Pergamon

Tetrahedron Letters 39 (1998) 5965–5966

TETRAHEDRON LETTERS

DMAP-Catalyzed Hydroxymethylation of 2-Cyclohexenones in Aqueous Medium Through Baylis-Hillman Reaction

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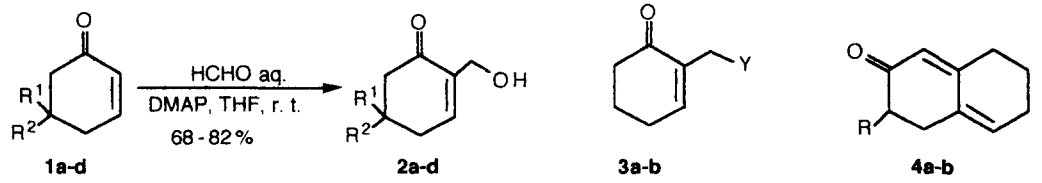
Received 1 April 1998; accepted 10 June 1998

Abstract: Reaction of 2-cyclohexenones **1a-d** with aqueous formaldehyde, catalyzed by DMAP in THF, affords the corresponding 2-(hydroxymethyl)-2-cyclohexenones **2a-d** in good yields.

2-(Hydroxymethyl)-2-cyclohexenone **2a** is a potential intermediate for the synthesis of products having biological properties[1,2]. For instance, acetate **3a** is effective against HELA cells growth[3] while amines **3b** derivatives have an analgesic activity[4]. Furthermore, we have recently developed a simple and convenient method for the synthesis of allylic amines **3b**[5] and bicyclic dienones **4a-b**[6] via the reaction of synthon **3a** and a variety of nucleophiles. However, up to now, 2-(hydroxymethyl)-2-cyclohexenone **2a** was prepared in two steps and in small-scale by reaction of 1,3-cyclohexanedione with paraformaldehyde in the presence of BF_3 etherate, followed by Dibal-H reduction of intermediate 1,3-dioxine vinylogous ester[7].

We assume that, under the influence of a suitable catalyst, Baylis-Hillman[8,9] coupling reaction of cyclic enone **1a** with formaldehyde, which has been reported rarely[10], would be a simple method for preparing alcohol **2a**. We report herein, a new and efficient procedure for direct α-hydroxymethylation of enones **1a-d** in one step, in aqueous medium and relatively in much higher scale.

Reaction of **1a** and HCHO in THF, catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO)[11-13], commonly used as a catalyst in the Baylis-Hillman reaction, led to the recovery of the starting materials. However, we have found that, at room temperature and in the presence of a catalytic amount (10 mol %) of 4-(dimethylamino)pyridine (DMAP) or 4-(pyrrolidino)pyridine (PPY), α,β-unsaturated ketone **1a** reacted with aqueous formaldehyde (2 equiv) in THF, to give 2-(hydroxymethyl)-2-cyclohexenone **2a** in 75-82 % yield.



1a-d **2a-d** **3a-b** **4a-b**

	a	b	c	d
R^1	H	H	Me	H
R^2	H	Me	Me	Ph
Yield (%)	82	76	68	71

3	a	b
Y	OAc	NR_2

4	a	b
R	H	Me

To our knowledge, this process is the first Baylis-Hillman reaction of cyclic enones with aldehydes catalyzed by a pyridine derivative. In order to explore the scope and limitations of the reaction described above, we have prepared a variety of 5-substituted-2-cyclohexenones **1b-d**[14-15] and we have studied their catalytic

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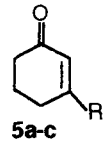
PII: S0040-4039(98)01206-4

hydroxymethylation with aqueous formaldehyde. Our experimental results and the required compounds **2b-d** obtained in 68-76 % yields, are summarized in the table below:

α,β-enones (mmol)	HCHO (x equiv)	DMAP (molar %)	T(°C)	Time (day)	Products	Yield(%)
1b (20)	4	15	25	3	**2b**	76
1c (20)	6	20	60	5	**2c**	68
1d (12)	4	20	25	6	**2d**	71

It is noteworthy that in the presence of 0.2 equiv of DMAP, the treatment of β-substituted 2-cyclohexenones **5a-c** with a large excess (6 equiv) of aqueous formaldehyde at 60 °C for 10 days, led to the recovery of the starting materials; this may be explained by the C (β) steric effects which prevent, in the first step of the Baylis-Hillman reaction, the Michael addition of DMAP to α,β-enones **5a-c**[16-17].



5a-c

5	**a**	**b**	**c**
R	Me	OEt	Cl

A representative experimental procedure for α-hydroxymethylation of enone **1a** is presented below:

A mixture of compound **1a** (24 g, 0.25 mol), 30 % aqueous formaldehyde (50 mL, 0.5 mol), 50 mL of THF and DMAP (3,05 g, 25 mmol), was stirred for 15 h at room temperature, then acidified dropwise with 1.5 N aqueous HCl. The reaction mixture was extracted with methylene chloride, washed successively with $NaHCO_3$ and brine. After usual work up, chromatography of the crude product on a silica gel column, using ether-methylene chloride (3:1) as eluent, gave a 82 % yield of pure **2a** as yellow oil.

IR ($CHCl_3$): 1670, 3580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (t, J = 4, 1H); 4.07 (s, 2H); 2.67-2.23 (m, 4H); 2.13-1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4; 146.8; 138.4; 60.8; 38.2; 25.7; 22.8; MS (m/e): 39 (100); 41 (88); 55 (82); 69 (82); 97 (44); 111 (29); 126 (M^+, 60).

In conclusion, 2-(hydroxymethyl)-2-cyclohexenones **2a-d** were prepared in one step and in mild conditions from the corresponding α,β-enones **1a-d** in good yields. This convenient methodology is inexpensive and can be successfully used in large-scale syntheses of cyclic 2-(hydroxymethyl) enones. Extension of this process to coupling several substituted cyclic α,β-enones with a variety of electrophiles, is in progress in our laboratory.

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