REACTION OF AZEPINES WITH PALLADIUM(II) ACETATE: FORMATION OF MUCONDIALDEHYDE AND DIHYDROAZEPINE DERIVATIVE

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Abstract —— Reaction of 1-carboethoxy-1H-azepine with palladium(II) acetate in chloroform or acetonitrile afforded trans-trans-mucondialdehyde together with ethyl carbamate. On the other hand, the analogous reaction in acetic acid gave 1-carboethoxy-2,3-diacetoxy-2,3-dihydro-1H-azepine. The same reaction but using 1-carboethoxy-1H-1,2-diazepine gave a nitrile derivative via a ring opening.

Much attention has been paid to the reactions of heterocycles with organometallic compounds to clarify that dimerizations, phenylations, or allylations occur in the reactions of furan or pyrrole derivatives.[1] While the reactions of organometallic compounds with five-membered heterocycles have been elucidated well, the reactivities of seven-membered heterocycles such as azepine or diazepine derivatives to organometallic compounds still remain unclear,[2] except the reactivities to carbonyl complexes of iron and chromium.[3] Contrary to the aromatic heterocycles such as furans or pyrroles, azepines and diazepines are known to behave as polyolefins, and as a result their reactivities are different from those of the aromatic heterocycles.[4] As a series of our research on the reactions of seven-membered heterocycles, we investigated the reactions of 1-carboethoxy-1H-azepine and 1-carboethoxy-1H-1,2-diazepine with palladium(II) acetate and could get some interesting results, which will be reported here.

1-Carboethoxy-1H-azepine (1) was allowed to react with an equimolar amount of palladium (II) acetate in the presence of five molar equivalents of sodium acetate using a series of solvents to give trans-trans-mucondialdehyde (2)[5] accompanied by ethyl carbamate (3). The details of the reactions were presented in Table 1. The yields of 2 were plotted against acceptor (AN) and donor numbers

(DN)[6] of the solvents as shown in Figures 1 and 2, respectively. A linear relationship was obtained for the acceptor number. On the other hand, a good relationship was not found for the donor number, however, it was shown that the more decrease in the donor number gave the better yields of 2.

When acetic acid was used as a solvent, the reaction was found to proceed in a different manner to afford 1-carboethoxy-2,3-diacetoxy-2,3-dihydro-1H-azepine (4) in 19% yield together with 9% yield of 2. On the other hand, 1-carboethoxy-1H-1,2-diazepine (5) afforded only resinous materials except a low yield (3%) of a nitrile compound (6).[2,7]

Table 1. Reactions of 1 with Palladium Acetate.

Solvents	AN	DN	Time (min)	Temp(°C)	Yield of 2 (%)
chloroform	23.1		80	60	31
acetonitrile	18.9	14.1	50	60	27
acrylonitrile			50	60	16
acetone	12.5	17.0	60	60	11
HMPA	10.6	38.8	60	60	11
tetrahydropyran			80	80	11
THF		20.0	60	60	10
diglyme	10.2		60	60	9
s-trioxane			80	80	7
n-hexane	0		60	60	4
piperidine		51	80	80	0

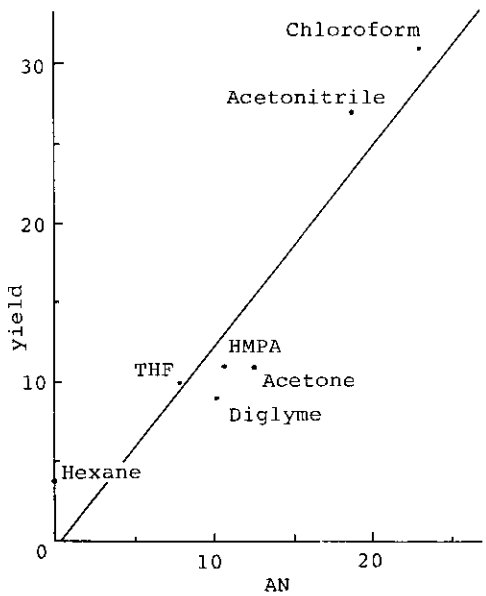


Figure 1

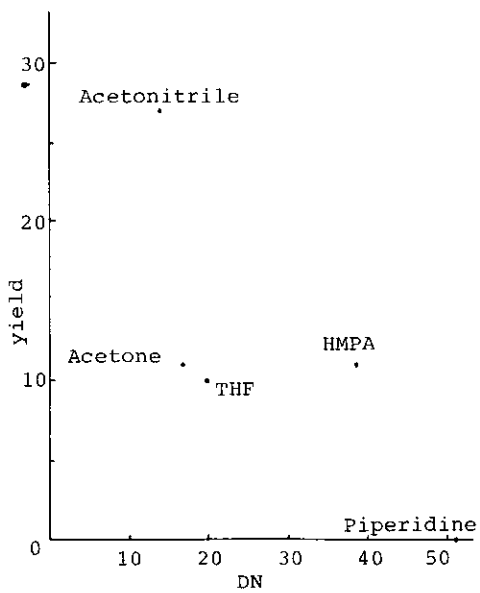
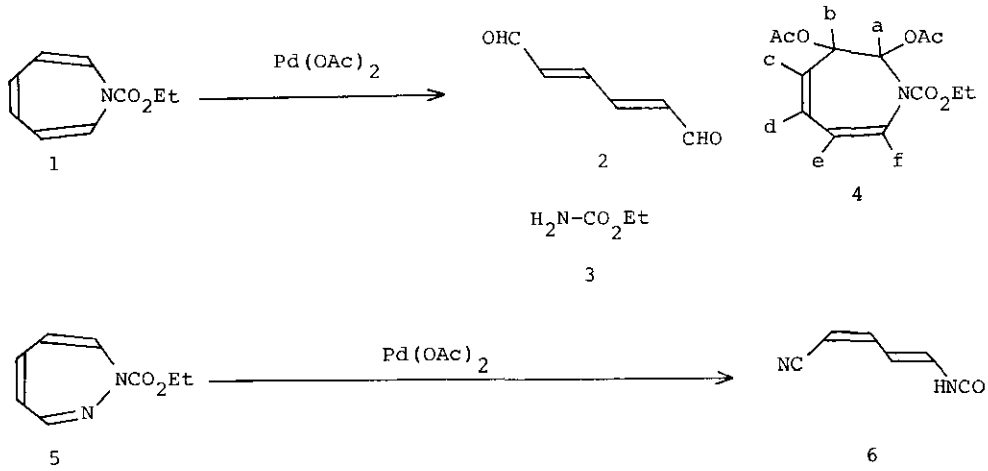


Figure 2

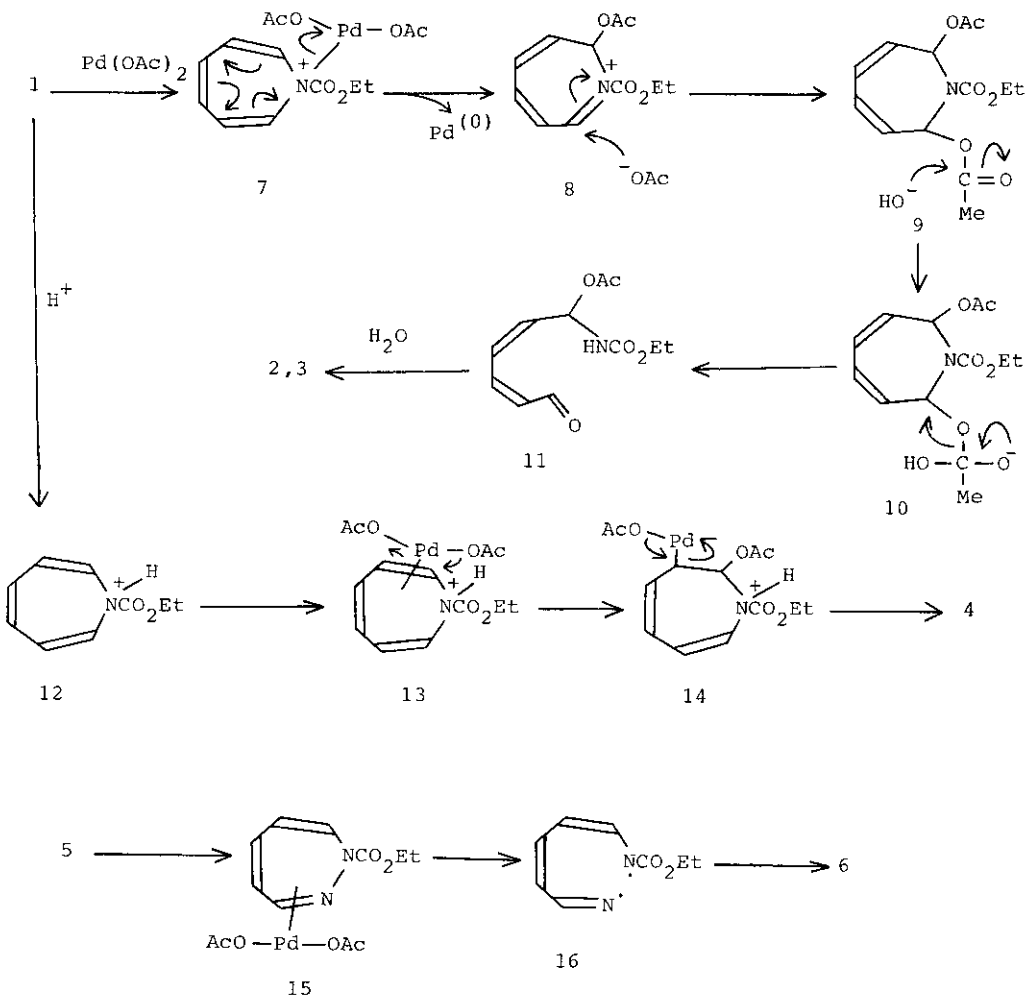
The structures of 2 and 6 were deduced from the spectral properties and confirmed by the agreements of their melting points with the literature values.[5,7] The structure of 4 was deduced on the basis of its spectral properties as follows:[8] The molecular ion peak in mass spectrum shows 4 to be a 1:2 adduct of 1 and acetoxyl group. ^{1}H Nmr spectrum tells that 4 is not a symmetric compound and that 4 has a continuity of six protons (H_a-H_f). A rather large value of coupling constant (10.9 Hz) between H_c and H_d suggests that there is a double bond between the two carbon atoms to which attached these two protons. These facts indicate the structure of 4 to be the one shown in the Figure, which was further confirmed by a resemblance of the absorption maximum in the uv spectrum of 4 to that of the analogous compound, 1-carbomethoxy-2,3-dihydro-1H-azepine (277 nm).[9]



1 2 3 4 5 6

Previously Sakakibara et al. reported that the nitrogen atom of N,N-dialkylaniline formed a cation radical through an oxidation by palladium(II) acetate.[10] The formation of 2 is considered to proceed through a similar oxidation mechanism as follows: Coordination of 1 with its lone pair electrons on the nitrogen atom to palladium affords a σ-complex (7) of palladium. Subsequent attack of the acetoxyl group at the 2-position of the azepine nuclei generates a cation intermediate (8), which further reacts with the other acetoxyl group to form 9, releasing palladium metal. Hydrolysis of 9 affords 2 and 3 via 10 and 11.[11] The improvement of the yields of 2 in the high-acceptor number solvents can be considered to be the result of the easier formation of the σ-complex (7) by palladium whose oxidation capacity is strengthened through an overflow of its electrons to the solvents.[6]

On the other hand, in the reaction in acetic acid, a protonation at the lone pair electrons on the nitrogen atom of 1 dominates the reaction. A coordination of the protonated ion (12) to palladium using the double bond forms a π-complex (13). Subsequent attack of the acetoxyl group at the 2-position of azepine moiety followed by a palladium-carbon bond formation affords a σ-complex (14). Reaction of the other acetoxyl group at the 3-position of the azepine moiety, and the simultaneous oxidative desorption of palladium afforded the final product 4 and palladium metal.[12] The formation process of 6 has been reported to be considered to proceed through a π-complex (15) and a diradical intermediate (16).[2]



EXPERIMENTAL

Nmr spectra were measured with a Varian XL 200 spectrometer with tetramethylsilane as an internal standard. Ir and mass spectra were measured with JASCO A-102 spectrophotometer and JMX-DX300 spectrometer, respectively. Melting points were recorded on a Yanagimito micro melting point apparatus and were uncorrected. Only typical reactions are mentioned below.

Reaction of 1 with Palladium Acetate in Chloroform. A mixture of 1 (500 mg, 3 mmol), palladium acetate (670 mg, 3 mmol), and sodium acetate (1200 mg, 15 mmol) in chloroform (32 ml) was stirred for 80 min at 60°C. After quenching with water, filtration, and extraction with ether, the solvent was removed on a rotary evaporator. The resulted residue was separated with column chromatography on silica gel to give yellow crystals 2 (100 mg, 31%, mp 114-118°C, lit.[5] 121°C) from elution with n-hexane-ethyl acetate (80:20 to 75:25).

Reaction of 1 with Palladium Acetate in Acetic Acid. A mixture of 1 (500 mg, 3 mmol), palladium acetate (670 mg, 3 mmol), and sodium acetate (1200 mg, 15 mmol) in acetic acid (32 ml) was stirred for 80 min at 60°C. After the same treatment as above the resulted residue was separated with column chromatography on silica gel. The elution with n-hexane-ethyl acetate (75:25) gave an yellow oily product which was then purified with thin-layer chromatography on silica gel using n-hexan-ethyl acetate (7:3) as a developing solvent to provide 4 (130 mg, 19%, R_f=0.54) as an yellow oil. The elution with n-hexane-ethyl acetate (7:3) gave 2 (29 mg, 9%) and the elution with n-hexane-ethyl acetate (4:1 to 1:1) was analyzed using glc (column PEG-20M, 180°C, Rt=7.9 min) to contain 3.

4: Hrms: Found: 283.1065. Calcd for $C_{13}H_{17}NO_6$: 283.1057. Ms m/z (rel intensity): 283 (M^+, 30), 181 (100). Uv (EtOH): 269 nm (log ε, 3.96). Ir (oil): 1730 cm^{-1}. ^1H Nmr ($CDCl_3$) δ =1.35 (t, J=7.1Hz, 3H, Me), 2.00 (s, 3H, Me), 2.02 (s, 3H, Me), 4.34 (q, J=7.1Hz, 2H, CH_2), 5.33 (dd, 1H, H_b), 5.71 (dd, 1H, H_e), 5.89 (dd, 1H, H_d), 6.23 (dd, 1H, H_c), 6.90 (d, 1H, H_a), 7.16 (d, 1H, H_f). Coupling constants in Hz: J_{ab}=5.0, J_{bc}=8.0, J_{cd}=10.9, J_{de}=7.0, J_{ef}=9.6.

Reaction of 5 with Palladium Acetate. A mixture of 5 (500 mg, 3 mmol), palladium acetate (670 mg, 3 mmol), and sodium acetate (1200 mg, 15 mmol) in 1,4-dioxane (32 ml) was refluxed for 7 h. After the usual workup the resulting mixture was separated with thin-layer chromatography on silica gel using n-hexane-ethyl acetate (2:8) as a developing solvent to provide 6 (13 mg, 2.6%, R_f=0.91) as pale yellow crystals.

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