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PALLADIUM CATALYZED ALLYLATION OF REFORMATSKY REAGENTS.
SYNTHESIS OF γ,δ-UNSATURATED ESTERS.

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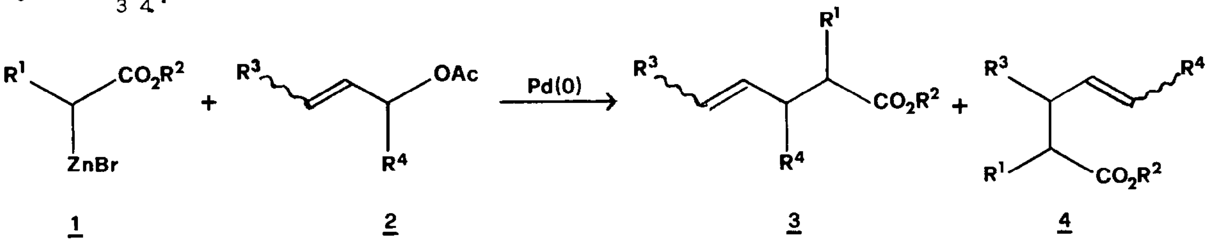
Abstract: Reformatsky reagents regioselectively react under mild conditions with allylic acetates in the presence of $Pd(PPh_3)_4$ to give γ,δ-unsaturated esters in good yields.

The direct α-alkylation of ester enolates has been rarely considered an effective synthetic methodology owing to the competition of the self-condensation reaction. To improve the yield of alkylation reactions several measures have been adopted, such as using hindered lithium amides to generate the ester enolate at -78°C or employing t-butyl esters[1].

Anyway the most widely used alternative to the direct α-alkylation of ester enolates is, still now, the classic malonic ester synthesis, which, on the other hand, suffers the drawback of requiring a later removal of the auxiliary ester group. Alternatively carboxylic acid dianions, or their synthetic equivalents[2], have been alkylated. Finally ketene silyl acetales[3] and "soft" anions derived from malonates and β-sulphonyl esters[4] give allylic substitution on allylic carbonates and acetates in the presence of palladium complexes.

More recently "hard" nucleophiles such as ketones enolates of tin[5a], zinc[5b] and lithium[5c] were employed in this kind of reaction. At our knowledge no direct Pd catalyzed allylation reaction of enolates of monoesters has been reported[6].

Here we wish to report the reaction of Reformatsky reagents with allylic acetates catalyzed by $Pd(PPh_3)_4$.



We prepared Reformatsky reagents, according to a procedure worked out in our laboratory[7], by dropping a solution of an α-bromo ester or lactone in THF over a suspension of 10% molar excess of highly dispersed zinc on the graphite surface (Zn-Gr) in the same solvent at 0°C. Alternatively the use of Zn-Cu couple[8] under similar conditions is possible.

The subsequent allylic substitution reaction is easily performed in situ, upon addition of $Pd(PPh_3)_4$ and the allylic acetate, and stirring the reaction mixture at room temperature. A first series of experiments was effected using cinnamyl acetate and ethyl zinc bromoacetate as model substrates to establish the best reaction conditions (Table I). A molar ratio 1:2 = 2:1 allows to obtain both good yields and reaction rates. The use of 8% of Pd catalyst is strongly indicated, while the addition of triphenylphosphine does not afford better results. The graphite used in the preparation of Zn-Gr plays an important role[9]. The preparation of ethyl zinc bromoacetate with Zn-Cu couple affords a final yield comparable with that of the other tests. This fact ensures that the way of preparation of the Reformatsky reagent is not a determinant factor in the subsequent reaction with the allylic substrate. In all the tests reported the 3/4 ratio is 93/7 and the 3E/3Z ratio is 94/6[10].

TABLE I

Reactions of ethyl zinc bromoacetate with cinnamyl acetate[a]

1:2 molar ratio	$Pd(PPh_3)_4$ moles %	PPh_3 moles %	Graphite[b]	t(h)	3 + 4 % yield
1.3:1	8	-	A	50	55
2:1	4	8	A	30	42
2:1	8	16	A	2	72
2:1	8	-	A	2	84
2:1	8	-	B	2	75
2:1	8	-	C	20	35
2:1	8	-	Zn-Cu	2	68

a) The reactions were performed on 2.5 mmoles of cinnamyl acetate in 25 ml of THF at room temperature. The Reformatsky reagent was previously prepared at 0°C by the addition of the reported ammount of ethyl bromoacetate over a suspension of 10% molar excess of Zn-Gr, obtained according to the literature.

b) Graphite samples used in the preparation of Zn-Gr were obtained from: Roth (A); Fluka (B); Carlo-Erba (C). Zn-Cu means that the Reformatsky reagent was prepared starting from Zn-Cu couple.

The results of reactions between several allylic acetates and Reformatsky reagents are reported in Table II. Significantly, also substrates bearing hydrogens in the α' position with respect to the double bond give good yields; careful analysis of the reaction mixture in entries 3 and 4 excluded the formation of 1,3-undecadiene[11].

TABLE II

Reactions of Reformatsky reagents with allylic acetates[a]

entry	1		2[b]		t(h)	Yields %[c]		E/Z[d]
	R^1	R^2	R^3	R^4		3	4	
1	H	Et	H	C_5H_{11}	"	8	59	99:1
2	H	Et	C_3H_7	H	"	57	8	92:8
3	H	Et	C_8H_{17}	H	18	46	6	93:7
4[e]	H	Et	C_8H_{17}	H	"	42	5.5	91:9
5	Me	Et	Ph	H	2	59	6	98:2
6	Me	Et	H	C_5H_{11}	"	3	71	97:3
7	$(CH_2)_2$		C_3H_7	H	"	76	2.5	96:4
8	$(CH_2)_2$		$(CH_2)_3$		2	75[f]		

a) To the Reformatsky reagent (5.5 mmoles) prepared as previously reported (cfr. Table I, note a) in THF (25 ml), $Pd(PPh_3)_4$ (0.2 mmoles, 8%), and of the allylic acetate (2.5 mmoles) were added. After stirring at room temperature for the time indicated, the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 ml) and worked-up. The products were purified through flash chromatography over silica gel[12].

b) The configuration of the double bond was always E except in entry 5.

c) Yields were determined on the purified mixture of 3 and 4, whose ratio was established by capillary GC (OV1, 25m, 0.1-0.15 m film thickness).

d) E/Z refers to the isomer ratio of the main product and was determined by capillary GC (CARBOWAX 20M, 25m, 0.4-0.45 m film thickness) The minor product was always a mixture of diastreoisomers; their ratio ranged from 8/2 to 6/4.

e) (Z)-2-undecen-1-yl acetate was used. This compound was prepared treating 2-undecyn-1-ol with Zn-Gr in EtOH for 10 h at reflux[13]. The isomeric purity (Z/E = 98:2) was tested by capillary GC (CARBOWAX 20M, 25m, 0.4-0.45 m film thickness).

f) Yield refers to the total amount of the two diasteromers whose ratio, determined by capillary GC (CARBOWAX 20M, 25m, 0.4-0.45 m film thickness) was 65:35. No attempt was made to establish the configuration of the major one.

The regiochemical course of this reaction is under steric control; the main product (3 or 4) always arises from the attack to the less substituted carbon, indipendently of the nature of the allylic acetate (entries 1 and 6). Starting from both Z or E allylic acetates (entries 3 and 4) the configuration of the double bond in the ester product is prevalently E.

The zinc derivative derived from α-bromo-γ-butyrolactone similarly reacts with allylic acetates (entries 7 and 8). In the reaction with 2-cyclohexen-1-yl acetate it seems to be more nucleophilic than ethyl zinc bromoacetate, the later affording a disappointingly low yield.

We think that the extension of the Pd-catalyzed allylic substitution to Reformatsky reagents derived from α-bromo esters and lactones represents an important achievement being alternative to the use of malonates and so avoiding the final decarboxylation step. Moreover the high degree of regio and stereoselectivity exhibited, makes this reaction attractive from a synthetic point of view.

Notes and References

1) N. Petragnani and M. Yonashiro, Synthesis, 541 (1982).
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5) a: B.M. Trost and E. Keinan, Tetrahedron Lett., 2591 (1980); b:E. Negishi and R.A. John, J. Org. Chem., 48, 4098 (1983); c: J.C. Fiaud and J.L. Malleron, J. Chem. Soc. Chem. Commun., 1159 (1981).
6) Alkylation of t-butyl zinc bromoacetate in dimethylsulphoxide was reported: F. Orsini and F. Pellizzoni, Synth Commun., 13, 523 (1983).
7) G.P. Boldrini, D. Savoia, E. Tagliavini, C. Trombini and A. Umani-Ronchi, J. Org. Chem., 48, 4108 (1983).
8) L.E. Rice, M. Craig Boston, H.O.Finkles, B.J. Suder, J.O. Frazier and T. Hudlicky, J. Org. Chem., 49, 1845 (1984).
9) Roth graphite and Fluka graphite show a similar X-Rays diffraction pattern, while the same analysis performed on Carlo-Erba graphite clearly indicated a less cristalline material. The Fluka product is more finely powdered than the Roth one and require a prolonged heating under stirring during the preparation of potassium-graphite.
10) As determined by capillary GC (CARBOWAX 20M, 25m, 0.4-0.45 m film thickness). ^{1}H-NMR spectrum showed the vinylic protons resonances at δ = 6.5 (d, J = 16Hz) and 6.2 (m) due to compound 3 and a resonance at δ = 5.1 (m) due to the vinylic methylene protons of compound 4 whose areas were in agreement with the composition measured by GC analysis.
11) The quantitative formation of myrcene and ocimene from the reaction of neryl and geranyl acetates respectively with propargyl zinc bromide was reported: H. Matsushita and E. Negishi, J. Org. Chem., 47, 4161 (1982). The reaction between allylic tin derivatives and allylic acetates catalyzed by Pd(Ph$_3$P)$_4$ cannot be performed with substrates bearing α' hydrogens (see ref. 5a).
12) All compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra.
13) See: M.H.P.J. Aerssens and L. Brandsma, J. Chem. Soc. Chem. Commun., 735 (1984); D. Savoia, C. Trombini and A. Umani-Ronchi, Pure Appl. Chem., 57, 1887 (1985).

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