HETEROCYCLES, Vol 26, No 6, 1987

METAL-CATALYZED INTRAMOLECULAR CYCLIZATION OF 2-DIAZO-4-(4-INDOLYL)-3-OXOBUTANOIC ACID ESTERS

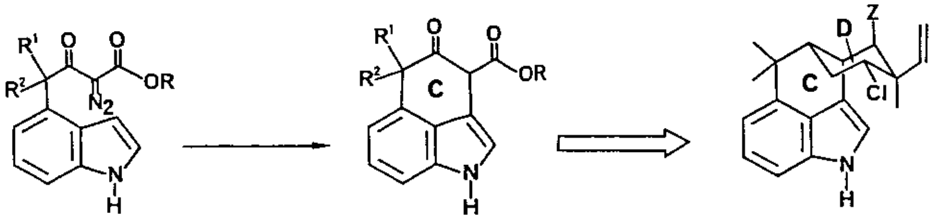
Masakatsu Matsumoto*, Nobuko Watanabe, and Hisako Kobayashi
Sagami Chemical Research Center,
Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

Abstract ——— $Rh_2(OAc)_4$-catalyzed decomposition of 2-diazo-4-(4-indolyl)-3-oxobutanoic acid esters (1) leads to indoles 3, whereas $Pd(OAc)_2$-catalyzed reaction of 1 gives indoles 2 with C-ring.

Intramolecular C-H bond insertion by diazoketones has become an excellent methodology to construct highly substituted cyclic ketones.[1,2] The recent development has, however, been focused on the aliphatic C-H bond insertion with carbenes and carbenoids generated by metal-catalyzed decomposition of diazo compounds. The intramolecular aromatic C-H bond insertion should be as well an interesting entry to cyclic system fused with aromatic ring. For this reaction, there have been a few examples known with acid catalysis.[1]

In the course of our study on the synthesis of 4-substituted indoles and related alkaloids, we examined whether 2-diazo-4-(4-indolyl)-3-oxobutanoic acid esters (1) led to the indoles 2 with C-ring via C-H bond insertion.[3]

Copper-catalyzed reaction of ethyl diazoacetate with indole is well known to afford 3-indoleacetic acid ester.[4] Accordingly, we expected that the diazoketone 1 would lead to a tricyclic compound 2, which should be a key intermediate with functionalities for further transformations toward ergot and clavine alkaloids, and also toward a new class of alkaloids such as hapalindoles.[5]



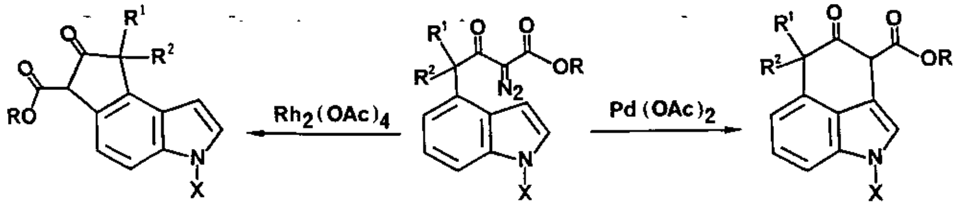
1

2

hapalindole A (Z= -N=C)
B (Z= -NCS)

A solution of the diazoketone 1a (100 mg) in toluene (2 ml) was heated in the presence of $Cu(acac)_2$ (2 mg) at 80°C for 6 h. After chromatographic separation, a tricyclic compound was obtained in ca. 20% yield. It was not the desired one 2a but a compound 3a derived from the intramolecular C-H bond insertion at the 5-position of 1a. The structure of 3a was determined by nmr(400MHz), ms, ir and elemental analyses.[6] In place of $Cu(acac)_2$, $Rh_2(OAc)_4$ was next used for the cyclization of 1a. The Rh-catalyzed reaction occurred smoothly at room temperature and the tricyclic compound 3a was produced in 89% yield after 30 min. For the Rh-catalyzed reaction of 1a, a variety of medium such as methanol, benzene and their mixtures were surveyed, but the results were not essentially different.

On the other hand, the Pd-catalyzed reaction of 1a gave completely different result from the case of Cu or Rh. When a solution of 1a (281 mg) and $Pd(OAc)_2$ (10 mg) in methanol (5 mL) at 0°C for 45 min, the desired cyclization product 2a was obtained in 71 % yield together with a slight amount of 3a (<1%). The physical properties of 2a were cited in



3 1 2

Table 1. Metal-catalyzed cyclization of 2-diazo-4-(4-indolyl)-3-oxobutanoic acid esters (1).

1					2			3		
R	R^1	R^2	X	Catalyst		Yield(%)	Mp (°C)		Yield(%)	Mp (°C)
(1a) Et	H	H	H	$Rh_2(OAc)_4$	(2a)	<1	110(dec)	(3a)	89	110-113
				$Pd(OAc)_2$		71			<1	
(1b) Et	H	H	Tosyl	$Rh_2(OAc)_4$	(2b)	0	---	(3b)	61	155.5-8.5
				$Pd(OAc)_2$		--	---		--	
(1c) Me	H	H	$PhCH_2$-	$Rh_2(OAc)_4$	(2c)	0	---	(3c)	86	120-1.5
				$Pd(OAc)_2$		0	---		51	
(1d) Et	Me	Me	H	$Rh_2(OAc)_4$	(2d)	0		(3d)	87	oil
				$Pd(OAc)_2$		77	143-4.5		17	
(1e) Et	i-Bu	H	H	$Rh_2(OAc)_4$	(2e)	1		(3e)	73	oil
				$Pd(OAc)_2$		55	86(dec)		0	

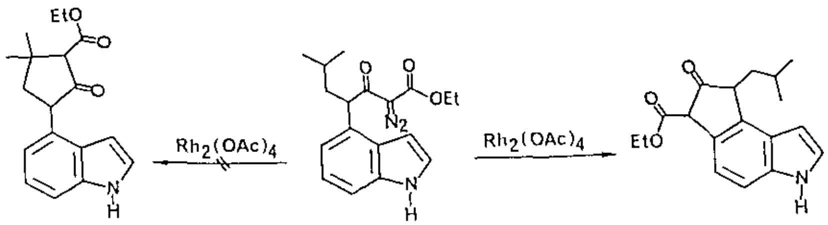
Note.[7] The other Pd-catalyst such as $PdCl_2(PhCN)_2$ and $(PdCl)_2(\pi\text{-}C_3H_5)_2$ was also moderately active for the transformation of 1a to 2a (40-60% yield). The older method with acid catalyst,[1] $HClO_4$, CF_3CO_2H, BF_3, and so on, was unsuccessful for the present purpose.

The Pd- and Rh-catalyzed reactions were further investigated for the diazoketones 1b-e with various substituents and the results were summarized in Table I. The results of 1b and 1c showed that the cyclization at the 3-position forming 2 was significantly affected by the N-substituent of indole 1. Similar trend in the reactivity of indoles is well recognized for electrophilic substitutions such as Vilsmeier-Haack reaction and Friedel-Crafts reaction.[8] A carbocationic species was strongly suggested to participate in the Pd-catalyzed reaction of 1. The following fact supported the suggestion: aprotic solvent such as CH_2Cl_2, benzene, and ethyl acetate was far less effective than protic solvent such as methanol for the $Pd(OAc)_2$-catalyzed cyclization of 1. The cyclization of 1 to 2 was formal C-H bond insertion of a carbene (carbenoid) and was likely an electrophilic substitution toward the indole skeleton.

The Rh-catalyzed intramolecular aliphatic C-H bond insertion has recently been found to prefer substantially for five-membered ring formation.[2a,b] A plausible mechanism seemed to include a six-membered ring transition state comprising of rhodium carbenoid and the hydrogen atom that is to be transfered.[2b] The Rh-catalyzed cyclization of 1 to 3 might proceed in a similar fashion. On the other hand, the cyclization to 2 would require a seven-membered transition state, which was probably less stable than the six-membered one mentioned above. This seemed a reason for the substantial preference for formation of 3 in the Rh-catalyzed reaction of 1.

The diazoketone 1e was formally capable of undergoing the aliphatic C-H bond insertion to yield a cyclopentanone 4. The $Rh_2(OAc)_4$-catalyzed reaction of 1e gave, however, 3e without 4. This fact was likely due to difference between acidity of hydrogen on the aromatic ring and that of saturated carbon.

A sterically congested diazoketone 1d gave also 2d and 3d, though the regioselectivity was somewhat blunt. It is worth to point out that the tricyclic compound 2d possesses a basic



4 1e 3e

skeleton with functionalities enough to build up the D-ring of hapalindoles.

The results described here can be summarized as follows: (i) transition metal such as Cu(II), Pd(II), and Rh(II) effectively catalyzed generation of the carbenoids from 1, to cause the intramolecular aromatic C-H bond insertion without addition to the C=C double bond of aromatic ring, which frequently leads to ring-expansion products and (ii) the regiochemistry of the C-H bond insertion extremely depended on the metal catalyst used.

REFERENCES AND NOTES

(1) For a review, see: S. D. Burke and P. A. Grieco, Org. React. (N. Y.), 1979, 26, 361.

(2) a) D. F. Taber and E. H. Petty, J. Org. Chem., 1982, 47, 4808. b) D. F. Taber and K. Raman, J. Am. Chem. Soc., 1983, 105, 5935. c) Cyclization through oxonium ylide: M. C. Pirrung and J. A. Werner, ibid., 1986, 108, 6060. E. J. Roskamp and C. R. Johnson, ibid., 1986, 108, 6062.

(3) The starting materials, 4-(4-indolyl)-3-oxobutanoic acid esters, were easily prepared from 5-halo-4-oxo-4,5,6,7-tetrahydroindoles: M. Matsumoto and N. Watanabe, Heterocycles, 1986, 24, 3149. The ketoesters were converted to the diazo compounds 1 by the standard procedure: M. Regitz, J. Hocker, and A. Liedhegener, "Organic Synthesis", Wiley (N. Y.) 1973, Collect. Vol. V. p197.

(4) S. S. Nametkin, N. N. Melnikov, and K. S. Bokarev, Zhur. Priklad. Khim., 1956, 29, 459.

(5) R. E. Moore, C. Cheuk, and G. M. L. Patterson, J. Am. Chem. Soc., 1984, 106, 6456.

(6) Enol form. NMR($CDCl_3$) δ1.47(t, J=7.1Hz, 3H), 3.73(s, 2H), 4.43(q, J=7.1Hz, 2H), 6.45(ddd, J=3.0, 2.0, and 0.7Hz, 1H), 7.21(dd, J=3.0 and 2.8Hz, 1H), 7.31(dd, J=8.4 and 0.7Hz, 1H), 7.56(d, J=8.4Hz, 1H), 8.03-8.21(m, 1H), 10.94-11.12(m,1H)ppm. IR(KBr) 3427, 1638, 1590, and 1485 cm^{-1}. Mass(m/z,%) 243(M^+, 17), 197(100), 169(34), and 141(96). Anal. Calcd.($C_{14}H_{13}NO_3$): C,69.12; H,5.39; N,5.76. Found: C,68.75; H,5.32; N,5.63.

(7) Enol form. NMR($CDCl_3$) δ1.46(t, J=7.1Hz, 3H), 4.13(s with fine coupling, 2H), 4.41(q, J=7.1Hz, 2H), 6.84(ddd, J=6.8, 2.3, and 1.0Hz, 1H), 7.07(dd, J=1.0 and 0.9Hz, 1H), 7.09(dd, J=8.1 and 0.9Hz, 1H), 7.14(dd, J=8.1 and 0.9Hz, 1H), 7.62-7.76(m, 1H), and 12.83(s, 1H). IR(KBr) 3370, 1647, and 1627 cm^{-1}. Mass (m/z,%) 243(M^+), 197(100), 169(45), and 141(56). High Mass(m/z) 243.0889 (er= -0.5mmu)(M^+, $C_{14}H_{13}NO_3$).

(8) For a review, see: W. A. Remers and R. K. Brown, "Indoles" part one in "Heterocyclic Compounds"; W. J. Houlihan Ed., Wiley (N.Y.) 1972.

Received, 24th February, 1987