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Alkylidenation of esters on solid support and traceless synthesis of 2-substituted benzofurans

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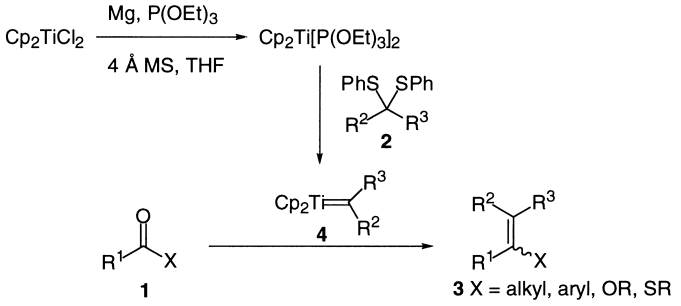
Abstract

Polymer-supported esters are smoothly converted into enol ethers using a titanocene alkylidene prepared by treatment of 2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal with the low valent titanium species $Cp_2Ti[P(OEt)_3]_2$. Treatment of the enol ethers with acid leads to the release of ketones from the Wang resin in high yield. Traceless solid-phase synthesis of 2-substituted benzofurans is achieved in a three-step termination procedure. © 2000 Published by Elsevier Science Ltd.

Keywords: solid-phase synthesis; benzofurans; titanium and compounds; thioacetals.

Takeda and co-workers recently reported the alkylidenation of carbonyl compounds **1** using thioacetals **2** and a low valent titanium complex, $Cp_2Ti[P(OEt)_3]_2$ (Scheme 1).[1,2]



Scheme 1.

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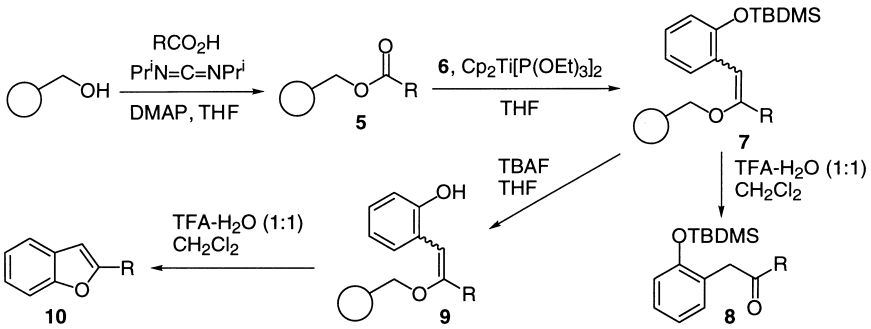
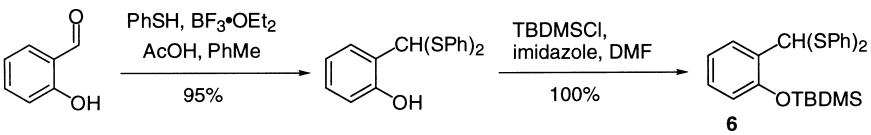
Esters **1** (X=OR) can be converted into enol ethers **3** (X=OR) using this procedure and like the reagents developed by Tebbe[3] and Petasis,[4] the active species is believed to be titanocene(IV) alkylidene **4**, but unlike these other reagents, R^1 and R^2 can have hydrogen atoms beta to the titanium atom. Furthermore, the thioacetal reactants are more easily made than the 1,1-dibromoalkanes required for the related Takai reagents,[5] which we have used extensively.[6]

We here report the first use of the Takeda reaction in solid-phase synthesis.[7,8] The new procedure avoids the problematic work-up that resulted in low yields of enol ethers when we used Takeda alkylidenation of esters in solution phase. We also report a novel alkylidenating agent that allows cyclative termination of solid-phase synthesis to give 2-substituted benzofurans. Substrates are often attached to polymer supports such as Merrifield, Wang or Tentagel resins by an ester link. After substrate modifications cleavage from the resin generally leaves a carboxylic acid derivative or alcohol at the site of attachment. This unnecessary functionality may contribute to the physiochemical and biological properties of the final compound, and so distort structure–activity relationships when used in agrochemical or pharmaceutical research. The benzofurans produced by our method show no trace of the site of attachment to the solid support and may, in theory, have substituents at any site.

We used 1,3-diisopropylcarbodiimide to couple carboxylic acids to Wang-resin (loading 1.7 mmol/g) contained in macrokans (0.29 mmol of alcohol per IRORI macrokan) to give resin-bound esters **5** (Scheme 2). Thioacetal **6** was synthesised in two steps from salicaldehyde (Scheme 3) and used to generate a novel alkylidenating reagent under Takeda conditions. Esters **5** were smoothly converted into enol ethers **7** using this reagent and the work-up consisted of simply washing the resin with various solvents. In each case, disappearance of the carbonyl absorption in the IR spectrum of esters **5** (obtained using the Golden Gate IR apparatus) and an appropriate weight gain confirmed complete conversion to enol ethers **7**. The steric bulk of R had little effect on the reaction (Table 1). Cleavage from the resin using 50% aqueous trifluoroacetic acid (TFA) in dichloromethane for 30 min gave pure ketones **8** in good overall yield from esters **5**. No chromatography was necessary.



Scheme 2.



Scheme 3.

Table 1

R	Yield of ketone 8 from ester 5 (%)	Yield of benzofuran 10 from ester 5 (%)
CH_3	69	38
$Ph(CH_2)_2$	79	83
$PhCH_2$	76	38
Ph	65	69

Enol ethers similar to enol ethers **7**, synthesised by palladium(0)-catalysed cross-coupling reactions, had been cyclised in solution phase using polyphosphoric or *p*-toluenesulfonic acid.[9] We attempted cleavage and cyclisation of enol ethers **7** using dry TFA over magnesium sulfate, but this gave a mixture of products. Consequently, phenol **9** was generated using tetrabutylammonium fluoride (TBAF), and treated with 50% aqueous TFA in dichloromethane for 30 min. This resulted in smooth cleavage from the resin to give benzofurans in good yield. Again, no chromatography was necessary.

Typical procedure for alkylidenation reaction: Triethylphosphite (4.0 ml, 23.3 mmol) in dry THF was added to titanocene dichloride (2.93 g, 11.8 mmol), magnesium (0.40 g, 16.5 mmol) and 4 Å molecular sieves (1.15 g) and the mixture was stirred at room temperature under argon for 3.5 h. A solution of thioacetal **6** (1.27 g, 2.90 mmol) in dry THF (11 ml) was added and the mixture stirred for a further 15 min. The resulting reagent was syringed into a dry flask containing two kans of preswollen (in 3 ml of dry THF) resin-bound ester **5** (0.29 mmol each of Wang resin with a loading of 1.7 mmol of ester/g). The mixture was stirred or shaken for 18 h, the THF removed and the kans washed (30 ml each wash) with THF, then alternately with methanol and CH_2Cl_2 ($\times$4), then methanol and finally ether. The resin-bound enol ether **7** was then dried under vacuum.

Procedure for deprotection reaction: TBAF (1 ml of a 1 M solution in THF) was added to one kan of resin-bound enol ether **7** (0.29 mmol) swollen in dry THF (5 ml) under argon and the mixture was shaken for 3 h. The THF was removed and the kan washed (30 ml each wash) with THF ($\times$3), and then as above. The resin-bound phenol **9** was dried under vacuum.

Procedure for cleavage: One kan of resin-bound enol ether **7** or **9** (0.29 mmol) was swollen in CH_2Cl_2 (4 ml) and treated with 50% aqueous TFA solution (2.5 ml). After 30 min stirring or shaking, the kan was washed with CH_2Cl_2 (3$\times$30 ml). The washings were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to give ketone **8** or benzofuran **10**. Traces of TBAF were removed from benzofuran **10** by dissolving in ether (30 ml) and washing with water (6$\times$30 ml), before drying ($MgSO_4$), and removing the solvent under vacuum.

In summary, we have demonstrated that the Takeda reaction can be performed on solid-phase and have developed a procedure for the traceless solid-phase synthesis of 2-substituted benzofurans.

Acknowledgements

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