PYRIDAZINE AND ITS RELATED COMPOUNDS. 15¹

PHOTOLYSIS OF 3-AZIDO-4,5-DIPHENYL-1H-PYRAZOLO[3,4-c]-PYRIDAZINE IN DIFFERENT SOLVENTS

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Keywords: 3-Azido-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine, photolysis in solvents; nitrene formation

The photochemistry of 3-azido-1H-pyrazolo[3,4-c]pyridazine ring-system has been investigated. The irradiation of 3-azido-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine 1 in various solvents brings to a photolytic nitrene intermediate, which involves into a ring-opening to give 3-substituted pyridazine derivatives. During the photolysis of 1 in toluene and/or anisole the photoattack reaction of nitrene with the solvents is faster than the ring opening thus the corresponding 3-(arylanilino)pyrazolo[3,4-c]pyridazine derivatives are formed. The photolysis in the presence of diethyl malonate led to a mixture of three pyridazine derivatives.

Introduction

Photolysis of aryl and heteroaryl azides is a well documented reaction² to give rise to a varied group of products, whose identity is influenced by many factors such as reaction medium, substituents, etc. The generally accepted pathway includes primary formation of an open-shell singlet nitrene³ by lose of N₂ followed by intersystem crossing (ISC) to the ground state triplet nitrene and/or cycladdition to a neighboring C=C double bond in arene system. On the other hand, pyridazine derivatives and heterocyclic annelated pyridazines continue to attract considerable attention for their application in agriculture and in practical for their biological activity for use as potential drugs.⁴

In a previous paper directed towards the synthesis of new pyridazine derivatives,¹ we presented the photolysis of 3-diazo-4,5-diphenylpyrazolo[3,4-c]pyridazine in different solvents. The present paper reports the photolysis (300 W, λ 320 nm) of the azido derivative in different solvents at room temperature.

Results and Discussion

3-Azido-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine 1 was prepared in 85% yield as a yellow crystals (mp 167°C) by addition of sodium azide in portion wise to 3-diazo-4,5-diphenylpyrazolo[3,4-c]pyridazine² in concd. HCl at room temperature. The processes are quick and are readily carried out in a beaker or open flask. The reaction progress was completed until no diazo compound could be detected by thin-layer chromatography as well as no coupling colour with β-naphthol.

Irradiation of the azido derivative 1 in methanol and/or ethanol resulted in the formation of 5,5',6,6'-tetraphenyl-[3,3'-bipyridazine]-4,4'-dicarbonitrile 2 in moderate yield. A mechanism for the transformation of 1 into 2 could involve the formation of a singlet nitrene followed by ring opening concerted with nitrogen molecule and hydrogen radical elimination producing the radical species which dimerized to form 2 (Scheme1).

Scheme 1. Caption should be given.

The structure of compound 2 was inferred from the analytical data and spectral feature. The IR spectrum had strong absorption band at 2239 cm⁻¹ due to CN stretching vibration. The mass spectrum exhibited a characteristic strong molecular ion peak at m/z 512 and the fragmentations are outlined as follows:

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The 1H-NMR spectrum showed a multiplet at δ 7.60-7.90 attributed to the aromatic phenyl protons (4 Ph).

When compound 1 was irradiated in dimethyl sulfoxide, a ring opening reaction was occurred with nitrogen and hydrogen molecules (there were detected these molecules or counted only form the formula? Other N-H compds can also be eliminanted !) elimination to give 3-((methylsulfinyl) methyl)-5,6-diphenylpyridazine-4-carbonitrile 3 as was evidenced by the analytical and spectral data.

Irradiation of 1 in benzene (or derivatives) showed the same patterns. Irradiation of 1 in benzene led to the isolation of 3,5,6-triphenylpyridazine-4-carbonitrile 4 in 50% yield, and irradiation of 1 in phenol or chlorobenzene gave pyridazines 5 and 6 in 89% and 51% yields, respectively.

Irradiation of a solution of 1 in nitrobenzene led to the isolation of the product 7. This result could be interpreted in terms of nitrobenzene is not reactive enough to attack the intermediate. The proof for the structures of compounds 4-7 results on their elemental analyses and spectral data and is summarized in experimental section.

On the other hand, the irradiation of 3-azido derivative 1 in toluene did not give the corresponding nitrile instead gave a mixture of ortho and para substituted anilino derivatives 8 and 9 of anilino compounds could be explained assuming that the photo attack reaction of the nitrene compound with toluene is faster than the ring opening to give the corresponding anilino derivatives.

In the photolysis of compound 1 with anisole, the behavior is analogous to that observed in toluene, leading to the corresponding products 10 and 11 (Scheme 2).

Lastly, compound 1 was irradiated in presence of diethyl malonate. The thin-layer chromatographic results of the crude product shows the presence of three products.

Separation by column chromatography on silica gel (20 – 600 mesh) led to the isolation of 3,4-diphenylpyridazine-5-carbonitrile 7 in 10.8% yield. The carboxamides 12, 13 were also obtained in 34.3% and 37.8% yields, respectively.

The structure of compounds 12 and 13 were established on the basis of their elemental and spectral data.

The photoreaction of 3-azido derivative 1 with a variety of reagents proceeds smoothly to yield substituted 4-cyanopyridazine, substitutd aminopyrazoloipyridazine and/or pyridazine-carboxamide derivatives, depending on the nature of the reagents, the photoreaction described here would be an efficient and novel method for their synthesis.

Experimental

Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. 1H-NMR spectra were obtained on a Bruker Ac 200 F instrument. Mass spectra were obtained at 70 eV by using a AEI MS 30 mass spectrometer. Elemental analysis (C, H, N) were carried out using a Perkin-Elmer 240C Microanalyzer the Microanalytical Laboratory-Cairo University. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm). The photoreactions were carried out in a Pyrex immersion apparatus equipped with 300 W high-pressure mercury lamps at room temperature. Commercially available reagents and solvents were usually reagent grade and distilled or recrystallized prior to use.
3-Azido-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine 1.

M.p. 167° (dec.). It was prepared from 3-diazoo-4,5-diphenylpyrazolo[3,4-c]pyridazine as follows: To a solution of 3-diazoo derivative (0.6 g, 2 mmol) in conc. hydrochloric acid (5 mL), sodium azide (0.4 g, 6 mmol) was added in portion-wise at room temperature with stirring. A yellow deposit product was separated, filtered and recrystallized from benzene (0.54 g, 85%), m.p. 167 °C; IR: 3150-3090 (NH), 2150 (N-J), 1650 (C=N) and 1520 cm\(^{-1}\) (C=C); \(^{1}H\)-NMR (DMSO-\(d_{6}\)): \(\delta\) 6.58 – 7.54 (m, 15H, 3Ph); MS \(m/z\): 333 (M\(^{+}\), 34.3%), 256 (M\(^{+}\) - Ph, 100%), 178 (M\(^{+}\) - 2Ph, 70.9%). Anal. Calcd for C\(_{23}\)H\(_{13}\)N\(_{9}\); C, 65.16; H, 3.54; N, 16.39. Found: C, 78.70; H, 4.20; N, 11.90.

Irradiation in phenol

Irradiation of compound 1 (0.5 g, 1.6 mmol) in phenol (50 mL) for 60 h. The reaction mixture was evaporated on a steam-bath and the residue was washed with diethyl ether, the solid product was filtered off and recrystallized from benzene to give (0.5 g, 89.6 %) of 3-(4-hydroxyphenyl)-5,6-diphenylpyridazine-4-carbonitrile 5, m.p. 165-166 °C; IR: 3454, 3360 (OH), 3146, 3054 (CH, aromatic), 2234 (CN), 1624 (C=N), 1444, 1382, 1231 cm\(^{-1}\); \(^{1}H\)-NMR (DMSO-\(d_{6}\)): \(\delta\) 6.80 (d, J=7.0, 2H, aromatic), 7.50 (d, J=7.0, 2H, aromatic), 7.66 – 7.90 (m, 10H, 2Ph), 12.99 (s, 1H, OH); MS \(m/z\): 349 (M\(^{+}\), 6.2%), 256 (M\(^{+}\) - C\(_{6}\)H\(_{4}\)OH, 75%). Anal. Calcd for C\(_{23}\)H\(_{13}\)NO: C, 79.06; H, 4.33; N, 12.04. Found: C, 78.90; H, 4.20; N, 11.90.

Irradiation in chlorobenzene

Irradiation of compound 1 (0.5 g, 1.6 mmol) in chlorobenzene (150 mL) for 16 h. The reaction mixture was evaporated on a steam-bath and the residue was washed with diethyl ether, the solid product was filtered off and recrystallized from benzene to give (0.3 g, 51.7 %) of 4,5-diphenylpyridazine-4-carbonitrile 4, m.p. 157-158 °C (from benzene); IR: 3057 (CH, aromatic), 2228 (CN), 1607 (C=N), and 1445, 1358, 1225, 1129 cm\(^{-1}\); \(^{1}H\)-NMR (DMSO-\(d_{6}\)): \(\delta\) 6.58 – 7.54 (m, 15H, 3Ph); MS \(m/z\): 333 (M\(^{+}\), 34.3%), 256 (M\(^{+}\) - Ph, 100%), 178 (M\(^{+}\) - 2Ph, 70.9%). Anal. Calcd for C\(_{23}\)H\(_{13}\)NO: C, 82.86; H, 4.54; N, 12.60. Found: C, 82.70, H, 4.40; N, 12.50.

Irradiation in nitrobenzene

Irradiation of compound 1 (0.5 g, 1.6 mmol) in nitrobenzene (150 mL) for 6 h, gave 3,4-diphenylpyridazine-5-carbonitrile 7 (0.3 g, 68.6%), m.p. 143-144 °C; IR: 3021 (CH, aromatic), 2129 (CN), 1605 (C=N), 1443, 1380, 1177 cm\(^{-1}\); \(^{1}H\)-NMR (DMSO-\(d_{6}\)): \(\delta\) 7.10 (d, \(J\) = 6.5, 2H, aromatic), 7.50 (d, \(J\) = 6.5, 2H, aromatic), 7.20 – 7.42 (m, 10H, 2Ph); MS \(m/z\): 368 (M\(^{+}\), 11.4%), 256 (M\(^{+}\) - C\(_{6}\)H\(_{4}\)Cl, 13.9%). Anal. Calcd for C\(_{23}\)H\(_{13}\)ClN\(_{2}\); C, 74.89; H, 3.83; N, 11.39. Found: C, 75.00, H, 3.90; N, 11.20.

Irradiation in toluene

Irradiation of compound 1 (0.5 g, 1.6 mmol) in toluene (250 mL) for 3 h. The resulting reaction mixture was concentrated to its third volume, the solid obtained was collected by filtration to give (0.3 g, 49.9 %) of 4,5-diphenyl-N-(toly1)-1H-pyrazolo[3,4-c]pyridazin-3-amine 8, m.p. 141 – 142 °C (from tolune). IR: 3420 (NH), 3040 (CH, aromatic) 2922, 2855 (CH, aliphatic), 1609 (C=N), 1580, 1428, 1382 and 753, 701 cm\(^{-1}\) attributed to the ortho substituted; \(^{1}H\)-NMR (DMSO-\(d_{6}\)): \(\delta\) 1.24 (s, 3H, CH\(_{3}\)), 6.88 – 7.23 (m, 4H, toluene aromatics), 7.39 – 7.64 (m, 2H).
Photolysis of 3-azido-4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazine

The filtrate was evaporated under reduced pressure and the residue was triturated with diethyl ether to give (0.15 g, 25 %) of 9, 4,5-diphenyl-N-(p-tolyl)-1H-pyrazolo[3,4-c]pyridazin-3-amine, m.p. 228 – 229 °C (from ethanol). IR: 3405, 3150 (NH), 3090 (CH, aromatic), 2927 (CH, aliphatic), 1633 (C=O); H-NMR (DMSO-d$_6$): δ 17.55 – 7.05 (m, 4H, toluene protons), 7.55 – 7.70 (m, 10H, 2Ph), 9.76 (s, 1H, NH), 12.55 (s, 1H, pyrazole NH); MS m/z: 377 (M$^+$, 9.5%), 376 (M$^+$ - 1, 10.5%), 286 (M$^+$ - C$_6$H$_5$CH$_3$, 10.1%), 271 (M$^+$ - NH$_2$CH$_2$CH$_3$, 77%, ion A), 256 (ion A - NH, 10.1%). Anal. Calcd for C$_{24}$H$_{20}$N$_2$: C, 76.36; H, 5.08; N, 18.56. Found: C, 76.20; H, 4.90; N, 18.90.

The filtrate was evaporated under reduced pressure and the residue was triturated with diethyl ether to give (0.2 g, 37.1 %) of 4,5-diphenyl-1H-pyrazolo[3,4-c]pyridazin-3-amine. IR: 3429, 3310 (NH), 3125, 3061 (CH, aromatic), 1663 (C=O amide), 1567 (C=N), 1269 cm$^{-1}$ (C-O amide), 1444, 1269, 1076 cm$^{-1}$ for the aromatic system: H-NMR (DMSO-d$_6$): δ 1.22 (s, 3H, CH$_3$), 4.05 (q, 2H, CH$_2$), 7.28 – 7.54 (m, 10H, 2Ph), 14.13 (s, 1H, NH$_2$); MS m/z: 347 (M$^+$, 1.6 %), 274 (M$^+$ - COOEt, 22.6 %, ion A), 273 (ion A – 74, 100 %, ion B), 157 (ion B – NH$_2$, 29.5%), 229 (M$^+$ - COONH$_2$, - COOEt, 11.2%). Anal. Calcd for C$_{24}$H$_{19}$N$_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.00; H, 4.80; N, 12.00.

REFERENCES


Received: 10.10.2013. Accepted: 12.12.2013.