapor. The product was purified by column chromatography on silica gel (100 to 200 mesh) using petroleum ether (40-60°) followed by dichloromethane as eluents. The analytical data of the compounds **3a-3j** were identical to those reported in the literature.[9,17-19]

Compound 3a, pale yellow viscous oil. ^{1}H NMR: δ 7.20-7.50 (m, 5H), 5.95 (s, 1H), 5.85 (s, 1H), 5.10 (s,1H), 3.6 (broad s, 1H). MS: (M^+) 159.

Compound 3b, pale yellow viscous oil. ^{1}H NMR: δ 7.25 (d, 2H, J = 8 Hz), 6.85 (d, 2H, J = 8 Hz), 6.05 (s, 1H), 5.95 (s, 1H), 5.15 (s, 1H), 3.25 (broad s, 1H). MS: (M^+) 189.

Compound 3c, pale yellow viscous oil. ^{1}H NMR: δ 7.28-7.50 (m, 4H), 6.10 (s, 1H), 6.05 (s, 1H), 5.25 (s, 1H), 2.28 (broad s, 1H). MS: (M^+) 193.

Compound 3d, pale yellow viscous oil. ^{1}H NMR: δ 6.55 (s, 2H), 6.08 (s, 1H) 5.95 (s, 1H), 5.10 (s, 1H), 3.85 (s, 6H), 3.75 (s, 3H), 3.0 (broad s, 1H). MS: (M^+) 249.

Compound 3e, pale yellow viscous oil. ^{1}H NMR: δ 7.15-7.31 (m, 4H), 6.09 (s, 1H), 5.98 (s, 1H), 5.22 (s, 1H), 2.95 (broad s, 1H), 2.34 (s, 3H). MS: (M^+) 173.

Compound 3f, pale yellow viscous oil. ^{1}H NMR: δ 8.21 (d, 2H, J = 8 Hz), 7.59 (d, 2H, J = 8 Hz), 6.15 (s, 1H), 6.05 (s, 1H), 5.41 (s, 1H), 3.31 (broad s, 1H). MS: (M^+) 204.

Compound 3g, pale yellow viscous oil. ^{1}H NMR: δ 7.51 (d, 2H, J = 8 Hz), 7.25 (d, 2H, J = 8 Hz), 6.13 (s, 1H), 6.02 (s, 1H), 5.36 (s, 1H), 2.85 (broad s, 1H). MS: (M^+) 238.

Compound 3h, pale yellow viscous oil. ^{1}H NMR: δ 7.15-7.45 (m, 5H), 6.68 (d, 1H, J = 15 Hz), 6.20 (d, 1H, J = 15 Hz), 6.05 (s, 1H), 5.95 (s, 1H), 4.80 (d, 1H, J = 3 Hz), 3.15 (broad s, 1H). MS: (M^+) 185.

Compound 3i, pale yellow viscous oil ^{1}H NMR: δ 8.05-7.95 (m, 1H), 7.90-7.75 (m, 2H), 7.60-7.40 (m, 4H), 6.05 (s, 1H), 5.98 (s, 1H), 5.35 (s, 1H), 3.10 (broad s, 1H). MS: (M^+) 209.

Compound 3j, pale yellow viscous oil. ^{1}H NMR: δ 7.81-7.98 (m, 4H), 7.41-7.59 (m, 3H), 6.14 (s, 1H), 6.01 (s, 1H), 5.42 (s, 1H), 3.12 (broad s, 1H). MS: (M^+) 209.

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