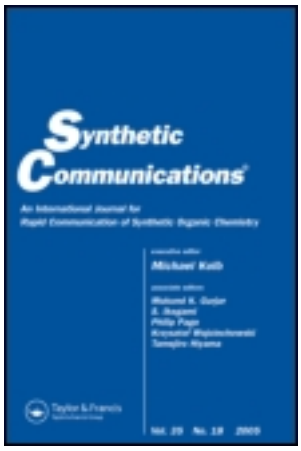

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The Use of DMAP as Catalyst in the Baylis-Hillman Reaction Between Methyl Acrylate and Aromatic Aldehydes

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ABSTRACT

We found an efficient methodology for the Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**1**), naphtaldehyde (**4a**), and pyperonal (**4b**) with methyl acrylate by using 4-dimethylaminopyridine (DMAP) as a catalyst, without solvent, additives, or any sophisticated equipment. A very important temperature effect was observed.

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The Baylis-Hillman reaction (Fig. 1) is an emerging method for carbon–carbon bond formation.[1–4] It involves the coupling of an activated alkene with an aldehyde or ketone. Usually, a tertiary amine or phosphine is required as a catalyst, and 1,4-diazabicyclo[2.2.2]octane (**Dabco**, Fig. 1) is the most popular one.

A great inconvenience of the Baylis-Hillman reaction is its slow rates. The literature reports reaction which could last up to 45 days.[1] Many efforts were done to accelerate the reaction, and there have been some examples of activation with Lewis acid,[5,6] lithium perchlorate,[7] the use of ultrasound technique,[8,9] high pressure,[10,11] or microwave irradiation.[12]

The 4-(*N*,*N*-dimethylamino)pyridine (DMAP), a very good nucleophilic catalyst,[13] is more basic than Dabco (pKa of the conjugated acids: Dabco = 8.5, DMAP = 9.7). DMAP is accessible in most of the organic synthesis laboratories, however Gaied and Rezgui describe the only example of its use as catalyst in the Baylis-Hillman reaction (hydroxymethylation reaction of 2-cyclohexanone).[14]

The objective of this article is to describe an efficient methodology for the Baylis-Hillman reaction between methyl acrylate and aromatic aldehydes using DMAP as catalyst under simple reaction conditions.

We began our studies by treating the *p*-nitrobenzaldehyde (**1**) with methyl acrylate (**2**) and 10% mol of DMAP as catalyst at room temperature. Several solvents were tested (methanol, THF, pyridine, and dioxane) but all were inefficient and no reaction or very poor yield was obtained (<10%). On the other hand, the use of methyl acrylate (excess) without solvent presented the most satisfactory result (72% yield) (Entry 2, Table 1).

We investigated the rate acceleration temperature effect of this reaction and found some very interesting effects. First, a great increase in yield and rate was obtained conducting the reaction at 76°C (Entries 1 and 2, Table 1). A yield of 93% was obtained (Entry 5, Table 1) when the reaction was carried out for only 15 min using a domestic microwave oven.[12] The use of ultrasound technique also seemed to cause an

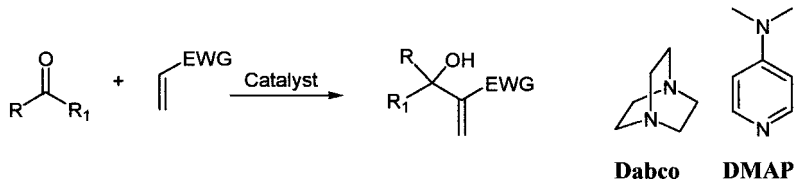
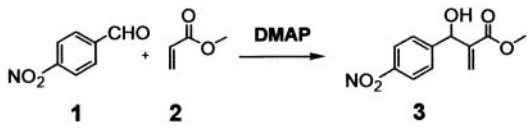


Figure 1. *R*, R_1 = H, Alkyl, Aryl. EWG = CO_2R, CN, COR.

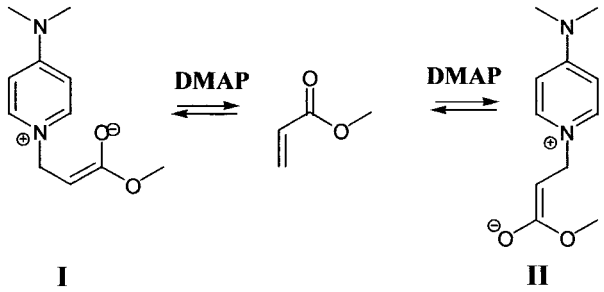
Table 1.



1 2 3

Entry	*T* (°C)	Time	Yield (%)[a]
1	76	5 h	>99
2	25	4 days	72 (97)[a]
3	−4	5 h 40 min	65 (75)[a]
4	−36	6 h	No reaction
5	Microwave[b]	15 min	93
6	Ultrasound[c]	3 h	85

[a]Considering the recovery of the departure aldehyde; [b]A domestic microwave (700 W) was used and all the reactions were carried out in sealed tube; [c]A Bransonic 2210R-MT ultrasound was used.

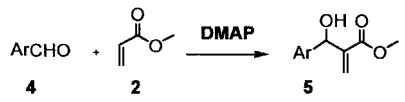


I **II**

Figure 2.

incremental increase in the reaction rate[8] (Entry 6, Table 1). Surprisingly, we also found that the reaction is faster at −4°C than at room temperature (Entry 3, Table 1). A few years ago, Rafel and Leahy also described this rate acceleration under low temperature.[15] One way to rationalize this is to consider the two purported ionic intermediates **I** and **II** (Fig. 2). These intermediates should be in equilibrium with the starting materials and react with *p*-nitrobenzaldehyde at different rates. Their relative concentration can be different at 0°C and at room temperature. The observed changes in the rates of the Baylis-Hillman reaction likely reflect this difference.[15] Unfortunately, no product was obtained conducting

Table 2.



Entry	Ar[a]	*T* (°C)	Time	Yield (%)
1	A	76	5 days	60 (85)[b]
2	A	25	12 days	47 (98)[b]
3	A	−4	6 days	65 (97)[b]
4	A	Microwave	3 h	15 (98)[b]
5	B	76	6 days	47 (70)[b]
6	B	25	15 days	44 (55)[b]
7	B	−4	4 days	No reaction
8	B	Microwave	1 h	No reaction

[a]Ar: A = β-Naphtyl; B = Pyperonyl; [b]considering the recovery of the aldehyde.

the reaction at −36°C possibly due to heterogeous reaction condition at this temperature.

In order to investigate this process we used naphtaldehyde (**4a**) and pyperonal[8] (**4b**) as starting materials (Table 2). Moderated results were obtained regarding increase in rate and yield when reaction was carried out at room temperature. (Entries 2 and 6). The reaction with **4a** is completed in 12 days at r.t. in 47% yield, however in 5 days in 60% yield at 76°C (Entries 1 and 2). Only moderated yields were obtained for **4b** at room temperature (40%, 12 days, Entry 6) and 76°C (47%, 6 days, Entry 5), so far the best result described for **4b**.[8] Similar to the observation with aldeyde 1, we also found that the reaction for **4a** procceded faster upon cooling to −4°C then at r.t. (65% yield). No product was obtained for **4b** (Entries 3 and 7) under these condictions. Surprisingly, poor results were obtained when the reaction was performed in the microwave (Entries 4 and 8).

CONCLUSION

In this work, we developed a simple, economical, and efficient methodology for the Baylis-Hillman reaction with aromatic aldehydes, and DMAP as the catalyst in place of Dabco. In these cases, the use of DMAP was more efficient than Dabco. We obtained product **3** in 5 h at 76°C (quantitative yield) and in 15 min (93%), using a domestic microwave oven. We found the same rate acceleration temperature

effect conducting the reaction at $-4^{\circ}C$ as described by Leahy (using Dabco as catalyst). The compounds **5a–b** were prepared in satisfactory yields and rates, comparable with the literature.[8,9] The use of higher temperatures (76°C) is the best condition.

EXPERIMENTAL SECTION

General Methods

The Baylis-Hillman adducts are known[3,8,9] and were characterized by ^{1}H NMR Varian Spectra (200 MHz) in $CDCl_3$ with $CHCl_3$ as internal reference (δ 7.26 ppm) and ^{13}C NMR Varian Spectra (50 MHz) in $CDCl_3$ solution with $CHCl_3$ (77.0 ppm) as internal reference. Chromatographic methods: A Lachrom HPLC system Merck equipped with a model D7000 interface, an L-7100 pump, an L-7450A diode array detector (DAD) and an L-7612 solvent degasser was used. Shim-Pack C-8 column (250 × 10 mm); 5 micron 100 ANG A. Separation were done in gradient mode, using acetonitrile:water ($t_0 = 20\%$water and $t_{30} = 100\%$ acetonitrile) at a flow rate of 2.0 mL/min with an injection volume of 20 μL and UV detection was at 280 nm. The analysis time was about 30 min. UV detection was performed using DAD in the range 210–300 nm.

General Procedure for the Aducts 3, 5a, and 5b

In a mixture of 1 mmol of the aromatic aldehyde, 10% mol of 4-*N*,*N*-dimethylaminopyridine (DMAP), 0.5 mL of methyl acrylate was added. The mixture was conducting at $T^{\circ}C$ until the end of the reaction (TLC analysis, 2:8 ethyl acetate/hexane). The mixture was evaporated and filtered in silica gel. Purification of the products by silica-gel column chromatography (1:9 ethyl acetate/hexane) gave **3**,[3] **5a**,[3] and **5b**[8] in *X*% yield (Tables 1 and 2).

Product 3: ^{1}H NMR ($CDCl_3$): δ 1.57 (s, 1H), 3.74 (s, 3H), 5.63 (d, $J = 6.32$ Hz, 1H), 5.87 (s, 1H), 6.40 (s, 1H), 7.61 (m, 2H), 8.25 (m,2H). ^{13}C NMR ($CDCl_3$): δ 52.066 (CH_3), 72.528 (CH), 123.460 (CH), 127.063 (CH_2), 127.209 (CH), 140.865 (C), 147.307 (C), 148.490 (C), 166.222 (C). HPLC: $t_R = 12.7$ min, >99%.

Product 5a: ^{1}H NMR ($CDCl_3$): δ 1.57 (s, 1H), 3.73 (s, 3H), 5.75 (d, $J = 5.77$ Hz, 1H), 5.88 (t, $J_1 = 1.14$ Hz, $J_2 = 1.10$ Hz, 1H), 6.39 (s, 1H),

7.50 (m, 3H), 7.78 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 51.857 (CH_3), 73.184 (CH), 124.453 (CH), 125.399 (CH), 125.909 (CH), 126.018 (CH_2), 126.800 (CH), 127.510 (CH), 127.983 (CH), 128.056 (CH), 132.896 (C), 133.105 (C), 138.482 (C), 141.767 (C), 166.669 (C). HPLC: $t_R =$ 15.63 min, >99%.

Product 5b: ^{1}H NMR ($CDCl_3$): δ 1.57 (s, 1H), 3.73 (s, 3H), 5.49 (d, $J = 5.49$ Hz, 1H), 5.86 (t, $J_1 = 1.26$ Hz, $J_2 = 1.21$ Hz, 1H), 5.96 (d, $J = 0.86$ Hz, 2H), 6.33 (t, $J_1 = 1.09$ Hz, $J_2 = 0.8$ Hz, 1H), 6.87 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 51.784 (CH_3), 72.655 (CH), 100.887 (CH_2), 107.038 (CH), 107.939 (CH), 120.030 (CH), 125.571 (CH_2), 135.161 (C), 141.821 (C), 146.998 (C), 147.544 (C), 166.541 (C). HPLC: $t_R = 11.6$ min, >99%.

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