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Reducing the complexity of photoreaction pathway of pyrazoles: photochemistry of 4,5-cycloalkanopyrazoles

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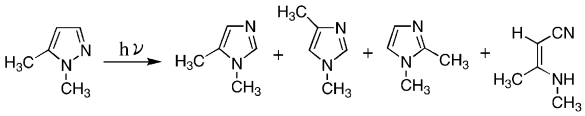
Abstract

Products from photoirradiation of 4,5-cycloalkanopyrazoles have been isolated and characterized. The simpler product mixtures relative to the parent systems are in agreement with the hypothesis that the extra carbocyclic ring could reduce the possible number of reaction pathways. Relative reactivities and secondary photoreaction pathways have also been determined. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: 4,5-Cycloalkanopyrazoles; Photochemistry

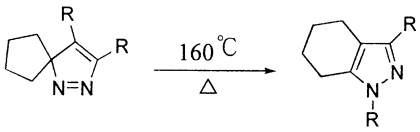
1. Introduction

The multiple reaction pathways available to pyrazoles during photoirradiation [1] represent a fascinating story of this five-membered heterocyclic-ring system. Thus, it was shown that from 1,5-dimethylpyrazole (**1a**), the product mixtures contained three different skeletal rearranged products, 1,5-dimethylimidazole (**2a**), 1,4-dimethylimidazole (**3a**) and 1,2-dimethylimidazole (**4a**) and the ring-opened 3-(*N*-methylamino)butenenitrile (**5a**) (Eq. (1)) [2]. These reactions are further more different from its analog's thermal reactions. For example, the 3,5-dimethylpyrazole (**1b**) undergoes thermal reaction to form 3,5-dimethyl-3*H*-pyrazole (**2b**) and subsequently loses nitrogen to give an olefin (Scheme 1) [3].



(1)

It occurred to us that the relatively complex photochemical reaction pathways of pyrazoles could possibly be simplified if the pyrazole ring is constrained by the presence of another carbocyclic ring. Recently, in a study of thermal rearrangement of 3,3-spiroalkanopyrazoles [4], some 4,5-cycloalkanopyrazoles became available (Eq. (2)).



1c; R = H
1d; R = CO_2Me

2c; R = H (98%)
2d; R = CO_2Me (70%)

(2)

They allowed us to test the hypothesis of possibly reducing complexity of photoproduct mixtures. This paper describes results of photoirradiation of four such ring constraint pyrazoles.

2. Experimental details

Gas chromatography (GC) analyses were performed on an HP 5890 chromatograph using an HP-5 (30 m) or a Carbowax (30 m) capillary column. Mass spectra were recorded using an HP 5890 and 5970 MSD. IR spectra were obtained on a Perkin-Elmer 2000 FT-IR. ^{1}H NMR spectra were determined on a Bruker AC-250 spectrometer in $CDCl_3$ with TMS as an internal standard.

2.1. Materials

1-Methyl-4,5,6,7-tetrahydroindazole (**1f**) [5,6], 1-phenyl-4,5,6,7-tetrahydroindazole (**1g**) [6,7], 1-methyl-4,5,6,7-tetrahydrobenzimidazole (**2f**) [8], 2-methylamino-1-cyclo-

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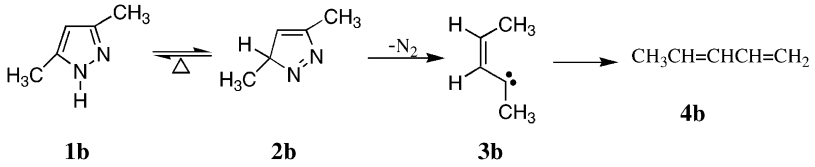


Scheme 1.

hexene-1-carbonitrile (**3f**) [8] were synthesized according to the procedures described in the literature.

*2.1.1. 1-Methyl-4,5,6-trihydroindazole (**1e**)*

The synthesis of **1e** was carried out as described by literatures [5] in an overall yield of 29%. IR (neat): 3417, 3092, 2944, 2860, 1436, 1280, 994, 790 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 2.48–2.68 (m, 6H), 3.74 (s, 3H), 7.11 ppm (s, 1H). MS, *m*/*z* (%): 122 (M^+, 100), 121 (95), 94 (26), 80 (19), 67 (24).

*2.1.2. 1-Methyl-4,5,6-trihydrobenzimidazole (**2e**)*

A solution of **1e** (200 ml, 2×10^{-1} M) in acetonitrile was irradiated with a medium pressure Hg lamp in a quartz immersion well for 10 min. The resulting solution was concentrated, and the residue was subjected to Al_2O_3 chromatography eluting with ether/*n*-hexane = 2/1 to afford **2e** (27% yield). ^1H NMR ($CDCl_3$), δ: 2.40–2.80 (m, 6H), 3.56 (s, 3H), 7.27 ppm (s, 1H). ^{13}C NMR ($CDCl_3$), δ: 22.0, 24.9, 28.2, 32.3, 134.8, 140.0, 147.1 ppm. IR (CH_2Cl_2): 3018, 2954, 2862, 1718, 1505, 1216 cm^{-1}. MS, *m*/*z* (%): 122 (M^+, 100), 121 (76), 94 (25), 80 (20), 68 (19). HRMS calcd. for $C_7H_{10}N_2$: 122.0843; found: 122.0836.

*2.1.3. 1-Phenyl-4,5,6,7-tetrahydrobenzimidazole (**2g**)*

Product **2g** was prepared by the same procedure from the irradiation of 1-phenyl-4,5,6,7-tetrahydroindazole (1.0×10^{-1} M) in methanol; yield: 68%. ^1H NMR ($CDCl_3$), δ: 1.70–2.00 (m, 4H), 2.54 (t, 2H, J = 5.4 Hz), 2.68 (t, 2H, J = 5.6 Hz), 7.20–7.60 ppm (m, 6H). ^{13}C NMR ($CDCl_3$), δ: 21.8, 23.2, 24.4, 124.2, 127.5, 129.5, 135.0 ppm. IR (neat): 3390, 2933, 2849, 1599, 1505, 1480, 1440, 1382, 920 cm^{-1}. MS, *m*/*z* (%): 198 (M^+, 100), 170 (89), 169 (76), 77 (33). Anal. calcd. for $C_{13}H_{14}N_2$: C, 78.75; N, 14.13; H, 7.12. Found: C, 77.51; N, 14.33; H, 7.38. HRMS calcd. for $C_{13}H_{14}N_2$: 198.1157; found: 198.1156.

*2.1.4. 2-Methylamino-1-cyclopentene-1-carbonitrile (**3e**)*

To a solution of 2-cyanocyclopentanone (1.5 g, 14 mmol), glacial acetic acid (0.4 ml) and benzene (103 ml) was added methylamine (0.5 g, 15 mmol) in benzene (5 ml). The reaction mixture was heated to reflux for 5.5 h and water was collected in a Dean–Stark trap. The reaction solution was concentrated in vacuo, and the residue was subjected to Al_2O_3 chromatography eluting with ether/*n*-hexane = 2/1 to obtain **3e** (1.1 g, 66% yield). ^1H NMR ($CDCl_3$), δ: 1.89–1.92 (m, 2H), 2.44 (t, 2H, J = 7.5 Hz), 2.56 (t, 2H, J = 7.0 Hz), 3.03 (d, 3H, J = 5.2 Hz), 4.36 ppm (brs, N–H). ^{13}C NMR ($CDCl_3$), δ: 21.8, 31.5, 32.2, 33.7, 69.9, 120.8, 162.9 ppm. IR (KBr): 3328, 3084, 2910, 2861, 2171 (CN), 1613, 1555, 1418, 1358, 1163 cm^{-1}. MS, *m*/*z* (%): 122 (M^+, 55), 121 (100), 94 (8), 80 (9). HRMS calcd. for $C_7H_{10}N_2$: 122.0843; found: 122.0842.

*2.1.5. 2-Phenylamino-1-cyclohexene-1-carbonitrile (**3g**)*

The preparation of **3g** followed the above mentioned procedure using 2-cyanocyclo-hexanone, aniline, glacial acetic acid and benzene in the same molar ratios; yield: 43%; m.p. 97.5–99 °C (Lit [9] 95–98 °C). ^1H NMR ($CDCl_3$), δ: 1.50–1.80 (m, 4H), 2.10–2.40 (m, 4H), 6.49 (brs, 1H), 6.90–7.50 ppm (m, 5H). ^{13}C NMR ($CDCl_3$), δ: 21.8, 21.9, 25.0, 26.9, 93.1, 124,1, 124.7, 129.1 ppm. IR (KBr): 3300, 3050, 2925, 2853, 2189 (CN), 1617, 1596, 1499, 1393, 1302, 1148, 901, 766 cm^{-1}. MS, *m*/*z* (%): 198 (M^+, 100), 197 (54), 169 (67), 170 (39), 118 (42), 77 (33).

*2.1.6. 1-Benzyl-4,5,6,7-tetrahydroindazole (**1h**) [10]*

To a suspension of 35% of KH (2.4 g, 20 mmol) in anhydrous DMF (13 ml) at 0 °C was added dropwise a solution of 4,5,6,7-tetrahydroindazole (2.4 g, 20 mmol) in DMF (19 ml). When the addition was complete (**1h**), the cooling bath was removed and the mixture stirred at room temperature for 1 h, then a solution of benzyl chloride (2.6 g, 20 mmol) in DMF (2 ml) was added. After stirring at room temperature under nitrogen for 20 h, the reaction mixture was poured into water (63 ml) and extracted with ether. The organic phase was washed with water, brine, dried and concentrated in vacuo. The residue was purified by column chromatography (Al_2O_3), eluting with hexane/ether = 3/1, to afford pure **1h** (1.2 g, 29% yield). ^1H NMR ($CDCl_3$), δ: 1.50–1.87 (m, 4H), 2.30–2.60 (m, 4H), 5.21 (s, 2H), 7.09–7.35 ppm (m, 6H). ^{13}C NMR ($CDCl_3$), δ: 20.7, 21.4, 22.7, 22.9, 52.7, 116.4, 127.0, 127.5, 128.6, 136.9, 138.1 ppm. IR ($CHCl_3$): 3089, 3064, 3031, 2930, 2854, 1497, 1455, 1410, 1316 cm^{-1}. MS, *m*/*z* (%): 212 (M^+, 75), 183 (55), 121 (74), 91 (100), 65 (40).

*2.1.7. 1-Benzyl-4,5,6,7-tetrahydrobenzimidazole (**2h**)*

Product **2h** was prepared by the above procedure from 4,5,6,7-tetrahydrobenzimidazole and benzyl chloride in the same molar ratios; yield: 27%; m.p. 123.5–124 °C. ^1H NMR ($CDCl_3$), δ: 1.70–1.83 (m, 4H), 2.28–2.41 (m, 2H), 2.55–2.70 (m, 2H), 4.99 (s, 2H), 7.05–7.45 ppm (m, 6H). ^{13}C NMR ($CDCl_3$), δ: 20.6, 22.9, 23.2, 24.4, 48.4, 125.7, 126.8, 127.8, 128.9, 135.5, 136.6, 137.3 ppm. IR (KBr): 3090, 2920, 2845, 1491, 1438, 1231, 917, 738 cm^{-1}. MS,

m/z (%): 212 (M^+, 45), 184 (15), 121 (6), 91 (100). Anal. calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.17; H, 7.72; N, 13.07.

2.1.8. 2-Benzylamino-1-cyclohexene-1-carbonitrile (3h)

The preparation of **3h** followed the same procedure of **3g** using 2-cyanocyclo-hexanone, glacial acetic acid, benzylamine and benzene in the same molar ratios; yield: 48%; m.p. 85.5–86.5 °C. ^{1}H NMR ($CDCl_3$), δ: 1.52–1.70 (m, 4H), 2.16–2.26 (m, 4H), 4.36 (d, 2H, J = 6.0 Hz), 4.97 (brs, 1H, N–H), 7.22–7.40 ppm (m, 5H). ^{13}C NMR ($CDCl_3$), δ: 21.7, 21.9, 24.9, 25.7, 46.7, 72.8, 121.7, 126.8, 127.5, 128.8, 138.9, 157.5 ppm. IR (neat): 3340, 3025, 2923, 2167, 1600, 1415, 1169 cm^{-1}. MS, *m/z* (%): 212 (M^+, 14), 92 (9), 91(100), 65 (24). Anal. calcd. for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 78.93; H, 7.74; N, 13.41.

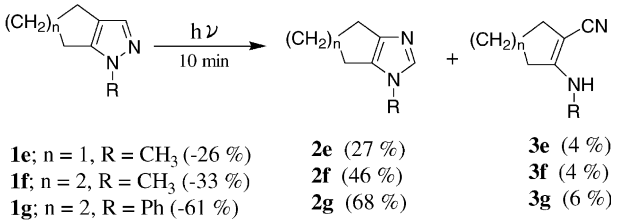
2.1.9. 2-Benzyl-4,5,6,7-tetrahydrobenzimidazole (4h) [11]

Product **4h** was prepared by the same procedure from the irradiation of 1-benzyl-4,5,6,7-tetrahydrobenzimidazole (200 ml, 1.0×10^{-2} M) in CH_3CN; yield: 11%. ^{1}H NMR ($CDCl_3$), δ: 1.70–1.90 (m, 4H), 2.40–2.60 (m, 4H), 4.06 (s, 2H), 7.10–7.50 ppm (m, 6H). IR (KBr): 3148, 3062, 2921, 2842, 1619, 1456, 1436, 1030 cm^{-1}. MS, *m/z* (%): 212 (M^+, 89), 184 (92), 91 (30), 44 (100).

Also isolated from the irradiation mixture of 1-benzyl-4,5,6,7-tetrahydrobenzimidazole (200 ml, 1.0×10^{-2} M) in CH_3CN was bibenzyl; yield: 8%. ^{1}H NMR ($CDCl_3$), δ: 2.92 (s, 4H), 7.01–7.40 ppm (m, 10H). IR (CH_2Cl_2): 3015, 2919, 2852, 1601, 1497, 1453, 1217, 1069, 1028, 755 cm^{-1}. MS, *m/z* (%): 182 (M^+, 25), 92 (8), 91 (100), 65 (23).

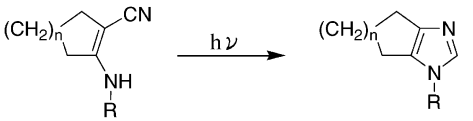
3. Results

The compounds used in this study are **1e**–**h**. Their preparation has been described in an earlier publication [5,6,10]. The UV absorption spectra of all these compounds exhibit a weak absorption band centered around 227–255 nm, followed by a strong absorption band below 200 nm. Expectedly for **1g**–**h**, each containing an additional phenyl ring, the long wavelength band is more intense. (The extinction coefficients for



1e; n = 1, R = CH_3 (-26 %) **2e** (27 %) **3e** (4 %)
1f; n = 2, R = CH_3 (-33 %) **2f** (46 %) **3f** (4 %)
1g; n = 2, R = Ph (-61 %) **2g** (68 %) **3g** (6 %)

Scheme 2.



3e; n = 1, R = CH_3 (-7 %) **2e** (16 %)
3f; n = 2, R = CH_3 (-8 %) **2f** (17 %)
3g; n = 2, R = Ph (-8 %) **2g** (22 %)

Scheme 3. Primary photoproducts of **3e**–**g**.

1g and **1h** were 1.6×10^4 and 4.2×10^3 l mol^{-1} cm^{-1}, respectively.) Hence, all irradiation was carried out with a 450 W medium pressure Hg lamp in a quartz immersion well. Progress of reactions was monitored by GLC. Product isolation in preparative irradiation was accomplished by terminating irradiation at various stages of irradiation where a maximal amount of a given product was reached. Products were isolated by column chromatography and characterized by comparison of spectral data (H and C NMR, MS, IR and UV) with those of previously reported or homologs of related structures. All yields in this paper are determined by quantitative GLC and based on the number of moles of reactant consumed.

The major products obtained from **1e** to **g** are respectively **2e** and **3e**, **2f** and **3f** or **2g** and **3g** although the relative amounts of the two products varied significantly for the three compounds and the ratio seemed to change during the course of irradiation. In preparative runs, these products were obtained in the following isolated yields: **2e** (27%), **2f** (46%), **2g** (68%), **3e** (4 %), **3f** (4 %), **3g** (6%) (Scheme 2).

The course of photoreaction of these compounds is shown separately in Fig. 1.

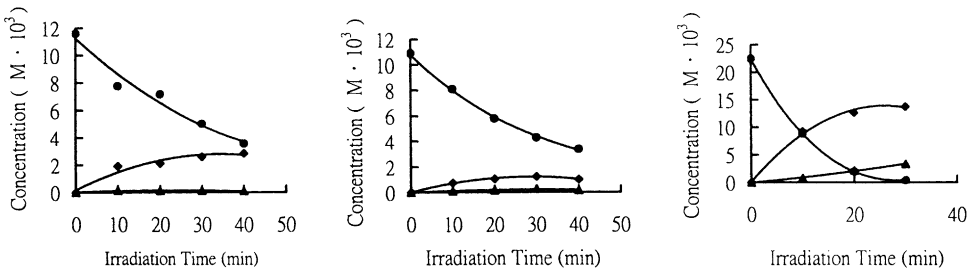
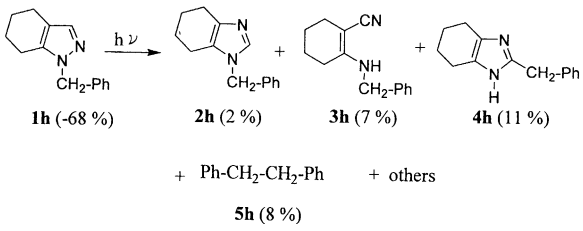


Fig. 1. Progress of photoreactions of pyrazoles **1e**, **1f**, **1g** (●) was monitored by GLC and appearance of products **2e**, **2f**, **2g** (◆) and **3e**, **3f**, **3g** (▲); left (**1e**), middle (**1f**) and right (**1g**).

The curves show the general trend that while the amounts of products **2** increase with irradiation time, the amounts of products **3** either remain constant (**3e–f**) or increased a little with time (**3g**). The latter trend suggested that products **3** likely underwent secondary photochemical reaction but at varying efficiencies. Indeed, alkene **3** with push–pull substituents absorb in the range 275–290 nm. Irradiation of isolated **3e**, **3f** or **3g** resulted in its producing the corresponding imidazoles (**2e**, **2f** or **2g**) (Scheme 3).

While pyrazole **1h** gave initially two similar photoproducts **2h** and **3h**, their amounts never exceeded 2 and 7%, respectively. Two new final products **4h** and **5h** were subsequently isolated (11 and 8%, respectively) (Eq. (3)) and characterized by their spectral data. The nature of the secondary reactions was determined in the following additional experiments. Irradiation of a solution of an isolated sample of **3h** was found to give initially exclusively **2h**, followed by gradual appearance of **4h** and **5h** (Eq. (4)). And, irradiation of a solution of isolated **2h** was found to give exclusively **4h** and **5h** in a ratio of 7:1 (Eq. (5)). Thus, the complete sequences of reaction during irradiation of **1h** can be summarized in the following manner:



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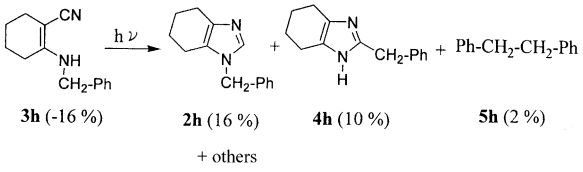

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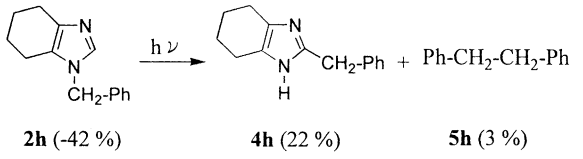

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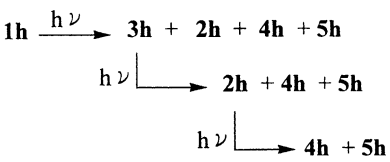


Sensitized irradiations of **1e–g** were carried out in acetone (E_T = 79–82 kcal/mol) [12]. All of these reactants were found to be unreactive as triplets.

4. Discussion

Formation of the primary products **2e–g** and **3e–g** likely followed the reaction pathways proposed by Pavlik [13]. The photochemistry of **1e–g** has been suggested to involve cleavage of the N–N bond resulting in the formation of a species **6** that can be described as either a diradical (**6**) or a zwitterion (**7**). Two possible pathways are envisioned (Scheme 4) for this species. First, rotation about the C-3–C-4 bond of **7** to form **8** followed by H-atom transfer (path A) from C-3 to N-1 would yield the observed **3**. This species **3** could undergo cyclization to form **2**. Alternatively, it has also been suggested that **6** could undergo intramolecular cyclization to form the iminoazirine **9**, as originally suggested by Schmid and coworkers [14]. The iminoazirine **9** would undergo ring opening to yield the nitrile ylide **10** followed by H-transfer to form isocyanide **11**. Both of these species could undergo cyclization to form **2** (Scheme 4).

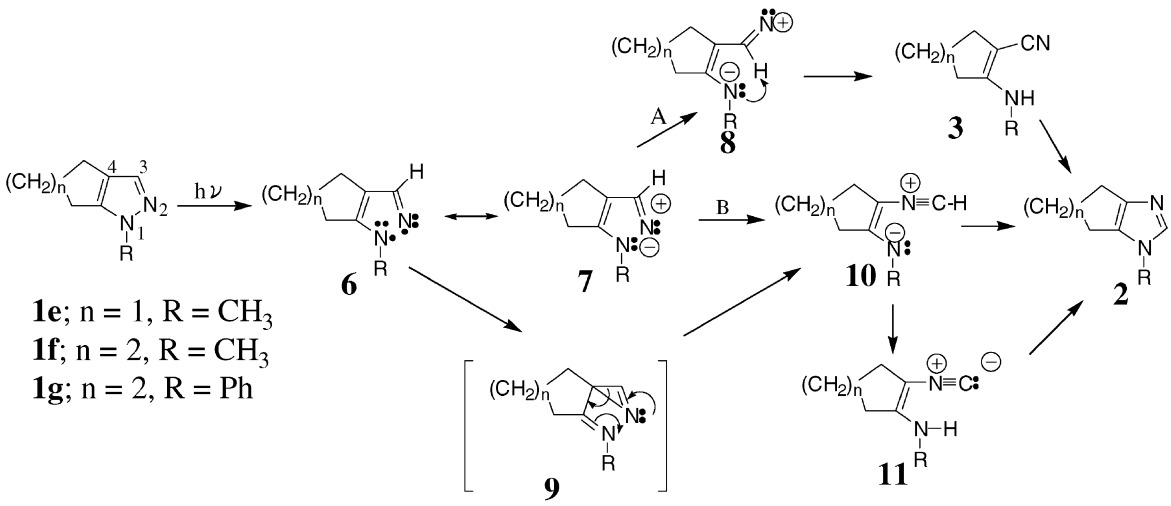
In the parent case of 1,5-dimethylpyrazole, it was reported [2] and noted above that the formation of products **2a** and **3a** was accompanied by a copious amount of the 1,2-skeletal rearranged product **4a**. The latter type of products (**4e–g**) were noticeably absent in the current study.

Formation of **4a** was believed to proceed via the following reaction pathway: electrocyclic ring closure results in the formation of 1,5-diaza intermediate **12**, which can undergo 1,3-sigmatropic shift of nitrogen. Rearomatization of the isomeric 2,5-diaza intermediate **13** would produce **4a** (Scheme 5).

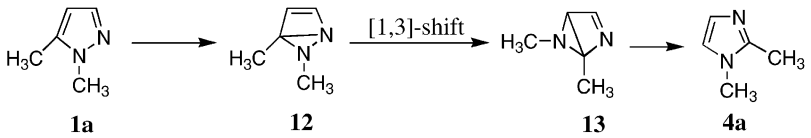
The current absence of such compounds (**4e–g**) could be a reflection of the expected higher strain-energy that would be present in the corresponding 2,5-diazatricyclo intermediate **15**, making this pathway not competitive against other rearrangement or fragmentation (Scheme 6). Hence, it appears that the presence of an additional fused ring indeed accomplished the stated goal to simplify the photochemical reaction pathways of pyrazoles.

A few other points shown by the data above worth brief comments. The high yield of the rearranged product **2g** (68%) in the case of phenyl pyrazole **1g**, which also exhibited a higher reactivity than **1e** and **1f**, was clearly due to stability of the diradical intermediate making the fragmentation process a more facile process. In fact, in this case, we were able to obtain one chromatographic fraction during separation of the photoproducts that exhibited the unusual IR absorption at 2115 cm^{-1} (for –NC, isonitrile) [15] with significantly the simultaneous absence of a 2185 cm^{-1} band (for –CN). Such structural features are in agreement with the intermediate structure **11** in the above proposed mechanism. Unfortunately, the compound was too unstable for accumulation of sufficient amounts for further characterization, e.g. recording its NMR spectrum.

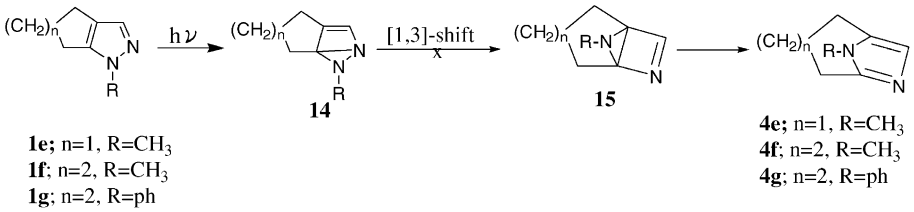
On the other hand, the observed low yields of products **2h** from the benzylpyrazole **1h** was clearly not due to a lack of its initial reactivity. Rather, it must be due to



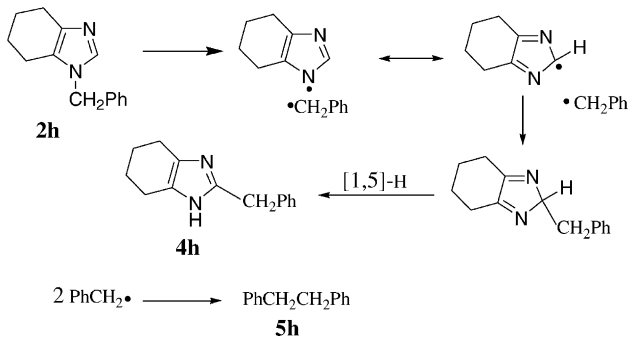
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

efficient secondary photochemical reactions, dictated by ready formation of the stable benzyl radical and the subsequent formation of radical addition product **4h** and radical coupling product **5h** (Scheme 7).

Acknowledgements

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