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Palladium Catalyzed Chemoselective Cleavage of β-Propargyloxy-α, β-Unsaturated Esters: Approach to γ-Protected Hydroxy-β-Ketoesters#

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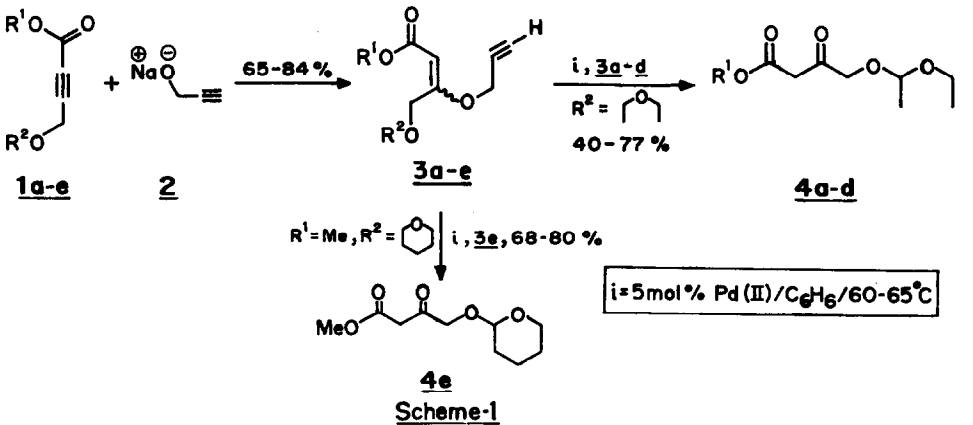
Abstract: *β-Propargyloxy-α, β-unsaturated esters **3a-e** chemoselectively cleave in the presence of catalytic amount of Palladium (II) complexes to afford acid sensitive β-ketoesters **4a-e** in good yields.*

In order to overcome limitations associated with the base induced Claisen condensation approaches[1,2] to β-diketones and β-ketoesters, alternate routes *via* the hydrolysis of latent carbonyl functionalities like alkynones, β-alkoxy / alkylthio substituted α, β-unsaturated ketones and esters have been established[3]. However, the necessity of acid and toxic mercury[4] and thallium[5] complexes for performing the hydrolytic transformations makes these methodologies unsuitable for systems with acid sensitive groups. In view of the easy availability of these intermediates[6] and usefulness of the resulting β-diketones and esters as building blocks in organic synthesis[7] and biocatalytic conversions[8], development of efficient routes for carrying out such reactions under neutral conditions are highly desirable. The intrinsic ability of palladium in catalytically influencing synthetic transformations[9-11] through complexation with oxygen atoms prompted us to consider its utility for the desired scissoring. Described herein are our preliminary results in this direction.



Scheme-1

TABLE 1

β-Ketoesters 4a-e prepared from 3a-e

Entry	Enolether 3 *(Cis:Trans)*[a]	Product	R^1	R^2	Palladium complex[b]	Time (h)[c]	Isolated Yield(%)
1	3a (1:1)	4a	Me	DEE[d]	$Pd(OAc)_2$	11	59
2	3a (1:1)	4a	Me	DEE	$PdCl_2(PhCN)_2$	11	77
3	3b (1:3)	4b	Et	DEE	$PdCl_2(PhCN)_2$	08	71
4	3b (1:3)	4b	Et	DEE	$Pd(OAc)_2$-BBEDA[f]	12	66
5	3c (1:2)	4c	^{n}Bu	DEE	$Pd(OAc)_2$	14	70
6	3d (1:3)	4d	Bz	DEE	$Pd(OAc)_2$	14	40
7	3d (1:3)	4d	Bz	DEE	$PdCl_2(PhCN)_2$	12	56
8	3e (1:1)	4e	Me	THP[e]	$Pd(OAc)_2$	12	67
9	3e (1:1)	4e	Me	THP	$Pd(OAc)_2$+2PPh_3	15	80
10	3e (1:1)	4e	Me	THP	$PdCl_2(PhCN)_2$	11	69

[a]Determined by ^{1}H-NMR[13], [b]5 mol %, [c]Unoptimized, [d]Diethyl ether, [e]Tetrahydropyran, [f]Bisbenzylideneethylenediamine

The required enolether esters **3a-e** were prepared in 65-84% yield as a variable mixture of *cis* and *trans* isomers by conjugate addition[12] of sodium propargyl oxide **2** to **1a-e** (Scheme 1). These were found to undergo smooth chemoselective cleavage at the enolether site in the presence of 5 mol % of palladium (II) complexes. Thus, upon heating **3b** (R^1=Et, R^2=DEE) at 60-65 °C for 8h in dry benzene in the presence of 5 mol % $PdCl_2(PhCN)_2$, the required β-ketoester **4b** was isolated in 71 % yield. The cleavage of the propargyl group in **3b** was equally facile with $Pd(OAc)_2$-bisbenzylideneethylenediamine (BBEDA) complex (5 mol %) and **4b** was formed in 66% yield.

The transformation was found to be general and enolether esters **3a** and **3c-e** could also be selectively and catalytically cleaved in the presence of various palladium complexes under identical experimental conditions to afford the required β-ketoesters **4a** and **4c-e** respectively in moderate to high isolated yield (Table 1). The extremely mild nature of the transformation is clearly demonstrated by the survival of the highly sensitive benzyl ester group in the conversion of **3d** to **4d** (entries 6 & 7). The deprotection of the acid labile diethylether (DEE) and tetrahydropyran (THP) groups was not at all detected under the reaction conditions employed.

In summary, the methodology described above provides a versatile route for chemoselective removal of an acid stable moiety in the presence of a highly acid sensitive protective group in a catalytically efficient manner to yield protected hydroxy β-ketoesters from the corresponding propargyloxy enolesters. Efforts are currently underway to generalize the transformation and to understand the precise mechanism of this novel deprotective methodology.

Representative Experimental Procedure:

To a stirred suspension of $PdCl_2(PhCN)_2$ (10 mg, 0.025 mmol) in dry benzene under an atmosphere of argon, the propargyloxy enol ester **3b** (128 mg, 0.5 mmol) was added. After 15 minutes of stirring at room temperature, the mixture was heated at 60-65 °C for 8h after which the *TLC* showed the reaction to be complete. The reaction mixture was filterd through a small pad of silicagel to remove the palladium complex and evaporated on rotavapor to give the crude ketoester **4b**. Purification by column chromatography on silicagel yielded pure **4b** as a colourless oil. Yield=77 mg (71%).

4b: **^{1}H-NMR** (200.13 MHz, $CDCl_3$) δ = 1.10-1.35(2t+1d, 9H); 3.65(m, 4H); 4.05-4.25(2q, 4H); 4.75(q, 7Hz, 1H). **^{13}C-NMR with DEPT** (50.32 MHz, $CDCl_3$) δ = 14.0(+), 15.01(+), 19.50(+), 45.96(-), 61.13(-), 61.62(-), 69.95(-), 100.15(+), 166.93(ϕ), 201.41(ϕ). **IR** (cm^{-1}) ν = 935, 953, 1152, 1327, 1385, 1633, 1732, 1741, 2940.; **MS**. m/e = 146 (M^+-C_4H_6O), 128(146-H_2O).

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[f]NCL Communication No. 5798.

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