

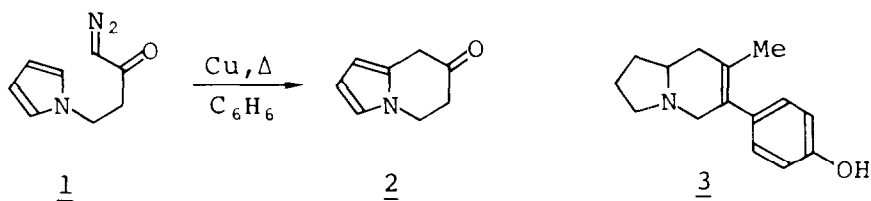
## COMPETITIVE INTRAMOLECULAR CARBENOID REACTIONS OF PYRROLE DERIVATIVES

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**Abstract.** Rhodium(II) acetate-catalyzed decomposition of 1-diazo-3-phenyl-4-(pyrrol-1-yl)-butan-2-one and its p-methoxy derivative resulted in their intramolecular cyclization to form the 6-phenyl-5,6-dihydroindolizin-7(8H)-ones and 1-(pyrrol-1-yl)methylindan-3-ones as major and minor products respectively in high yields (77-89%). The p-nitrophenyldiazo compound cyclized exclusively to the 5,6-dihydroindolizin-7(8H)-one in 76% yield.

The reaction of  $\alpha$ -diazocarbonyl compounds with aromatic molecules has received much attention [1]. The decomposition of  $\alpha$ -diazoketones and esters by thermal, photolytic and transition metal catalysis affords an  $\alpha$ -ketocarbene or carbenoid species which adds to the benzene ring to give a norcaradiene which subsequently tautomerizes to a cycloheptatriene. Both inter and intramolecular examples are known [1-2]. Polynuclear aromatic and  $\pi$ -excessive heteroaromatics containing oxygen or sulfur atoms generally undergo cyclopropanation with cleavage [1-3]. In contrast, pyrroles are usually alkylated [6-8] unless strong electron-withdrawing substituents make them behave like dienes [4,5]. The reaction of ethyl diazoacetate with pyrroles is typical in giving 2- and 3-pyrroleacetic acids [8,9].

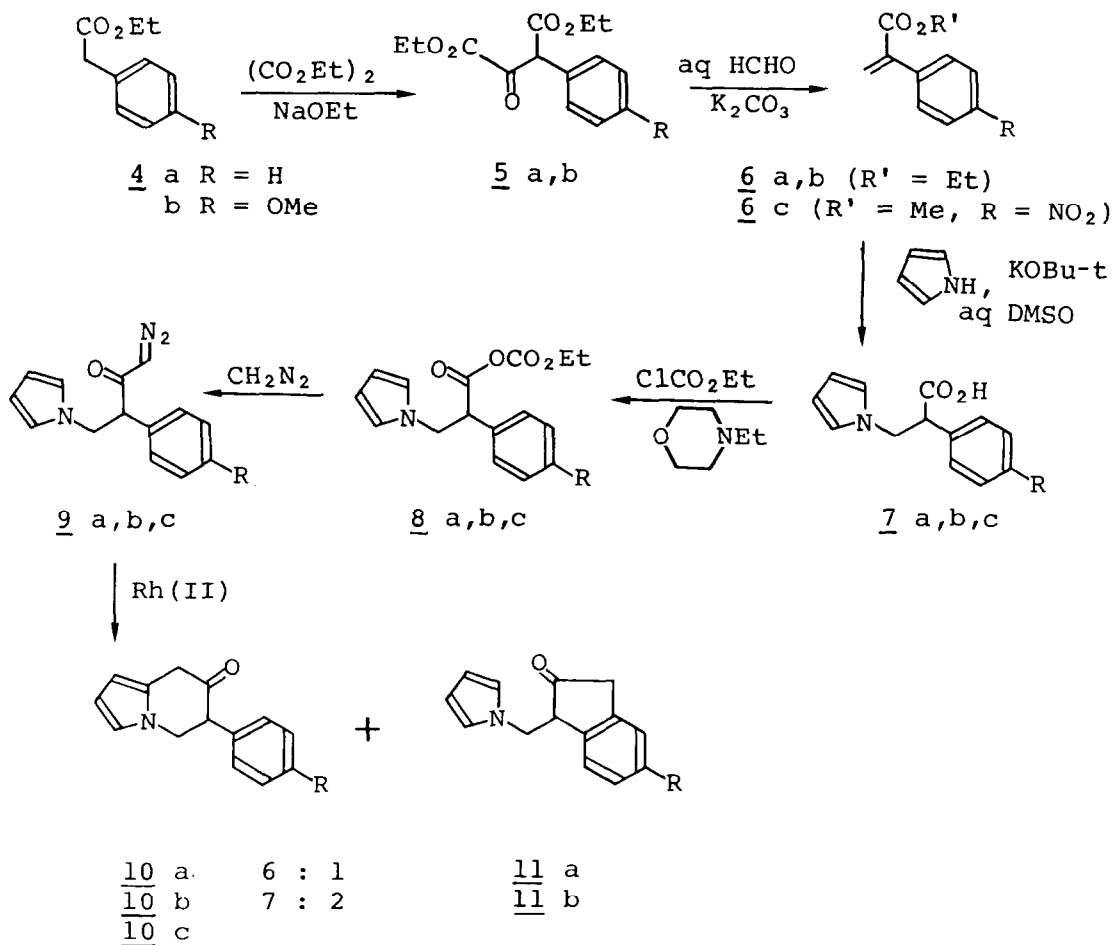
Scheme 1



We recently reported the first, efficient intramolecular version [10,11], namely the decomposition of 1-diazo-4-(pyrrol-1-yl)butan-2-one (1) which gave the dihydroindolizinone (2) in nearly quantitative yield (Scheme 1). As we were interested in exploiting this cyclization for synthesizing alkaloids possessing phenyl-substituted azabicyclic rings such as ipalbidine (3), the behavior of suitable precursors needed to be tested. The logical choice falls on 1 substituted at C3 with a phenyl group together with its p-methoxy and p-nitro derivatives in order to monitor electronic effects. We now report on the results obtained from the decomposition of three diazobutanones (9a,b,c) in which phenyl and pyrrole rings can compete for the nascent carbenic center.

1-Diazo-3-phenyl-4-(pyrrol-1-yl)butan-2-one and its p-methoxy derivative (9a,b) were prepared from the corresponding ethyl phenylacetates 4a,b [12] (Scheme 2). The treatment of 4 with diethyl oxalate in the presence of sodium methoxide [13] gave the oxosuccinates 5a,b in 94 and 89% yield. Their conversion occurred in 93 and 86% yield to the propenoates (6a,b) on treatment with aqueous formaldehyde in the presence of potassium carbonate [14]. Michael addition of pyrrole anion to the propenoate was readily accomplished in aqueous dimethyl sulfoxide giving the required propanoic acids 7a,b in 73 and 51% yield. Conversion to their mixed anhydrides 8a,b [15], followed by the action of diazomethane furnished the desired starting materials 9a,b in 44 and 58% yield. The p-nitrophenyl analogue 9c was similarly prepared from the known methyl 2-(p-nitrophenyl)propenoate (6c) [16]. The sole difference was that saponification did not occur spontaneously on addition of pyrrole, this step was performed separately to give the acid 7c.

Scheme 2



Unlike the unidirectional cyclization (1→2) which worked well with copper powder in refluxing benzene [10], the diazoketones 9 decomposed slowly, requiring hours, both with copper and copper acetylacetonate [8]. Moreover, the resulting mixtures were difficult to purify. Fortunately, on using rhodium(II) acetate instead [17,18] in catalytic amounts in dichloromethane, the decomposition of 9a and 9b was dramatically accelerated and was over in 30 min at room temperature. Inspection of the reaction mixture by NMR spectroscopy showed that substitution in the two senses had occurred with cyclization being overwhelmingly favored on the pyrrole ring. The 3-phenyldiazo compound (9a) gave the indolizinone 10a and indanone 11a in a 6:1 ratio, whereas the p-methoxy derivative (9b) altered the ratio of 10b and 11b to 7:2. In both cases the yields were high (75-88%). The p-nitrophenyldiazo compound 9c also decomposed cleanly with the rhodium catalyst. The cyclization was not only efficient (76%), but gave just one product the indolizinone 10c.

Formally, the products are the result of insertion by carbenic carbon into the carbon-hydrogen bonds at the  $\alpha$  positions of the pyrrole and benzene rings. The high proportion of pyrrole substitution is undoubtedly a reflection of its pronounced nucleophilic character which is only offset when the benzene ring bears an electron-donating substituent. In the latter case no ring enlarged products were detected, probably owing to the geometric impossibility of cyclopropanation. We will discuss elsewhere applications of this method to the synthesis of ipalbidine.

We thank the Swiss National Science Foundation (grant No. 2.036-0.83) for support of this work.

#### REFERENCES

- [1] V. Dave, E.W. Warnhoff, *Org. React.* 1970, 18, 270; A.P. Marchand, N.M. Brockway, *Chem. Rev.* 1974, 74, 431.
- [2] S.D. Burke, P.A. Grieco, *Org. Reactions* 1979, 26, 361.
- [3] M.N. Nwaji, O.S. Onyiriuka, *Tetrahedron Lett.* 1974, 2255.
- [4] S.R. Tanny, J. Grossman, F.W. Fowler, *J. Am. Chem. Soc.* 1972, 94, 6495.
- [5] J.F. Biellman, M.P. Goeldner, *Tetrahedron* 1971, 27, 2957.
- [6] F. Šorm, *Coll. Czech. Chem. Commun.* 1947, 12, 245.
- [7] A. Gossauer, "Die Chemie der Pyrrole", Springer Verlag, Berlin 1974; R.A. Jones, G.P. Bean, "The Chemistry of Pyrroles", Academic Press, London 1977.
- [8] B.E. Maryanoff, *J. Heterocycl. Chem.* 1977, 14, 177; *J. Org. Chem.* 1979, 44, 4410; *J. Org. Chem.* 1982, 47, 3000.
- [9] C.D. Nenitzescu, E. Solomonica, *Chem. Ber.* 1931, 64, 1924.
- [10] C.W. Jefford, W. Johncock, *Helv. Chim. Acta* 1983, 66, 2666.
- [11] The pyrolysis of ethyl 2-diazo-4-(pyrrol-1-yl)butanoate gave Z and E olefins by hydride rearrangement, but also afforded cyclized product (E. Galeazzi, A. Guzmán, A. Pinedo, A. Saldaña, D. Torre, J.M. Muchowski, *Can. J. Chem.* 1983, 61, 454).

[12] All new compounds gave satisfactory elemental analyses and mass spectroscopic data. Some selected characteristics are listed below.

9a: yellow platelets ( $\text{CCl}_4$ ), mp. 71-72°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  3.81(m, 1H, H-C(3)), 4.10(dd, 1H, J=13.5, 6.0Hz, H-C(4)), 4.73(dd, 1H, J=13.5, 8.0Hz, H-C(4)), 5.09(s, 1H, H-C(1)), 6.07(t, 1H, J=3.5Hz,  $\beta$ -pyrrolyl), 6.56(t, 1H, J=3.5,  $\alpha$ -pyrrolyl), 7.18(m, 2H, H-C(3'), H-C(5')), 7.32(m, 3H, H-C(2'), H-C(4'), H-C(6')).

9b: colorless needles ( $\text{CCl}_4$ ), mp. 70°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  3.81(s, 3H, OMe), 3.77(dd, 1H, J=8.0, 6.0Hz, H-C(3)), 4.09(dd, 1H, J=14.0, 6.0Hz, H-C(4)), 4.69(dd, 1H, J=14.0, 8.0Hz, H-C(4)), 5.08(s, 1H, H-C(1)), 6.07(t, 2H, J=2.0Hz,  $\beta$ -pyrrolyl), 6.54(t, 2H, J=2.0Hz,  $\alpha$ -pyrrolyl), 6.87(AA' of AB system, 2H, H-C(3'), H-C(5')), 7.13(BB', 2H, H-C(2'), H-C(6')).

9c: pale yellow platelets (ether/hexane), mp. 122.5-124°C(dec.).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  3.96(br. t, 1H,  $^2J=14.0$ ,  $^3J=7.5$ Hz, H-C(4)), 5.15(s, 1H, H-C(1)), 6.09(t, 2H, J=2.0Hz,  $\beta$ -pyrrolyl), 6.51(t, 2H, J=2.0Hz,  $\alpha$ -pyrrolyl), 7.41(d, 2H, J=8.5Hz, H-C(2'), H-C(6')), 8.20(d, 2H, J=8.5Hz, H-C(3'), H-C(5')).

10a: colorless needles (ether/hexane), mp. 84-85°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  3.75(dd, 1H, J=20.5, 1.0Hz, H-C(8)), 3.83(dd, 1H, J=20.5, 1.0Hz, H-C(8)), 3.92(dd, 1H, J=8.5, 6.0Hz, H-C(6)), 4.41(dd, 1H, J=13.0, 8.5Hz, H-C(5)), 4.43(dd, 1H, J=13.0, 6.0Hz, H-C(5)), 6.00(m, 1H, H-C(1)), 6.18(dd, 1H, J=3.25, 2.5Hz, H-C(2)), 6.65(dd, 1H, J=2.5, 1.75Hz, H-C(3)), 7.06(dd, 2H, J=7.5, 2.0Hz, H-C(2'), H-C(6')), 7.31(m, 3H, H-C(3'), H-C(4'), H-C(5')).

11a: colorless oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 360 MHz):  $\delta$  3.33(d, 1H, J=23.0Hz, H-C(3)), 3.53(d, 1H, J=23.0Hz, H-C(3)), ca. 3.8(1H, H-C(8)), 4.29(dd, 1H, J=14.0, 7.0Hz, H-C(1')), 4.51(dd, 1H, J=14.0, 4.0Hz, H-C(1')), 6.08(t, 2H, J=2.0Hz,  $\beta$ -pyrrolyl), 6.50(t, 2H, J=2.0Hz,  $\alpha$ -pyrrolyl), 6.92(br. d, 1H, J=7.5Hz, H-C(7)), 7.29(m, 3H, H-C(4), H-C(5), H-C(6)).

[13] G.M. Ksander, J.E. McMurry, M. Johnson, J. Org. Chem. 1977, 42, 1180.

[14] A.S. Howard, G.C. Gerrans, J.P. Michael, J. Org. Chem. 1980, 45, 1713.

[15] L. Thijs, F.L.M. Smeets, P.J.M. Cillissen, J. Harmsen, B. Zwanenburg, Tetrahedron 1980, 36, 2141.

[16] C. Mannich, L. Stein, Berichte 1925, 58, 2659; J.H. Schauble, E. Herz, J. Org. Chem. 1970, 35, 2529; J.H. Schauble, E.H. Freed, M.D. Swerdloff, J. Org. Chem. 1971, 36, 1302.

[17] A.J. Anciaux, A.J. Herbert, A.F. Noels, N. Petiniot, P. Teyssie, J. Org. Chem. 1980, 45, 695.

[18] M.A. McKervey, S.M. Tuladhar, M.F. Twohig, J. Chem. Soc., Chem. Commun. 1984, 129.

(Received in Germany 13 August 1985)