CHEMCOMM Communication
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A novel precipitating auxiliary approach to the purification of Baylis–Hillman adducts†

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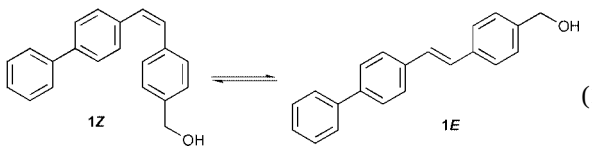
Received (in Cambridge, UK) 3rd May 2001, Accepted 27th June 2001
First published as an Advance Article on the web 9th August 2001

Diaryl alkene alcohol 1 is a 'precipiton', a precipitating auxiliary that is used to aid the isolation of Baylis–Hillman adducts.

There is a need for new methods of product isolation which rely on simple purification procedures, eliminate the need for distillation or chromatography, and can be easily automated and used for parallel chemical syntheses.[1] While solid-phase organic synthesis (SPOS) remains the most popular method, there are several disadvantages associated with SPOS: the supports can be expensive; loading capacities can be low (0.1–1.0 mmol g^{-1}); solid-phase reactions often require extensive optimization of reaction conditions; and monitoring of reaction progress is difficult. To address the shortcomings of SPOS, molecules can be attached to 'phase-tags'. Fluorous synthesis,[2] soluble polymer-supported organic synthesis (SPSOS),[3] dendrimer-supported organic synthesis,[4] and acid/base tags[5] are examples of this approach. With these methods, tagged compounds can be easily separated from untagged compounds by a phase-transfer event (precipitation or liquid–liquid partition).

We recently introduced an approach to product isolation based on a solubility switch activated by structural isomerization.[6] Diaryl alcohol **1** is a 'precipiton', a group of atoms



(1)

(molecular fragment) that is purposefully attached to a reactant molecule and that can be activated {in this case isomerized [equilibrium (1)]} after the reaction in order to cause precipitation of the attached product. Our method has been applied to the synthesis and isolation of isoxazolines[6] and α-substituted β-ketoesters.[7] In this communication, we describe the precipiton approach for the synthesis of pure Baylis–Hillman adducts.

The Baylis–Hillman reaction[8] is a C–C bond forming reaction between an activated alkene and an aldehyde in the presence of a tertiary amine, tertiary phosphine, or chalcogenide.[9] This reaction provides useful multifunctional intermediates that can be used for subsequent transformations. One of the drawbacks associated with the Baylis–Hillman reaction is that one of the components must be used in an excess to drive the reaction to completion.[10] This often leads to a need to use chromatography to separate the desired product from the excess reactant. In order to avoid chromatography we sought to use our methodology to isolate pure Baylis–Hillman adducts.

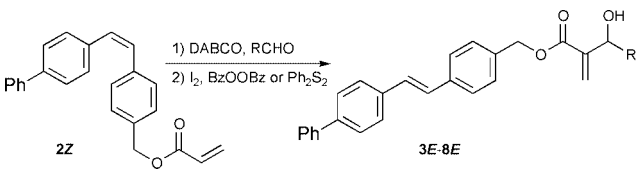
Alcohol **1*Z*** was prepared as previously described from 4-biphenylcarbaldehyde and *p*-bromobenzyl alcohol *via* a Negishi coupling.[7] Acrylate **2*Z*** was then readily prepared by treatment of **1*Z*** with acryloyl chloride in the presence of NEt_3.[6]

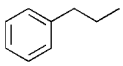
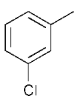
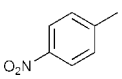
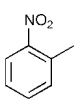
† Electronic supplementary information (ESI) available: full experimental details. See http://www.rsc.org/suppdata/cc/b1/b103969p/

The precipiton Baylis–Hillman reactions were performed on a 0.52 to 2.43 mmol scale with respect to the acrylate. The acrylate **2*Z*** was treated with a catalytic amount of DABCO and an excess of aldehyde at room temperature.[11] Upon completion of the reaction (depending upon the nature of the aldehyde, reactions were complete in 1 to 10 days) the crude mixture was diluted with a suitable solvent and treated with I_2 and dibenzoyl peroxide or PhSSPh.[12] The isomerization process was monitored by ^{1}H NMR (isomerizations were complete in 4–24 h). Upon completion of the isomerization event, the crude reaction mixture was diluted with $CHCl_3$. Aqueous work-up with bisulfite, followed by evaporation of the organic layer, gave a crude product, that was then purified simply by trituration with hexanes, ether, or MeOH, followed by filtration. This protocol afforded Baylis–Hillman adducts in good yields and with purities of ≥95% (Table 1).[13]

The precipiton-bound products were cleaved from the precipiton by hydrolysis (LiOH in THF–H_2O).[14] These reactions were performed on a 22 to 188 μmol scale. The acids were isolated by filtration of the insoluble precipiton, acidification of the solution, followed by extraction with EtOAc. Removal of the EtOAc furnished the desired acids in good yields and with purities of ≥95% (Table 2).[13] Several other conditions,

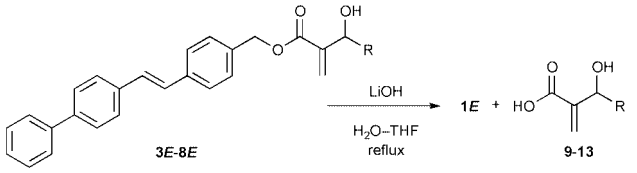
Table 1 Precipiton Baylis-Hillman reaction with acrylate **2*Z***

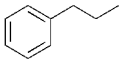
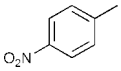


Entry	R	Time/d	Isomerization catalyst(s)	Product	Yield (%)
1		20	I_2/BzOOBz	**3*E***	70
2		5	I_2/BzOOBz	**4*E***	58
3		5	I_2/BzOOBz	**5*E***	78
4		3	I_2/BzOOBz	**6*E***	76
5		4	I_2/BzOOBz	**7*E***	76
6		1	I_2/BzOOBz	**8*E***	81
7		2	Ph_2S_2	**8*E***	75

 DOI: 10.1039/b103969p

Table 2 Hydrolytic removal of product from the precipiton



Entry	Starting material	R	Product	Yield (%)
1	**3*E***		9	72
2	**4*E***		10	74
3	**5*E***		11	85
4	**6*E***		12	83
5	**7*E***		13	72

methanolysis and the Weinreib aminolysis, were examined for cleavage of the precipiton but were found ineffective. The acid derived from compound **8*E*** is a zwitterionic compound which could not be conveniently isolated.

These experiments demonstrate an application of the precipiton approach to product isolation. This method does not require chromatography, which is often a necessity in the Baylis–Hillman reaction. This process can be automated and has been successfully applied to very small scale reactions. It therefore may be found useful for preparing small quantities of pure compound for biological screening. We expect the method will be equally useful for large-scale preparations of compounds.

Notes and references

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12 The isomerization using I_2 and benzoyl peroxide was effected by dilution of the crude residue with Et_2O or CCl_4 followed by irradiation with a 250 W sunlamp. The isomerization conditions with PhSSPh involved dilution of the crude residue with THF followed by heating at reflux.
13 All products were fully characterized. Reactions were monitored by TLC or ^{1}H NMR. Purities were determined by ^{1}H NMR and were $\geqslant$95% for all isolated compounds. Experimental procedures are presented in the supporting information.
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