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A new base-mediated photocyclization to 1,2,4-triazolo[3,4-*b*]-1,3-(4*H*)-benzothiazines via 1,2,4-triazole-3-thiones

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Abstract—The photocyclization of substituted 1,2,4-triazole-3-thiones, under base-mediated conditions, afforded 1,2,4-triazolo[3,4-*b*]-1,3-(4*H*)-benzothiazines along with the desulfurization product. © 2002 Elsevier Science Ltd. All rights reserved.

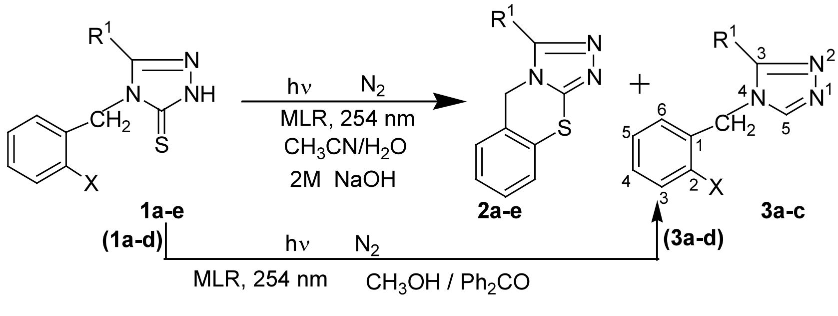
Generally 1,2,4-triazole fused heterocyclic ring systems are found to be associated with diverse pharmacological activity. A series of triazolobenzothiazines were tested for their ability to displace (3*H*)-funitrezepam from bovine brain membranes.[1] IDPH-791 an analogue of triazolobenzothiazine is a well known centrally acting muscle relaxant. It shows anticonvulsant activity and is active in inhibiting various spinal polysynaptic reflexes, crossed extensor, flexor and linguomandibular reflexes.[2] A number of triazolobenzothiazines were tested for CNS activity.[3,4]

Few methods have been reported for the synthesis of 1,2,4-triazolobenzothiazine analogs.[5–7] Recently, photochemical ring expansion of 1,2-benzisothiazole to 1,3-benzothiazine and the photocyclization of 2-chloroindole-3-thiocarbamate to thiazino indole have been reported.[8,9]

In continuation of our interest in the photochemical synthesis of benzothiazoles,[10,11] we have reported[12] the photochemical synthesis of triazolobenzothiazole. To the best of our knowledge there is no report of the photochemical synthesis of triazole-fused benzothiazines. We report here our results on the photocyclization of substituted 1,2,4-triazole-3-thiones to 1,2,4-triazolo[3,4-*b*]-1,3-(4*H*)-benzothiazines.

The required starting materials, 4-(2-halobenzyl)-5-substituted-1,2,4-triazole-3-thiones **1a–e**, were synthesized by refluxing the respective 4-(2-halobenzyl)-1-benzoyl thiosemicarbazide obtained from *o*-halobenzyl isothiocyanate and an acid hydrazide,[13] using a 10% K_2CO_3 solution.

Initially, the irradiation of **1a** under mild aqueous basic conditions (CH_3OH/0.5 M K_2CO_3 or CH_3OH/0.5 M



Scheme 1.

Keywords: photocyclization; basic conditions; photodesulfurization; benzophenone.

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Table 1. Photolysis of substituted 1,2,4-triazole-3-thiones **1a**–**e**

1	R^1	X	Irradiation time (h)	**2**		**3**	
				Yield (%)	Mp (°C)	Yield (%)	Mp (°C)
a	Phenyl	Cl	18 (62)	41	208–210	10 (67)	158–160
b	*p*-Tolyl	Cl	17 (53)	47	203–205	8 (60)	130–132
c	*p*-Anisyl	Cl	20 (47)	38	166–168	15 (48)	156–158
d	*o*-Tolyl	Br	11 (50)	50	173–175	(71)	108–110
e	Benzyl	Cl	21	45	162–164	–	–

The values shown in parenthesis are for the irradiation of triazole-3-thiones in the presence of benzophenone.

NaOH) in a multilamp reactor (MLR) (254 nm) under nitrogen resulted in the formation of desulfurized triazole **3a** as the major product. Nevertheless, when the irradiation of **1a** was carried out in 2 M NaOH/CH_3CN the expected 5-phenyl-1,2,4-triazolo[3,4-*b*]-1,3-(4*H*)-benzothiazine **2a** was isolated as the major product (Scheme 1) along with the desulfurized product **3a**.

Obviously, an increase in the concentration of base increases the concentration of the anion of the thioamide, which intramolecularly substitutes the *o*-halogen present in the *N*-benzyl moiety of the triazole-3-thione.

Similarly, the irradiation of triazole-3-thiones **1b**–**e** gave the respective triazolobenzothiazines **2b**–**e** as major products along with desulfurized triazoles **3b**–**c**. In the case of **1d**,**e** no desulfurized product was observed (Table 1). The structures of photoproducts **2** and **3** were consistent with their spectral data.[14] Further, the structures of **2a**[15] and **3a**[16] were confirmed by X-ray diffraction studies.

Next, the irradiation of **1a**–**d** was carried out in the presence of benzophenone (1.2 equiv.) as a sensitizer in methanol using an MLR, under nitrogen, to afford the desulfurized triazoles **3a**–**d** (Scheme 1) as sole products.

In conclusion, it has been shown that the irradiation of 4-(2-halobenzyl)-5-substituted-1,2,4-triazole-3-thiones under base-mediated conditions afforded the respective 1,2,4-triazolo[3,4-*b*]-1,3-(4*H*)-benzothiazines or desulfurized triazoles depending on the concentration of the base employed, whereas, for the irradiation of triazole-3-thiones in the presence of benzophenone, selective desulfurization of the thiones was observed.

The laser flash photolysis and excited state potential energy calculations for the desulfurization pathway will be published elsewhere.

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References

1. Perioli, L.; Ambrogi, V.; Grandolini, G.; Giusti, L.; Lucacchini, A.; Martini, C. *Farmaco* **1994**, *49*, 245.
2. Junnarkar, A. Y.; Singh, P. P.; Patnaik, G. K.; Shrotri, D. S. *Pharmacol. Res.* **1992**, *26*, 131.
3. Grandolini, G.; Tiralti, M. C.; Rossai, C.; Ambrogi, V.; Orzalesi, G.; De Regis, M. *Farm Ed. Sci.* **1987**, *42*, 43.
4. Grandolini, G.; Rossi, C.; Tiralti, M. C.; Orzalesi, G.; De Regis, M. *Farm Ed. Sci.* **1985**, *40*, 221.
5. Fodor, L.; Sohar, P. *Heterocycles* **1984**, *22*, 537.
6. Liu, K. C.; Shih, B. J.; Chern, J. W. *J. Heterocycl. Chem.* **1990**, *27*, 391.
7. Mishra, A. R.; Singh, S.; Wahab, A. *Indian J. Chem.* **2001**, *40B*, 252.
8. Elghamry, I.; Dopp, D. *Tetrahedron Lett.* **2001**, *42*, 5651.
9. Kutschy, P.; Suchy, M.; Andreani, A.; Dzurilla, M.; Rossi, M. *Tetrahedron Lett.* **2001**, *42*, 9281.
10. Paramasivam, R.; Palaniappan, P.; Ramakrishnan, V. T. *J. Chem. Soc.*, *Chem. Commun.* **1979**, 260.
11. Jayanthi, G.; Muthusamy, S.; Ramakrishnan, V. T. *J. Photochem. Photobiol. A: Chem.* **1998**, *116*, 103.
12. Jayanthi, G.; Muthusamy, S.; Paramasivam, R.; Ramakrishnan, V. T.; Ramasamy, N. K.; Ramamurthy, P. *J. Org. Chem.* **1997**, *62*, 5766.
13. Iqbal, R.; Rama, N. H.; Ahmed, N.; Zamani, K.; Ebrahim, S.; Iqbal, N. *Indian J. Chem.* **1998**, *37B*, 506.
14. Spectral data of compound **2a**: UV: 261, 241 nm (CH_3OH); IR (KBr): 1613, 1473, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.16 (s, 2H, CH_2), 7.18–7.76 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.68, 126.37, 127.36, 127.94, 127.96, 128.67, 129.15 (more intense; two CH), 129.45, 130.18, 130.37, 147.79, 153.99 (C=N); ^{13}C NMR–*DEPT-135* ($CDCl_3$, 50 MHz): δ 47.68 (↓), 126.37, 127.36, 127.95, 128.67, 129.16 (more intense; two CH), 130.38; MS, *m*/*z* (%): 265 (M^+, 100), 264 (36), 193 (20), 161 (26), 135 (20), 134 (48), 121 (34), 108 (8), 103 (4), 102 (6), 90 (8), 89 (24), 77(30). Spectral data of compound **3a**: UV: 238 nm (CH_3OH); IR (KBr): 1575, 1502, 1469 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.30 (s, 2H, CH_2), 6.88 (d, $J = 7.36$ Hz, 1H, C_6-ArH), 7.22–7.58 (m, 8H, ArH), 8.18 (s, 1H, C_5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 46.60, 126.47,

127.64, 128.52, 128.73, 128.97, 130.08, 130.28, 132.65, 132.90, 144.44 (C_5-H), 154.34 (C=N): MS, m/z (%): 269 (M^+, 60) [271, 19], 234 (76), 166 (2), 165 (2), 138 (2), 131 (4), 125 (100) [127, 32], 104 (8), 103 (6), 90 (10), 89 (35), 77(6).

15. Velmurugan, D. Professor, Department of Crystallography and Biophysics, University of Madras, personal communication.
16. Rajakannan, V.; Govindasamy, L.; Velmurugan, D.; Sekar, D.; Senthilvelan, A.; Shanmugasundararaj, S.; Fun, H. K. *Cryst. Res. Technol.* **2002**, *2*, 301.