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The Reactions of Aryl Acrylates Under Baylis-Hillman Conditions.

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Abstract: The use of aryl acrylates in the Baylis-Hillman reaction is reported. In contrast to their alkyl counterparts these acrylates react very rapidly with aldehydes, often yielding cyclic products arising from reaction of the initial adduct with a second molecule of aldehyde.

The DABCO-catalysed coupling of acrylates with aldehydes (Scheme 1) was first reported in a patent by Baylis and Hillman in 1972.¹ The first study of this method to appear in the open literature was published in 1983.² Since then several applications in organic synthesis of this simple process have been reported.³ Other than in the original patent no mention has been made of the use of *aryl* acrylates. Table 1 contains the results from such reactions with aromatic aldehydes (Scheme 1, R = Ar, R' = Ar').



Scheme 1.

From Table 1 (entries 1-7) it is clear that these aryl acrylates⁴ react much faster than, e.g. methyl acrylate (entry 8).⁵ For example, whereas reaction of benzaldehyde with methyl acrylate takes six days at room temperature (entry 8),² the same yield may be obtained by reacting *phenyl* acrylate at 0°C for only eight hours (entry 2). The more reactive 3-pyridylcarboxaldehyde,² also reacted well at 0°C, providing the adduct 3 (R = Ph, R' = 3-pyridyl) in 54% yield with a reaction time of only ten minutes (entry 3). The use of an

Entry	Rb	R'	Reaction time	Temp. (°C)	Yield ^c (%)
1	Ph	Ph	3h	rt	78
2	Ph	Ph	8h	0	39
3	Ph	3-Pyridyl	10 min	0	54
4	Ph	2-Furyl	8h	rt	21
5	4-NP	Ph	72h	rt	16 ^d
6	2,6-DMP	Ph	72h	rt	49d
7	4-MP	Ph	24h	rt	10
8	Me	Ph	6d	rt	39

Table 1. Results from the DABCO-catalysed Coupling of Aryl Acrylates with Aromatic Aldehydes (Scheme 1, R = aryl).^a

a. Reaction conditions: neat, r.t.; ratio of reactants (acrylate:aldehyde:DABCO) = (1:1:0.1). b. 4-MP: 4-methoxyphenyl; 2,6-DMP = 2,6-dimethylphenyl: 4-NP = 4-nitrophenyl. c. Isolated yield unless indicated otherwise. d. 0.5M in CHCl₃, 1.5 equiv. of DABCO.

electron-deficient aromatic ester, 4-nitrophenyl, led to rapid consumption of starting materials yielding a complex mixture of products. By running the reaction in chloroform and using an excess of DABCO a low yield (16%) of the Baylis-Hillman product could be obtained (entry 5). Employing electron-donating aromatic esters led to a very significant rate reduction and a concomitant reduction in yields. However a reasonable yield (49%) was achievable with a more-hindered ester (2,6-dimethylphenyl) by again running the reaction in chloroform using excess DABCO (entry 6). Attempts to use the electron-rich ester (4-methoxyphenyl) gave a low yield of the coupled product (entry 7) as did the reaction of phenyl acrylate with 2-furaldehyde.

The reaction of phenyl acrylate with *aliphatic* aldehydes was not only very fast but yielded the cyclic acetals **6** instead (Scheme 2). This type of reaction has been observed before for the acrylate ester of pantolactone.⁶ Several examples of this process are collected in Table 2. The number of equivalents of either



Scheme 2.

reactant seemed to matter little to the final outcome (see entries 1 to 4) as the second reaction (acetal formation) is apparently at least as fast as the first (normal Baylis-Hillman coupling).

Entry	Ar	R	No. Equiv	Time	Temp.	Ratio (5:6)	Yield (%) ^a
1	Ph	Me	5	2h	rt	0:1	57
2	Ph	Me	1	10h	rt	0:1	52
3	Ph	i-Pr	5	24h	rt	0:1	95
4	Ph	i-Pr	1.5	14h	rt	1:1	25°
5	4-MP	Me	5	8h	rt	0:1	69
6	2,6-DMP	Me	1	14h	rt	4:1	26 ^c
7	2,6-DMP	Me	1	6h	0	6:1	36 ^c
8	2,4,6-TMP ^b	Me	1	14h	rt	7:1	43°

 Table 2.
 Results from the reaction of anyl acrylates with aliphatic aldehydes (Scheme 2).

a. Isolated yields. b. 2,4,6-TMP= 2,4,6-trimethylphenyl. c. Isolated yield of 5, after preparative t.l.c. on silica.

Although these cyclic acetal products are of great synthetic interest⁷ we were also concerned with being able to control the reaction so that the Baylis-Hillman product could be isolated. Variation of the substitution pattern of the aromatic moiety led to the observation that the use of 2,6-dimethylphenyl acrylate or, better, 2,4,6-trimethylphenyl acrylate gave predominantly the normal Baylis-Hillman product in reactions with *one equivalent* of acetaldehyde (entries 6-8).

The aryl ester-derived Baylis-Hillman products reacted well with aliphatic aldehydes yielding the expected cyclic acetals. For example 5 (Ar = R = Ph) or 8 (Ar = 2,4,6-TMP, R = Me) each reacted with acetaldehyde in the presence of DABCO in high yields (Scheme 3). (Negligible reaction occurred when the methyl ester corresponding to 5 in Scheme 3 was employed, again demonstrating the increased reactivity of aryl esters compared to alkyl esters). No reaction occurred when benzaldehyde was treated with 5 or 8 under similar conditions.



Scheme 3.

These results strongly imply that the *in situ* process as well as the stepwise method proceed through a common intermediate (e.g. 9, Scheme 4).⁸



In summary, the DABCO-catalysed reactions of aryl acrylates with aldehydes proceeds at significantly greater rates than that for alkyl acrylates. By simply varying the aryl group in the acrylate, reactions with alkanals can be controlled to produce either the normal Baylis-Hillman product (i.e. 5) or the cyclic acetal (6).

Caution. One of the nmr operators in our Department has developed symptoms indicative of hypersensitivity to some of these aryl acrylates, especially the 2,6-dimethylphenyl and 2,4,6-trimethylphenyl esters, as well as products contaminated with these acrylates.

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^{4.} All the aryl acrylates described here were prepared from acryloyl chloride and the appropriate phenol using a method described in Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. (eds) "Vogels's Textbook of Practical Organic Chemistry" Fifth Edn. Longman, Burnt Mill, 1989, p. 705.

^{5.} All new compounds reported here gave satisfactory spectroscopic and combustion analysis.

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^{7.} For example, see Zimmermann, J.; Seebach, D. Helv. Chim. Acta 1987, 70, 1104.

It is also notable that the cyclic acetals were produced with very high diastereoselectivity in favour of the di-equatorial derivatives⁶ (eg 10).