

269. Intramolecular Carbenoid Reactions of Pyrrole Derivatives

Efficient Syntheses of Pyrrolizinone and Dihydroindolizinone¹⁾

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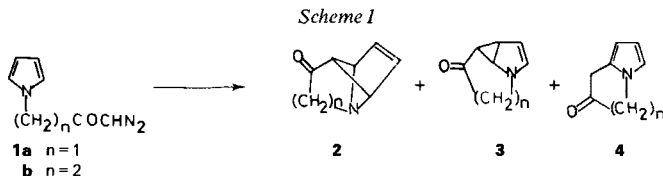
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Summary

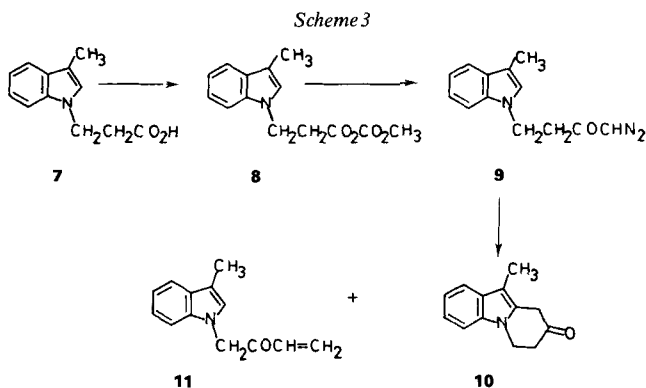
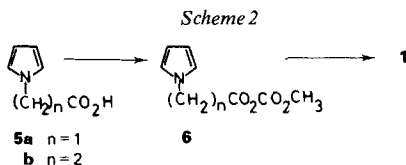
The copper-catalyzed pyrolysis of 1-diazo-3-(pyrrol-1-yl)-2-propanone (**1a**) and 1-diazo-4-(pyrrol-1-yl)-2-butanone (**1b**) in benzene solution gave 1*H*-pyrrolizin-2-(3*H*)-one (**4a**) and 5,6-dihydroindolizin-7(8*H*)-one (**4b**), respectively, in quantitative yield. Similar pyrolysis of 1-diazo-4-(3-methylindol-1-yl)-2-butanone (**9**) was less efficient giving 1-methylbenzo[*b*]-5,6-dihydroindolizin-7(8*H*)-one (**10**) and 4-(3-methylindol-1-yl)-but-1-en-3-one (**11**) in 7% and 24% yield, respectively.

Introduction. – The reactions of diazoacetates and diazomalonates with a wide variety of unsaturated compounds have received considerable attention over the last 30 years [1]. In most instances, loss of N₂ produces a carbene or carbenoid which gives a cyclopropane adduct in an intermolecular process. Although the intramolecular version possesses great synthetic potential, comparatively few examples have been reported [2]. In the present paper we are concerned with the possible intramolecular reactions of pyrroles bearing an *N*-substituted α -diazoketo group **1** (Scheme 1). In principle, three different courses are possible; 1,4-addition would give the cyclopentene derivative **2**, 1,2-addition the cyclopropane **3** and substitution at the α -position of the ring, the bicyclic product **4**. Nonetheless, it is recognized at the outset that cyclopropanation is not usually observed with pyrroles [3] and that 1,4-addition, despite a few special cases, is unlikely [4]. Moreover, adducts **2** and **3** would be expected to collapse to the substitution product **4**. In any event, these reactions would be of synthetic value as they permit the incorporation of the *N*-pyrrole entity into a complex bicyclic structure in a single step.



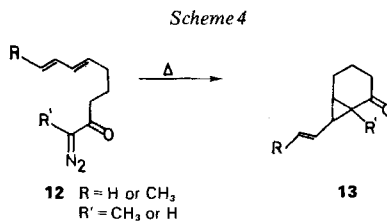
¹⁾ This work was presented at the autumn meeting of the Swiss Chemical Society, Berne, October 14, 1983.

Results. – The three diazoketones chosen, **1a**, **1b** and **9**, were prepared in good yield using conventional procedures. (1-Pyrrolyl)acetic (**5a**) and 3-(1-pyrrolyl)propionic acids (**5b**) were converted into their mixed anhydrides **6a** and **6b** and treated with CH_2N_2 to give **1a** and **1b** (*Scheme 2*). Submission of 3-(3-methyl-1-indolyl)propionic acid (**7**) to the same sequence gave the anhydride **8** and then its diazoketone derivative **9** (*Scheme 3*).



Pyrolysis of the diazoketone was carried out in dilute solutions of benzene containing a gram atom equiv. of Cu which were heated under reflux. Both pyrrole derivatives **1a** and **1b** gave quantitative yields of pyrrolizinone **4a** and dihydroindolizine **4b**. No other products were detected. In contrast, pyrolysis of the indole diazoketone **9** led to a complex mixture of products of which two were isolated and characterized. Unfortunately, cyclization only occurred to a minor extent to produce the dihydroindolizine **10** in 7% yield. The other product, the enone **11** obtained in 24% yield, was the result of rearrangement.

Discussion.—The cyclization of the simple pyrrole diazoketones is remarkable in that a sole product is formed in 100% yield. Such a result is expected of intramolecular carbene reactions for reasons of entropy, however, in practice, mixtures of products in variable yield are often obtained. For example, intramolecular cyclopropanations of diazonona-6,8-dien-2-ones (**12** → **13**, *Scheme 4*) occurred in yields between 38 and 95% depending on

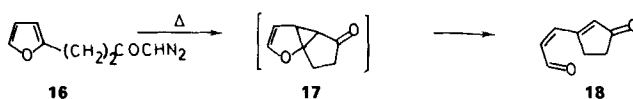


the nature of the substituents [5]. The 2-cyclohexenyl ester of α -substituted α -diazo acetic acid **14** gave the cyclopropane **15** in 32% yield, accompanied by a pair of dimers of unknown structure in 20% yield [6] (*Scheme 5*). When the olefin is replaced by a nucleophilic heterocycle, more efficient cyclization should be seen. The diazoketo derivative of furan **16** gave (*Z*)-3-(3-oxo-1-cyclopenten-1-yl)propenal (**18**) in 60% yield *via* the cyclopropane adduct **17** (*Scheme 6*) [7].

Scheme 5

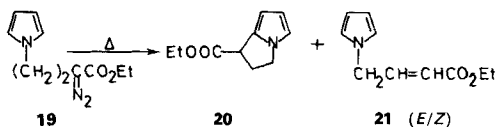


Scheme 6



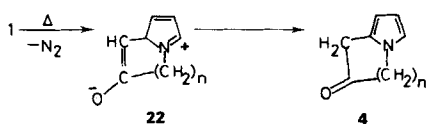
However, our results can be best compared with the behaviour of ethyl 2-diazo-4-(pyrrol-1-yl)butanoate (**19**) which provided the first example of an intramolecular attack of an α -keto carbenoid on the pyrrole nucleus [8]. Unfortunately, the reaction was not preparatively useful as the decomposition of **19** gave a mixture of (*Z*)- and (*E*)- α,β -unsaturated esters **21** together with the bicyclic product **20** in a yield of 35%, at best (*Scheme 7*). Clearly, the structure of the diazoketone **19** favours hydride shift despite competition offered by the nucleophilicity of the pyrrole ring.

Scheme 7

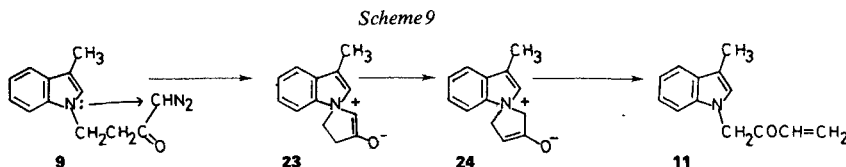


The advantage of the pyrrole diazoketones **1a** and **1b** is that hydride shift is not possible. Moreover, the use of Cu-catalyst ensures that a *Wolff* rearrangement is suppressed. Consequently, addition of the carbenoid to the α -position of the pyrrole proceeds unhampered to give the zwitterion **22** which, by prototropy, furnishes **1** (*Scheme 8*). The intermolecular counterpart of this reaction is the well-tried method for preparing α -pyrrole acetic acids which owes its success to the pronounced nucleophilic character at the α -position. Even so, some addition at the β -position occurs and yields are rarely better than 53% [9].

Scheme 8



The failure of the indole diazoketone **9** to cyclize in satisfactory yield can be attributed to the diminished nucleophilic character at the α -position of the indole nucleus [10]. The rearrangement which takes place instead is unusual, perhaps unprecedented. A plausible mechanism is that the electrophilic carbenoid centre engendered in **9** is attacked directly by the N-atom to produce the azaspirocyclic zwitterion **23** which, on isomerization to the new zwitterion **24**, then affords **11** by cleavage (*Scheme 9*).



Conclusion. – Having available a simple, efficient chemoselective method for preparing the pyrrolizinone and indolizinone rings in substantial quantities, it should be possible to accomplish in a straightforward manner syntheses of a wide variety of alkaloids possessing the aforementioned structural features which in the past have required complex multi-step procedures [11]. Three classes which should be accessible are the necine bases [12], pyrrolo[1,2-*a*]indoles such as mitosene [13] and the elaeo-carpus alkaloids [14]. Pertinent illustrations of our method will be reported in due course.

We thank Messrs. *J.-P. Saulnier* and *A. Pinto* for performing the NMR spectral measurements.

Experimental Part

General. Thin layer chromatography (TLC): silica gel 60 F_{254} Merck. Column chromatography (CC): silica gel 60, 230–400 mesh ASTM. All solvents were analytical grade Merck. Melting points (m.p.): Reichert hot-stage microscope (uncorrected). IR spectra: Perkin-Elmer 681 spectrometer. ^1H -NMR spectra (chemical shifts in ppm relative to internal TMS (= 0 ppm), coupling constants *J* in Hz: Varian XL 100 spectrometer or Bruker WH 360 spectrometer. ^{13}C -NMR spectra (chemical shifts in ppm relative to internal tetramethylsilane (= 0 ppm): Bruker WH 360 spectrometer. Et_2O was dried over LiAlH_4 and distilled prior to use. Elemental analyses were carried out by Drs *H.* and *K. Eder*, Service de Microchimie, Institut de Chimie Pharmaceutique, University of Geneva.

Ethyl (pyrrol-1-yl)acetate (ethyl ester of **5a**). The ethyl ester of glycine hydrochloride (7 g, 50.0 mmol) and KOAc (8 g, 82.0 mmol) were dissolved in the minimum amount of H_2O and added to glacial AcOH (50 ml). The solution was heated to reflux and 2,5-dimethoxytetrahydrofuran (6.6 g, 50.0 mmol) was added. The mixture was then heated at reflux (4 h) [15]. The resulting solution was neutralized with solid NaHCO_3 and extracted with AcOEt. The org. phase was separated, washed with brine, dried (Na_2SO_4) and then evaporated giving a light brown oil which on distillation under reduced pressure gave pure ester (5.9 g, 77% yield), b.p. $56^\circ/1$ Torr ([16]: $112^\circ/20$ Torr).

(Pyrrol-1-yl)acetic acid (5a). Ethyl (pyrrol-1-yl)acetate (1 g, 6.54 mmol) and a 20% solution of KOH in abs. MeOH (25 ml) were stirred at 20° for 12 h. Removal of solvent by evaporation gave a colourless solid which was dissolved in H_2O (25 ml) and carefully acidified with 5 M HCl. The solution was then extracted with 4 aliquots of Et_2O . The combined extracts were washed with brine and dried over Na_2SO_4 . Filtration and evaporation of the solvent afforded pure acid **5a** (0.81 g, 100%), m.p. 91.5° ([16]: 91.0°).

1-Diazo-3-(pyrrol-1-yl)-2-propanone (1a). Acid **5a** (0.7 g, 5.6 mmol) was converted to diazoketone **1a**, a yellow oil (0.83 g, 100%) in the same way as that used for **1b** (*v. infra*). IR (film): 2100 (C=N), 1635 (C=O). ^1H -NMR (100 MHz, CDCl_3): 4.58 (s, CH_2); 4.72 (s, CH=N); 6.24 (t, $J = 2$, 2H, β -pyrrolyl); 6.64 (t, $J = 2$, 2H, α -pyrrolyl).

3-(Pyrrol-1-yl)propionic acid (5b). Pure **5b** was prepared in 60% yield. m.p. 62.5° ([17]: 62°).

1-Diazo-4-(pyrrol-1-yl)-2-butanone (1b). Acid **5b** (1 g, 7.19 mmol) was converted to the mixed anhydride **6b** with methyl chloroformate and *N*-methylmorpholine in anh. Et_2O [18]. The solution so obtained was filtered and

added dropwise to an Et₂O-solution of CH₂N₂ prepared from *N*-nitroso-*N*-methyl-4-toluensulfonamide (3.2 g, 15.0 mmol) [19]. The solution was stirred at 20° for 4 h, filtered through *Celite* and evaporated to give pure diazoketone **1b** as a yellow oil (1.17 g, 100%). IR (film): 2105 (C=N), 1640 (C=O). ¹H-NMR (100 MHz, CDCl₃): 2.76 (t, *J* = 7, CH₂CO); 4.25 (t, *J* = 7, NCH₂); 5.14 (s, HC=N); 6.16 (t, *J* = 2.5, β-pyrrolyl); 6.67 (t, *J* = 2.5, α-pyrrolyl).

3-(3-Methylindol-1-yl)propionic acid (7). The reaction of 3-methylindole and acrylonitrile [20] followed by hydrolysis with aq. KOH *in situ* gave acid **7** in 50% yield, m.p. 80–81° ([21]: 81°).

1-Diazo-4-(3-methylindol-1-yl)-2-butanone (9). Acid **7** (0.4 g, 1.97 mmol) was converted quantitatively into diazoketone **9** (0.44 g) *via* the mixed anhydride **8**. IR (film): 2100 (C=N); 1635 (C=O). ¹H-NMR (100 MHz, CDCl₃): 2.35 (d, *J* = 1, CH₃); 2.78 (t, *J* = 7, CH₂CO); 4.45 (t, *J* = 7, NCH₂); 5.06 (s, CH=N); 6.90 (m, 1H, arom. H); 7.03–7.40 (m, 3H, arom. H); 7.54–7.66 (m, 1H, arom. H).

1H-Pyrrolizine-2(3H)-one (4a). A solution of diazoketone **1a** (167 mg, 1.12 mmol) and Cu-powder (70 mg, 1.12 mg-atom) in benzene (200 ml) was heated under reflux for 7 h. Workup (*cf.* **1b**, **4b**) gave pyrrolizone **4a** as a colourless solid which darkened on standing (135 mg, 100%); m.p. 105° (dec.). IR (CCl₄): 1765 (C=O). ¹H-NMR (360 MHz, CDCl₃): 3.53 (s, 2H–C(1)); 4.41 (s, 2H–C(3)); 6.05 (m, 1H–C(7)); 6.30 (t, *J* = 3, 1H–C(6)); 6.80 (m, 1H–C(5)). ¹³C-NMR (90.56 MHz, CDCl₃): 39.27 (t, C(1)); 54.22 (t, C(3)); 101.71 (d, C(7)); 111.12 (d, C(6)); 115.31 (d, C(5)); 130.05 (s, C(8)); 209.35 (s, C=O).

C₇H₇NO (121.14) Calc. C 69.41 H 5.83 N 11.56% Found C 69.63 H 6.01 N 11.39%

5,6-Dihydroindolizin-7(8H)-one (4b). Diazoketone **1b** (200 mg, 1.23 mmol) in dry benzene (200 ml) was heated under reflux. The reaction was monitored by observing the disappearance of the IR absorption at 2105 cm^{–1} (due to the diazo group) and was complete after 7 h. Filtration through *Celite*, and evaporation of the solvent yielded a yellow oil which became green on standing and which was judged from its NMR spectra to be pure **4b** (160 mg, 100%). Rapid CC (silica gel 60/CH₂Cl₂) produced a colourless oil which turned green on standing. IR (film): 1720 (C=O). ¹H-NMR (360 MHz, CDCl₃): 2.77 (t, *J* = 6, 2H–C(6)); 3.68 (d, *J* = 1, 2H–C(8)); 4.25 (t, *J* = 6, 2H–C(5)); 5.98 (m, 1H–C(1)); 6.14 (t, *J* = 3, 1H–C(2)); 6.68 (t, *J* = 3, 1H–C(3)). ¹³C-NMR (90.56 MHz, CDCl₃): 38.03 (t, CH₂); 39.45 (t, CH₂); 101.73 (d, arom. C); 111.32 (d, arom. C); 115.30 (d, arom. C); 124.87 (s, C(9)); 205.64 (s, C=O).

C₈H₉NO (135.17) Calc. C 71.09 H 6.71 N 10.36% Found C 71.12 H 7.00 N 9.90%

Pyrolysis of 1-diazo-4-(3-methylindol-1-yl)-2-butanone (9). A solution of **9** (297 mg, 1.31 mmol) in benzene (200 ml) containing Cu-powder (90 mg, 1.42 mg-atom) was heated under reflux for 2½ h. Filtration through *Celite* and evaporation of the solvent afforded a yellow oil (152 mg, 58%) which on TLC (silica gel, CH₂Cl₂) revealed two main products and many minor polar products. By flash CC (silica gel, CHCl₃/light petroleum ether (4:1)) *4-(3-methylindol-1-yl)but-1-en-3-one (11)* was obtained as a yellow oil (62 mg, 24%). IR (film): 1700 (C=O). ¹H-NMR (360 MHz, CDCl₃): 2.42 (s, CH₃); 4.90 (s, NCH₂); 5.79, 5.82, 6.21, 6.24, 6.25, 6.28, 6.33, 6.42 (m, CH₂=CH); 6.85 (s, 1H); 7.17–7.30 (m, 3H); 7.68 (m, 1H). ¹³C-NMR (90.56 MHz, CDCl₃): 9.47 (q, CH₃); 53.70 (t, NCH₂); 108.74 (d, arom. C); 111.82 (s, arom. C); 119.14 (d, arom. C); 119.20 (d, arom. C); 122.01 (d, arom. C); 125.82 (d, arom. C); 129.02 (s, arom. C); 130.00 (t, =CH₂); 131.94 (d, =CH); 136.79 (s, arom. C); 194.85 (s, C=O).

C₁₃H₁₃NO (199.25) Calc. C 78.36 H 6.58 N 7.03% Found C 78.78 H 6.85 N 7.33%

*1-Methylbenzof[*b*]-5,6-dihydroindolizin-7(8H)-one (10)* was also obtained as a yellow oily solid, slightly impure (17 mg, 7%); IR (CCl₄): 1730 (C=O). ¹H-NMR (360 MHz, CDCl₃): 2.20 (s, CH₃); 2.29 (t, *J* = 6, CH₂CO); 3.78 (s, 2H–C(1)); 4.33 (t, *J* = 6, NCH₂); 7.10–7.30 (m, 3H, arom. H); 7.52 (d, *J* = 8, 1H, arom. H). ¹³C-NMR (90.56 MHz, CDCl₃): 8.03 (q, CH₃); 38.00 (t, CH₂); 39.23 (t, CH₂); 39.42 (t, CH₂); 108.32 (d, arom. C); 118.43 (d, arom. C); 119.24 (d, arom. C); 121.16 (d, arom. C); 128.54 (s, arom. C); 135.44 (s, arom. C); 136.05 (s, arom. C); 204.90 (s, C=O).

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