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Competing O–H Insertion and β-Elimination in Rhodium Carbenoid Reactions; Synthesis of 2-Alkoxy-3-arylpropanoates

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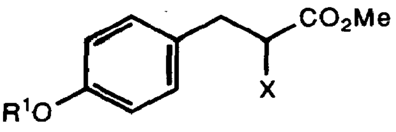
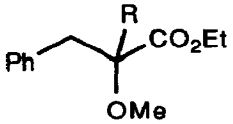
Abstract: *Rhodium(II) carboxylate catalysed decomposition of diazo esters 3 and 4 in the presence of alcohols or water results in formation of 2-alkoxy- or 2-hydroxy-3-arylpropanoates respectively by O–H insertion in competition with cinnamates by elimination; the ratio of insertion to elimination is dramatically affected by the carboxylate ligand on rhodium. Use of methanol-d as the alcohol confirms that the alkene does not arise by elimination from the initial alkoxyester product.*

During some recent studies, we required access to a range of 2-alkoxy-3-arylpropanoates **1**.[1] Since attempts to prepare these compounds by reaction of the chloride **2**[2] with alkoxides were unsatisfactory, we considered an alternative approach starting from methyl 2-diazo-3-(4-hydroxyphenyl)propanoate **3**,[3] readily prepared from commercially available tyrosine methyl ester, and employing a rhodium carbenoid O–H insertion reaction.[4]



1 $R^1 = H, X = OR^2$
2 $R^1 = CH_2Ph, X = Cl$



5a $R = {}^1H$
5b $R = {}^2H$

Thus addition of a solution of the diazo compound **3** in the alcohol R^2OH to a stirred mixture of the alcohol and rhodium(II) acetate (1 mol%), followed by heating the mixture under reflux for several hours gave, after aqueous work-up, the desired alkoxyesters **1** in varying yield (Table 1). Methanol gave the best yield (Entries 1-3), with other alcohols generally giving lower yields; increasing the bulk of the alcohol (2-propanol) (Entry 6) or reducing its nucleophilicity (2,2,2-trifluoroethanol) (Entry 7) caused a reduction in yield. Benzyl alcohol, methyl glycolate and propargyl alcohol (Entries 8 - 10) also gave low yields of the corresponding alkoxyesters **1**. In general the reaction is most conveniently carried out neat (for simple alcohols), although benzene is a suitable co-solvent.

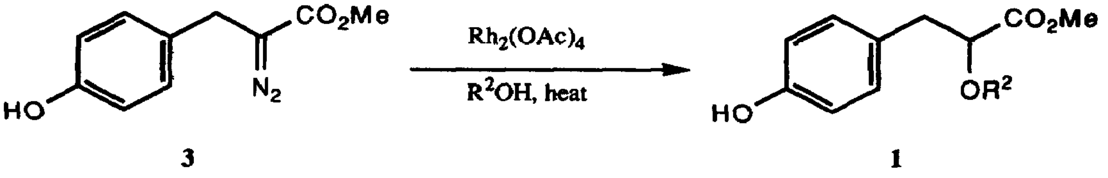


Table 1. Rhodium(II) acetate mediated O–H insertion reactions of diazo tyrosine **3**

Entry	*Alcohol* R^2OH	*Method*	*Temperature* (°C)	*Time* (h)	*Isolated Yield* **1** (%)
1	MeOH	a	65	5	44
2	MeOH	b	65	5	49
3	MeOH	c	80	5	40
4	EtOH	a	78	5	40
5	*n*-PrOH	a	80	3.5	30
6	*i*-PrOH	b	80	3	29
7	CF_3CH_2OH	a	80	4	32
8	$PhCH_2OH$	b	80	4	<20†
9	MeO_2CCH_2OH	d	80	0.5	25
10	$HC{\equiv}CCH_2OH$	c	80	5	24

Method (a) Addition at room temperature; (b) Addition at the reaction temperature; (c) This reaction was performed using benzene as a solvent and 5 equiv. alcohol; (d) 2 equiv. $HOCH_2CO_2Me$ were used in benzene as solvent; † Product not isolated; yield estimated by ^1H NMR.

The major byproduct in all cases was methyl 3-(4-hydroxyphenyl)propenoate, as detected in the ^1H NMR spectrum of the crude reaction mixture, and by isolation (15-20%) in some cases. The alkene presumably arises from β-hydride elimination in the intermediate carbenoid, rather than by elimination of R^2OH from **1** since the ethoxy compound **1** (R^2 = Et) was recovered unchanged from heating in ethanol in the absence or presence of rhodium(II) acetate. Proof that the alkene arises directly from the intermediate carbenoid came from carrying out parallel insertion reactions in both methanol and methanol-d. Thus rhodium(II) acetate catalysed decomposition of ethyl 2-diazo-3-phenylpropanoate **4**[5] in methanol gave the expected O–H insertion product **5a** (52%) along with ethyl cinnamate (*ca.* 16%). When the reaction was repeated in MeOD, the O–D insertion product **5b** was formed in 69% yield; careful analysis of **5b** by ^1H, ^{13}C and ^2H NMR established its structure and ~100% deuterium content. The cinnamate (*ca.* 16%) that was formed along with **5b** was also analysed by ^2H NMR and established to contain less than 5% deuterium, thereby confirming that the major route to the alkene is not by elimination from the alkoxyester insertion product.

Such elimination reactions to give alkenes have been noted previously with related diazo ketones and diazoesters,[6] and in certain cases it has been shown that rhodium mediated intramolecular C–H insertion (to give cyclopentanes) can compete effectively with alkene formation.[6c] However, nothing is known about the relative ease with which the rhodium carbenoid intermediate undergoes O–H insertion as opposed to β-hydride elimination, and therefore we undertook a more detailed study of this competition process. For simplicity of product analysis, we again used the diazoester **4** and water as the hydroxylic component; a range of rhodium(II) carboxylates was employed as catalysts.[7] The reactions were carried out by dissolving the diazoester **4** in ether saturated with water (*ca.* 6%), adding the rhodium catalyst (1-2 mol%) and stirring the mixture at room temperature until TLC indicated complete disappearance of the diazo compound. The ratio of O–H insertion (formation of ethyl 2-hydroxy-3-phenylpropanoate **6**[8]) to β-hydride elimination (formation of ethyl cinnamate **7**) was determined by ^{1}H NMR and is shown in Table 2 for the various catalysts used. The cinnamate **7** was formed largely as its Z-isomer; catalysts which gave the largest amount of cinnamate also gave the highest Z:E ratios. Related catalyst effects have been observed in the reaction of methyl 2-diazotetradecanoate which undergoes elimination to give the Z-isomer of methyl 2-tetradecenoate, in competition to intramolecular C–H insertion.[6c] In contrast, the elimination reactions of diazoester **3** which were conducted at *elevated* temperatures gave a 1:1 mixture of E- and Z-cinnamates, although at room temperature there was a slight preference for the Z-isomer, the exact ratio depending on the catalyst used.[9] Although it is possible that the initial Z-isomer readily isomerises because of the presence of the *para*-hydroxy group, control experiments suggested that this was unlikely.[10] Therefore it is likely that in all these experiments the geometry of the alkene is determined in the transition-state for the rhodium carbenoid mediated elimination.[6b]

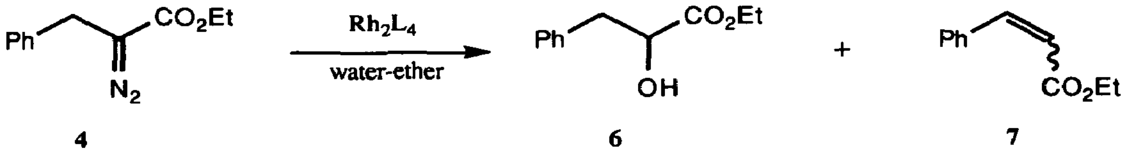


Table 2. Rhodium mediated O–H insertion *vs* elimination reactions of diazoester **4**

Entry	L	Ratio **6**	Ratio **7**
1	2-Ph-$C_6H_4CO_2$-	16.5	1.0
2	2,4,6-Me_3-$C_6H_2CO_2$-	10.3	1.0
3	1-$C_{10}H_7CO_2$-	8.0	1.0
4	9-$C_{14}H_9CO_2$-	7.6	1.0
5	$MeCO_2$-	4.6	1.0
6	2-HO-$C_6H_4CO_2$-	1.8	1.0
7	CF_3CONH-	1.7	1.0
8	CF_3CO_2-	1.0	2.1
9	$C_3F_7CO_2$-	1.0	5.1

It is clear from Table 2 that the ligand on the rhodium(II) carboxylate has a striking effect, the more strongly electron withdrawing ligands favouring elimination. When two of these catalysts [$Rh_2(OCOR)_4$; R = 1-$C_{10}H_7$ and R = 9-$C_{14}H_9$) were applied to the decomposition of **3** in methanol, good yields (69, 63%) of O–H insertion product were obtained (*cf.* 66% with $Rh_2(OAc)_4$ under identical conditions), and although alkene formation was not completely suppresssed, change in catalyst did markedly increase the Z/E-ratio from 3:1 for $Rh_2(OAc)_4$ to 15:1 for the anthracene derived catalyst.

The results add substance to Taber's speculation that the intermediacy of a rhodium carbenoid bearing electron withdrawing ligands favours the less entropically demanding β-hydride elimination (earlier transition state).[6c] Bulkier, more electron releasing ligands, on the other hand, favour the intermolecular reaction with water. Such catalysts may find use in other rhodium carbenoid O–H insertion reactions.

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REFERENCES AND NOTES

1. Compounds of type **1** can be prepared *via* Heck, aldol or olefination sequences, followed by reduction of the resulting double bond. For example, see: Sakamoto, T.; Kondo, Y.; Kashiwagi, Y.; Yamanaka, H. *Heterocycles*, **1988**, *27*, 257; Horner L.; Renth, E.-O. *Liebigs Ann. Chemie*, **1967**, *703*, 37; and especially Grell, W.; Machleidt, H. *Liebigs Ann. Chemie*, **1966**, *699*, 53.
2. Hindley, R.M. *International Patent Appl., Publication No.* WO 9202520, **1992**. For similar reactions of analogues of the chloride **2** with thiols see Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3563.
3. Takamura, N.; Mizoguchi, T. *Tetrahedron Lett.*, **1971**, 4495.
4. For other examples of rhodium carbenoid mediated O–H insertion reaction see: Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.*, **1973**, 2233; Noels, A. F.; Demonceau, A.; Petiniot, N.; Hubert, A. J.; Teyssie, P. *Tetrahedron*, **1982**, *38*, 2733; Adams, J.; Spero, D. M. *Teytrahedron*, **1991**, *47*, 1765; Davies, M. J.; Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1; Cox, G. G.; Kulagowski, J. K.; Moody, C. J.; Sie, E.-R. H. B. *Synlett*, **1992**, 975.
5. The diazoester **4** (Schöllkopf, U.; Rieber, N. *Chem. Ber.*, **1969**, *102*, 488) was used for these experiments since the resulting deuterated ethyl cinnamates are known compounds.
6. (a) Takamura, N.; Mizoguchi, T.; Yamada, S. *Tetrahedron Lett.*, **1973**, 4267; (b) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *ibid.*, **1981**, *22*, 4163; (c) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436, and references therein.
7. Of the catalysts used only that derived from naphthalene-2-carboxylic acid is a new compound; all catalysts were prepared from rhodium(II) acetate by ligand exchange in the usual way.
8. Ethyl 2-hydroxy-3-phenylpropanoate **6** is formed in a related insertion type reaction when an *N*-acetyl-*N*-nitroso compound is used a diazo precursor; see: Chow, Y. L.; Polo, J. *J. Chem. Soc., Chem. Commun.* **1981**, 297.
9. When the diazoester **3** was decomposed in methanol at room temperature in the presence of rhodium(II) acetate, rhodium(II) trifluoroacetate or rhodium(II) trimethylbenzoate, the ratios of Z- to E-alkene obtained were 3.4:1, 3.6:1 and 1.9:1 respectively.
10. One such control experiment involved further heating of a 3.6:1 Z- to E- mixture of alkenes in methanol in the presence of rhodium(II) trifluoroacetate. After 6 h the ratio of Z- to E-alkenes was determined to be 2.2:1; *i.e.* although there is a slow but detectable double bond isomerisation, it cannot account for the 1:1 mixtures of alkenes that were formed in the original rhodium carbenoid mediated step.

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