THE STUDIES OF METAL ION CATALYZED CARBON-HYDROGEN INSERTION OF α-ALKOXY-α'-DIAZOKETONES DERIVED FROM MANDELIC AND LACTIC ACIDS

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Abstract - The cupric acetylacetonate is the best catalyst to induce the carbon-hydrogen inserted reaction for the α-alkoxy-α'-diazoketones derivatives (5 and 6). The side reactions such as aromatic carbon-hydrogen insertion and rearrangement could be prevented.

Intramolecular cyclization via a carbenoid C-H insertion in geometrically rigid system is a highly favored process.[1] The reactivity of the C-H bond inserted by the carbenoid is in the order of tertiary C-H > secondary C-H > primary C-H.[2] Similarly, it was found that an ester group deactivated both α- and β-methylene groups toward C-H insertion.[3] In other words, the electronic factor is very important to the regioselectivity. In contrast to the above observation, the C-H bond adjacent to the ether oxygen was found to be the preferred site of insertion, compared to a normal aliphatic C-H bond.[4] Therefore, we wanted to take advantage of this observation to study the possibility of making the heterocyclic compounds containing oxygen via carbenoid route. During the study of this work, we found that the reactivity and selectivity of the C-H insertion reaction are dependent on the type of catalysts used. In this communication, we would like to describe our discoveries.

The α-hydroxy acids (1 and 2) were mono-O-alkylated by treatment with sodium hydride and benzyl bromide in refluxing THF solution.[5] The resulted compounds (3 and 4)[6] were treated with oxalyl chloride followed by reacting with excess diazomethane to give compound (5 and 6)[7] respectively.(Scheme 1) When compound (5) was treated with 3 weight % $Rh_2(OAc)_4$ in dichloromethane, four products (7, 8, 9 & 10) were formed.[8] (Scheme 2, Table 1) To our surprise, one of the reaction products is benzyl trans-cinnamate (7) which was not observed in the similar

Scheme 1
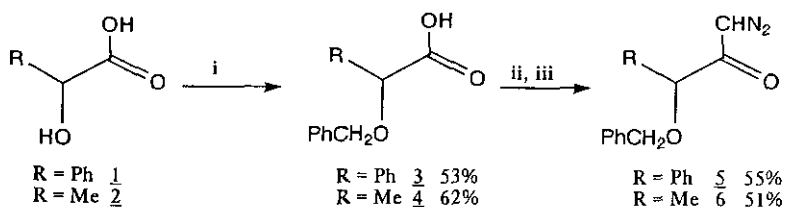
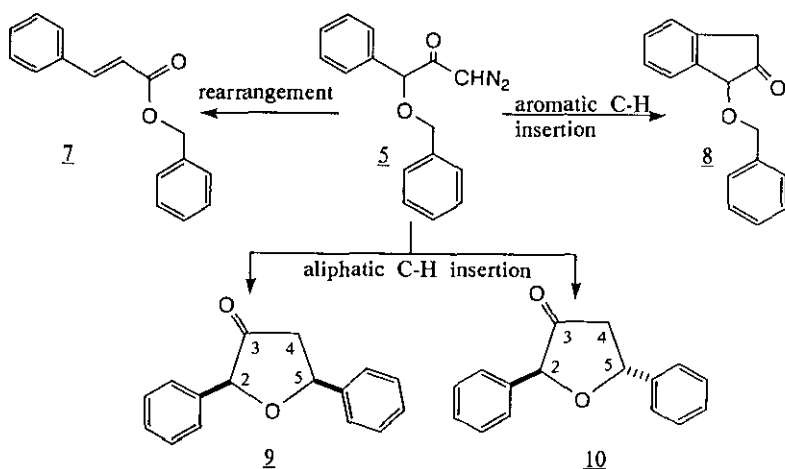Reagents (i) 3 eq. NaH, 1.5 eq. PhCH$_2$Br, THF, reflux   (ii) oxalyl chloride, PhH, reflux   (iii) excess CH$_2$N$_2$, ether

Scheme 2

Table 1 : Products distribution variated with different catalysts used for compound (5)

entry	catalyst / solvent	7	8	9	10	chemical yield (%)
1	Rh$_2$(OAc)$_4$ / CH$_2$Cl$_2$	10%	43%	20%	17%	30
2	Cu / benzene	50%	0%	40%	10%	58
3	CuSO$_4$ / benzene	13%	0%	68%	19%	37
4	CuCl / benzene	30%	0%	56%	14%	57
5	Cu(acac)$_2$ / benzene	0%	0%	83%	17%	53

studies.[9,10] The possible mechanism is described in Scheme 3. The carbenoid species underwent
Wolff rearrangement to form the ketene intermediate which subsequently migrated via {1,3}
sigmatropic shift to give benzyl trans-cinnamate (7).[11] The other possibility was the ether oxygen
added nucleophilically to the ketene intermediate to form the four-membered ring oxonium-enoate
which then underwent ring opening to give compound (7). (Scheme 3) The 2-tetrahydrofuranone
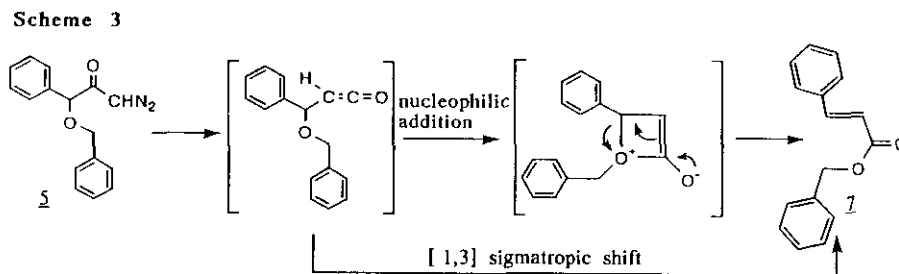
Scheme 3

derivatives (9 and 10) were formed via aliphatic C-H bond insertion and the 2-indanone derivative
(8) was formed via aromatic C-H bond insertion. (Scheme 2) The structures of the compound (9 and
10) were justified by their ^{1}H nmr spectra. The chemical shifts of the C_2-H and C_5-H of the minor
isomer are downfield ($\Delta\delta = 0.25$ ppm) compared with the corresponding proton of the major isomer.[12]
Both C_2-H and C_5-H on the trans isomer are affected by the ring current of two benzene rings and
their chemical shifts should be slightly downfield. Therefore, the cis isomer is the major product.
The poor yield and selectivity in the formation of the tetrahydrofuranone derivatives provoke us to
look for better reaction conditions to improve our results. Among the catalysts we tried, cupric
acetylacetonate $(Cu(acac)_2)$ is the best catalyst for the tetrahydrofuranone ring formation. All the
side reactions, including rearrangement and aromatic C-H insertion, were completely prevented.
(entry5, Table 1)

However, compound(12 and 13) were the products derived from compound (6) treated with 3%
weight $Rh_2(OAc)_4$ in dichloromethane.[13,14] No rearranged product was formed in any catalysts
we had tried. (Scheme 4, Table 2) The difference in compound (5) and (6) is the substituent α to
the keto group. So far it is not clear why the phenyl and methyl group make so much difference

in their reaction pathways. Fortunately, we found that the cupric acetylacetonate is the best
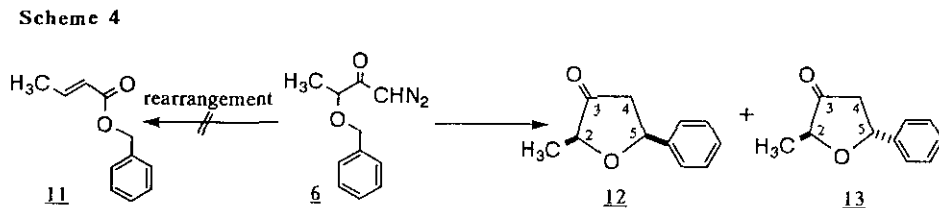
catalyst for both compound ($\underline{5}$) and ($\underline{6}$).

Scheme 4

Table 2 : Products distribution variated with different catalysts used for compound ($\underline{6}$)

entry	catalyst / solvent	$\underline{12}$	$\underline{13}$	chemical yield (%)
1	$Rh_2(OAc)_4$ / CH_2Cl_2 (0.03M)	75%	25%	36
2	$Rh_2(OAc)_4$ / CH_2Cl_2 (0.01M)	83%	17%	32
3	Cu / benzene	86%	14%	65
4	$CuSO_4$ / benzene	88%	12%	60
5	CuCl / benzene	88%	12%	56
6	$Cu(acac)_2$ / benzene	86%	14%	58

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5. The concentration of mandelic acid in the reaction mixture is crucial to the success of this reaction. Otherwise, 2-benzyl-2-benzyloxyphenylacetic acid will be formed as the side product. However, the mono-$\underline{O}$-alkylated product was formed in high yield if the concetration of the mandelic acid was kept at 0.3M in THF.

6. Compound ($\underline{3}$): ^{1}H nmr (CDCl$_3$) δ 4.62 and 4.54 (ABq, J= 11.8 Hz, 2H, O-CH$_2$-Ph), 4.94 (s, 1H, Ph-CH-O), 7.25-7.49 (m, 10H, aromatic protons), 8.96 (brs, 1H, COOH); ^{13}C nmr (CDCl$_3$) δ 70.094, 79.001, 127.331, 127.967, 128.365, 128.608, 128.837, 135.466, 136.558, 175.666.
    Compound ($\underline{4}$): ^{1}H nmr (CDCl$_3$) δ 1.50 (d, J= 6.9 Hz, 3H, CH$_3$-C-O), 4.11 (q, J= 6.9 Hz, 1H, C-CH-CO), 4.72 and 4.52 (ABq, J= 11.6 Hz, 2H, O-CH$_2$-Ph), 7.32-7.38 (m, 5H, aromatic protons); ^{13}C nmr (CDCl$_3$) δ 18.251, 71.902, 73.333, 127.837, 128.317, 137.027, 178.566.

7. Compound ($\underline{5}$): ^{1}H nmr (CDCl$_3$) δ 4.62 and 4.53 (ABq, J= 11.7 Hz, 2H, O-CH$_2$-Ph), 4.59 (s, 1H, Ph-CH-O), 5.83 (s, 1H, CHN$_2$), 7.33-7.43 (m, 10H, aromatic protons); ^{13}C nmr (CDCl$_3$) δ 52.602, 71.249, 84.819, 126.652, 127.657, 127.903, 128.416, 128.562, 136.642, 136.983, 193.814.
    Compound ($\underline{6}$): ^{1}H nmr (CDCl$_3$) δ 1.38 (d, J= 6.8 Hz, 3H, CH$_3$-C-O), 3.97 (q, J=6.8 Hz, 1H, C-CH-O), 4.15 and 4.60 (ABq, J= 11.7 Hz, 2H, O-CH$_2$-Ph), 5.79 (s, 1H, CHN$_2$), 7.30-7.37 (m, 5H, aromatic protons); ^{13}C nmr (CDCl$_3$) δ 18.360, 52.015, 71.940, 127.647, 127.994, 128.551, 137.335, 197.463.

8. Compound ($\underline{7}$): ^{1}H nmr (CDCl$_3$) δ 5.25 (s, 2H, O-CH$_2$-Ph), 6.44 (d, J= 16 Hz, 1H, Ph-C=CH-), 7.30-7.53 (m,10H, aromatic protons), 7.69 (d, J= 16 Hz, 1H, Ph-CH=C-); ^{13}C nmr (CDCl$_3$) δ 66.304, 117.85, 128.053, 128.209, 128.540, 128.834, 130.289, 134.327, 145.137, 166.721.
    Compound ($\underline{8}$): ^{1}H nmr (CDCl$_3$) δ 3.51 (s, 2H, O-CH$_2$-Ph), 4.98 and 4.80 (ABq, J=11.7 Hz, 2H Ph-CH$_2$-C-O), 4.91 (s, 1H, Ph-CH-CO), 7.29-7.46 (m, 9H, aromatic protons); ^{13}C nmr (CDCl$_3$) δ 41.350, 71.683, 79.396, 124.994, 125.667, 127.828, 128.087, 128.344, 129.158, 136.652, 139.002, 213.855.

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11. H. Meier and K.-P. Zeller, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32. In this review article, the authors mentioned that rhodium and palladium catalysts usually stabilized the carbenoid and the Wolff rearrangement no longer occurred or became very difficult. In our reaction system, however, the rhodium catalyst did not inhibit the Wolff rearrangement to occur.

12. Compound (9) : ^{1}H nmr (CDCl$_3$) δ 2.63 (dd, J=17.8 and 11.0 Hz, 1H, C$_4$-H), 2.95 (dd, J= 17.8 and 5.7 Hz, 1H, C$_4$-H), 4.91 (s, 1H, C$_2$-H), 5.31 (dd, J= 11.0 and 5.7 Hz, 1H, C$_5$-H), 7.33-7.55 (m, 10 H, aromatic protons). Compound (10) : ^{1}H nmr (CDCl$_3$) δ 2.73 (dd, J= 18.1 and 7.4 Hz, 1H, C$_4$-H), 2.98 (dd, J= 18.1 and 7.4 Hz, 1H, C$_4$-H), 5.15 (s, 1H, C$_2$-H), 5.58 (t, J= 7.4 Hz, 1H, C$_5$-H), 7.31-7.53 (m, 10H, aromatic protons).

13. Compound (12) : ^{1}H nmr (CDCl$_3$) δ 1.34(d, J= 6.7Hz, 3H, C$_2$-Me), 2.45(dd, J= 18.1 and 10.7 Hz, 1H C$_4$-H), 2.77(dd, J= 18.1 and 5.8 Hz, 1H, C$_4$-H), 3.93 (q, J=6.7 Hz, 1H, C$_2$-H), 5.06 (dd, J=10.7 and 5.8 Hz, 1H, C$_5$-H), 7.20-7.55 (m, 5H, aromatic protons). Compound (13) : ^{1}H nmr (CDCl$_3$) δ 1.58(d, J=7.0 Hz, 3H, C$_2$-Me), 2.53(dd, J = 18.1 and 7.3 Hz, 1H, C$_4$-H), 2.87 (dd, J= 18.1 and 7.3 Hz, 1H, C$_4$-H), 4.12 (q, J= 7.0 Hz, 1H, C$_2$-H), 5.32 (t, J= 7.3 Hz, 1H, C$_5$-H), 7.21-7.55 (m, 5H, aromatic protons).

14. Compounds (3-13) are in the oil form. They are all colorless oil except compounds (5 and 6) are yellow.