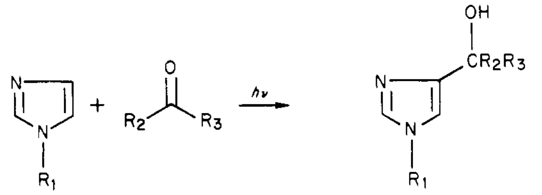
Regioselective Photoaddition of Pyrroles and Aliphatic Carbonyl Compounds. A New Synthesis of 3(4)-Substituted Pyrroles

Summary: Photolysis of a series of pyrroles in the presence of alkanals or alkanones gives 3-(1-hydroxyalkyl)pyrroles (imidazoles behave similarly); the 3-substituted pyrroles, which result from Paterno–Büchi photocycloaddition followed by rearrangement, are easily dehydrated to 3-(1-alkenyl)pyrroles or oxidized to 3-acylpyrroles.

Sir: Access to 3(4)-substituted pyrroles has been a stubborn problem in synthetic heterocyclic chemistry.[1] All general methods require several steps and/or the simultaneous introduction of several ring substituents.[2] We wish to report a convenient preparation of pyrroles substituted cleanly in the 3(4) position with groups having varied functionality. The sequence of reactions is based on the photochemical addition of pyrroles and aliphatic carbonyl compounds.

Irradiation through Vycor or Corex of a series of pyrroles and alkanals or alkanones using standard equipment (450 W lamp, immersion well, nitrogen purge) resulted in a rapid conversion of starting materials which included pyrrole (**1**), *N*-methylpyrrole (**2**), 1,2,5-trimethylpyrrole (**3**), 1-(2-cyanoethyl)pyrrole (**4**), acetaldehyde (**5**), butyraldehyde (**6**), and acetone (**7**) (Chart I). Photoproducts were obtained cleanly by vacuum distillation and identified as the hydroxyalkylpyrroles **8** based on IR, NMR, and MS spectral data and microanalysis. The important regiochemical assignment for the photoadducts was based on NMR data[3] and a chemical correlation described below.

Most runs were made to moderate conversion of addends so that isolated yields (Table I) based on limiting reagent were relatively low. Correction for recovered starting material showed that intrinsic yields are generally good (numbers in parenthesis). Pyrrole itself (**1**) appeared to be the most reluctant to photoadd, whereas **2**–**4** gave adducts similarly well. 1,2,5-Trimethylpyrrole (**3**) yielded volatile side products which have been tentatively identified.[5] Success with **4** suggested that photoreaction tolerates at least modest additional functionality. Imidazoles were also suitable addends; several combinations of imidazole (**10**) and 1-methylimidazole (**11**) with prototype carbonyls gave adducts **12** in 64–88% (adjusted) yield. The site of addition (4 position) was verified by comparison of the *p*-nitrobenzoate of **12b** (mp 119–120 °C) with the known *p*-nitrobenzoate derivatives of 1-methyl(1-hydroxyethyl)imidazoles (2, 4, and 5 isomers), mp 101–102 °C, 114–116 °C, and 127–128 °C, respectively.[6,7]

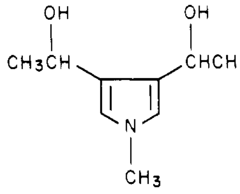


10, **11**

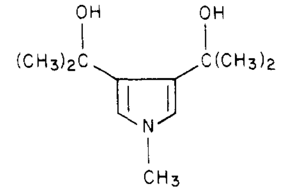
12a, $R_1 = R_2 = H$; $R_3 = CH_3$
b, $R_1 = R_3 = CH_3$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_2CH_2CH_3$
d, $R_1 = R_2 = R_3 = CH_3$

Pyrrole photoadducts were obtained on a respectable scale under a variety of conditions. On photolysis in acetonitrile (Corex filter, 17 h, 0.5 M) *N*-methylpyrrole (**2**; 9.1 g, 0.11 mol) and butyraldehyde (**6**; 8.2 g, 0.11 mol) gave 5 g of virtually pure **9e** after removal of solvent and unreacted addends and simple vacuum distillation. In a scaled up experiment **2** (53 g, 0.74 mol) and **6** (55 g, 0.68 mol) were photolyzed through Vycor for 48 h without solvent and yielded 27 g (26%) of **9e**.

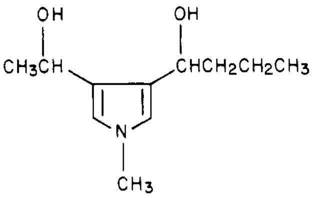
Extended irradiation of **1**–**4** with excess carbonyl compound resulted in formation of higher molecular weight products assigned 2:1 adduct structures. "Double addition" to the pyrrole nucleus was most successfully carried out in sequential photolyses. Thus, distilled adducts **8d** and **8f** were photolyzed in acetonitrile with acetaldehyde, butyraldehyde, or acetone and gave diols **13** [bp 145–150 °C (0.2 mm)], **14** (mp 141–143 °C), and "cross adduct" **15** [bp 158–162 °C (0.1 mm)] in about 50% yield (based on unrecovered starting material).



13



14



15

Photoadducts **8** were not stable for extended periods and were particularly susceptible to dehydration. In two cases (**8i** and **8k**) alkenylpyrroles **9** accompanied initial photoadducts as distillation products. In other cases gas chromatography of adducts resulted in formation of derivatives **9** which were isolated and identified from spectral data.[8] Synthetically useful yields of alkenylpyrroles were obtained by vapor-phase pyrolysis (quartz tube, 500 °C, nitrogen flow, 170 mL/min) [e.g., **9d**, bp 45–47 °C (3 mm), 84%; **9f**, bp 55–57 °C (2 mm), 75%].

Another potentially useful series of compounds was obtained by oxidation of **8a,d,e**. Thus, treatment of photoadducts with MnO_2/CH_2Cl_2 (reflux temperature, 16 h) gave ketones **16** (71–77%). The more stable acyl-

---

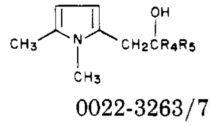
[1] R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, New York, 1977, Chapter 3.

[2] (a) C. E. Loader and H. J. Anderson, *Tetrahedron*, **25**, 3879 (1969); (b) M. W. Rommi and S. F. MacDonald, *Can. J. Chem.*, 48, 1689 (1970); (c) J.-V. Valnot, *Synthesis*, 590 (1978).

[3] The 2- and 5-hydrogens of 1-alkyl-3-(1-hydroxyalkyl)pyrroles have a chemical shift near δ 6.3 (2 H) and the 4-hydrogen absorbs near δ 5.8 (1 H), whereas the 5-hydrogen of 1-methyl-2-(1-hydroxyethyl)pyrrole has a chemical shift of δ 6.2 and the 3- and 4-hydrogens absorb at δ 5.7.[4]

[4] G. T. Bruice, A. R. Cooksey, and K. J. Morgan, *J. Chem. Soc., Perkin Trans.* 2, 553 (1975).

[5] The NMR and IR spectral data as well as C, H, and N analysis are consistent with the structure



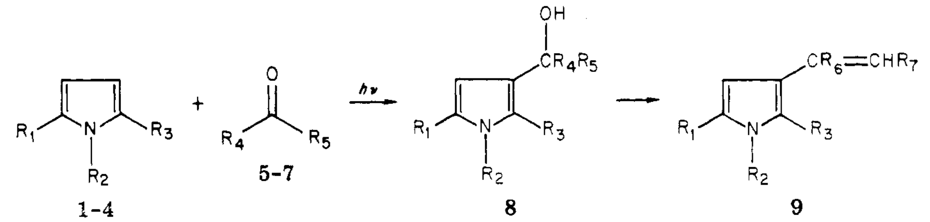
[6] D. S. Noyce and G. T. Stowe, *J. Org. Chem.*, **38**, 3765 (1973).

[7] The ^1H NMR spectrum ($CDCl_3$) of the *p*-nitrobenzoate of **12b** is δ 1.78 (d, 3, $\mathbf{CH_3}CH(OH)-$), 3.68 (s, 3, CH_3N), 6.12 (q, 1, $\mathbf{CH}(OH)CH_3$), 6.97 (br, s, 1, 5-H), 7.35 (br, s, 1, 2-H) and 8.10 (s, 4, $C_6H_4NO_2$). These chemical shifts compare favorably with those reported for the 4-substituted imidazole but not for the 2- or 5-substituted imidazoles.

[8] Spectral data for a typical alkene (**9d**): ^1H NMR ($CDCl_3$) δ 3.45 (s, 3, CH_3N), 4.71 (d of d, J = 10.5 and 2.0 Hz, 1, terminal methylene) 5.12 (d of d, J = 17 and 2 Hz, 1, terminal methylene), and 5.09–6.53 (m, 4, 2,4,5-pyrrole and 1-vinyl H); IR 1660 cm^{-1} (C=C stretch); MS *m/e* (rel intensity) 107 (mol ion, 72), 106 (61), 65 (47), 51 (41), 42 (64), and 39 (100). GLC analysis suggested that stereoisomeric alkenylpyrroles were formed. Ratios of 77:23 and 75:25 (trans configuration presumeably predominating) were obtained for **9e** and **9h**, respectively.

0022-3263/79/1944-2949$01.00/0

Chart I



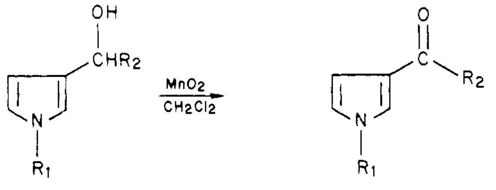
1-4 5-7 8 9

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
a	H	H	H	H	CH_3		
b	H	H	H	H	$CH_2CH_2CH_3$		
c	H	H	H	CH_3	CH_3		
d	H	CH_3	H	H	CH_3	H	H
e	H	CH_3	H	H	$CH_2CH_2CH_3$	H	CH_2CH_3
f	H	CH_3	H	CH_3	CH_3	CH_3	H
g	CH_3	CH_3	CH_3	H	CH_3	H	H
h	CH_3	CH_3	CH_3	H	$CH_2CH_2CH_3$	H	CH_2CH_3
i	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	H
j	H	CH_2CH_2CN	H	H	$CH_2CH_2CH_3$	H	CH_2CH_3
k	H	CH_2CH_2CN	H	CH_3	CH_3	CH_3	H

Table I. Physical Properties and Yields of Photoadducts 8

3-(1-hydroxyalkyl)-pyrroles (8)	bp, °C (mmHg)	yield, %[a]
8a	115-120 (0.1)	12 (28)
8b	154-155 (2.2)	(24)
8c	103-105 (2.5)	(6)
8d	70-74 (0.2)	38 (74)
8e	98-102 (2.0)	29 (60)
8f	62-64 (0.1)	40 (92)
8g	77-79 (0.2)	3 (5)
8h	99-112 (0.2)	11 (15)
8i	83-120 (0.4)	31 (56)[b]
8j	173-178 (0.4)	43 (85)
8k	149-150 (0.1)	31 (52)

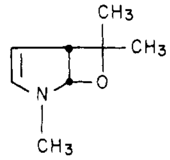
[a] Isolated yield based on limiting reagent. Numbers in parenthesis are yields corrected for recovered starting material. [b] Photoadduct 8i obtained contaminated with small amounts of 9i and side-chain substitution product (see ref 5) (NMR analysis).



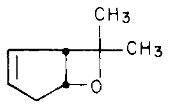
16a, $R_1 = H; R_2 = CH_3$
b, $R_1 = CH_3; R_2 = CH_3$
c, $R_1 = CH_3; R_2 = CH_2CH_2CH_3$

pyrroles were identified from spectral data and microanalysis. the IR[9] and ^1H NMR[10] spectra of 3-acetylpyrrole (**16a**) were identical with that reported. The ^1H NMR spectrum[11] and boiling point[4] of **16b** compared favorably with data reported for 3-acetyl-1-methylpyrrole but not for 2-acetyl-1-methylpyrrole which is readily available.[13] The latter ketone was reduced with $NaBH_4$ to the known[4] 2-(1-hydroxyethyl)-1-methylpyrrole (mp 23–25 °C), which was shown to be different from **8d**.

The mechanism of photoaddition of pyrroles and aliphatic carbonyl compounds is not yet known with certainty. The precedent, however, is strong for the involvement of oxetanes **17** as intermediates and a rearrangement of the expectedly unstable amino ether linkage. Paterno–Büchi cycloaddition of furans and aliphatic carbonyls is known[13] and the catalyzed rearrangement of furan photoadducts to hydroxyalkylfurans has been reported.[14] Electron-deficient pyrroles and aryl ketones have been shown to give stable oxetane photoadducts,[15] and the addition of ketones and imidazoles giving hydroxyalkyl derivatives has been reported.[16,17]



17



18

Careful ^1H NMR analysis of photolysates provided evidence that oxetanes are indeed formed. Irradiation of **2** in acetone (solvent) at room temperature or at 0 °C provided solutions showing minor absorptions at δ 0.99, 1.44, and 3.08 along with signals for **8f**. The equally intense singlets which disappeared on concentration of the photolysate were assigned to the *endo*-methyl, *exo*-methyl, and *N*-methyl groups of the expected adduct **17**. The *C*-methyl resonances compared favorably with those found for cyclopentadiene–acetone adduct **18** (δ 1.06 and 1.47).[18] Similar examination prior to workup of photolysate from irradiation of **11** and acetone also suggested formation of an oxetane.

Studies of the mechanism of pyrrole–carbonyl photoaddition and synthetic application of the now readily available 3-substituted heterocycles are currently underway.

Acknowledgments. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 1, 109-97-7; 2, 96-54-8; 3, 930-87-0; 4, 43036-06-2; 5, 75-07-0; 6, 123-72-8; 7, 67-64-1; **8a**, 70749-40-5; **8b**, 70714-16-8; **8c**, 70714-17-9; **8d**, 70702-65-7; **8e**, 70702-66-8; **8f**, 70702-67-9; **8g**,

---

(9) A. J. Castro, J. R. Lowell, Jr., and J. P. March, Jr., *J. Heterocycl. Chem.*, 207 (1964).

(10) K. J. Morgan and D. P. Morrey, *Tetrahedron*, **27**, 245 (1971).

(11) We thank Professor H. J. Anderson for providing spectral and other data for 3-acetyl-1-methylpyrrole.

(12) Obtained from Aldrich Chemical Co.

(13) (a) S. Toki, K. Shima, and H. Sakurai, *Bull. Chem. Soc. Jpn.*, **38**, 760 (1965); (b) K. Shima and H. Sakurai, *ibid.*, **39**, 1806 (1966).

(14) A. Zamojski and T. Kozluk, *J. Org. Chem.*, **42**, 1089 (1977).

(15) C. Rivas, M. Velez, M. Cacarella, R. A. Bolivar, and S. E. Flores, *Aceta Cient. Venezolana*, **22**, 145 (1971); C. Rivas and R. A. Bolivar, *J. Hetrocycl. Chem.*, **13**, 1037 (1976).

(16) T. Matsuura, A. Banba, and K. Ogura, *Tetrahedron*, **27**, 1211 (1971).

(17) T. Nakano, C. Rivas, C. Perez, and J. M. Larrauri, *J. Heterocycl. Chem.*, **13**, 173 (1976).

(18) E. H. Gold and D. Ginsberg, *Angew. Chem., Int. Ed. Engl.*, **5**, 246 (1966).

(19) On sabbatical leave from Southwestern at Memphis, Memphis, Tennessee.

70702-68-0; **8h**, 70702-69-1; **8i**, 70702-70-4; **8j**, 70702-71-5; **8k**, 70702-72-6; **9d**, 70702-73-7; **9e**, 70702-74-8; **9f**, 70702-75-9; **9g**, 70702-76-0; **9h**, 70702-77-1; **9i**, 70702-78-2; **9j**, 70702-79-3; **9k**, 70702-80-6; **10**, 288-32-4; **11**, 616-47-7; **12a**, 70702-81-7; **12b**, 70702-82-8; **12b** *p*-nitrobenzoate, 41507-39-5; **12c**, 70702-83-9; **12d**, 45786-14-9; **13**, 70702-84-0; **14**, 70702-85-1; **15**, 70702-86-2; **16a**, 1072-82-8; **16b**, 932-62-7; **16c**, 62128-46-5; **17**, 70702-87-3; **18**, 5202-71-1; 2-acetyl-1-methylpyrrole, 932-16-1; 2-(α-hydroxyethyl)-1-methylpyrrole, 56423-58-6; 2-(β-hydroxypropyl)-1,5-dimethylpyrrole, 70702-88-4; 2-(β-hydroxypentyl)-1,5-dimethylpyrrole, 70702-89-5; 2-(2-hydroxy-2-methylpropyl)-1,5-dimethylpyrrole, 70702-90-8.

Guilford Jones, II,* Helmuth M. Gilow,[19],* Julie Low
Department of Chemistry, Boston University
Boston, Massachusetts 02215

Received March 15, 1979

Base Decomposition of Azides Leading to Nitriles

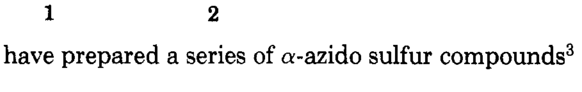
Summary: α-Azido sulfides, sulfoxides, sulfones, and nitriles bearing an α-hydrogen atom react with base to give nitriles.

Sir: We wish to point out a generally unrecognized property of the azide group: its ability to function under basic conditions as an intramolecular oxidizing agent.

There are scattered reports in the literature[1] of the reactions of α-azido ketones with base to give α-diketones (or α-imino ketones) and one report of the reaction of an allylic azide with strong base to give (upon aqueous workup) an α,β-unsaturated aldehyde.[2] It was suggested that these reactions involved the intermediacy of α-azido carbanions which lose molecular nitrogen to give imines that are readily hydrolyzed to ketones or aldehydes. We now present results which are consistent with the above proposed pathway and further extend these reactions by noting that when the electron-withdrawing group attached to the α-carbon atom of a primary or secondary azide is a leaving group, nitriles are produced. This is most dramatically illustrated by the conversion of phenylacetonitrile to benzonitrile in 90% yield in a simple two-step procedure.

$$PhCH_2CN \xrightarrow[\text{2. excess } N_3^-/Me_2SO]{\text{1. NBS/CCl}_4} PhCN + N_2 + CN^- \quad (1)$$

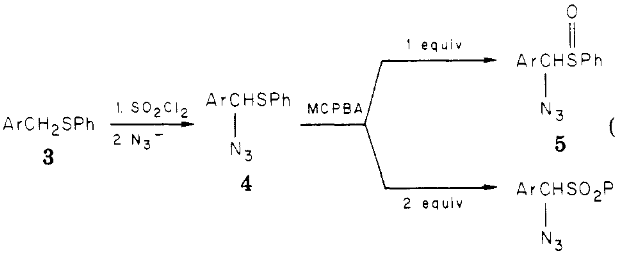
The crude α-bromophenylacetonitrile is added to a solution of excess sodium azide in Me$_2$SO at room temperature, whereupon copious amounts of gas (presumably N$_2$) are evolved. The α-azido nitrile (**1**) presumably is formed, but under the reaction conditions, azide ion is sufficiently basic to deprotonate **1** giving carbanion **2** which then ejects nitrogen and cyanide ion (eq 2).



(2)

1 **2**

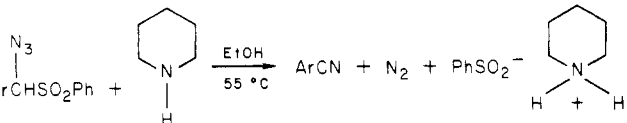
We have prepared a series of α-azido sulfur compounds[3] (eq 3) and have studied in detail the reactions of α-azido sulfones with base which give nitriles. The syntheses of the α-azido sulfides were accomplished in good yields except in the case where the aryl group was *p*-nitrobenzyl. Although α-chlorination proceeded smoothly,[4] treatment of the resulting α-chloro-*p*-nitrobenzyl phenyl sulfide with sodium azide gave *p*-nitrobenzonitrile, a reaction analogous to that observed with α-bromophenylacetonitrile (eq 2).



3 **4** **5** **6** (3)

a, Ar = C_6H_5
b, Ar = m-ClC_6H_4
c, Ar = p-ClC_6H_4
d, Ar = p-CNC_6H_4
e, Ar = p-$CH_3C_6H_4$

Azides **4**, **5**, and **6** all react with base to give the corresponding benzonitriles, although as expected stronger bases are required as one goes from sulfone to sulfoxide to sulfide.[5] Because of the ease of reaction of azido sulfones with base, the scope of this reaction was investigated. The α-azidobenzyl phenyl sulfones **6** react readily with piperidine in ethanol at 55 °C to give benzonitriles in 70–90% yield. Benzenesulfinate was methylated (CH$_3$I) and isolated as methyl phenyl sulfone (eq 4).



(4)

a, Ar = C_6H_5
b, Ar = m-ClC_6H_4
c, Ar = p-ClC_6H_4
d, Ar = p-CNC_6H_4
e, Ar = p-$CH_3C_6H_4$

Treatment of α-azido-β-phenethyl phenyl sulfone (**7**) with sodium methoxide at 60 °C gave phenylacetonitrile in 85% yield. Similarly, the adamantylazido sulfone **8** gave 1-adamantanecarbonitrile in 90% yield when treated with potassium *tert*-butoxide in THF. Weaker base systems proved less effective with these azides presumably due to their lower acidity. On the other hand, typical α-azidoalkyl phenyl sulfones, e.g. **9** and **10**, reacted with these stronger base systems liberating nitrogen, but gave no isolable nitriles. Control experiments showed that the expected nitriles did not survive the strongly basic reaction conditions.

In conclusion, we note that when an azido group is attached to a carbon bearing both a hydrogen atom and an electron-withdrawing group, the carbon atom is readily oxidized (–N$_3$ being reduced to molecular nitrogen) under basic conditions. If the electron-withdrawing group is also a potential leaving group (e.g. –CN or –SO$_2$Ph), then

---

[1] (a) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **87**, 826 (1903); **91**, 867 (1907); (b) J. H. Boyer and F. C. Canter; *Chem. Rev.*, **54**, 1 (1954); (c) O. E. Roberts and K. K. Purushothaman, *Can. J. Chem.*, **42**, 712 (1964).

[2] A. Hassner and J. S. Teeter, *J. Org. Chem.*, **35**, 3397 (1970).

[3] The details of the syntheses and thermal reactions will be presented in a full paper. Analytical data and physical properties of compounds **6a–e**, **7**, **8**, **9**, and **10** are presented in the supplementary table.

[4] Chlorination of *p*-methoxybenzyl phenyl sulfide resulted in the formation of benzenesulfenyl chloride and benzyl chloride (carbon–sulfur bond cleavage). Based on previous work, this result was not unexpected: see B. B. Jarvis and M. M. Evans, *J. Org. Chem.*, **39**, 643 (1974), and references cited therein.

[5] Although the α-azidobenzyl sulfones reacted with relatively weak bases, α-azidobenzyl sulfides required significantly stronger base systems (e.g. potassium *tert*-butoxide) in order to lose molecular nitrogen. Use of milder bases (e.g. cyclohexylamine) typically gave substitution reactions: