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Precipiton strategies applied to the isolation of α-substituted β-ketoesters†

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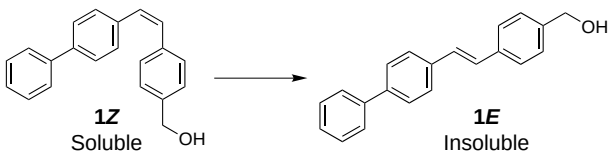
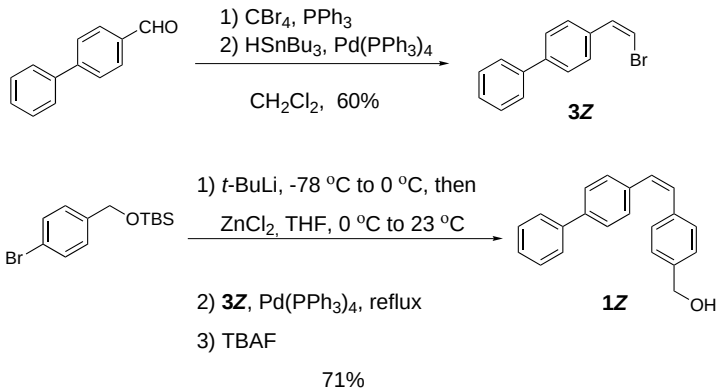
Abstract—Diaryl alkene **1*Z*** is a 'precipiton', a protecting group that allows reaction products to be isolated by simple filtration. Here we illustrate the use of this protecting group for the preparation and isolation, without distillation or chromatography, of pure α-substituted β-ketoesters. The precipiton **1*Z*** was prepared in 43% overall yield. It is anticipated that development of precipiton-based syntheses will provide a new alternative for automated reaction product isolation that may be useful for bench-scale and process-scale chemical preparations. © 2001 Elsevier Science Ltd. All rights reserved.



Advances in high through-put screening and parallel synthesis have stimulated interest in new approaches to product separation.[1] Often the most costly stage in a synthetic transformation is purification of the product. Solid-supported organic synthesis, also called solid-phase organic synthesis (SPOS), is the dominant method for automated syntheses because it allows excess reagents, catalysts, and solvent to be removed from the resin-bound products. However, there are disadvantages associated with SPOS: the supports can be expensive; typical loading capacities range from 0.1 to 1.0 mmol/g—resulting in effective molecular weights of 1,000–10,000 and making large scale or even multi-gram SPOS impractical; reaction conditions developed for homogeneous processes often must be re-optimized for SPOS; and reaction progress is difficult to monitor. Alternatives to SPOS (i.e. fluorous synthesis,[2] soluble polymer-supported organic synthesis or SPSOS,[3] and dendrimer-supported organic synthesis[4]) attach a reactant molecule to a 'phase-tag' which facilitates product isolation by a phase-transfer event (solvent-induced precipitation or liquid–liquid partition).



Scheme 1.

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† This paper is dedicated to Professor Ronald Breslow on the occasion of his 70th birthday.

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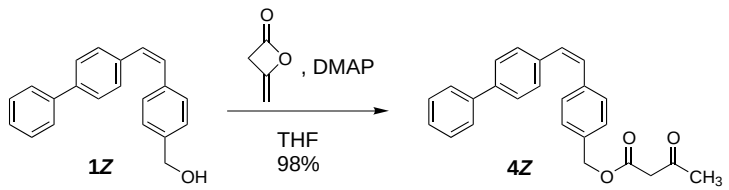
We have recently described an approach to product separation based on a change in solubility caused by structural isomerization of an ancillary portion of the desired product.[5] This auxiliary we term a 'precipiton', a group of atoms (molecular fragment) that is purposefully attached to a reactant molecule and that can be isomerized after the reaction in order to cause precipitation of the attached product. Our first-generation precipiton was benzyl alcohol **1*Z***, which is freely soluble in most organic solvents in the *Z* form and nearly insoluble in the *E* form.[5] In our earlier work, isomerization (with a concomitant change in solubility) was achieved by heating the *cis*-olefin with diphenyldisulfide. In this communication, we describe a more efficient synthesis of precipiton **1*Z***, new isomerization conditions, and the use of our method for the synthesis and isolation of pure α-substituted β-ketoesters.

Our first synthesis of precipiton **1*Z*** employed a Wittig olefination that gave a 1.2:1.0 mixture of *E* and *Z* isomers. A better synthesis was realized by applying a variant of Negishi's process[6a,b] to form the stilbene system (Scheme 1). Commercially available 4-biphenylcarboxaldehyde was converted to the dibromoalkene under standard Corey–Fuchs conditions.[7] The resulting dibromide was then selectively reduced with tributyltin hydride in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0).[8] These two steps could be carried out in 'one pot' to give a 60% isolated yield of **3*Z***.[9] The bromide **3*Z*** was then coupled to TBS-protected *p*-bromobenzyl alcohol.[6b] Deprotection of the product by tetra *n*-butyl ammonium fluoride (TBAF) provided **1*Z*** in 71% yield for two steps. This two-pot synthesis yields **1*Z*** in 43% overall yield.

To demonstrate the usefulness and to extend the scope of our method we prepared a family of α-substituted β-ketoesters. These products serve as useful intermediates in the preparation of heterocyclic compounds[10] and can also be chemoselectively and diasteroselectively reduced to form aldol-type products.[11] Both solid-phase[12] and soluble polymer-supported[13] protocols for the synthesis of α-substituted β-ketoesters have been reported.

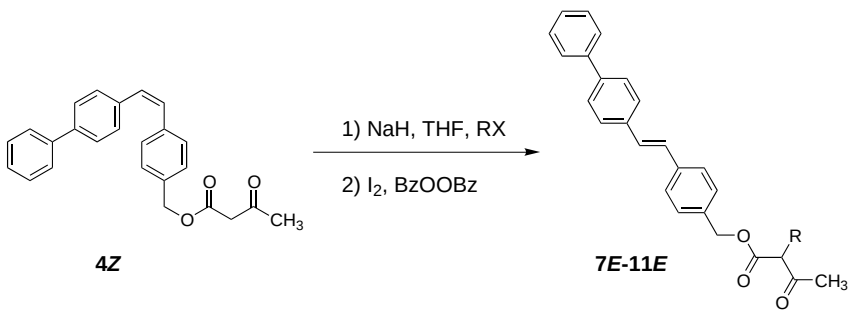
Acetoacetate ester **4*Z*** was prepared by treatment of **1*Z*** with diketene and a catalytic amount of *N*,*N*-dimethylamino pyridine (Scheme 2). An advantage of our approach to product isolation is that it allows an excess of alkylating reagent to be used. This excess, which can increase reaction rates and product yields, may be removed without the use of chromatography or distillation.

The β-ketoester **4*Z*** was deprotonated with sodium hydride to generate the enolate, which was then treated with an excess of an alkylating agent.[14] Upon completion of the alkylation event (generally in 3 h at 23°C)



Scheme 2.

Table 1. Alkylations of β-ketoester **4*Z***



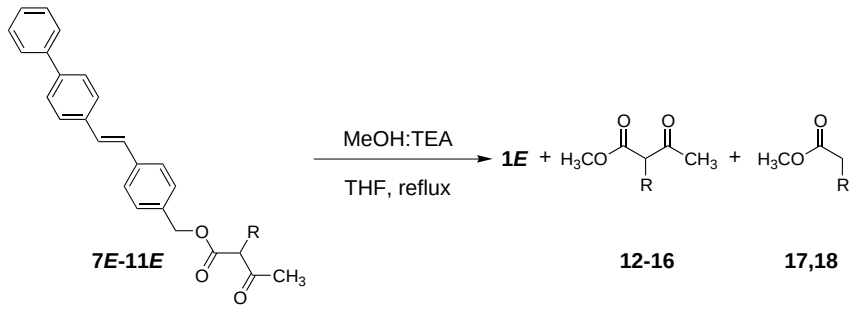
Entry	RX	Product	Yield (%)
1	EtO_2CCH_2Br	**5*E***	91
2	CH_3I	**6*E***	84
3	$PhCH_2Br$	**7*E***	70
4	$PhCOCH_2Br$	**8*E***	89
5	$CH_3CH_2CH_2I$	**9*E***	64
6	$CH_3(CH_2)_{10}CH_2I$	**10*E***	41[a]
7	*p*-$OMePhCH_2$	**11*E***	72

[a] This flocculent, waxy solid was difficult to filter.

the reaction mixture was partitioned between EtOAc and aqueous NH_4Cl. The organic layer was evaporated and the residue was dissolved in Et_2O or CCl_4 containing I_2 and benzoyl peroxide. The isomerization process (monitored by NMR) was complete in 4–24 h. An aqueous work-up with bisulfite, followed by evaporation of the organic layer, gave crude product, that was then purified simply by trituration with ether, hexanes, and/or methanol. All contaminants not bound to the precipiton were removed by this trituration. This protocol afforded precipiton-bound products in good yields and with purities over 95%[15] (Table 1).

The precipiton-bound products are quite insoluble in ether, hexanes, and methanol, but slightly soluble in THF. They can be cleaved from the precipiton by methanolysis (MeOH/TEA in THF, reflux, 1–2 h)[15] (Table 2). After the reaction mixture was evaporated to dryness, the desired methyl esters were separated from the ether-insoluble benzyl alcohol precipiton **1*E*** by trituration with ether or MeOH. Evaporation of the volatile components from the filtrates furnished the methyl β-ketoesters **12** through **16** in good yields and with purities over 95%. Complete deacylation of compound **8*E*** and partial deacylation of **11*E*** were observed

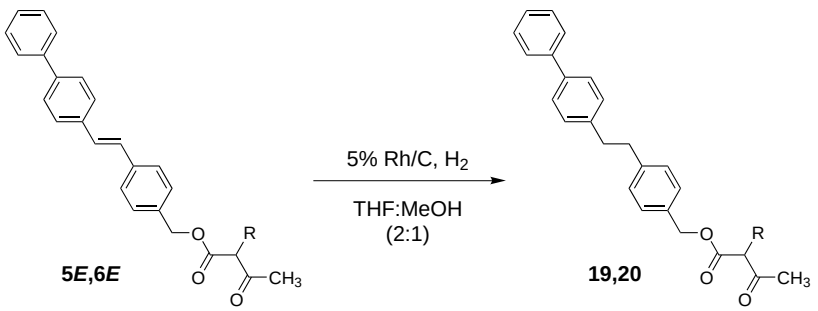
Table 2. Methanolytic removal of product from precipiton



Entry	Starting material	RX	Product	Yield (%)
1	**7*E***	$PhCH_2Br$	**12**	78
2	**8*E***	$PhCOCH_2Br$	**15**[a]	91
3	**8*E***	$PhCOCH_2Br$	**17**[b]	63
4	**9*E***	$CH_3CH_2CH_2I$	**13**	85
5	**10*E***	$CH_3(CH_2)_{10}CH_2I$	**14**	85
6	**11*E***	*p*-$OMePhCH_2Cl$	**16**[c]	71
7	**11*E***	*p*-$OMePhCH_2Cl$	**16**:**18**[d]	65:29

[a] Reflux 1.5 h.
[b] Reflux 22 h.
[c] Reflux 0.75 h.
[d] Reflux 4 h.

Table 3. Hydrogenation of β-ketoesters **5*E*** and **6*E***



Entry	RX	Compound	Product	Yield (%)
1	EtO_2CC	H_2Br	**5*E***	**19**
2	CH_3I	**6*E***	**20**	91

with longer methanolysis reaction times. In those cases the methyl esters **17** and **18** were isolated. (Table 2, entries 3 and 7) Shorter reaction times for methanolysis of **8*E*** and **11*E*** afforded only the β-ketoester products (Table 2, entries 2 and 6). The methyl esters arising from the cleavage of compounds **5*E*** and **6*E*** were too volatile to conveniently isolate.

In cases involving volatile cleavage products it is useful to retain the larger protecting group during subsequent transformations. By design, however, the *trans*-ester is not easily dissolved in solvents used for organic reactions. We expected that reduction of the olefin would yield a product soluble in standard organic solvents. Hydrogenation over 5% Rh/C in THF:MeOH (2:1) reduced the alkene of β-ketoesters **5*E*** and **6*E*** in high yield (Table 3). The products were soluble in both Et_2O and toluene at concentrations greater then 0.5 M.

These experiments demonstrate a new application of the precipiton approach to product isolation. The method does not require distillation or chromatography steps to provide α-substituted β-ketoesters in high purity and in yields equal to other methods. The loading capacity of the precipiton reported here is over 3 mmol/g and, even without precipiton recycling, the costs are competitive with SPOS. The process can be automated and may be especially useful in large-scale preparations.

Acknowledgements

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14. Side products arising from incomplete reaction and/or dialkylation could be eliminated by washing the 60% sodium hydride mineral oil dispersion with pentane and drying the residue in vacuo prior to use.
15. All products were fully characterized. Reactions were monitored by TLC or ^{1}H NMR. Purities were determined by ^{1}H NMR and were greater then 95% for all isolated compounds. Experimental procedures may be obtained from the corresponding author.