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Reaction of Baylis–Hillman products with Swern and Dess–Martin oxidants

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Abstract—The Baylis–Hillman adducts of aryl aldehydes and alkyl acrylates are efficiently oxidized to the corresponding α-methylene-β-keto esters with the Dess–Martin periodinane. The attempted Swern oxidation of the same adducts resulted in S_N2'-type substitution of the allylic hydroxyl group by chloride.

The Baylis–Hillman[1] reaction provides an effective method for the synthesis of functionalized allylic alcohols.[2] The reaction is characterized by the simple conversion of an aldehyde and an activated alkene, usually an acrylate, into an allylic alcohol, under mild conditions by the action of an appropriate nucleophilic catalyst (e.g. **1**→**2**) (Scheme 1). The reaction, first documented in 1972 continues to attract great attention. Improvements to the breadth, scope, yield and selectivity of the reaction are regularly reported.[3–6] The closely associated functionality present in the product alcohols **2** accompanied by their rich chemistry combines to provide potentially important synthetic building blocks.

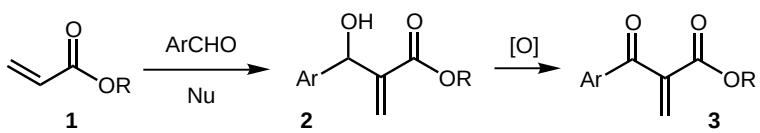
Our interest in new electrophilic anticancer agents[7] prompted us to investigate the biological activity of α,β-unsaturated carbonyl compounds derived from the Baylis–Hillman reaction. The ability of similar α,β-unsaturated carbonyl derivatives, such as sesquiterpene α-methylene lactones, to act as biological alkylating agents is well documented.[8] We therefore developed a program to investigate the use of Baylis–Hillman adducts and selected derivatives as potential alkylating agents. Ketones of type **3** (Scheme 1) represented an important target, since possessing a doubly activated alkene they are highly electrophilic. We report herein some surprising aspects of the synthesis of these α-methylene-β-keto esters.

The desired allylic alcohols **2** were obtained using previously reported conditions for the Baylis–Hillman reaction (Table 1) with either DABCO™ or DBU as the catalyst. In general the reaction proceeded well for

Table 1.

	Ar	R	Yield **2** (%)	Yield **4** (%)
a	Ph	Me	84[a]	58
b	Ph	Et	76[a]	66
c	2-ClC_6H_4	Et	64[b]	70
d	4-MeC_6H_4	Et	73[b]	62

[a] DBU (1 equiv.), methyl or ethyl acrylate (1 equiv.), ArCHO (1 equiv.), rt, overnight (Ref. 5)
[b] DABCO™ (0.5 equiv.), ethyl acrylate (2 equiv.), ArCHO (1 equiv.), rt (1–7 days) (Ref. 13).



1 2 3

Scheme 1.

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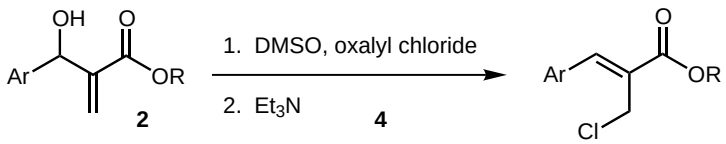
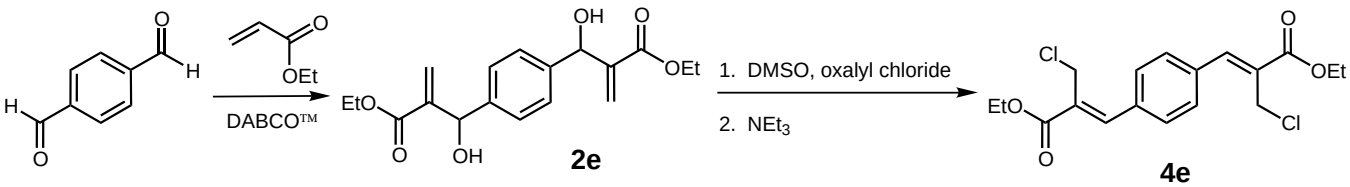
benzaldehydes possessing electron-withdrawing substituents, as is usual for the Baylis–Hillman reaction. This suited our requirements, since these types of aryl groups should ultimately give rise to enones of type **3** that are highly electrophilic.

We first chose to oxidize the alcohol **2a** by using the Swern reaction.[9] The Swern reaction has been used to successfully oxidize many simple and complex allylic alcohols.[10,11] The alcohol was treated with a mixture of DMSO and oxalyl chloride at −60°C in the usual manner (Scheme 1). However, it was clear that the oxidation had not proceeded as expected. The isotope pattern of the molecular ion in the mass spectrum revealed that chlorine had been incorporated into the product. The key ^{1}H NMR diagnostic signals (δ 4.55 ppm, 2H, singlet; δ 7.94 ppm, 1H, singlet) indicated that the product was actually the allylic chloride *Z*-**4a**.[12] The reaction is highly stereoselective; no other isomer was detectable in the ^{1}H NMR spectrum. The substitution process is not unique to **1a**. Other substrates were also subjected to the conditions of the Swern reaction and also yielded the corresponding allylic chloride (Table 1 and Schemes 2 and 3). It is interesting to note that substitution products **4** are also good electrophiles, and still worthy of biological study. The adduct **2e**, derived from terephthalaldehyde gave the bisallylic chloride **4e**, which we hoped would act as a biological cross-linking agent (Scheme 3).

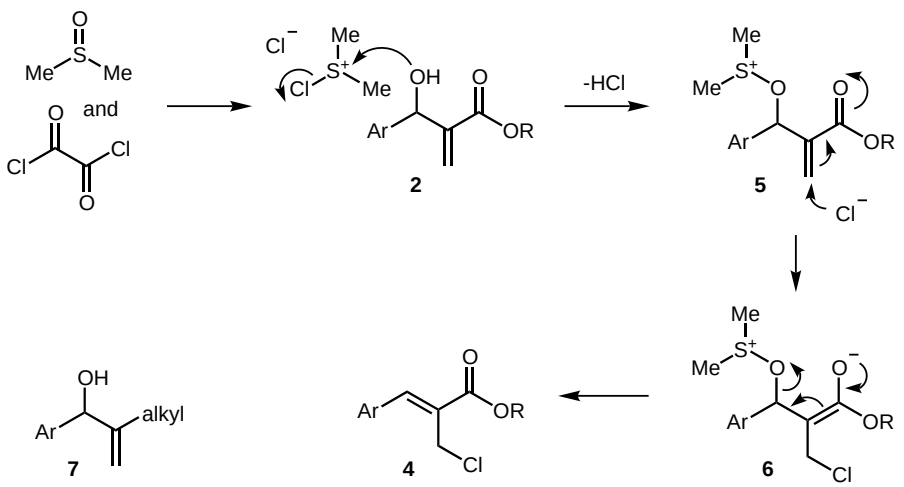
The product clearly arises from a substitution pathway probably after the alcohol has been activated by the Swern reagent system. The alkoxy(dimethyl)sulfonium salt **5** formed from **2** by the action of the chlorodimethylsulfonium chloride, must be highly susceptible to attack by chloride ion as indicated in Scheme 4. This substitution process may occur via a simple S_N2' mechanism. However, the Swern oxidation of the related alcohols of type **7** occurs in the normal way without competing substitution.[11] To emphasize the influence of the ester group the mechanism is drawn as a sequential conjugate addition/elimination process via the enolate **6**. Allylic chlorides of type **4** have also been obtained from Baylis–Hillman adducts by other reagents which transform the hydroxyl into a nucleofuge in the presence of chloride.[12,14] It is interesting to note that the Corey–Kim[15] reaction of alcohols of type **1**, in which the aryl group has been replaced by an alkyl group, with NCS/Me_2S generate the allylic chloride analogous to **4**.[16] This supports the general mechanism shown in Scheme 4.



Scheme 2.



Scheme 3.



Scheme 4.

Table 2. Oxidation of Baylis–Hillman adducts **2** with the Dess–Martin periodinane

	Ar	R	Yield **2** (%)	Yield **2**→**3** (%)
a	Ph	Me	See Table 1	84
b	Ph	Et	See Table 1	78
c	2-ClC_6H_4	Et	See Table 1	71
d	4-MeC_6H_4	Et	See Table 1	67
f	3,4-$F_2C_6H_3$	Et	86[a]	63
g	4-FC_6H_4	Me	78[a]	64
h	4-$(CF_3)C_6H_4$	Me	72[a]	51

[a] DABCO™ (0.5 equiv.), ethyl or methyl acrylate (2 equiv.), ArCHO (1 equiv.), rt (1–7 days) (Ref. 13).

The successful oxidation of Baylis–Hillman adducts has been achieved by Hoffmann and co-workers[17] using Jones reagent. However we were concerned that trace toxic chromium-containing residues might possibly complicate the subsequent assessment of the cytotoxicity of the ketones and sought an alternative reagent. The Dess–Martin periodinane is often used when a mild, selective oxidant is required (Table 2).[18] Significantly for us it has been used to effect the synthesis of α-methylenecycloalkanones from the corresponding alcohol.[19] We soon found that the reagent met our requirements and was able to efficiently transform the Baylis–Hillman adducts into the desired α-methylene-β-keto esters. Clearly the reaction mixture does not contain a species sufficiently nucleophilic to react with the product.

In conclusion we have shown that Baylis–Hillman adducts are efficiently oxidized by the Dess–Martin periodinane but not by DMSO/oxalyl chloride. The biological activity of the ketones **3** and the unintentional series of allylic chlorides **4** will be reported in due course.

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