Phototransposition Chemistry of 1-Methyl-4-phenylpyrazole. A New Intermediate on the P_4 Pathway

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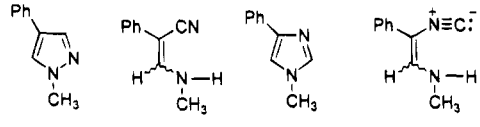
1,4-Disubstituted pyrazoles are known to undergo phototransposition to 1,4-disubstituted imidazoles *via* a P_4 permutation process.[1-4] These reactions are known to proceed by way of a photocleavage–photocyclization pathway involving isolable enaminonitriles[1,5-7] and by a less well-defined pathway not involving an enaminonitrile intermediate.[1] Although by analogy with isoxazole phototransposition chemistry[8] this alternate pathway has been suggested to involve iminoazirine intermediates,[1,2] no such compounds have been isolated in the pyrazole → imidazole transposition. We now wish to report that this alternative pathway involves an isocyanide intermediate.

A solution of 1-methyl-4-phenylpyrazole (**1**) (3.0 mL, 2.0×10^{-2} M) in methanol was irradiated at 254 nm for 3.0 h while the solution was continuously purged with a fine stream of nitrogen. Gas–liquid chromatographic (GLC) analysis of the resulting solution showed that irradiation was accompanied by the consumption of 98% of **1** and the formation of 3-(*N*-methylamino)-2-phenylpropenenitrile (**2**) and 1-methyl-4-phenylimidazole (**3**), identified by direct chromatographic and spectroscopic comparison with authentic samples of these compounds synthesized in this laboratory. ^{1}H NMR analysis of the residue left after evaporation of the irradiated solution showed singlets at δ 3.92 and 3.70 due to the *N*-methyl groups of **1** and **3**, respectively, and also two doublets (J = 4.5 Hz) of essentially equal area at δ 2.93 and 3.06 due to the *N*-methyl groups of the (*E*) and (*Z*) isomers of **2**. The yields of (*E*)-**2**, (*Z*)-**2**, and **3**, determined by quantitative GLC and ^{1}H NMR analyses, were 6.2%, 5.6%, and 70.8%, respectively.[9]



1 2 3 4

A solution of **2** (97% *Z*:3% *E*, 3.0 mL, 2.0×10^{-2} M) was also irradiated at 254 nm for 3.0 h. Quantitative ^{1}H NMR analysis of the residue left after evaporation of the solvent showed the presence of a singlet at δ 3.70, confirming the formation of **3** in 33% yield and also revealed that the ratio of the doublets at δ 2.93 and 3.06 due to the *N*-methyl groups of the *E* and *Z* isomers of **2** had changed from 1:32 before photolysis to 1:2.5 after irradiation as a result of a 42% consumption of **2** (*Z*) and the formation of **2** (*E*) in 36% yield. These results show that **2** undergoes both *E*/*Z* photoisomerization and photoconversion to **3**. This confirms that the photocleavage–photocyclization pathway *via* enaminonitrile **2** constitutes one pathway for the phototransposition of **1** to **3**. When, however, solutions of **1** and **2** (3.0 mL, 2.0×10^{-2} M) in methanol were irradiated simultaneously for 3.0 h on a merry-go-round apparatus, GLC and ^{1}H NMR analyses showed that 99% of **1** and 13% of **2** had been consumed and that 1-methyl-4-phenylimidazole (**3**) was formed in 71% yield from **1** and in 33% yield from **2**. Since these yields represent relative quantum yields, they clearly indicate that the transposition pathway *via* **2** cannot be the only route for the formation of **3** from **1**.

Monitoring the photoreaction by UV-absorption spectroscopy further confirmed this suggestion. Thus, when a solution of 1-methyl-4-phenylpyrazole (**1**) (3.0 mL, 2.0×10^{-2} M) in methanol was subjected to four consecutive 15 min irradiations, GLC analysis of the final solution showed 76.4% consumption of pyrazole (**1**). After each 15 min of irradiation, an aliquot was removed and diluted 1:500. Analysis of the resulting solutions by UV absorption spectroscopy showed a continuous increase in the optical density at 312 nm, where enaminonitrile **2** is known to absorb, until it reached a value of 0.34 after 60 min of irradiation. On the basis of the known extinction coefficient for **2** at 312 nm of 11 480, this optical density would require the formation of enaminonitrile **2** in a yield of 90%. This is substantially larger than the total yield of **2** subsequently detemined by ^{1}H NMR analysis to be 16.4%. Furthermore, although experiments show that enaminonitrile **2** in methanol is unchanged by the addition of a small quantity of HCl, acidification of the irradiated solution resulted in the immediate decrease in the optical density at 312 nm from 0.34 to almost 0. These results show that after 60 min of irradiation most of the absorption at 312 nm cannot be due to enaminonitrile **2** but must be due to some other compound which has a much larger extinction coefficient than **2** and which is very sensitive to acid.

^{1}H NMR analysis of the residue left after evaporation of the solvent showed the expected singlet at δ 3.70 due

(1) Pavlik, J. W.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6313.
(2) Pavlik, J. W.; Connors, R. E.; Burns, D. S.; Kurzweil, E. M. *J. Am. Chem. Soc.* **1993**, *115*, 7645.
(3) For a discussion of permutation pattern analysis in aromatic phototransposition chemistry and in five-membered heteroaromatic phototransposition chemistry see: Barltrop, J. A.; Day, A. C. *J. Chem. Soc. Chem. Commun.* **1975**, 177. Barltrop, J. A.; Day, A. C.; Ward, R. W. *J. Chem. Soc., Chem. Commun.* **1978**, 131.
(4) For five-membered ring heterocycles containing two heteroatoms there are 12 different ways of transposing the five ring atoms resulting in 12 permutation patterns identified P_1–P_{12}. For a table showing these permutation patterns, see ref 1.
(5) Barltrop, J. A.; Day, A. C.; Mack, A. G.; Sharisa, A.; Wakamatsu, S. *J. Chem. Soc., Chem. Commun.* **1981**, 604.
(6) Wakamatsu, S.; Barltrop, J. A.; Day, A. C. *Chem. Lett.* **1982**, 667.
(7) For additional examples of the photocyclization of enaminonitriles see: (a) Ferris, J. P.; Kuder, J. E.; Catalano, A. W. *Science* **1969**, *166*, 765. (b) Ferris, J. P.; Kuder, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 2527. (c) Ferris, J. P.; Trimmer, R. W. *J. Org. Chem.* **1976**, *41*, 19. (d) Koch, T. H.; Rodehorst, R. M. *J. Am. Chem. Soc.* **1974**, *96*, 6707. (e) Ferris, J. P.; Narang, R. S.; Newton, T. A.; Rao, V. R. *J. Org. Chem.* **1979**, *44*, 1273.
(8) (a) Kurtz, D. W.; Schechter, H. *J. Chem. Soc., Chem. Commun.* **1966**, 689. (b) Ullman, E. F.; Singh, G. *J. Am. Chem. Soc.* **1966**, *88*, 1844; **1967**, *89*, 6911. (c) Singh, A.; Azeig, A.; Gallivan, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 1199. (d) Nishiwaki, T.; Nakano, A.; Matsuoka, H. *J. Chem. Soc. C* **1970**, 1825. (e) Nishiwaki, T.; Fujiyama, F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1456. (f) Wamhoff, H. *Chem. Ber.* **1972**, *105*, 748. (g) Good, R. H.; Jones, G. J. *Chem. Lett.* **1973**, 111. (i) Goth, H.; Gagneux, A. R.; Eugster, C. B.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 137. (j) Padwa, A.; Chen, E.; Kua, A. *J. Am. Chem. Soc.* **1975**, *97*, 6484. (k) Kietliker, K.; Gilgen, P.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1976**, *59*, 2074.
(9) All yields reported are percent yields determined by quantitative GLC and/or ^{1}H NMR and are based on the number of moles of reactant consumed.

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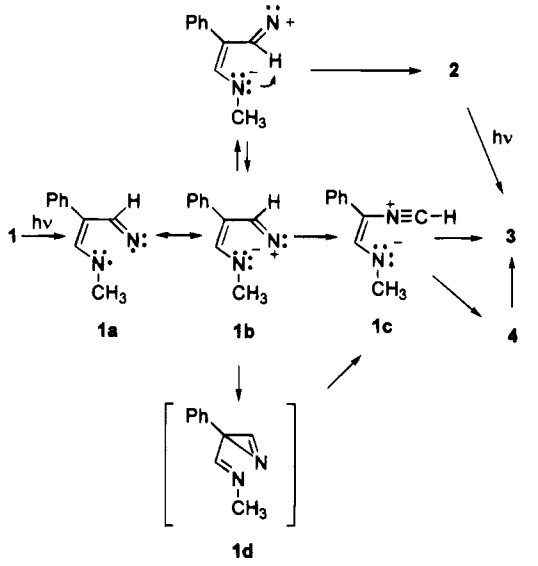
to the presence of imidazole **3** formed in 28.6% and the doublets at δ 2.93 and 3.06 due to the formation of *E* and *Z* isomers of **2** in yields of 8.3% and 8.1%, respectively. Interestingly, however, the spectrum also revealed a second pair of doublets at δ 2.86 and 3.10 that were not present in the spectrum recorded after 3 h of irradiation. Although the integrated areas of these two new doublets were approximately equal, their areas were substantially greater than the areas of the doublets due to **2**. Thin layer chromatography confirmed the presence of an additional component in the solution. Thus, TLC analysis showed the presence of imidazole **3** (R_f = 0.10), pyrazole **1** (R_f = 0.40), the *E* and *Z* mixture of **2** (R_f = 0.75), and an unknown component (R_f = 0.90).

The residue remaining after irradiation of 1-methyl-4-phenylpyrazole (**1**) (50 mL, 2.0×10^{-2} M) for 60 min to maximize the optical density at 313 nm was subjected to careful flash column chromatography on silica gel. This led to the isolation of 1-methyl-4-phenylimidazole (**3**) (fraction 34, 0.011 g), 1-methyl-4-phenylpyrazole (**1**) (fractions 26–33, 0.057 g), a mixture of the *E* and *Z* isomers of enaminonitrile **2** (fractions 10–18, 0.009 g), and a white crystalline compound **4** (fraction 7, 0.018 g), mp 97.5–98.0 °C. The UV-absorption maximum at 313 nm (log ϵ = 4.10) and its sensitivity to acid confirmed that this material is the component detected in the small-scale reaction. The high-resolution mass spectrum (*m/e* 158.0850) and the elemental analysis confirm that this compound is isomeric with enaminonitrile **2**.[10] Furthermore, the ^{1}H NMR spectrum, which exhibits signals at δ 3.1 (d, J = 4.5 Hz, 3H), 4.2 (br s, 1H), 6.8 (d, J = 12.6 Hz, 1H), and 7.1–7.3 (m, 5H), shows that the β-(*N*-methylamino)styryl moiety found in **2** remains intact in **4**. The infrared spectrum, however, shows no signal at 2200 cm^{-1} confirming the absence of a nitrile functional group, but does exhibit an absorption band at 2105 cm^{-1}, which is characteristic of an isocyanide functionality.[11] This absorption, the extreme sensitivity of the compound toward acid, and the characteristic penetrating odor of the compound lead us to assign its structure as the isocyanide **4**. Although the ^{1}H NMR spectrum of the residue after irradiation showed the presence of both stereoisomers of **4** in equal concentrations, only the *Z*-isomer was isolated by flash column chromatography.[12] Whereas the isolated yields of **2**, **3**, and **4** were 8.9%, 10.9%, and 17.8%, respectively, quantitative GLC and ^{1}H NMR of the residue before chromatography indicated yields of 12.0%, 17.2%, and 68.1%, respectively.

A reasonable mechanism for the photoisomerization of **1** to yield nitrile **2** and isocyanide **4** is shown in Scheme 1. Thus, cleavage of the N–N bond in **1** is suggested to result in an acyclic species that can be viewed as diradical **1a** or zwitterion **1b**. Rotation about the C_3–C_4 bond and either H-atom or proton transfer would result in the formation of the photocleavage product **2**. Alternatively, one can also envision a 1,2-shift of C_4 from C_3 to the electron deficient nitrogen to yield nitrile ylide **1c** which can cyclize directly to the P_4 imidazole or rearrange *via* a proton transfer to yield the observed isocyanide **4**.

Scheme 1



Finally, it is also plausible that **1a** or **1b** could cyclize to an undetected iminoazirine **1d**. Interestingly, photochemical ring opening of the azirine would be expected to result in the same nitrile ylide **1c** formed by the 1,2-shift pathway. Thus, the net effect of azirine formation and ring opening is a 1,2-shift of C_4 from carbon to nitrogen and can occur *via* an azirine intermediate or an azirine-like species on the reaction coordinate.

A solution of (*Z*)-**4** (3.0 mL, 1.44×10^{-2} M) in methanol was irradiated at 254 nm for 5 min. UV and ^{1}H NMR spectroscopic analysis of the resulting solution showed a 24.1% consumption of (*Z*)-**4**. In addition to the doublet at δ 3.10 due to residual (*Z*)-**4**, the NMR spectrum showed a second doublet at δ 2.86 due to the formation of (*E*)-**4** in 51.1% yield (*Z*:*E* = 6.2:1.0) and a singlet at δ 3.70, confirming the formation of imidazole **3** in 27.6% yield. These results clearly show that (*Z*)-isocyanide **4** undergoes *Z* → *E* photoisomerization and photocyclization to imidazole **3**.[13] This confirms that the photocleavage–photocyclization pathway *via* isocyanide **4** constitutes a second phototransposition pathway. No evidence, however, could be detected for the formation of enaminonitrile **2** from isocyanide **4**. Thus, contrary to our earlier suggestion,[1] enaminonitriles are not formed from pyrazoles *via* isocyanide intermediates.

The involvement of isocyanides in the pyrazole → imidazole phototransposition appears to occur with other pyrazoles.[14] Thus, ^{1}H NMR examination of the crude reaction mixtures obtained after irradiation of 1,4-dimethylpyrazole or 1,5-dimethylpyrazole showed pairs of doublets at δ 2.81 and 2.92 (J = 5 Hz) or at δ 2.69 and 2.95 (J = 5 Hz) due to the *N*-methyl groups of the *E* and *Z* enaminonitriles and a second pair of doublets at δ 2.78 and 2.88 (J = 5 Hz) or δ 2.58 and 2.86 (J = 5 Hz) consistent with the presence of the (*E*)- and (*Z*)-isocyanides. Further work on the intermediacy of isocyanides in the pyrazole → imidazole phototransposition is currently in progress.

Supporting Information Available: Procedures, characterization data, and spectra (10 pages).

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(10) **4**(*Z*): mp 97.5–98.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.1–7.3 (m, 5H), 6.8 (d, J = 12.6 Hz, 1H), 4.2 (br s, 1H), 3.1 (d, J = 4.5 Hz, 3H); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ 137.2, 132.0, 128.9, 125.3, 121.4, 34.4; IR (thin film) 3319, 2105, 1654, 748, 637 cm^{-1}; UV (CH_3OH) λmax (log ϵ) 225 (3.98), 263 (3.86), 298 (4.15), 313 (4.10); HRMS calcd for $C_{10}H_{10}N_2$ 158.0844, found 158.0850. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.75; H, 6.38; N, 17.71. Found: C, 75.76; H, 6.26; N, 17.73.

(11) Silverstein, R. M.; Bassler, G. C.; Morrill T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; Wiley: New York, 1991; p 126.

(12) The fate of the (*E*)-isocyanide on the silica gel column is not clear at this time but is under further investigation.

(13) Isocyanide **4**(*Z*) also undergoes thermal cyclization to imidazole **3** at 80 °C.

(14) Although isocyanides have not been previously observed as intermediates in the pyrazole to imidazole phototransposition, they have been spectroscopically detected as intermediates in the analogous P_4 isoxazole to oxazole phototransposition. See: Ferris, J. P.; Antonucci, F. R. *J. Am. Chem. Soc.* **1974**, *96*, 2014. Ferris, J. P.; Trimmer, R. W. *J. Org. Chem.* **1976**, *41*, 13.