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REGIOCONTROL BY ELECTRON WITHDRAWING GROUPS IN THE Rh-CATALYZED C-H INSERTION OF α-DIAZOKETONES

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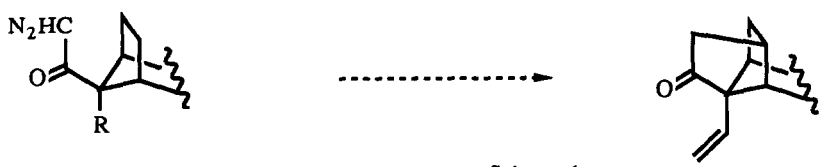
Summary: It is possible to control the regiochemistry of the Rh-catalyzed insertion of α-diazoketones into C-H bonds by taking advantage of the greatly reduced rate of insertion into methylenes which are α or β to a carboxyl function. The 2-carboxyethyl group is especially useful for this purpose because it can be transformed eventually into a variety of other substituents.

In the course of an approach to the synthesis of gelsemine we required the transformation shown in Scheme 1. This required finding a group R which would 1) survive the Rh-catalyzed C-H insertion reaction of a diazoketone; and 2) be easily transformable into a vinyl substituent. Simple possibilities such as, *inter alia*, a vinyl group (R = $CH{=}CH_2$ [1]) or oxygen-containing groups (*e.g.* R = CO_2R [2] or CH_2OR [3]), are unsuitable because they undergo metal-catalyzed reactions with diazoketones .

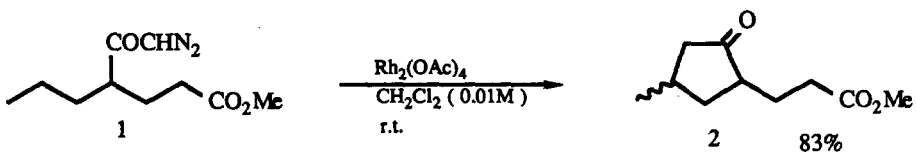


Scheme 1

In the course of their extensive studies on Rh(II)-catalyzed C-H insertion reactions,[4] Taber and Ruckle reported that electron withdrawing substituents, such as vinyl and phenyl groups, decrease the reactivity of the adjacent C-H bond to such insertions.[4a] In the reaction of α-diazo-β-keto esters catalyzed by $Rh_2(OAc)_4$, an aliphatic methylene was preferred over an allylic or a benzylic methylene by factors of 2.3 and 2.9, respectively.[5] This suggested the possibility that more electron

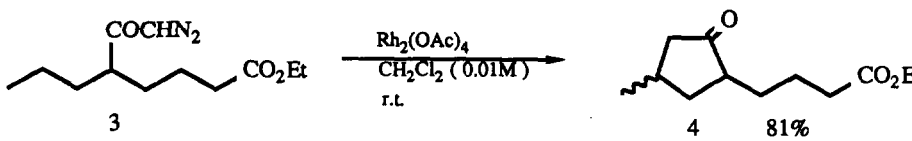
withdrawing groups, such as ketones or esters, might protect not only their α, but their β C-H bonds as well, against the insertion reaction. Should this hypothesis prove correct, the resulting selectivity should be generally useful since a propionate substituent (R=$CH_2CH_2CO_2Me$) can be transformed not only into a vinyl group (*e.g.* by oxidative decarboxylation of the corresponding acid with lead tetraacetate and cupric acetate[6]), but also into a variety of other substituents.

We now show that an ester group indeed steers diazo ketone insertion away from its α as well as from its β methylenes. Cyclization of 1 clearly shows the protection of the α-methylene to the ester: to a 0.01M solution of 1[7] (133mg) in 63ml of CH_2Cl_2, $Rh_2(OAc)_4$ (14mg, 5mol%) was added at room temperature. After gas evolution ceased (ca. 5min.) the solvent was removed *in vacuo*. The residue was diluted with ether and washed with water. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The ^{1}H-NMR spectrum of the crude products (106mg) showed no triplet methyl signals, but there were now two doublet signals, one at 1.09ppm (J=6.5Hz) and the other at 1.14ppm (J=6.5Hz). After purification by flash chromatography, the cyclopentanone ester 2[8] (96mg, 83% yield) was obtained as a mixture of two stereoisomers.



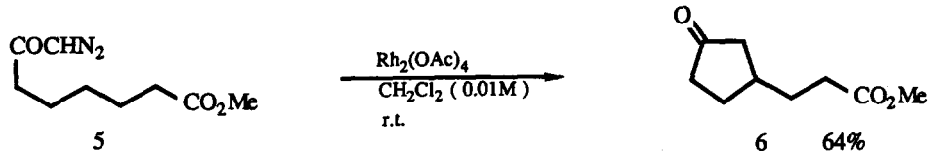
1 2 83%

Result of the competition between the two possible cyclopentanones from the cyclization of 3[9] shows that the protection by the ester function extends to the β-methylene group: The Rh(II)-catalyzed reaction of diazoketone 3 led, after flash chromatography, to an 81% yield of cyclopentanone 4, as a mixture of two stereoisomers.[8]



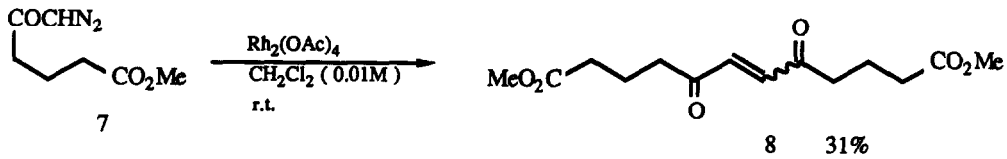
3 4 81%

As might be expected, protection against insertion is no longer effective once the γ-carbon to the ester is reached. Reaction of 5 proceeds "normally" to give cyclopentanone 6 in 64% yield by insertion into the γ-CH_2 to the ester.

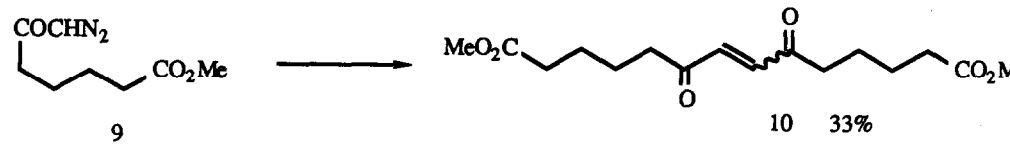


5 6 64%

Finally, one might wonder what would result if the only possible insertion were into the α or the β-methylenes to an ester function. In such situations, the reactions give rise to complex mixtures and low recovery. Cyclopentanone formation was, at best, a minor pathway and the major isolated products (~30%) were the result of "dimerization" as in 7 to 8 and 9 to 10.[10,11]



7 8 31%



9 10 33%

We believe that the ability of a carboxyl and, presumably, other strongly electron withdrawing groups to protect C-H bonds against diazoketone insertion should prove a useful feature in extending the range of these important reactions.

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References and Notes.

† Research Associate

1) For a general review of intramolecular cyclopropanation, see S.D.Burke and P.A.Grieco, *Organic Reactions*, 26, 361 (1979). For references of vinylogous Wolff rearrangement of β,γ-unsaturated diazoketones, see A.B.Smith,III, B.H.Toder and S.J.Branca, *J. Am. Chem. Soc.*, 106, 3995 (1984).

2) A.Gillon, D.Ovadia, M.Kapon and S.Bien, *Tetrahedron*, 38, 1477 (1982).

3) a) M.C.Pirrung and J.A.Werner, *J. Am. Chem. Soc.*, 108, 6060 (1986).
b) E.J.Roskamp and C.R.Johnson, *ibid.*, 108, 6062 (1986).

4) a) D.F.Taber and R.E.Ruckle,Jr., *J. Am. Chem. Soc.*, 108, 7686 (1986).
b) K.Nakatani, *Tetrahedron Lett.*, 28, 165 (1987) and references cited therein.

5) Regioselectivity may also vary depending on the specific type of diazoketone: cf relative insertion rates into aromatic vs. aliphatic C-H of α-diazo-β-keto-esters and α-diazoketones. Compare ref. 4a and ref. 4b.

6) R.A.Sheldon and J.K.Kochi, *Organic Reactions*, 19, 279 (1972).

7) Prepared from the dibenzyl ester of propylmalonic acid in 4 steps (cat. NaOMe, methyl acrylate / H_2, 5% Pd-C, EtOAc / xylene reflux / $(COCl)_2$, PhH / CH_2N_2).

8) Products were identified by ^{1}H-NMR, IR and mass spectral data.

9) Prepared form the dibenzyl ester of propylmalonic acid in 4 steps; NaH, $BrCH_2CH_2CH_2CO_2Et$ / H_2, 5% Pd-C, EtOAc / xylene reflux / $(COCl)_2$, PhH / CH_2N_2.

10) Each insertion reaction mentioned in this paper was carried out at least twice.

11) In the case of 9, a small amount (~9%) of the insertion product, the methylester of 3-oxocyclopentylacetic acid was isolated.

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