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Journal of Photochemistry and Photobiology A: Chemistry 116 (1998) 103–108

Journal of
Photochemistry
and
Photobiology
A:Chemistry

Photoreaction of *N*-arylcarbonyl-*N′*-arylthiourea derivatives

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Received 17 October 1997; received in revised form 27 April 1998; accepted 27 April 1998

Abstract

The thiourea derivatives containing an *o*-haloaryl substituent attached to the nitrogen of the thioamide gave the expected benzothiazole. In the absence of halogen, the thiourea derivatives give rise to different products in different solvents accountable by α-cleavage, γ-hydrogen abstraction and oxidative cyclization. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Photoreaction; Thiourea derivatives; Benzothiazole ring system

1. Introduction

Our interest on the photochemical synthesis of benzothiazole ring system [1–3] prompted us to investigate the photochemistry of thiourea derivatives. From the photoreaction of *N*-(2-chlorophenyl)thiourea **1a–c**, we have found the *ortho*-chloro substituent is necessary for the photochemical transformation of *N,N′*-diarylthiourea to benzothiazole. While *N′*-(2-chlorophenyl)-*N,N*-diphenylthiourea **1a**, on irradiation, gave 2-(*N,N*-diphenylamino)benzothiazole **2a**, the reaction with *N*-(2-chlorophenyl)-*N′*-phenylthiourea **1b** and *N*-benzoyl-*N′*-(2-chlorophenyl)thiourea **1c** gave other products in addition to the respective benzothiazoles **2b** and **2c** [4] (Scheme 1). Therefore, we investigated the substituent effect on the photoreaction of *N,N′*-substituted thioureas.

2. Experimental details

All the melting points are uncorrected. IR(KBr) spectra were recorded on a Perkin–Elmer 598 spectrophotometer. ^{1}H NMR spectra were recorded for $CDCl_3$ solution on a Varian EM-390 (90 MHz), a Jeol FX 90Q (90 MHz), and a Hitachi R-1100 (60 MHz) instruments using TMS as internal standard (chemical shift in δ ppm). Mass spectra were taken on a Hewlett-Packard 5985 (70 eV) and a Jeol-GSX-303 HF (70 eV) instruments. Purity of compounds was checked by TLC. The photochemical reactions were carried out in quartz vessel using a Rayonet RPR-208 (254 nm) and an Applied Photophysics reactor (254 nm).

2.1. Preparation of N-arylcarbonyl-N′-arylthiourea derivatives. N-Benzoyl-N′-(2-chlorophenyl)thiourea 1c

The compound **1c** was prepared from 2-chloroaniline (12.7 g, 0.1 mol) and benzoyl isothiocyanate (0.1 mol) in dry acetone as reported [4] earlier.

2.2. N-Benzoyl-N′-(3,4-dimethylphenyl)thiourea 5a

A freshly prepared acetone solution of benzoyl isothiocyanate (0.05 mol) was added dropwise to a solution of 3,4-dimethylaniline (6.05 g, 0.05 mol) in acetone (15 ml) with stirring. After the addition, the mixture was heated under reflux for 30 min and poured onto crushed ice with vigorous stirring. The isolated solid was filtered, washed with water, and dried to yield **5a**; yield: 13.7 g (96.5%), mp 134–135°C (lit., [5] 129–130°C); λ_{max} (MeOH)/nm 266 and 238; υ_{max}(KBr)/cm^{-1} 3210, 3000, 1670, 1590, 1500 and 1130; δ_H (90 MHz, $CDCl_3$) 2.3 (s, 6H, Ar CH_3), 7.2–7.9 (m, 8H, Ar H), 9.2 (br s, 1H, NH) and 12.6 (br s, 1H, NH).

2.3. N-(4-Chlorobenzoyl)-N′-(3,4-dimethylphenyl)thiourea 5b

Reaction of 4-chlorobenzoyl isothiocyanate (0.023 mol) and 3,4-dimethylaniline (2.8 g, 0.023 mol) in acetone (15 ml) gave **5b**; yield: 6.1 g (83.5%), mp 163–165°C; λ_{max} (MeOH)/nm 267.6; υ_{max} (KBr)/cm^{-1} 3220, 3110, 1660, 1580 and 1140; δ_H (90 MHz, $CDCl_3$) 2.25 (s, 6H, Ar CH_3), 7.30–7.85 (m, 7H, Ar H), 9.11 (br s, 1H, NH) and 12.36 (br s, 1H, NH).

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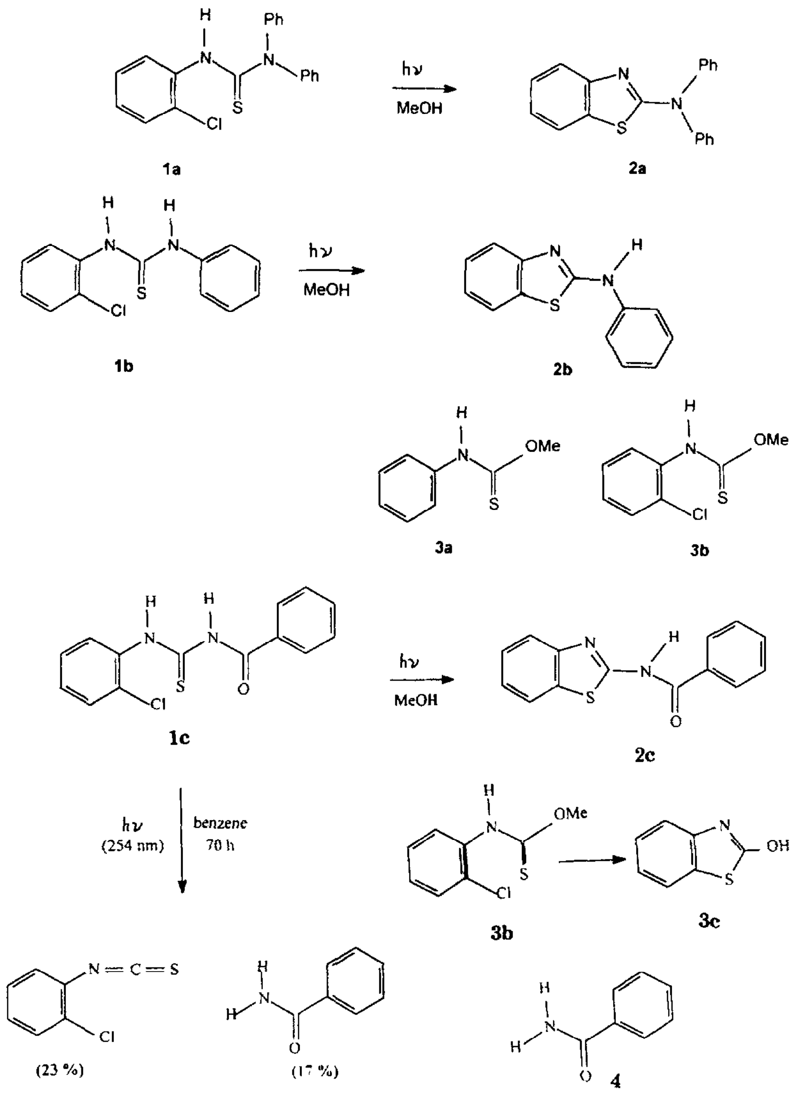


Scheme 1.

2.4. N-(2-Methylbenzoyl)-N′-(3,4-dimethylphenyl)thiourea 5c

The compound **5c** was prepared from *o*-toluoyl isothiocyanate (0.015 mol) and 3,4-dimethylaniline (1.8 g, 0.015 mol); yield: 1.4 g (31%), mp 94–95°C; λ_{max} (MeOH)/nm 263; υ_{max} (KBr)/cm^{-1} 3190, 3000, 1670, 1580, 1510 and 1120; δ_H (90 MHz, $CDCl_3$) 2.23 (s, 6H, Ar CH_3), 2.48 (s, 3H, Ar CH_3), 7.18–7.50 (m, 7H, Ar H), 9.00 (br s, 1H, NH) and 12.38 (br s, 1H, NH).

2.5. N-Benzoyl-N′-(4-methoxyphenyl)thiourea 5d

Thiourea **5d** was prepared from benzoyl isothiocyanate (0.05 mol) and *p*-anisidine (6.15 g, 0.05 mol); yield: 7.8 g (54.5%), mp 146–147°C (lit., [5] 150–154°C); λ_{max} (MeOH)/nm 271 and 235; υ_{max}(KBr)/cm^{-1} 3200, 3010, 1660, 1590, 1285 and 1130; δ_H (90 MHz, $CDCl_3$) 3.79 (s, 3H, OCH_3), 6.70–7.90 (m, 9H, Ar H), 9.25 (br s, 1H, NH) and 12.40 (br s, 1H, NH).

2.6. N-Benzoyl-N′-(4-methylphenyl)thiourea 5e

Reaction of benzoyl isothiocyanate (0.05 mol) and *p*-toluidine (5.35 g, 0.05 mol) furnished **5e**; yield: 8.1 g (60%), mp 150–152°C (lit., [5] 158–159°C); λ_{max} (MeOH)/nm 264; υ_{max}(KBr)/cm^{-1} 3220, 3000, 1660, 1580, 1340 and 1130; δ_H (60 MHz, $CDCl_3$) 2.30 (s, 3H, Ar CH_3), 6.95–7.80 (m, 9H, Ar H), 9.6 (br s, 1H, NH) and 12.50 (br s, 1H, NH).

2.7. N-Benzoyl-N′-(3-chlorophenyl)thiourea 5f

Treatment of 3-chloroaniline (6.35 g, 0.05 mol) with benzoyl isothiocyanate (0.05 mol) furnished **5f**; yield: 14.0 g (96.5%), mp 119–120°C (lit., [5] 127.5–128°C); λ_{max} (MeOH)/nm 262 and 238; υ_{max}(KBr)/cm^{-1} 3290, 2990, 1660, 1580 and 1130; δ_H (60 MHz, $CDCl_3$) 7.15–7.95 (m, 9H, Ar H), 9.18 (br s, 1H, NH) and 12.68 (br s, 1H, NH).

2.8. *N-(2-Chlorobenzoyl)-N′-(3,4-dimethylphenyl)thiourea 5g*

From 2-chlorobenzoyl isothiocyanate (0.02 mol) and 3,4-dimethylaniline (2.4 g, 0.02 mol) was obtained **5g**; yield: 5.8 g (91%), mp 130–132°C; υ_{max} (KBr)/cm^{-1} 3200, 3150, 1670, 1590 and 1280; δ_H (60 MHz, $CDCl_3$) 2.23 (s, 6H, Ar CH_3), 7.13–7.80 (m, 7H, Ar H), 9.36 (br s, 1H, NH) and 11.10 (br s, 1H, NH).

2.9. *N-(2-Chlorobenzoyl)-N′-(2,4-dimethylphenyl)thiourea 5h*

2-Chlorobenzoyl isothiocyanate (0.05 mol) was treated with 2,4-dimethylaniline (6.0 g, 0.05 mol) to furnish the thiourea **5h**; yield: 13.0 g (82%), mp 145–147°C; υ_{max} (KBr)/cm^{-1} 3200, 3140, 1670, 1590, 1280 and 1160; δ_H (60 MHz, $CDCl_3$) 2.3 (s, 6H, Ar CH_3), 7.2–7.8 (m, 7H, Ar H), 9.4 (br s, 1H, NH) and 11.8 (br s, 1H, NH).

2.10. *N-(2-Chlorobenzoyl)-N′-(4-methylphenyl)thiourea 5i*

A solution of 2-chlorobenzoyl isothiocyanate (0.05 mol) in acetone was treated with *p*-toluidine (5.14 g, 0.05 mol) to yield **5i**; yield: 12.0 g (79%), mp 164–166°C; λ_{max} (MeOH)/nm 300, 260; υ_{max} (KBr)/cm^{-1}; 3150, 3010, 1675, 1590 and 1160; δ_H (60 MHz, $CDCl_3$) 2.60 (s, 3H, Ar CH_3), 7.20–8.10 (m, 8H, Ar H), 9.36 (br s, 1H, NH) and 12.33 (br s, 1H, NH).

2.11. *N-Benzoyl-N′-methyl-N′-phenylthiourea 5j*

Treatment of benzoyl isothiocyanate (0.05 mol) with *N*-methylaniline (5.35 g, 0.05 mol) in acetone furnished **5j**; yield: 11.6 g (86%), mp 127–129°C. (lit., [6] 137°C); λ_{max} (MeOH)/nm 251; υ_{max} (KBr)/cm^{-1} 3180, 3010, 1690, 1590, 1480 and 1100; δ_H (60 MHz, $CDCl_3$) 3.65(s, 3H, N-CH_3), 7.00–7.55 (m, 10H, Ar H) and 8.52 (br s, 1H, NH).

2.12. *N-(2-Chlorobenzoyl)-N′-methyl-N′-phenylthiourea 5k*

Reaction of *N*-methylaniline (2.8 g, 0.0264 mol) with 2-chlorobenzoyl isothiocyanate furnished **5k**; yield: 2.9 g (36%), mp 105–108°C; λ_{max} (MeOH)/nm 286; υ_{max} (KBr)/cm^{-1} 3160, 3000, 1680, 1570, 1360 and 1120; δ_H (60 MHz, $CDCl_3$) 3.7 (s, 3H, N–CH_3), 7.1–7.2 (m, 8H, Ar

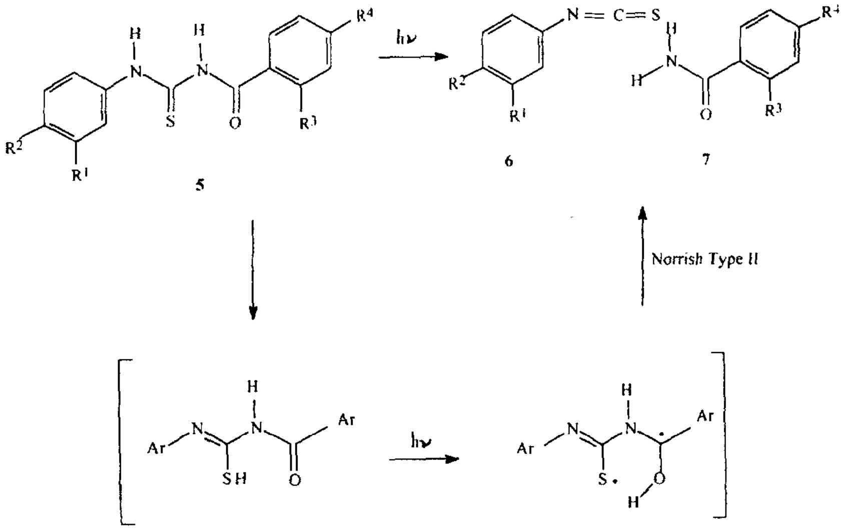


Table 1

Entry	R^1	R^2	R^3	R^4	Irrdn time/h^a	Solvent^b	Yield/% 6	7	Recovery of 5/%
5a	Me	Me	H	H	70	benzene	19.0	23	44
5b	Me	Me	H	Cl	61	benzene	6.6	0	43
5c	Me	Me	Me	H	60	benzene	20.8	0	40
5d	H	OMe	H	H	47	benzene	7.7	0	84
5e	H	Me	H	H	71	benzene	0	0	95.4
5f	Cl	H	H	H	45	benzene	0	0	55
5g	Me	Me	Cl	H	26 21	benzene acetone	0 46.0	0 52	70 0
5i	H	Me	Cl	H	65 60	acetone methanol	0 0	68 0	0 90

a. Irradiation of a solution containing 5a (0.35-0.9 g) by low pressure mercury lamp.
b. Benzene (180 ml), acetone (150 ml), methanol (180 ml)

Scheme 2.

H) and 8.2 (br s, 1H, NH); m/z 304 (M^+, 4%) [306, M + 2], 269 (100), 139(96) [141] and 111(60) [113].

2.13. *N-Benzoyl-N'-(1-chloro-2-naphthyl)thiourea* ***10***

N-(2-Naphthyl)benzamide was treated [7] with sulfuryl chloride to yield *N*-(1-chloro-2-naphthyl)benzamide, which was hydrolysed with 50% alcoholic KOH at 160–170°C in an oil bath, to obtain 1-chloro-2-naphthylamine [8]. The reaction of the amine (3.54 g, 20 mmol) with benzoyl isothiocyanate (3.26 g, 20 mmol) in dry acetone furnished the thiourea **10**; yield: 5.6 g (82%), mp 192–194°C; Analysis: calculated for $C_{18}H_{13}ClN_2OS$: C, 63.43; H, 3.84; N, 8.22; found: C, 63.31; H, 3.89; N, 8.10%; υ_{max} (KBr)/cm^{-1} 3260, 3020, 1665, 1590, 1510 and 1300; δ_H (60 MHz, $CDCl_3$) 6.7–7.6(m, 11H, Ar H), 8.4(br s, 1H, NH) and 11.8 (br s, 1H, NH); m/z 340 (M^+, 1%), 306 (28), 221(5), 219(15), 177(10), 149(7), 140(8), 106(8), 105(100) and 77(41).

2.14. *General procedure of photoreaction*

The thiourea **1c** (0.870 g, 3 mmol) in dry benzene (180 ml) was irradiated at 254 nm for 70 h. After removal of the solvent, the residue was chromatographed over a column of silica gel to afford (i) 2-chlorophenyl isothiocyanate (0.2 g, 23%), υ_{max}($CHCl_3$)/cm^{-1} 2060 (br), 1580, 1470 and 1440, (ii) unreacted **1c** (46%), and (iii) benzamide (0.15 g, 17%) using petroleum ether, benzene–petroleum ether (1:1) and chloroform–ethyl acetate (3:1) as eluents respectively.

The thioureas **5a–k** and **10** were irradiated following the above general procedure and the products were separated by column chromatography. Refer Table 1 for details.

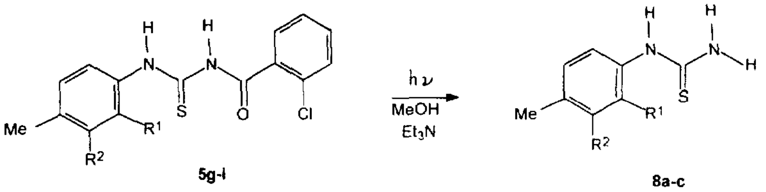
2.15. *2-Benzoylimino-3-methyl-2,3-dihydrobenzothiazole* ***9a***

Yield: 0.24 g, (60%), mp 152–153°C (lit., [9] 154°C); υ_{max} (KBr)/cm^{-1} 1610, 1490, 1450, 1350 and 1270, δ_H (90 MHz, $CDCl_3$) 3.98 (s, 3H, N–CH_3) and 7.3–8.4 (m, 9H, Ar H); m/z 268 (M^+, 56%), 191 (60), 163 (14), 137 (13) and 105 (81).

2.16. *2-(2-Chlorobenzoylimino)-3-methyl-2,3-dihydrobenzothiazole* ***9b***

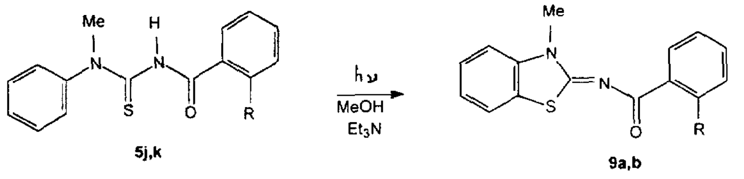
Yield: 0.13 g (43%), mp 166–167°C; Analysis: calculated for $C_{15}H_{11}ClN_2OS$: C, 59.50; H, 3.66; N, 9.25; found: C, 59.20; H, 3.62; N, 9.03%; υ_{max} (KBr)/cm^{-1} 1600, 1495, 1450, 1400, 1360 and 1290; δ_H (90 MHz, $CDCl_3$) 3.95 (s, 3H, N–CH_3) and 7.20–8.14 (m, 8H, Ar H); m/z 302 (M^+, 59%) [304, M+2], 267 (21), 258 (5) [260], 239 (19), 191 (63), 163 (11), 139 (86) [141] and 111 (94) [113].

Moreover the identification of **9b** was performed by comparison of ^1H NMR and IR spectra of **9b** with an authentic sample prepared as follows: The thiourea **5k** was treated with bromine (0.05 ml, 0.98 mmol) in glacial acetic acid (40 ml) under ice-cold conditions with stirring for 30 min. The reaction mixture was poured over crushed ice, stirred well, the



Entry	R^1	R^2	Irrdn time/h	Product (Yield/%)
5g^a	H	Me	14	**8a** (61)
5h^a	Me	H	15	**8b** (55)
5i^b	H	H	12	**8c** (60)

a. 1.0 g in 200 ml of methanol with 0.5 ml of triethylamine.
b. 0.6 g in 150 ml of methanol with 0.5 ml of triethylamine.



Entry	R	Irrdn time/h	Product (Yield/%)
5j^a	H	19	**9a** (60)
5k^a	Cl	28	**9b** (43)

a. 0.3-0.4 g in 180 ml of methanol and 0.5 ml of triethylamine.

Scheme 3.

solid obtained was filtered, washed with water and dried to get **9b**: yield: 0.24 g (80%), mp 164–166°C.

*2.17. 2-Benzoylamino naphtho[2,1-d]thiazole **11***

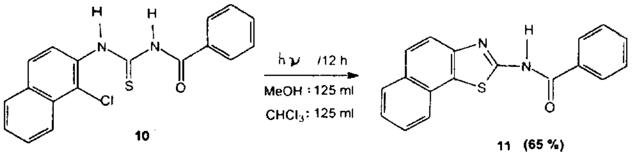
Yield: 0.58 g (65%), mp 210–212°C; Analysis: calculated for $C_{18}H_{12}N_2OS$: C, 71.03; H, 3.97; N, 9.20; found: C, 71.23; H, 3.85; N, 9.03%; υ_{max} (KBr)/cm^{-1} 3160, 1675, 1550 and 1300; δ_H (60 MHz, $CDCl_3$) 7.13–8.20 (m, 11H, Ar H), 8.40 (br s, 1H, NH) and 12.50 (br s, 1H, NH); m/z 305 (M^+ + H, 26%), 276 (5), 155 (3), 106 (7), 105 (100) and 77 (34).

3. Results and discussion

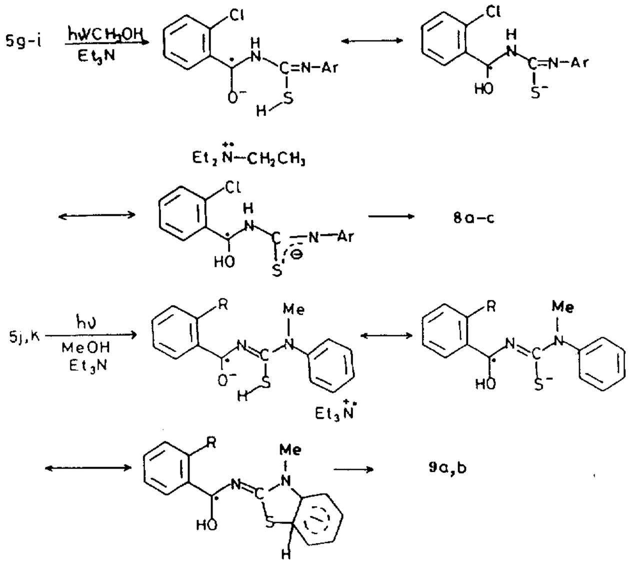
In the photochemistry of thiourea derivatives, it was found that trisubstituted thiourea **1a** gave the expected benzothiazole **2a**. Here we found new results that *N,N'*-disubstituted thiourea derivatives gave various products as shown in Scheme 1. The thiourea **1b** gave benzothiazole **2b** and thiocarbamates **3a** and **3b** by irradiation in MeOH, the latter two arising from α-cleavage at either side of the thiocarbonyl group of **1b**. The photoreaction of thiourea **1c** in MeOH gave **2c** and three additional products: **3b** and **3c** and **4**. It was already established that irradiation of **3b** in MeOH furnished **3c**. We have now established that **3b** is formed from *o*-chlorophenyl isothiocyanate by irradiation in MeOH. The irradiation of **1c** in benzene gave *o*-chlorophenyl isothiocyanate (23%) and benzamide (17%) with a 46% recovery of **1c**; the formation of these two products from **1c** can be explained by the Norrish Type-II reaction.

As an extension, the thioureas **5a–k** were prepared [5] and irradiated. The photolysis of the thioureas **5a–d** and **5g** furnished the respective aryl isothiocyanate **6** while **5a, 5g** and **5i** gave the respective benzamide **7** (Scheme 2). The thioureas **5e, 5f** did not give any isothiocyanate and the starting materials were recovered on irradiation in benzene. As expected, **5j** was recovered (90%) on irradiation in benzene for 48 h. These observations can be rationalized based on the Norrish Type II reaction. Since the irradiation of **5a–d** gave the respective isothiocyanate as a product, it can be viewed as arising from the γ-hydrogen abstraction from the SH instead of NH, by the excited carbonyl group, facilitated by the hydrogen bonding. The enol nature of the thioamide can be the reason for the downfield signal in the ^{1}H-NMR of **5a–d**. Moreover, K_b for 3,4-dimethylaniline, *p*-anisidine and *p*-toluidine are 14.79×10^{-10}, 15×10^{-10} and 12×10^{-10} respectively [10]. Since the basicity of *p*-toluidine is lower, the enolization is less efficient and hence no γ-hydrogen abstraction occurs in **5e**. The recovery of **5g** on irradiation in benzene may be explained on the basis of the reported less efficient hydrogen bonding by carbonyl oxygen due to the chlorine substituent at the *ortho* position.

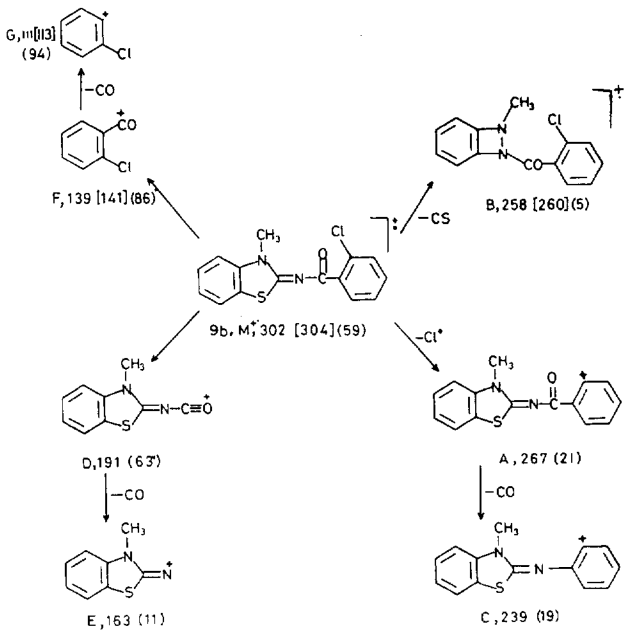
The irradiation of **5g** and **5i** in acetone giving products accountable by the γ-H abstraction process can be explained based on the hydrogen bonding between amide NH and acetone which will in turn increase the hydrogen bonding between amide carbonyl and thiol SH. Sensitization by acetone (E_T = 78 kcal mol^{-1}) [11] may not be the controlling factor since the irradiation of **5g** in benzene (E_T = 84 kcal mol^{-1}) did not lead to any product.



Scheme 4.



Scheme 5.



Scheme 6.

The thiourea **5i** remained unaffected on irradiation in MeOH. On the other hand, the irradiation of **5g–i** in MeOH in the presence of triethylamine furnished the respective thiourea **8a–c**, an α-cleavage product, probably involving an electron transfer mechanism. In the case of **5j,k**, the different type of photoreaction proceeded since no enolization in the thioamide moiety of **5j,k** occurred due to *N*-methyl substituent. The photolysis of **5j** and **5k** in MeOH in the presence of triethylamine gave the respective benzothiazole **9a** and **9b** (Scheme 3). Extension of the above work to *N*-benzoyl-*N′*-(1-chloro-2-naphthyl)thiourea **10** in the absence of Et_3N, however, furnished 2-benzoylaminonaphtho[2,1-*d*]thiazole **11** similar to our earlier observation [12] (Scheme 4).

Recently, we have reported the mechanistic studies on the formation of benzothiazoles from *o*-halothioacetanilides [13]. The formation of **8a–c** and **9a,b** can be rationalized involving electron transfer mechanism (Scheme 5). Electron transfer reaction and the participation of triethylamine in such reaction have been explained in a detailed manner [10,11,14]. The mass spectral fragmentation pattern of **9b** is depicted in Scheme 6.

4. Conclusion

The present results indicate that the thiourea derivatives give rise to the expected benzothiazoles, when the NH of the thioamide has an *o*-haloaryl substituent. In addition, Norrish Type I reaction and Norrish Type II reaction have been observed. Oxidative cyclization occurs in the photolysis of suitably substituted thioureas. An electron transfer mechanism has been proposed for α-cleavage and oxidative cyclization processes.

Acknowledgements

We wish to thank the CSIR, New Delhi, for the Research Fellowship (GJ), University Grants Commission, New Delhi, for the Special Assistance Programme to our Department and late Prof. J.H. Boyer, University of New Orleans and Prof. J. Kagan, University of Illinois at Chicago, USA for mass spectral data.

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