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Solid state photochemistry of 1,4-dihydropyridines

Hamid R. Memarian* and Arsalan Mirjafari

Department of Chemistry, Faculty of Science, University of Isfahan, 81746-73441 Isfahan, Iran

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Abstract—Photochemical behavior of some 1,4-dihydropyridines has been investigated in the solid state. Whereas upon irradiation of 1,4-dihydropyridines in solution phase, their photo-oxidation and formation of pyridine derivatives have been observed, irradiation of these compounds in the solid state decreases their light sensitivity. In many cases photo-oxidation has been observed only in very low yields.

1. Introduction

1,4-Dihydropyridines are interesting compounds and play an important role in synthetic, therapeutic and bioorganic chemistry.[1–4] The most interesting aspect of dihydropyridines can be attributed to the coenzyme reduced nicotinamide adenine dinucleotide (NADH) and the unique ability of these compounds in biological systems to reduce unsaturated functionalities and also strained ring systems (carbonyls, conjugated olefins, epoxides, etc.).[5–8] Phototoxicity of nifedipine, one of the 1,4-dihydropyridine classes, has also been reported.[9] Oxidation of 1,4-dihydropyridine compounds with various oxidizing agents has been extensively studied.[10,11] Photo-oxidation of 1,4-dihydropyridines is also of great interest and is still under intensive investigation. Recently, we have reported on the photochemical behavior of these compounds and investigated the effect of the type and the nature of the 4-substituent and also the presence or absence of oxygen on the rate of photo-oxidation.[12,13] Since the presence of the acetyl groups instead of the ester groups on 3- and 5-positions could also affect the rate of photo-oxidation, we have synthesized some novel keto-dihydropyridines and studied their photochemical reactions.[14,15]

Solid state photochemistry of 1,4-dihydropyridines is not widely investigated. Solid state and solution photodimerization of N-substituted and non-substituted Hantzsch-type dihydropyridines without any substituents at 2- and 6-positions takes place through two regioselective and consecutive [2+2]-cycloaddition and affords the formation of cage dimer.[16–18] Recently, solid state photochemistry of only one 2,6-dimethyl-1,4-dihydropyridine and formation of head to tail cage dimer have been reported.[19] Most of the 1,4-dihydropyridines exhibit pharmaceutical activity and this property is due to the presence of dihydropyridine ring; therefore, because of their light sensitivity especially in the solution phase, protection from light during their preparation has been recommended[12,20] to prevent photo-oxidation to the pyridine ring. In the course of our studies on the chemistry of 1,4-dihydropyridines, we investigated solid state photochemistry of various dihydropyridines to elucidate their light sensitivity in the solid state versus the solution phase.

2. Results and discussion

Direct irradiation ($\lambda \geqslant 280$ nm) of 0.03 mol of each of the powdered 1,4-dihydropyridine-3,5-diesters (**1a**–**1p**) or 3,5-diacetyl-1,4-dihydropyridines (**4a**–**4n**) in the solid state was carried out on a water cooled plate with admission of air for 50 h and the progress of the reaction was followed by thin layer chromatography (TLC). Since the aim of this work was to compare the photochemical behavior of 1,4-dihydropyridines in the solution phase and solid state, the same amount of **1a**–**1p** and **4a**–**4n** was dissolved in 3 ml $CHCl_3$ and exposed to UV-light simultaneously with the powdered dihydropyridine until total disappearance of the dissolved dihydropyridine was observed.[21] The results are summarized in Tables 1 and 2.

Keywords: 1,4-Dihydropyridines; Photodehydrogenation; Photo-oxidation; Solid state photochemistry.

* Corresponding author. Tel.: +98 311 793 2707; fax: +98 311 668 9732; e-mail: memarian@sci.ui.ac.ir

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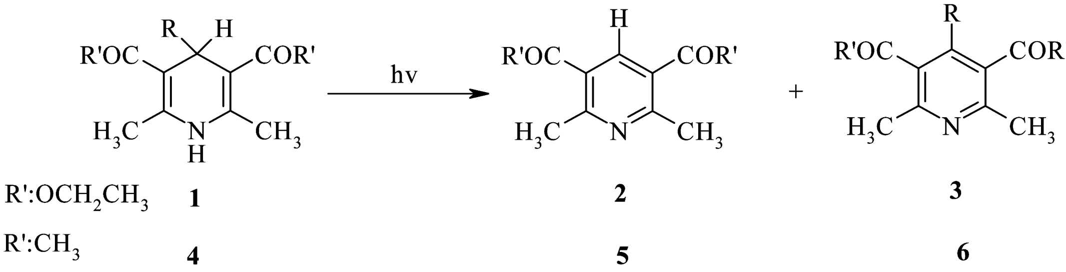

Table 1. Solid state and competitive solution photochemistry of 1,4-dihydropiridine-3,5-diesters (**1a**–**1p**) at $\lambda \geqslant 280$ nm

Compound	R	Solid photochemistry[a]		Solution photochemistry	
		Product	Yield (%)	Product	Time (h)[b]
1a	H	**2**	95[c]	**2**	8
1b	CH_3	—	—	**3b**	16
1c	*i*-Pr	**2**	63[c]	**2**	12
1d	$PhCH_2$	**2**	7[d]	**2**	7
1e	Ph	—	—	**3e**	15
1f	$2\text{-}CH_3OC_6H_4$	**3f**	Trace[e]	**3f**	12
1g	$2,5\text{-}(CH_3O)_2C_6H_3$	**3g**	Trace[e]	**3g**	14
1h	$4\text{-}HO\text{-}3\text{-}H_3COC_6H_3$	—	—	**2**	15
1i[f]	$2\text{-}NO_2C_6H_4$	**3i**	30[c]	**3i**	8
1j	$3\text{-}NO_2C_6H_4$	**3j**	Trace[e]	**3j**	13
1k	$4\text{-}(CH_3)_2NC_6H_4$	—	—	**3k**	11
1l	$4\text{-}ClC_6H_4$	**3l**	Trace[e]	**3l**	12
1m	1-Naphthyl	**3m**	Trace[e]	**3m**	21
1n	2-Furyl	**2**	16[d]	**2**	10
1o	5-Methyl-2-furyl	**2**	7[d]	**2**	10
1p	2-Thienyl	**2**	Trace[e]	**2**	11

[a] Irradiation of powdered 1,4-dihydropyridines was carried out for 50 h.

[b] Irradiation was continued until total disappearance of 1,4-dihydropyridines was observed.

[c] Isolated yield.

[d] The yield was determined by the comparison of the integral ratios of the characteristic ^1H NMR peaks in the starting materials and products.

[e] Formation of trace amount of products was detected on the TLC.

[f] **1i** was converted to brownish oil after 15 min irradiation and the reaction was stopped.

Table 2. Solid state and competitive solution photochemistry of 3,5-diacetyl-1,4-dihydropyridines (**4a**–**4n**) at $\lambda \geqslant 28$ nm

Compound	R	Solid photochemistry		Solution photochemistry	
		Product	Yield (%)[a]	Product	Time (h)[b]
4a	CH_3	—	—	**6a**	15
4b	Ph	—	—	**6b**	15
4c	$2\text{-}CH_3OC_6H_4$	—	—	**6c**	13
4d	$3\text{-}CH_3OC_6H_4$	—	—	**6d**	12
4e	$4\text{-}CH_3OC_6H_4$	—	—	**6e**	13
4f	$2,5\text{-}(CH_3O)_2C_6H_3$	—	—	**6f**	22
4g	$3,4\text{-}(CH_3O)_2C_6H_3$	—	—	**6g**	21
4h	$3\text{-}NO_2C_6H_4$	**6h**	Trace[c]	**6h**	21
4i	$4\text{-}NO_2C_6H_4$	**6i**	Trace[c]	**6i**	20
4j	$4\text{-}ClC_6H_4$	**6j**	Trace[c]	**6j**	13
4k	2-Furyl	**5**	8[d]	**5**	18
4l	5-Methyl-2-furyl	**5**	7[d]	**5**	18
4m	2-Thienyl	**5**	Trace[c]	**5**	19
4n	2-Pyridinyl	**6n**	Trace[c]	**6n**	13

[a] Irradiation of powdered 1,4-dihydropyridines was carried out for 50 h.

[b] Irradiation was continued until total disappearance of 1,4-dihydropyridines was observed.

[c] Formation of trace amount of products was detected on the TLC.

[d] The yield was determined by the comparison of the integral ratios of the characteristic ^1H NMR peaks in the starting materials and products.

The results presented in Tables 1 and 2 show that the light sensitivity of many of the 1,4-dihydropyridines investigated in this work in the solid state is very low and these compounds are resistant to the UV-light. In comparison, their photo-oxidations have been observed successfully in the solution. The loss of the substituent in position 4 has been observed earlier in photochemical reactions of Hantzsch esters only in the cases of carboxy group,[22] some heterocyclic groups[12] and secondary alkyl and benzyl groups.[12] The possible argument for the expulsion of these substituents as in **1c**, **1d**, **1n** and **1o** is the higher stability of these groups with radical or carbocation character compared with the other groups. The interesting point in our reactions is the expulsion of these groups even in the solid state, which we do not have the effect of solvation due to the absence of a solvent. This reflects only the higher light sensitivity of dihydropyridines with these groups in position 4 compared to the other groups listed in Tables 1 and 2.

3. Conclusion

In conclusion, we have found that the light sensitivity of 1,4-dihydropyridines in the solid state is decreased drastically in comparison to that in their solution state and that they have a good resistance to UV-light. Therefore, due to their pharmaceutical activity, protection from light of the reaction mixture during their preparation is necessary; however, protection during packing as a tablet or capsule is not important, which is important for drug designers and manufacturers.

4. Experimental

Dihydropyridine crystals (3 mol) were ground in a mortar and strewn on the glass surface (15 cm × 15 cm), which was laid on the water cooled plate and exposed to the 400 W high pressure mercury light source of a reflector at a distance of 40 cm from the glass surface. The light of the reflector was passed through a Pyrex glass. The same amount of dihydropyridines was dissolved in 3 ml $CHCl_3$, put in a vial and exposed to the UV light simultaneously with the powdered dihydropyridines.

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