AN IMPROVED SYNTHESIS OF 3-CARBOMETHOXY-4*H*-QUINOLIZONE VIA PALLADIUM(II) ASSISTANCE[1a]

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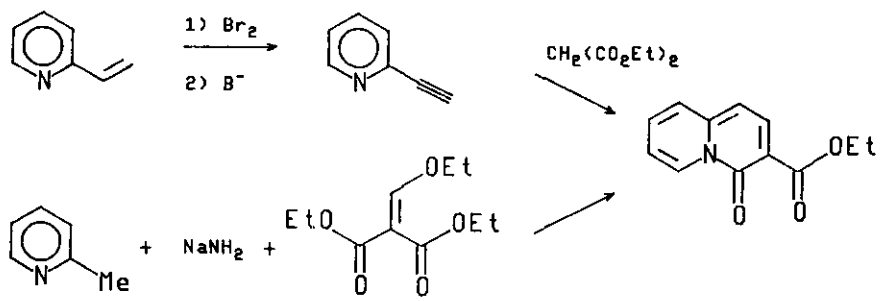
Abstract - The synthesis of 3-carbomethoxy-4-quinolizone from 2-vinylpyridine, dimethylmalonate and $PdCl_2$ under mild conditions is described. A mechanism is discussed in which Pd(II) facilitates initial attack by malonate anion on 2-vinylpyridine and then acts as an oxidant to give the final product. When the reaction is conducted in MeCN, a condensation of malonate with MeCN occurs as a competing reaction. X-ray crystal structures of this side product as well as 3-carbomethoxy-4-quinolizone are presented.

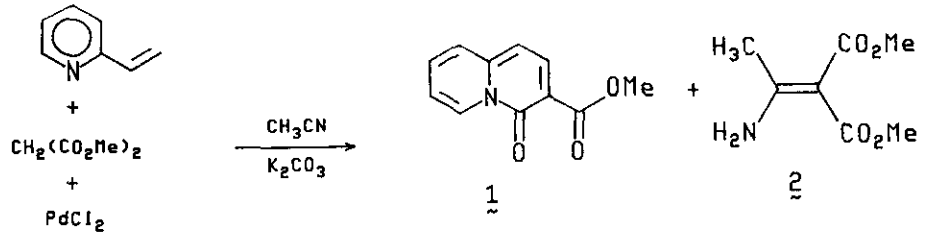
Since the parent and reduced quinolizine ring structures are found not only in the free state in nature but also as part of numerous alkaloids,[2,3] the herein facile synthesis of substituted 4*H*-quinolizones was pursued. Substituted carbalkoxy-4-quinolizones have generally been prepared by the condensation of the α-anion of an activated picoline with ethoxymethylene derivatives of active methylene compounds.[3b-d] Thus, 1-carbomethoxy-3-carbethoxy-4-quinolizone was prepared from methyl 2-pyridylacetate and diethyl ethoxymethylidenemalonate in 73% yield.[4] Unfortunately attempted monodecarbalkoxylation of 1,3-disubstituted 4-quinolizones gave exclusively the more stable 1-substituted product. Bohlmann reported the synthesis of 3-carbethoxy-4-quinolizone by reaction of the α-anion of 2-picoline, generated in situ from



Scheme 1.

picoline with $NaNH_2$, with the same above electrophile; the yield was unreported.[5] Another synthesis involved initial generation of 2-ethynylpyridine, prepared in two steps from 2-vinylpyridine, which was then condensed with diethyl malonate to give the desired quinolizone in a meager 8% overall yield from the olefin[6] (Scheme 1).

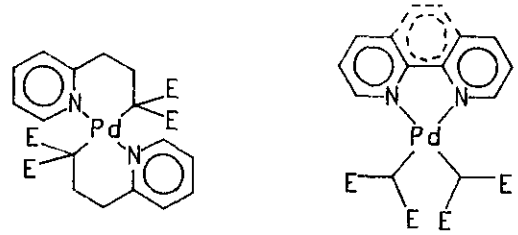
When the reaction depicted in Scheme 2 was conducted, the only isolable products were quinolizone 1 and enamine 2; no complexes were isolated. The addition of malonate to nitriles has generally been limited to activated nitriles (i.e. α-di- and tri-halo,[7,8] cyanogen,[9] benzoyl,[10] ethyl cyanoformate[11] and imidates[12]), thus the condensation of malonate and acetonitrile to give enamine 2 was unexpected. Recently however $SnCl_4$ in refluxing 1,2-dichloroethane was reported to promote the addition of malonates to simple alkyl nitriles in fair yields.[13] The new synthesis herein reported offers at least two distinct advantages over current procedures in that the Pd(II)-promoted addition is not moisture sensitive and gives comparable or improved yields.



1 2

Scheme 2.

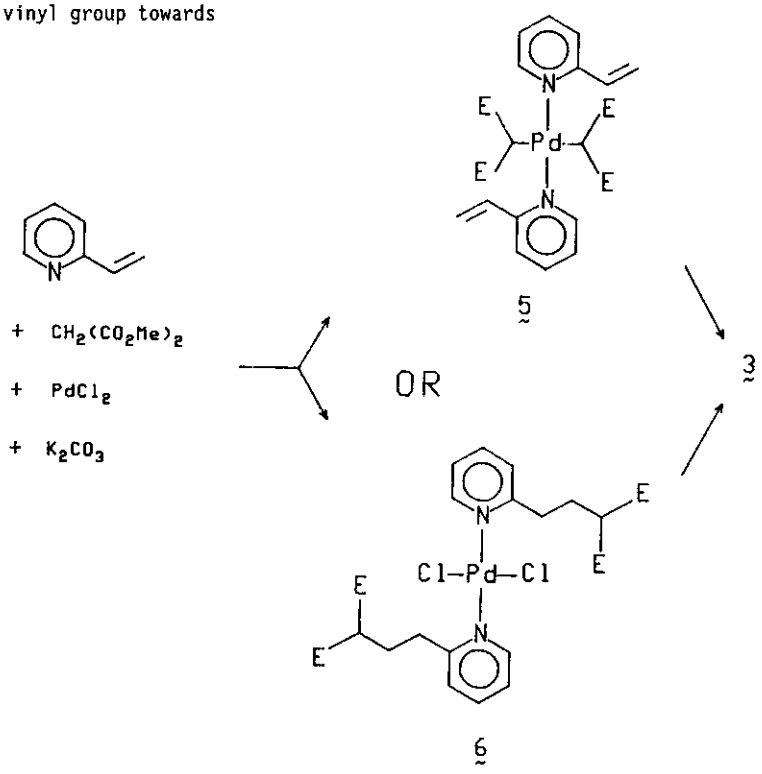
During the spontaneous synthesis of the cyclometalated Pd(II) complex 3 from its individual components (i.e. 2-vinylpyridine, dialkyl malonate and $PdCl_2$) in a one-pot synthesis, the unanticipated 1 and 2 were isolated. To be noted the synthesis of 3 was accomplished by Michael addition of 2-vinylpyridine with sodiomalonate, without transition



3 E=CO_2R 4 E=CO_2R

metal catalysis, followed by Pd(II)-*N* complexation and subsequent cyclometalation.[14] In addition *C*-malonato Pd(II) complexes 4 were also prepared,[15] thus it was of interest to determine if the attempted one-pot synthesis of 3 would proceed through the bis(malonato) complex 5 (analogous to 4) or if Michael addition would occur first to give 6 (the previously reported precursor to 3), followed then by cyclization.

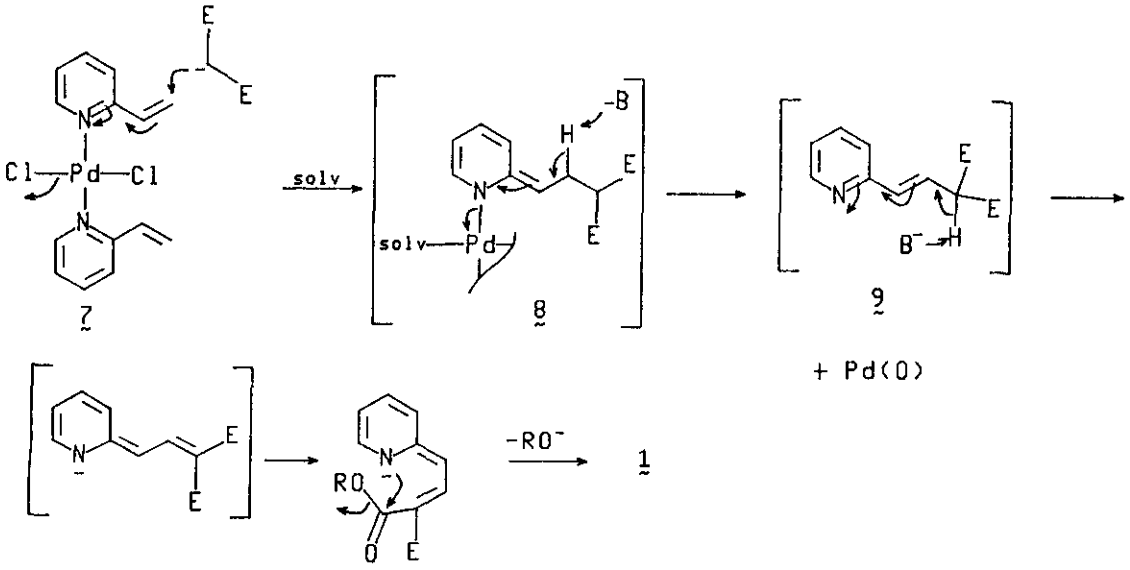
However when the one-pot reaction was carried out, no Pd complex was obtained and only 1 and 2 were isolated. Due to the very mild reaction conditions, it became apparent that Pd(II) was activating the vinyl group towards



Michael addition. [In the absence of Pd(II), addition of malonate to 2-vinylpyridine requires alkoxide, as base, under *refluxing* alcohol temperatures (ca. 80°C).] To determine if the effect was an inductive one or if a Pd π-bond was present, the bis(2-vinylpyridine)$PdCl_2$ complex **7** was isolated by mixing 2-vinylpyridine and $PdCl_2$ in a 2:1 ratio (to avoid Cl-bridged dimer formation) in MeCN; the desired complex **7** precipitated. An X-ray crystal structure determination of **7** clearly showed exclusive *N*-coordination and that *no Pd-vinyl interactions exist*. Thus the Pd(II) activation of the olefin to nucleophilic addition must be an inductive electron withdrawing effect.

A mechanism which invokes palladium assistance is given in Scheme 3. In the reaction of **7** with methyl sodiomalonate, the electron withdrawing effect of Pd(II) on the pyridine ring caused an S_N2' reaction to proceed [rather than exclusive 1,2-addition as in the absence of Pd(II)] with sequential elimination of chloride ion from Pd(II) to give **8**. Abstraction of the acidic β-hydrogen of **8** afforded pyridine **9** with concomitant reduction of Pd(II) to Pd(0). Based on the fact that no Pd(0) was isolated from, or observed in, the reaction mixture, the Pd(0) may then form a π-complex with unreacted 2-vinylpyridine, which can decompose on work-up. Loss of the labile allylic proton under the basic conditions and cyclization gave **1**. Although

quinolizone 1 was obtained when other solvents were used (e.g. MeOH, EtOH, acetone, DMF and DMSO). DMF was the best solvent medium in that the highest yields (ca. 39%) were realized, although the reaction conditions were not optimized.



Scheme 3.

Although disorder in the crystal of 7 (Figure 1) prevented an accurate structure determination, several salient features were evident. There are no inter- or intra-molecular Pd-vinyl interactions. The geometry around Pd is square planar with the two trans pyridine rings being nearly coplanar and both orthogonal to the line defined by Cl-Pd-Cl. The Pd-Cl bonds are 2.287(2) Å and Pd-N average 2.02(3) Å.

Because of the lack of precedence for the formation of 2 under such conditions an X-ray crystal structure determination of 2 was undertaken to prove its solid state structure (Figure 2). It exists in the enamine form rather than the imine form as seen by the shortened C(2)-C(3) bond [1.394(2) Å]. The carboxylate trans to the amino group is not coplanar with the rest of the molecule and is oriented such that the torsion angle O(2)-C(4)-C(3)-C(2) is 135.6°; the rest of the molecule is essentially planar. The second *H*-atom on *N* could not be located although all other *H* positions are evident in difference maps. This *H*-atom is thought to be disordered in spite of the potential N-O(3) intramolecular contact of 2.613(2) Å. This structure determination supports the conformation predicted from vibrational spectroscopy.[13,16]

Quinolizone 1 is planar (Figure 3) and exists as the monohydrate with water forming a nearly symmetric bridge between O(1) and O(2). In the pyridine moiety, the C(1)-C(2) and C(3)-C(4) bonds are shortened [1.341(2) and 1.343(2) Å, respectively]. In the other ring the C(8)-C(9) distance is short [1.358(2) Å] and the C(9)-N bond long [1.468(2) Å]. The external angles about the ring carbonyl carbon (C(8)-C(9)-O(1) [129.18(14)°] and N-C(9)-O(1)

[116.49(13)°]) indicate that the oxygen is tilted slightly toward the ring nitrogen perhaps because of *N*-electron delocalization into the ring and onto the oxygen although not directly between C(9)-N [1.468(2) Å].

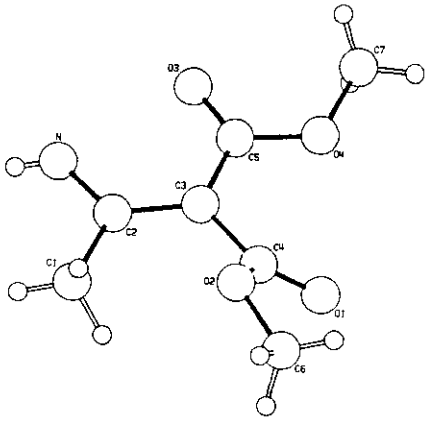


Figure 2. ORTEP drawing of **2**

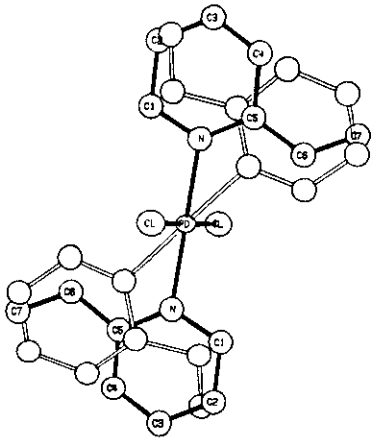


Figure 1. ORTEP drawing of **7**

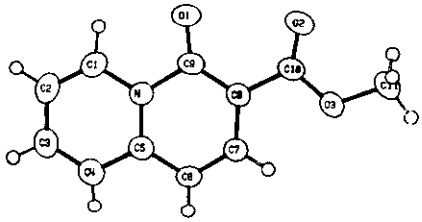


Figure 3. ORTEP drawing of **1**

EXPERIMENTAL

All melting points were taken in capillary tubes with a Thomas-Hoover Uni-melt apparatus and are uncorrected. ^{1}H and ^{13}C nmr were recorded on either an IBM NR/80 or IBM AF/100 spectrometer using $CDCl_3$ as solvent (unless otherwise specified) with Me_4Si and $CDCl_3$ as respective internal standards. ^{13}C nmr data were assigned using selective ^{1}H decoupled experiments. Mass spectral (ms) data (70eV) were determined by Mr. D. A. Patterson on a Hewlett-Packard HP 5985 GC/mass spectrometer and reported as (assignment, relative intensity). Preparative thick-layer chromatography (ThLC) was performed on 20 x 40 cm glass plates coated with a 2-mm layer of Brinkman silica gel PF-254-366.

Intensity data for 1, 2 and 7 were collected on an Enraf-Nonius CAD4 diffractometer equipped with Mo Kα radiation (λ=0.71073 Å) and a graphite monochromator. The crystal of 2 was sealed in a capillary to prevent sublimation. Variable scan rates were employed in the ω-2θ scans in order to achieve approximately equal relative precision for all observable data. One quadrant of data was collected for the monoclinic crystal, one hemisphere for the triclinic crystals. Crystal data and angular limits for each compound are given in Table 1. Data reduction included corrections for background, Lorentz, and polarization effects. Absorption corrections for 7 were based on ψ scans of reflections near χ=90°; the minimum relative transmission coefficient was 61.24%. Equivalent data were averaged; data having $I>3\sigma(I)$ were used in the refinement for 2, those having I>0 for 1 and 7.

The structures of 1 and 2 were solved using MULTAN, that of 7 by heavy-atom methods. Refinements of 1 and 2 were full-matrix least squares based on F with weights $w=\sigma^{-2}(F_o)$, treating nonhydrogen atoms anisotropically, with H atoms located by ΔF and refined isotropically. Disorder in 7 prevented routine refinement. Only Pd and Cl atoms were treated anisotropically, while half-populated vinylpyridine ligand atoms were treated isotropically. Well resolved half-atoms in the disordered region were refined by full-matrix least squares, while positions of C2, C5, C7 and their equivalents in the alternate orientation were adjusted with the aid of difference maps. Ordered models in possible alternate space groups *C2* and C_c led to high correlations and did not lead to improved agreement with the data, and thus were abandoned. Final R factors and residual electron densities are given in Table 1.

Dichlorobis(2-vinylpyridine)palladium(II) 7. Freshly distilled 2-vinypyridine (181mg, 1.72mmol) was added to $PdCl_2$ (132mg, 0.74mmol) in dry MeCN (30ml) and stirred for 12h at 25°C. The precipitated complex was filtered and washed with a small amount of MeCN to give (74%) 7, as a bright yellow solid: 214mg; mp 178-180°C(decomp.); ^{1}H nmr δ 5.94 (d, β-CH$_{(trans)}$, $J_{\alpha,\beta(trans)}$=11.2Hz, 1H), 6.10 (d, β-CH$_{(cis)}$, $J_{\alpha,\beta(cis)}$=17.5Hz, 1H), 7.16-7.35 (m, 5-pyr*H*, 1H), 7.56-7.64 (m, 3-pyr*H*, 1H), 7.66-7.87 (m, 4-pyr*H*, 1H), 8.59 (dd, α-C*H*, $J_{\alpha,\beta(cis)}$=17.5Hz, $J_{\alpha,\beta(trans)}$=11.2Hz, 1H), 8.98 (ddd, 6-pyr*H*, $J_{5,6}$=5.6, $J_{4,6}$=1.7, $J_{3,6}$=0.8Hz, 1H).

3-Carbomethoxy-4*H*-quinolizone (1). Method A. Reaction in DMF. Dimethyl malonate (823mg, 6.24mmol) and anhydrous K_2CO_3 (1.62g, 11.7mmol) were added to dichlorobis(2-vinylpyridine)-palladium(II) (7, 302mg, 6.24mmol) in reagent grade DMF (50ml). After stirring at 50°C for 12h, the solvent was removed in vacuo, the residue dissolved in $CHCl_3$ and filtered. The $CHCl_3$ soluble material was purified by ThLC eluting with 5% MeOH/$CHCl_3$ to give 1 as yellow microcrystals: 61mg (39%); mp116.5-117.3°C(pet. ether); ^{1}H nmr δ 3.95 (s, C*H*$_3$, 3H), 6.66 (dd, 1-quin*H*, $J_{1,2}$=8.5, $J_{1,8}$=0.6Hz, 1H), 7.20 (ddd, 6-quin*H*, $J_{5,6}$=7.3, $J_{6,7}$=4.8, $J_{6,8}$=3.4Hz, 1H) 7.57-7.65 (m, 7,8-quin*H*, 2H), 8.41 (d, 2-quin*H*, 1H), 9.40 (dd, 5-quin*H*, $J_{5,7}$=0.9Hz, 1H); ^{13}C nmr δ 52.0 (*C*H$_3$), 101.6 (*C*1), 115.9, 124.7 (*C*7 & *C*8), 133.0 (*C*5), 140.4 (*C*2), 166.1 (3-*C*O),

167.2 (C4); ms m/z 203 (M^+,10), 188 (M^+-CH_3, 8), 172 (M^+-OCH_3, 11), 160 (M^+-$C_2H_3O_2$, 21), 132 (M^+-$C_3H_3O_3$, 37), 106 (M^+-$C_5H_5O_2$, 39), 78 (M^+-$C_6H_5O_3$, *100*).

Method B. Reaction in CH_3CN. Using the same procedure as with DMF, gave **1** (20%) and methyl 3-amino-2-carbomethoxy-2-butenoate (**2**) as colorless microcrystals: R_f=0.5; mp 83.5-84.5°C (lit.[13] mp 83-84°C); Subl. 50°C (2mm); ^1H nmr δ 2.15 (s, CCH_3, 1H), 3.71 (s, OCH_3, 1H), 3.74 (s, OCH_3, 1H); ^{13}C nmr δ 22.2 (CCH_3), 51.1 (OCH_3), 51.7 (OCH_3), 164.1 (*C*O), 169.0 (*C*O); ms m/z 173 (M^+, 48), 142 (M^+-CH_3O, *100*), 141 (M^+-CH_4O, 88), 110 (26), 83 (22).

Table 1. Crystal Data and Data Collection Parameters.

Compound:	**1**	**2**	**7**
Formula:	$C_{11}H_9NO_3 \cdot H_2O$	$C_7H_{11}NO_4$	$PdCl_2C_{14}H_{14}N_2$
Formula Wt:	221.2	173.2	387.6
Crystal System:	Triclinic	Triclinic	Monoclinic
Space Group:	*P*$\bar{1}$	*P*$\bar{1}$	*C2/c*
a(Å):	6.905(2)	7.669(2)	15.403(5)
b(Å):	7.789(2)	8.930(2)	7.268(2)
c(Å):	10.458(2)	7.094(2)	14.699(4)
α(°):	70.63(2)	111.10(2)	--
β(°):	75.48(2)	109.21(2)	113.82(3)
γ(°):	74.48(2)	94.61(2)	--
V(Å^3):	503.1(3)	417.0(5)	1505(2)
Z:	2	2	4
D_c(gcm^{-3}):	1.460	1.379	1.710
T(°C):	25	27	22
μ(cm^{-1}):	1.05	1.06	15.6
Crystal size (mm):	0.12x0.16x0.36	0.32x0.40x0.52	0.06x0.26x0.32
θ limits(°):	1-27	1-30	1-30
Scan Speeds (° min^{-1}):	0.59-4.0	0.63-4.0	0.74 4.0
Unique Data:	2189	2421	2186
Observed Data:	1633	1415	1755
Variables:	190	149	62
R:	0.036	0.049	0.076
R_w:	0.038	0.065	0.080
Extinction:	9.7(17)x10^{-7}	--	--
Res. Density(eA^{-3}):	0.24	0.20	0.93
H atoms:	refined	refined	ignored

ACKNOWLEDGMENTS

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