Unusual Symmetric Compounds from Preparation of the Unsymmetric Dihydropyridine Derivatives
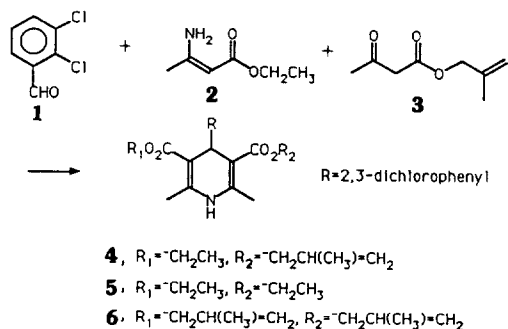
Young Key Shim*, Young Soon Cho, Wan Joo Kim

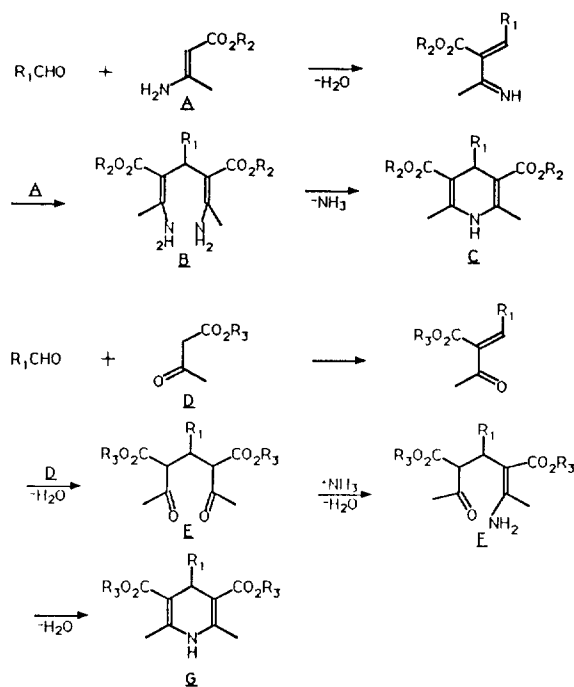*Korea Research Institute of Chemical Technology, Dae-Jeon 302-343. Received July 23, 1988*

The well known Hantsch reaction[1] has been applied widely for the preparation of dihydropyridine (DHP) derivatives which are used as cardiovascular drugs.[2] For the symmetric compounds aromatic aldehyde, two moles of acetoacetates, and ammonia water were refluxed altogether in lower alcohol for several hours (Scheme 1). The reaction of aromatic aldehyde with two moles of aminocrotonates to give symmetric compouns was also reported[3] (Scheme 2). By the way the unsymmetric compounds were obtained from the aromatic aldehyde, acetoacetate, and aminocrotonate (Scheme 3).

Generally the unsymmetric compounds were not found in the classical Hantsch reaction using aromatic aldehyde, acetoacetate, and aminocrotonate and most of the unsymmetric DHP derivatives have been synthesized by this system.[4] Recently the unusual formation of symmetric diallyl ester derivatives along with unsymmetric one from the reaction mixture of the 3-nitrobenzaldehyde, allyl 3-aminocrotonate, and *t*-butylacetoacetate was reported[5]. Now we report the results that gave the formation of symmetric DHP derivatives along with the unsymmetric one in Hantsch reaction.
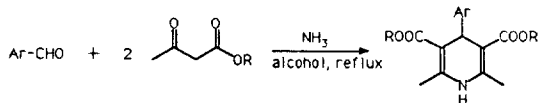
When we tried to prepare the various unsymmetric DHP derivatives which containing 2,3-dichlorophenyl and substituted or non-substituted ally esters we found two other spots on the TLC which were characterized as two different symmetric compounds (Scheme 4). Reactions with allyl 3-aminocrotonate as the amine source and methyl acetoacetate instead of methyl 3-aminocrotonate and allyl acetoacetate gave the same composition of the products. We tried various acetoacetates and aminocrotonates with 2,3-dichlorobenzaldehyde to obtain the pure unsymmetric compound, but the mixture of 3 compounds were always obtained. The formation of the unsymmetric product **4** and the symmetric product **5** which were derived from aminocrotonate can be explained reasonably from the classical Hantsch reaction. The formation of the other symmetric compound **6** which
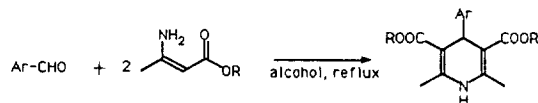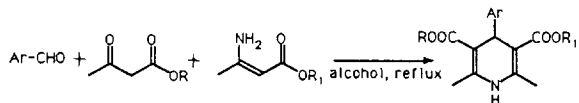
4, $R_1 = {}^-CH_2CH_3$, $R_2 = {}^-CH_2CH(CH_3) = CH_2$
5, $R_1 = {}^-CH_2CH_3$, $R_2 = {}^-CH_2CH_3$
6, $R_1 = {}^-CH_2CH(CH_3) = CH_2$, $R_2 = {}^-CH_2CH(CH_3) = CH_2$

Scheme 4

Scheme 5

was derived from two acetoacetates, however cannot be rationalized by the classical way. Now we postulate the possible mechanism of intermolecular amination of the diketo intermediate **E**. The two moles of the aminocrotonates and the aldehyde gave the acyclic dienamine intermediate **B**, the other-hand two moles of the acetoacetates and the aldehyde gave the diketo intermediate **E**. During the cyclization of the dienamine intermediate **B** the expelled ammonia did intermolecular attack to the one carbonyl of the diketo intermediate **E** to give the enamine **F** which underwent cyclization by the known Hantsch reaction to give another symmetric DHP derivatives **G** (Scheme 2). The same results from the switch of the ester function of the aminocrotonate

Scheme 1

Scheme 2

Scheme 3

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and the acetoacetate support the above postulation.

The role of the aromatic aldehyde and the alkenyl ester function seemed to be crucial because no byproducts were obtained from the reactions with electron defficient aldehyde, for example 3-nitrobenzaldehyde, alkyl acetoacetates and alkyl aminocrotonates but 3-nitrobenzaldehyde with allyl acetoacetate gave the symmetric one[5]. 2,3-Dichlorobenzaldehyde with simply alkyl acetoacetates and alkyl 3-aminocrotonates also gave the byproducts. The extend researches are being undergone with various substituted aromatic aldehydes, alkyl or alkenyl aminocrotonates and acetoacetates. To avoid the formation of the minor side products the benzylidene intermediate should be applied[6].

Representative Procedure

The same molar amount (4.4 mmol) of 2,3-dichlorobenzaldehyde **1**, ethyl 3-aminocrotonate **2**, and 2-methyl-2-propenyl acetoacetate **3** was heated up to reflux in isopropyl alcohol with stirring for 6 hours. After cooling the solvent was removed in vacuo to give the oily product which was chromatographed on the silica gel with 30% ethyl acetoacetate in toluene.

The first running eluent (rf = 0.52) was collected and the solvent evaporated to give an oily product which was identified as di-2-methyl-2-propenyl 2,6-dimethyl-4 (2′,3′-dichlorophenyl)-3,5-dicarboxylate **6** in 13.3% yield (by HPLC) [NMR(CDCl$_3$) δ =1.58, 1.70(each s, 3H,-CH$_3$), 2.80(s, 6H,

-CH$_3$), 4.45(s, 4H, -OCH$_2$-), 4.65~4.90(m, 4H, =CH$_2$), 5.50(s, 1H, C$_4$-H), 5.66(b, 1H, = NH), 6.85~7.40(m, 3H, -Ph)]. The second eluent(rf = 0.49) was the major product which was turned out in NMR spectroscopy as ethyl 2-methyl-2-propenyl 2,6-dimthyl-4-(2′,3′-dichlorophenyl)-3,5-dicarboxylate **4** in 72.6% yield (by HPLC) [NMR(CDCl$_3$) δ = 1.20(t, 3H, -CH$_3$), 1.60 (s, 3H, -CH$_3$), 2.30(s, 6H, -CH$_3$), 4.07(q, 2H, -CH$_2$-), 4.45(s, 2H, -OCH$_2$-), 4.65~4.85 (m, 2H, =CH$_2$), 5.46(s, 1H, C$_4$-H), 5.80(b, 1H, = NH), 6.85~7.35(m, 3H, -Ph)], The third eluent(rf = 0.45) was turned out as diethyl 2,6-dimethyl-4-(2′, 3′-dichlorophenyl)-3,5-dicarboxylate **5** in 12.5% yield (by HPLC) [NMR(COCl$_3$) δ = 1.18(t, 6H, -CH$_3$) 2.31(s, 6H, -CH$_3$), 4.07(q, 4H, -CH$_2$-), 5.46(s, 1H, C$_4$-H), 5.70(b, 1H, = NH), 7.06~7.32 (m, 3H, -Ph)].

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C-H Bond Activation and C-C Bond Activation: A New Synthesis of β,γ-Unsaturated Ketones *via* Acylrhodium(III) 1-Methylallyl Complexes Through a Hydride Insertion into Coordinated-Butadiene

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The activation of carbon-hydrogen bond[1] and carbon-carbon bond[2] by transition metal complexes has been one of the recent interests in organometallic chemistry. Especially a carbon-hydrogen bond of aldehyde can be easily broken by transition metals such as Wilkinson's catalyst, and subsequent decarbonylation gives alkanes[3]. This decarbonylation problem may be overcome through a cyclometallation to produce cyclopentanones since a five-membered ring is supposed to be a right size of a stable metallacycle complex[4]. The carbon-hydrogen bond of aromatic aldehydes can be activated by transition metals to give cyclometallated complexes without showing any decarbonylated products[5]. Also carbon-carbon bond activation in unstrained molecules having quinoline moieties has been reported[6]. Among them α,β-unsaturated ketones were not cleaved by rhodium(I) complexes even under vigorous conditions[7]. One of the target molecules to study is β,γ-unsaturated ketone since it was reported that the C-C bond of β,γ-unsaturated ketone is cleaved in a process of sigmatropic rearrangements in photo-

chemical reactions via stable allyl radical species[8]. The synthesis of β,γ-unsaturated ketone is not facile[9]. This paper describes new synthesis of β,γ-unsaturated ketone through a C-H bond activation and a hydride insertion into butadiene coordinated to Rh(I) complex prepared by olefin exchange with bis-cyclooctene rhodium(I) chloride dimer[10].

8-quinolinecarboxaldehyde **1** reacted with a solution of (C$_4$H$_6$)$_2$RhCl in benzene within 10 min to give an insoluble chlorine-bridged dimer **4**, which was isolated with pentane in 87% yield (scheme 1): decomp.>300 °C; Anal. Calcd for C$_{28}$H$_{26}$Cl$_2$N$_2$O$_2$Rh$_2$: C, 48.07; H, 3.72; N, 4.01. Found: C, 48.00; H, 4.08; N, 4.00. **4** can be solubilized by one equivalent of pyridine-d$_5$ to give the acylrhodium(III) 1-methylallyl complex **5**, five-coordinate species. η^3-1-methylallyl rhodium(III) complex **5** consists of two isomers, *anti*-η^3-1-methylallyl rhodium complex **5a** and *syn*-η^3-1-methylallyl rhodium complex **5b** in 62:38 ratio determined by ^{1}H NMR spectra: the methyl peaks of η^3-1-methylallyl group in **5a**; ^{1}H NMR(CDCl$_3$) δ(ppm) 0.5(d, 3H J = 6.0Hz, CH$_3$), those of η^3-