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Regioselective Intramolecular Carbon-Hydrogen Insertion in Copper-Catalyzed Carbenoid Decompositions of cis-1-Methyl-3-Arylcyclohexane-1-Diazomethyl Ketones : Some Synthetic Applications

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REGIOSELECTIVE INTRAMOLECULAR CARBON-HYDROGEN INSERTION IN
COPPER-CATALYZED CARBENOID DECOMPOSITIONS OF CIS-1-METHYL-3-
ARYLCYCLOHEXANE-1-DIAZOMETHYL KETONES : SOME SYNTHETIC
APPLICATIONS.

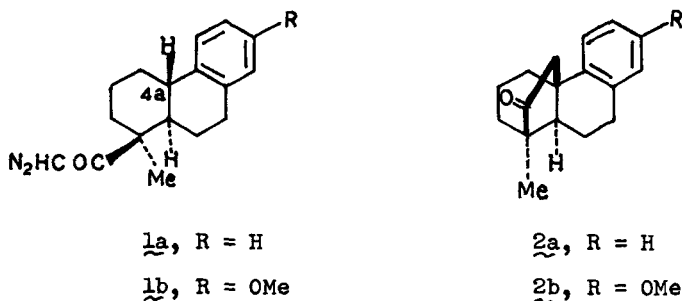
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Recently, we have developed¹ a new route for the stereo-
specific introduction of an angular carboxyl or functionalized
methyl groups² in a rigid hydrophenanthrene moiety. The key step
in this approach is a regioselective intramolecular α -keto
carbenoid insertion across the benzylic C-H bond (at C-4a) in
CuSO₄-catalyzed thermal decomposition of the diazoketones 1a
and 1b to the corresponding tetracyclic ketones 2a and 2b in
moderate to good yields. A modified procedure³ of carbenoid decom-
position of these diazoketones, in the presence of Cu₂O under
irradiation with tungsten filament lamp, improves the yields of
the desired C-H insertion products. Thus, the ketones 2a and 2b
have been prepared now in consistently higher yields (53-55%)
from the pure diazoketones 1a, m.p. 125-127^o, and 1b, m.p.

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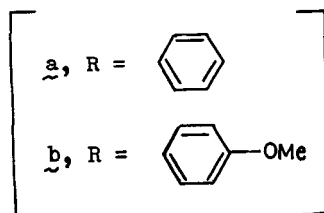
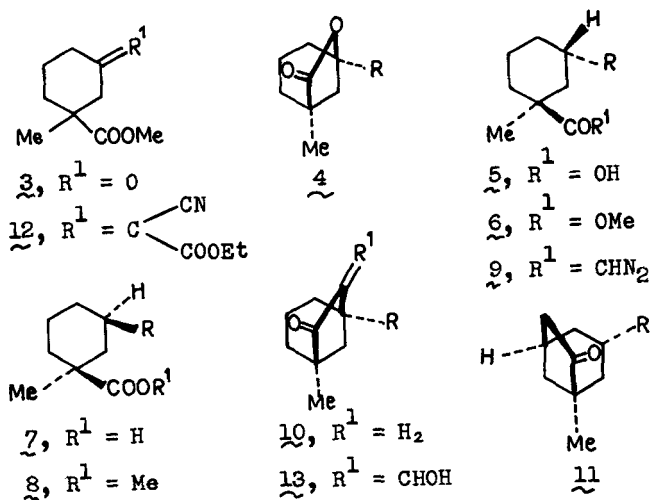
108-110^o, by slow additions (ca.3-4h) of the dilute solutions (ca. 0.02M) in anhyd cyclohexane - THF (1:1) to well-stirred refluxing suspensions of freshly prepared dry Cu₂O in cyclohexane under irradiation with tungsten lamps and continuing the reaction until the disappearance of the diazoketone band at ca 2110 cm⁻¹. We report herein a detailed investigation on the regioselectivity in the intramolecular C-H insertions in the copper-catalyzed carbenoid decompositions of two relatively flexible⁴ cyclohexane substrates, cis-1-methyl-3-phenylcyclohexane-1-diazomethyl ketone (9a)*, and the related p-methoxyphenyl derivative (9b).



Our studies demonstrate that in addition to the steric circumstances in the reacting molecules^{1,3-5} which play a dominant role on the regioselectivity in the C-H insertions, other factors such as the mode of the copper-catalyzed decomposition⁶ and electronic environment⁷ of the reaction sites also have important directive influences in this reaction.

* Compounds described here are all racemates. New compounds gave satisfactory analytical and spectral data. Unless otherwise stated nmr (δ , 60 MHz) and ir (ν , cm⁻¹) spectra were measured in CCl₄ and CHCl₃ respectively.

The precursors 5a and 5b for the diazoketone substrates have been synthesized by a stereocontrolled route⁸ through the respective γ -lactones 4a and 4b. Condensation of the known keto-ester 3^{9,10} with C_6H_5MgBr in ether, followed by treatment of the crude product with *p*-TsOH in refluxing C_6H_6 and saponification (5% aq-EtOH-KOH, reflux 2h) afforded after acidification (hot, 6N HCl) the lactone 4a, m.p. 92-93^o, ν : 1775. Acidic products on lactonization (conc. H_2SO_4 -



$C_6H_6, \sim -10^\circ$) afforded more 4a (total yield 50%). Following a similar sequence, 3 was reacted with $p\text{-MeOC}_6\text{H}_4\text{MgBr}$ to produce lactone 4b, m.p. 89° (84% yield). In parallel to our previous observations⁸, $\text{Li-NH}_3(1)\text{-NH}_4\text{Cl}$ induced reductive cleavage of the benzylic bond in 4a produced a mixture (ca. 100%) of the diastereomeric acids 5a and 7a in a ratio of 77:23 (100 MHz nmr of Me-esters); 5a, m.p. $125\text{-}126^\circ$; 6a (CH_2N_2), nmr : 1.17 (s, 3H), 2.50 (m, 1H), 3.70 (s, 3H). Hydrogenolysis⁸ (Pd-C , EtOH) of 4a produced only the epimer 7a, m.p. $109\text{-}110^\circ$; 8a (CH_2N_2), nmr (CDCl_3), 1.30 (s, 3H), 2.70 (m, 1H), 3.63 (s, 3H). Similarly, $\text{Li-NH}_3(1)\text{-NH}_4\text{Cl}$ cleavage of 4b gave diastereomers 5b and 7b in a ratio of ca. 85 : 15 (nmr). Acid 5b, m.p. 138° ; 6b, nmr : 1.16 (s, 3H), 2.43 (m, 1H), 3.66 (s, 3H), 3.70 (s, 3H); $\text{H}_2\text{-Pd-C}$, EtOH produced pure 7b, m.p. 118° ; 8b, nmr : 1.28 (s, 3H), 2.60 (m, 1H), 3.60 (s, 3H), 3.70 (s, 3H).

The acids 5a and 5b were converted into the semisolid diazoketones 9a and 9b, in the usual manner¹¹ in excellent yields and purified by column chromatography on neutral alumina using ether-light petroleum as eluents. Although a variety of copper catalysts and conditions were investigated for the decompositions, best results were obtained by slow addition (3-4 h) of dilute solution (0.01-0.02 M) of the diazoketones to refluxing suspensions of freshly prepared anhydrous Cu_2O (4-5 molar equivalent) in boiling cyclohexane under irradiation with two 250 W tungsten lamps and continuing the reaction until the disappearance of the diazoketone band in ir (3-4 h). Thus diazoketone 9a on decomposition under this condition and distillation of the volatile products afforded a colourless liquid (55-60%), which solidified

on keeping, was recrystallized to give the pure ketone 10a¹², m.p. 80°, ir : 1735; nmr : 1.05 (s, 3H), 1.68 (m, 6H), 2.01 (br s, 2H), 2.38 (br dd, 2H), 7.26 (m, 5H). Comparison of the nmr spectrum and glc of the crude product with that of 10a indicated the presence of only ca. 10-15% of the regioisomer 11a along with a small amount of possibly the solvent insertion product^{4a}. The crude volatile product (58-60%) from 9b also showed similar distribution of the corresponding insertion products and from which was crystallized out the pure regioisomer 10b, m.p. 70°, ir : 1730; nmr : 1.05 (s, 3H), 1.63 (m, 6H), 1.93 (br s, 2H), 2.37 (m, 2H), 3.70 (s, 3H), 6.90 (ABq, 4H, J_{AB} 8Hz). The similarity of the nmr spectral data of 10b with the desmethoxy analogue 10a confirms its assigned structure.

In contrast, the thermal decomposition of the diazoketones in presence of CuSO₄ under usual conditions^{4a} (without irradiation) afforded monomeric C-H insertion products with much decreased regioselectivity : 9a produced the volatile products (65-70%) consisting the regioisomers 10a and 11a in ratio of ca. 70 : 30 (nmr) along with some solvent insertion product^{4a}, from which the major isomer 10a was partially separated by careful chromatography followed by crystallization. The liquid isomer 11a, ir : 1735 : nmr : 1.00 (s, Me), 2.70 (m, benzylic H), so far could not be isolated in pure condition (80% purity from nmr), and the structure assignment is based upon the spectral and analytical data. The methoxy analogue 9b gave a mixture (75% yield) consisting 10b and 11b in a ratio of ca. 60 : 40 (nmr); the partly purified minor isomer gave spectral data,

ir : 1730; nmr : 1.00 (s, Me) 2.66 (m, benzylic H), 3.73 (s, OMe), 6.83 (ABq, J_{AB} 8Hz).

To exemplify the synthetic usefulness, we briefly record here a high yield (90-95%) transformation¹ of 10a and 10b to 14a, m.p. 209-210° [dimethyl ester 15a (CH_2N_2), m.p. 74°, nmr : 1.16 (s, 3H) 3.50 (s, 3H) and 3.63 (s, 3H)] and 14b, m.p. 196-197° [dimethyl ester 15b, m.p. 103-104° ir : 1730; nmr 1.16 (s, 3 H), 3.50 (s, 3H), 3.60 (s, 3H), 3.73 (s, 3H)] through the hydroxymethylene (NaH, HCOOEt) derivatives 13a and 13b, followed by oxidation with alkaline hydrogen peroxide.

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10. This compound was prepared in an overall yield of 46-50% from 3-methylcyclohex-2-enone by a modified sequence of conjugate HCN addition (aq-KCN-EtOH, reflux), alkaline hydrolysis in situ (aq KOH, reflux) and esterification (MeOH-H₂SO₄-cat.H₃BO₃, reflux) of the crude acid.
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12. The ketone 10a has been synthesized in an unambiguous route from 3 in an overall yield of ca. 10% through the following sequence. Conversion^{4b} of 3 to 12 (bp 135-137°/0.6 mm) followed by conjugate addition of C₆H₅MgBr in presence of CuI, saponification (aq-ethylene glycol-KOH, reflux), decarboxylation (180-200°), esterification with ethereal soln. of CH₂N₂, Dieckmann cyclisation of the resulting diester (t-BuOK-C₆H₆, reflux), and finally decarboxylation (5% aq. EtOH-KOH, reflux) of the crude β-ketoester to 10a.

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