269. Intramolecular Carbenoid Reactions of Pyrrole Derivatives

Efficient Syntheses of Pyrrolizinone and Dihydroindolizinone[1])

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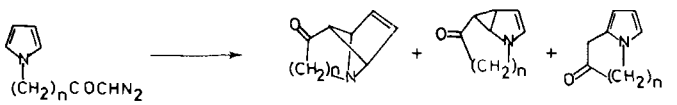
Summary

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 N_2 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.

Scheme 1



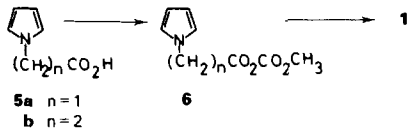
1a n=1
b n=2

2 **3** **4**

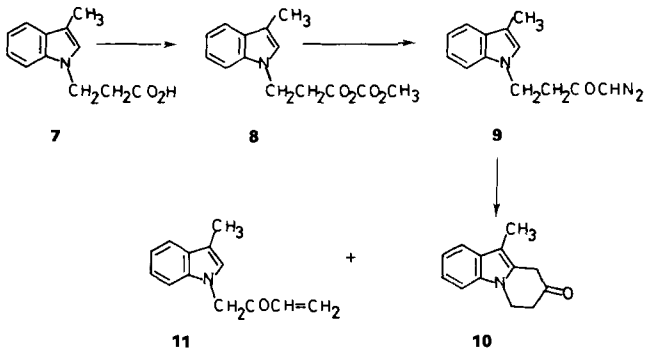
[1]) This work was presented at the autumn meeting of the Swiss Chemical Society, Berne, October 14, 1983.

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)*.

Scheme 2



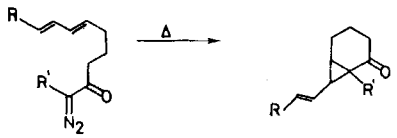
Scheme 3



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 dihydroindolizinone **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 dihydroindolizinone **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

Scheme 4



12 R = H or CH_3
R' = CH_3 or H

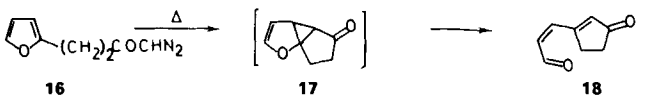
13

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

14 **15**

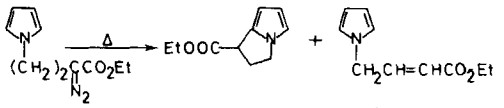
Scheme 6



16 **17** **18**

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.

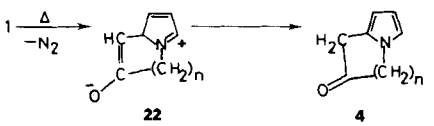
Scheme 7



19 **20** **21** (*E*/*Z*)

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].

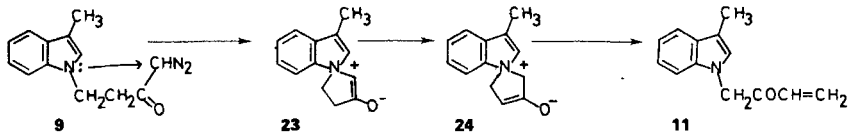
Scheme 8



22 **4**

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)*.

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 elaeocarpus 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. ^{1}H-NMR spectra (chemical shifts in ppm relative to internal TMS (= 0 ppm), coupling constants *J* in Hz: *Varian XL 100* spectrometer or *Brucker 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°/1 Torr ([16]: 112°/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=0). ^{1}H-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 Et_2O-solution of CH_2N_2 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). ^{1}H-NMR (100 MHz, $CDCl_3$): 2.76 (*t*, *J* = 7, CH_2CO); 4.25 (*t*, *J* = 7, NCH_2); 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). ^{1}H-NMR (100 MHz, $CDCl_3$): 2.35 (*d*, *J* = 1, CH_3); 2.78 (*t*, *J* = 7, CH_2CO); 4.45 (*t*, *J* = 7, NCH_2); 5.06 (*s*, CH=N); 6.90 (*m*, 1 H, arom. H); 7.03–7.40 (*m*, 3 H, arom. H); 7.54–7.66 (*m*, 1 H, 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 pyrrolizinone **4a** as a colourless solid which darkened on standing (135 mg, 100%); m.p. 105° (dec.). IR (CCl_4): 1765 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 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)). ^{13}C-NMR (90.56 MHz, $CDCl_3$): 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).

C_7H_7NO (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 benezene (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/CH_2Cl_2) produced a colourless oil which turned green on standing. IR (film): 1720 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 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)). ^{13}C-NMR (90.56 MHz, $CDCl_3$): 38.03 (*t*, CH_2); 39.45 (*t*, CH_2); 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).

C_8H_9NO (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 $2^1/_2$ h. Filtration through *Celite* and evaporation of the solvent afforded a yellow oil (152 mg, 58%) which on TLC (silica gel, CH_2Cl_2) revealed two main products and many minor polar products. By flash CC (silica gel, $CHCl_3$/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). ^{1}H-NMR (360 MHz, $CDCl_3$): 2.42 (*s*, CH_3); 4.90 (*s*, NCH_2); 5.79, 5.82, 6.21, 6.24, 6.25, 6.28, 6.33, 6.42 (*m*, CH_2=CH); 6.85 (*s*, 1H); 7.17–7.30 (*m*, 3H); 7.68 (*m*, 1H). ^{13}C-NMR (90.56 MHz, $CDCl_3$): 9.47 (*q*, CH_3); 53.70 (*t*, NCH_2); 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*, $=CH_2$); 131.94 (*d*, =CH); 136.79 (*s*, arom. C); 194.85 (*s*, C=O).

$C_{13}H_{13}NO$ (199.25) Calc. C 78.36 H 6.58 N 7.03% Found C 78.78 H 6.85 N 7.33%

1-Methylbenzo[b]-5,6-dihydroindolizin-7(8H)-one (**10**) was also obtained as a yellow oily solid, slightly impure (17 mg, 7%): IR (CCl_4): 1730 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 2.20 (s, CH_3); 2.29 (*t*, *J* = 6, CH_2CO); 3.78 (*s*, 2H–C(1)); 4.33 (*t*, *J* = 6, NCH_2); 7.10–7.30 (*m*, 3H, arom. H); 7.52 (*d*, *J* = 8, 1H, arom. H). ^{13}C–NMR (90.56 MHz, $CDCl_3$): 8.03 (*q*, CH_3); 38.00 (*t*, CH_2); 39.23 (*t*, CH_2); 39.42 (*t*, CH_2); 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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