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A CONTROLLED SYNTHESIS OF α-*(E)*-1-ALKENYL KETONES FROM β-KETO BENZYL ESTERS

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Summary: *A regio- and stereocontrolled method for the synthesis of α-(E)-1-alkenyl ketones from β-keto benzyl esters has been developed by devising the sequence of a modified Pinhey's alkenylation and a reductive removal of a benzyloxycarbonyl group with Raney nickel in the presence of triethylamine.*

The synthetic significance of α-alkenyl ketones as useful intermediates for a wide variety of transformations, *inter alia*, ring expansion reactions through Cope,[1] anionic oxy-Cope,[2] or Cope-Claisen[3] rearrangement, has stimulated considerable interest in expedient methods for the introduction of an alkenyl group α to the carbonyl of the ketones. Despite the great deal of work,[4-8] however, there exists a continuing demand for versatile and practical procedures enabling the regiocontrolled introduction of a stereo-defined alkenyl group onto unsymmetrical ketones. In the course of our studies directed toward the convergent synthesis of (+)-isocarbacyclin,[9] we were encountered with the problem of converting a bicyclic β-keto ester to a bicyclic ketone with ω-appendage α to the carbonyl. While this problem was recently solved by exploiting Pinhey's α-alkenylation[10] of the β-keto benzyl ester with the alkenyllead(IV) reagent prepared *in situ* from $Pb(OAc)_4$ and $(R\omega)_2Hg$ (Rω: ω-appendage equivalent), and devising a reductive removal of a benzyloxycarbonyl group with W-2 Raney nickel[11] in the presence of triethylamine,[9] one disadvantage for this sequence lay in a use of excess of the precious ω-appendage equivalent. We have now found that the use of alkenylzinc chloride instead of dialkenylmercury makes Pinhey's method more effective and economical. Herein we wish to report that the new version coupled with the salient debenzyloxycarbonylation method has advantages in providing a facile entry to α-*(E)*-1-alkenyl ketones with essentially complete regio- and stereocontrol, and including operational simplicity.

A wastage of one alkenyl group inherent in Pinhey's alkenylation method is due to the formation of the unreactive alkenylmercury acetate (eq. 1). Thus, we explored the feasibility of developing a more efficient method for the preparation of alkenyllead(IV) triacetate (eq. 2), through the reaction of a mixture of $Pb(OAc)_4$ and each of *(E)*-1-hexenylmetals containing $Al(i\text{-}Bu)_2$, $BO_2C_6H_4$, CdCl, $CeCl_2$, $SnBu_3$, and ZnCl with benzyl 2-oxocyclopentanecarboxylate. Among the metals screened, *(E)*-1-hexenylzinc chloride (2.1 equiv.) proved to be the

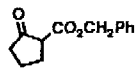
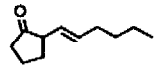
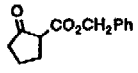
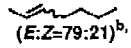
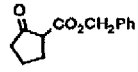
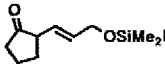
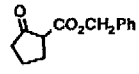
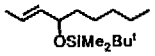
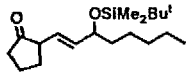
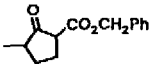
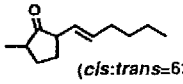
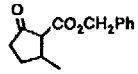
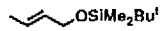
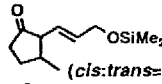
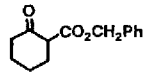
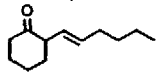
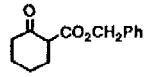
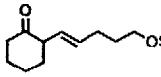
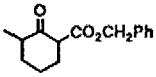
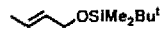
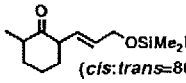
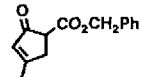
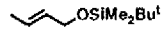
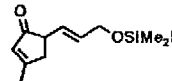
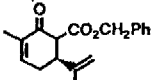
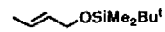
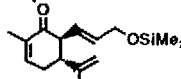
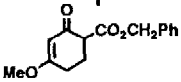
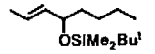
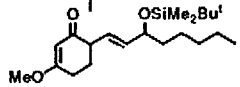
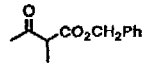
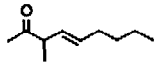
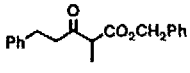
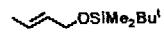
$$R_2Hg + Pb(OAc)_4 \longrightarrow RPb(OAc)_3 + RHgOAc \qquad (1)$$

$$RML_n + Pb(OAc)_4 \longrightarrow RPb(OAc)_3 + L_nMOAc \qquad (2)$$

R : alkenyl group

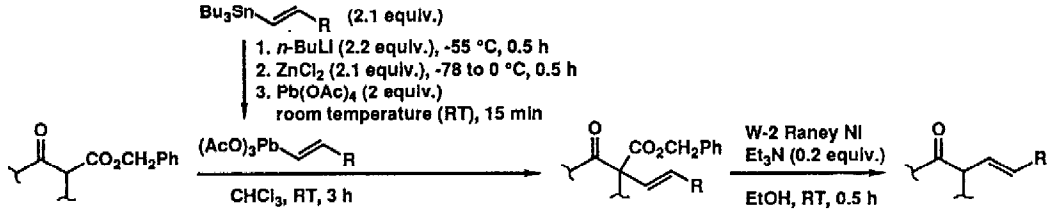
superior choice, giving the desired adduct[12] in 57% yield (85% yield based on the recovered keto ester).[13] The yield compared well with the 54% (82%) yield obtained by the use of di[*(E)*-1-hexenyl]mercury (2.1 equiv.). In stark contrast, the reaction with the other hexenylmetals afforded a complex mixture of products. On this positive note, the

Table 1. Synthesis of α-(*E*)-1-Alkenyl Ketones from β-Keto Benzyl Esters.

entry	substrate	alkenyl group	adduct % yield[a]	product / % yield
1			57 (85)	 83
2		 (*E*:*Z*=79:21)[b, c]	53 (87)	
3			58 (86)	 81
4			61 (86)	 83
5			54 (88)	 (*cis*:*trans*=63:37)[c] 81
6			60 (88)	 (*cis*:*trans*=14:86)[c] 80
7[d]			46 (83)	 84
8[d]		 (*E*:*Z*=85:15)[b, c]	46 (88)	 86
9[d]			60 (82)	 (*cis*:*trans*=86:14)[c] 77
10			62 (84)	 84
11[d]			59 (89)	 87
12[d]			53 (90)	 85
13[d]			49 (81)	 78
14[d]			41 (84)	85

[a] Values in parentheses are based on recovered starting material. [b] The alkenylstannane (2.5 equiv.), *n*-BuLi (2.6 equiv.), $ZnCl_2$ (2.5 equiv.), and $Pb(OAc)_4$ (2.4 equiv.) were used. [c] The ratio was determined by ^1H NMR analysis. [d] The corresponding sodium enolate generated with NaH was used.

Scheme 1



synthesis of a variety of α-alkenyl ketones based on the improved Pinhey's alkenylation / reductive debenzyloxycarbonylation sequence was investigated (Scheme 1).[14] Some representative results are presented in Table 1, in which several features deserve comment.

(1) α-*(E)*-1-Alkenylation of a variety of cyclic or acyclic β-keto benzyl esters proceeded smoothly to give the corresponding adducts in moderate to good yields, in which little variation in recovery yields of the starting materials was observed even when the large excess of the reagent was used. Except for cyclopentanone derivatives, the sodium enolates of β-keto esters gave better results.

(2) The stereochemical purities of the α-*(E)*-1-alkenyl ketones obtained upon debenzyloxycarbonylation[15] were confirmed to be >99% by their spectroscopic (400 MHz ^{1}H NMR) comparison with the corresponding α-*(Z)*-1-alkenyl ketones,[16] and furthermore, no trace of the saturated ketones or the conjugated enones could be detected.

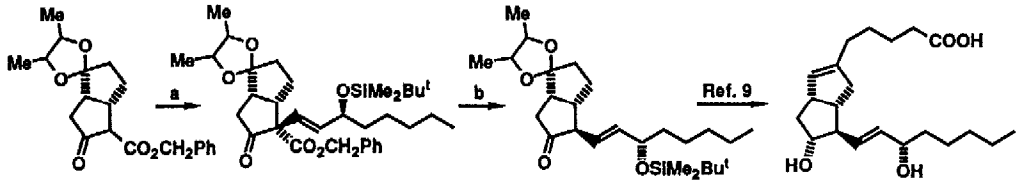
(3) α-Alkenylation with *(Z)*-alkenyl groups did not proceed under the present conditions. Thus, an *E/Z* mixture of the alkenylstannanes prepared by hydrostannation of 1-alkynes can serve as an alkenyl source for the formation of α-*(E)*-1-alkenyl ketones (entries 2 and 8), making the present procedure much simpler than the existing methods. It is important to note that the alkenylstannane as an alkenyl source is crucial to the success of this alkenylation, since the alkenyllithium generated from the corresponding alkenyl iodide gave much inferior results.

(4) Since the cyclic β-keto benzyl esters can be readily prepared by trapping the kinetic enolates of cyclic ketones or the intermediate enolates generated *via* organocopper conjugate addition to cyclic enones with benzyl cyanoformate,[17,18] the present method constitutes an efficient procedure for the controlled α-alkenylation of unsymmetrical cyclic ketones (entries 5, 6, and 9-12).

(5) Noteworthy is the fact that a conjugated enone moiety is compatible with the present debenzyloxycarbonylation conditions (entries 10-12), enabling access to α-*(E)*-1-alkenyl cyclic enones otherwise difficult to prepare.

The protocol developed here could be successfully applied to the synthesis of (+)-isocarbacyclin intermediate as shown in Scheme 2,[9] in which the ω-appendage equivalent, (+)-(3*S*)-*(E)*-3-(*tert*-butyldimethylsilyl)oxy-1-octene, $[\alpha]_D^{23}$ +6.3 ° (c 1.36, $CHCl_3$), recovered in 54% yield, could be converted back into the starting alkenylstannane, $[\alpha]_D^{23}$

Scheme 2



(a) RωZnCl (2.1 equiv.), $Pb(OAc)_4$ (2.0 equiv.), $CHCl_3$, RT, 0.5 h, then the β-keto ester added, RT, 3 h, 55% (86% based on recovered starting material). (b) W-2 Raney Ni (5 ml of sediment in EtOH per mmol), Et_3N (0.2 equiv.), RT, 0.5 h, then Et_3N (1 equiv.) added, 0 °C, 15 min, 75%.

-15.9 ° (c 1.52, $CHCl_3$), for reuse in 56% yield by a three-step operation (i, Br_2, CCl_4, -10 °C, 0.5 h; ii, $NaNH_2$, liq. NH_3, -40 °C, 15 min; iii, Bu_3SnH, AIBN, 100 °C, 2 h).

In conclusion, we have developed a facile and controlled method for the synthesis of a variety of α-*(E)*-1-alkenyl ketones. Exploitation of this method to the synthesis of biologically interesting compounds as well as mechanistic studies is currently in progress.

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References and Notes

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12. All new compounds were fully characterized by ^1H NMR (400 MHz), IR, and high resolution mass spectral analysis.
13. A small amount of benzyl 1-chloro-2-oxocyclopentanecarboxylate (*ca.* 8%) was formed as a by-product, which was reduced back to the starting keto ester with Zn dust during the workup.
14. The following procedure for the preparation of 2-[*(E)*-3-(*tert*-butyldimethylsilyl)oxy-1-propenyl]cyclopentanone is representative. To a stirred suspension of anhydrous $ZnCl_2$ (3.15 mmol) in THF (2 ml) at -78 °C was added a precooled(-78 °C) solution of the alkenyllithium in THF (3 ml) prepared by the transmetallation of *(E)*-3-(*tert*-butyldimethylsilyl)oxy-1-(tri-*n*-butylstannyl)-1-propene (3.15 mmol) with *n*-butyllithium (1.59 M in hexane, 3.3 mmol) at -55 °C over 0.5 h. After the bath temperature was raised to 0 °C over 0.5 h, the solution was transferred to a well stirred solution of $Pb(OAc)_4$ (3 mmol) in chloroform (20 ml) at -20 °C. After 15 min of stirring at room temperature, to the resultant yellow mixture was added a solution of benzyl 2-oxocyclopentanecarboxylate (327 mg, 1.5 mmol) in chloroform (3 ml), and stirring was continued at room temperature for 3 h. The reaction mixture was quenched with sald. aq. NH_4Cl (8 ml), treated with Zn dust (500 mg), and then extracted with ether-hexane (10:1, 70 ml). The organic layer was washed successively with 0.5N HCl, aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and then concentrated *in vacuo*. Column chromatography (silica gel, 15:1 hexane-ethyl acetate) provided the adduct (338 mg, 58%) and the starting keto ester (106 mg, 32%). To a stirred solution of the adduct (310 mg, 0.80 mmol) and Et_3N (16mg, 0.16 mmol) in EtOH (1 ml) was added W-2 Raney nickel (4 ml of sediment in EtOH) in three portions over 15 min at room temperature. After 15 min, the mixture was diluted with ether (25 ml), and the catalyst was filtered off. Usual extractive workup followed by column chromatography (silica gel, 15:1 hexane-ethyl acetate) afforded the product (165 mg, 81%) as a colorless oil.
15. Selective cleavage of benzyl and (benzyloxy)methyl ethers by W-2 Raney nickel without concomitant reduction of a double bond in a ring system has recently been reported. Y.Oikawa, T.Tanaka, K.Horita, and O.Yonemitsu, *Tetrahedron. Lett.*, **25**, 5397 (1984); H.Venkataraman and J.K.Cha, *J. Org. Chem.*, **54**, 2505 (1989).
16. The preparation of α-*(Z)*-1-alkenyl ketones will be reported in due course.
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