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RESEARCH ARTICLE

PHOTOCHEMICAL STUDIES OF THIOAMIDE DERIVATIVES

Rajalakshmi, S. and *Aruna, S.

Department of Chemistry, Queen Mary's College (A), Chennai - 600 004, Tamilnadu, India

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ABSTRACT

Photochemistry, a sub discipline of chemistry is the study of interactions between light and atoms or molecules. Photochemistry describes chemical reactions that proceed with the absorption of light. Everyday examples include photosynthesis, the degradation of plastics and the formation of vitamin D with sunlight. Photochemical reaction of thioamide derivatives gave the cyclised, oxidized and dehalogenated compounds. Thioamide derivatives are well known for their antimicrobial activities and they have drawn much attention because of their novel heterocyclic chemistry. Light is clearly manifesting itself as a unique reagent in organic synthesis as many of the novel reactions involve photochemical reaction as a key step. The synthesized thioamides are characterized by IR, ^{1}H, ^{13}C, Mass and analytical spectral data.

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INTRODUCTION

Our interest on the photochemical synthesis of benzothiazine ring system prompted us to investigate the photochemistry of thiourea derivatives. The photochemical synthesis of heterocyclic system has become a versatile method, in respect to its applicability to many ring systems. We have previously explored (Paramasivam *et al.*, 1979) the photochemical synthesis of benzothiazoles and the benzothiazoloquinazolinones (Muthusamy *et al.*, 1992) from suitably substituted thioacyl derivatives. Following extensive research on the photochemistry of thiones, we found that the photochemical cyclization of 4-(2-halophenyl)-1,2,4-triazole-5-thiones to their corresponding benzothiazoles in a multi lamp reactor (MLR) proceeded slowly 30-60 hrs, whereas the photocyclization of 4-(2-halobenzyl)-1,2,4-triazole-5-thiones to benzothiazine in a MLR in an alkaline medium (sodium hydroxide in acetonitrile) required a shorter reaction time. In the later case, we also observed photo desulfurized products along with the anticipated photocyclized product. (Jayanthi *et al.*, 1998; Senthilvelan and Ramakrishnan 2002) Triazolobenzothiazole formation through a singlet state involves a photo substitution of the anionic thiocarbonyl sulphur of triazolothione which intra molecularly displaces the halogen of the halo arene in an S_N (ET) Ar* mechanism (Horspool and Song 1995). A similar mechanism for the formation of triazolobenzothiazine through a singlet state and desulfurization through a triplet state has been proposed earlier (Senthilvelan *et al.*, 2004). Since compound gave the desulfurized product, along with the cyclization product, a triplet state of would also have been involved due to the presence of the napthyl ring (heavy atom effect) (Depuy *et al.*, 1998). The irradiation of thiones under the basic conditions described above using a TFR, furnished the respective triazolobenzothiazoles. The thiones on irradiation under the same conditions, furnished the thiazole and the desulfurized product. There are many methods for the preparation of 1,4-diazepines (Katritzky 1967) and 1,2-diazepines (Katritzky 1967), only a few methods are available for the synthesis of 1,3-diazepines (Katritzky 1967; Wang and Ramachandra 2001; Kobayashi *et al.*, 1981; De Stevens and Dughi 1961; Kharida *et al.*,1960; Berger *et al.*,1963).

MATERIALS AND METHODS

All the melting points are uncorrected, IR Spectra were recorded on FTIR-8300 Shimadzu spectrometer. ^{1}H-NMR spectra were recorded on Jeol-FXQ (90MHz), Jeol GSX (400 MHz) and DPX 200 (200MHz). Mass spectra were recorded on Jeol-JMS-DX 303 HF.

RESULTS AND DISCUSSION

Irradiation was carried out at 254nm using thin film reactor. The thioamides1a-f gave unexpected photochemical products 2a-f respectively. Irradiation of 1a was chosen to find out whether the photochemical ring formation would lead to a benzothiazole or a benzothiazine system. The formation of benzothiazole ring is observed. It has been found that the thiourea 1a has a preference to yield a five membered benzothiazole ring over a six-membered [1,3]-4H-benzothiazine ring 1b. Irradiation of thiourea 1b-d gave the reduction of halogen, instead of the expected benzothiazine 2b-

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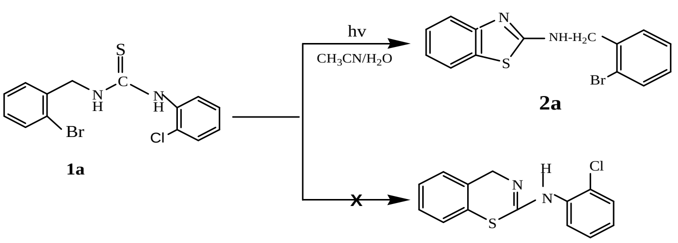
***Corresponding author: Aruna, S.** *Department of Chemistry, Queen Mary's College (A), Chennai - 600 004, Tamilnadu, India.*

d. Likewise, the thiourea 1e ,1f was irradiated under the same condition afford the product 2e and 2f an oxidation product instead of thiazine 2e and 2f.

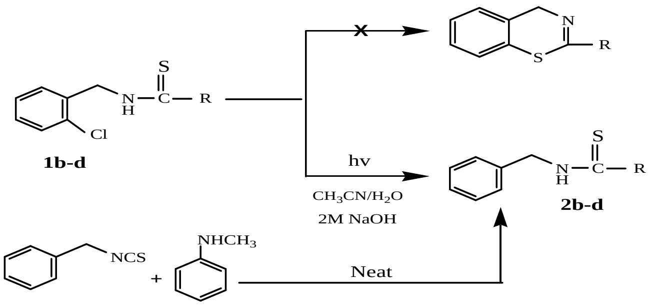
Scheme I

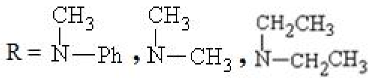
Synthesis of 2-(2-Bromobenzylamino)-benzothiazole: 2a



Scheme II

Synthesis of N-Benzyl-(N’- substituted)- thiourea: (2b-d)





$R = \overset{CH_3}{\overset{|}{N}}-Ph,\ \overset{CH_3}{\overset{|}{N}}-CH_3,\ \overset{CH_2CH_3}{\overset{|}{N}}-CH_2CH_3$

Characterization

N-(2-Bromobenzyl)-N’-(2-chlorophenyl) thiourea: (1a)

Reaction of 2-chlorophenyl isothiocyanate (1g, 0.006m) with 2-bromobenzylamine (1.10g, 0.006m) furnished the thiourea 1a. The solid obtained was filtered and washed with benzene. It was recrystallized from ethanol. Yield: 1.6g (75%), M.P.:201-202 ^{0}C. IR (KBr):3367, 3091, 2928, 1446, 1352, 721cm^{-1}. ^{1}H-NMR: δ4.9(d,2H,CH_2,*J*=5.7Hz),6.6(s,1H,NH),7.6, (s,1H,NH), 7.1-7.5(m,Ar-H, 8H). ^{13}C-NMR: δ49.27 (CH_2), 123.66, 127.69, 127.01, 128.60, 128.37, 129.51, 130.83, 130.94, 132.75, 133.24, 136.10, 180.84 (C=S). MS :m/z: 319 (M^+-Cl), 240, 186, 184, 171, 169, 153, 150, 107, 91, 90, 77. Analysis of $C_{14}H_{12}N_2SClBr$: Calculated: 355.40, %C: 47.37, %H: 3.40, %N: 7.91. Found: %C: 47.48, %H : 3.52, %N: 7.84.

N-(2-Chlorobenzyl)-N’-methyl-N’-phenyl thiourea: (1b)

Reaction of 2-chlorobenzyl isothiocyanate (1.83g, 0.01m) and N-methyl aniline (1g, 0.01m) gave the thiourea **1b.** It was recrystallised from ethanol. Yield: 2.1g (72%). M.P: 188-189 ^{0}C. ^{1}H-NMR: δ3.6 (s,3H, N-CH_3), 4.8 (d, 2H, CH_2, *J* = 5.7Hz), ($CDCl_3$,400 MHz): 5.9 (s, 1H, NH), 7.1-7.5 (m, Ar-H, 8H). ^{13}C-NMR: δ43.44 (CH_3), 47.37 (CH_2), 126.82, 127.1, 128.59, 128.75, 129.43, 130.41, 130.58, 133.39, 135.39, 142.53, 182.01 (C=S). MS, m/z:290,292.

N-(2-Chlorobenzyl)-N’,N’-dimethyl thiourea: (1c)

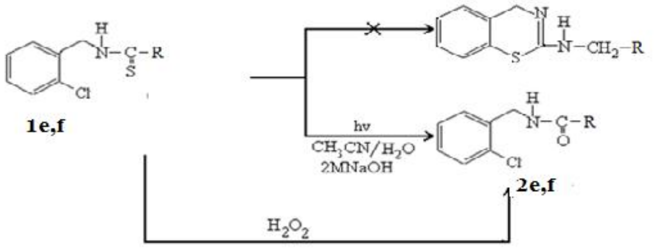
Treatment of 2-chlorobenzyl isothiocyanate (0.92g, 0.005m) with aqueous solution of N, N-dimethyl amine (0.23g, 0.005m) afforded the thiourea **1c.** Yield: 0.90g (79%). M.P: 177-178 ^{0}C. ^{1}H-NMR: δ3.2 (s, 6H, 2CH_3), 4.9(d, 2H, CH_2, *J* = 5.7 Hz), ($CDCl_3$, 400 MHz): 5.8(s, 1H, NH), 7.2-7.5(m, Ar-H, 5H). ^{13}C-NMR: δ40.12 (CH_3), 47(CH_2), 127.06, 129.09, 129.49, 131.16, 135.60.MS,m/z:229,231.

Table : Irradiation of 1 to give 2.

Compound	M. P.^{o}C	Yield (%)	Irradiation Time (h)	Solvent	Product	Yield (%)	M. P.^{o}C
1a	188-189	72	2	CH_3CN	2a	75	86-88
1b	177-178	79	2	CH_3CN	2b	80	93-95
1c	187-188	76	2	CH_3CN	2c	70	110-112
1d	201-202	75	2.5	CH_3CN	2d	60	180-182
1e	127-128	80	2.5	CH_3CN	2e	50	225-227
1f	210-211	80	2.5	CH_3CN	2f	60	182-183

Scheme III

Synthesis of N, N’-Di-(2-substituted) urea: (2e-f)



R = 2-Chloro aniline
2-Bromo aniline

N-(2-Chlorobenzyl)-N’, N’-diethyl thiourea: (1d)

Treatment of 2-chlorobenzyl isothiocyanate (0.85g, 0.004m) with aqueous solution of N, N-diethyl amine (0.23g, 0.005m) afforded the thiourea 1d. Yield0.65 (80%). M.P.: 187-188 ^{0}C. ^{1}H-NMR: δ1.9 (s, 6H, 2CH_3),δ3.9 (t, 4H, 2CH_2), 4.9(d, 2H, CH_2, *J* = 5.7 Hz), -($CDCl_3$, 400 MHz): 5.9(s, 1H, NH), 7.2-7.7(m, Ar-H, 5H). ^{13}C-NMR: δ40.12 (CH_3), 43.10 (CH_2), 47(CH_2), 125.06, 128.09, 129.49, 135.16, 139.60.MS,m/z:257,259.

N, N’-Di-(2-chlorobenzyl)-thiourea: (1e)

Treatment of 2-chlorobenzyl isothiocyanate (0.92g, 0.005m) with 2-chlorobenzyl amine (0.70g, 0.005m) afforded the thiourea 1e.Yield: 1.30g (80%). M.P.: 127-128^{0}C. ^{1}H-NMR: δ4.8(d, 2H,CH$_2$, *J* = 1.8 Hz), 6.3(t, 1H, NH). (CDCl$_3$, 400MHz): 7.1-7.7 (m, Ar-H, 10H), 7.73 (t, 1H, NH). ^{13}C-NMR: δ44.93 (CH$_2$), 59.78 (CH$_2$), 126.10, 127.57, 128.01, 128.38, 128.43, 128.84, 128.97, 131.99, 132.12, 132.31, 135.36, 136.71, 157.75.MS,m/z:324,326.

N, N'-Di-(2-bromobenzyl) thiourea: (1f)

Treatment of 2-bromobenzyl isothiocyanate (1.8g) with 2-bromobenzyl amine (0.70g, 0.005m) afforded the thiourea 1f.Yield: 1.30g (80%). M.P.: 210-211^{0}C. ^{1}H-NMR: δ45.1 (d, 2H,CH$_2$, *J* = 5.9 Hz), 6.5(t, 1H, NH). (CDCl$_3$, 400MHz): 7.1-7.7 (m, Ar-H, 10H), ^{13}C-NMR: δ43.32 (CH$_2$), 58.94 (CH$_2$), 127.10, 127.97, 128.01, 128.23, 128.54, 128.84, 128.97, 131.99, 133, 134.31, 135.61, 136.11. .MS, m/z:379, 381.

2-(2-Bromobenzylamino)-benzothiazole: (2a)

An acetonitrile (150ml) solution of thiourea 1a(0.3g,0.85m) containing 2M NaOH (30ml) was flushed with nitrogen for 1 h and irradiated in a thin film reactor for 2.5 h. After completion of the reaction, checked by TLC, the solvent was removed under reduced pressure. The residue obtained was extracted with ethyl acetate. The ethyl acetate layer was separated; the aqueous layer neutralized with dil. HCl and it was extracted with ethyl acetate. The ethyl acetate layers were combined and concentrated. The residue obtained was chromatographed over a column of silica gel; elution with petroleum ether ethyl acetate (2:3) afforded the benzothiazole 2a. Yield: 0.16g (60%). M.P.: 180-182^{0}C. IR (KBr): 3377, 1623, 1562, 1056 cm^{-1}. ^{1}H-NMR: δ4.7 (s, 2H, CH$_2$), 7.0-7.58 (m, Ar-H, 8H). (CDCl$_{3,}$400MHz). ^{13}C-NMR: δ49.52 (CH$_2$), 118.9, 120.9, 122.0, 126.1, 127.7, 129.25, 129.90, 133.05 (all CH), 116.5, 122.8, 123.8, 130.2 (all C). MS, m/z: 318 (M$^+$, 16), 320 (M+2, 17), 239, 186, 184, 171, 169, 149, 135, 134, 90, 89. Analysis of $C_{14}H_{11}N_2SBr$: Calculated: 319.22, %C: 52.67, %H: 3.47, %N: 8.77. Found %C: 52.79, %H: 3.64, %N: 8.62.

N-Benzyl-N'-methyl-N'-phenyl thiourea: (2b)

An acetonitrile (150ml) solution of thiourea 1b (0.3g, 0.001m) containing 2M NaOH (30ml) was flushed with nitrogen for 1 h and irradiated in a thin film reactor for 2.5h. Usual work up gave the thiourea 2b. Yield: 0.20g (75%). M.P.: 86-88 ^{0}C. IR (KBr): 3750, 3652, 2362, 2342 cm^{-1}. ^{1}H-NMR: δ3.68 (s, 3H, N-CH$_3$), 4.85-4.87 (d, 2H, *J* = 5.86 Hz, N-CH$_2$), 5.8 (s, 1H, NH), 7.1-7.5 (m, 10H, Ar-H), (CDCl$_{3,}$ 400MHz). ^{13}C-NMR: δ43.47 (CH$_3$), 47.48 (CH$_2$), 126.88, 127.09, 128.61, 128.80, 129.41, 130.61, 130.52 (all CH), 135.53, 142.74 (all C), 182.25 (C=S). MS, m/z: 256, 183, 149, 117, 107, 106, 105, 91, 65. The authentic sample was prepared from benzyl isothiocyanate (1.5g, 0.001m) and N-methyl aniline (0.86g, 0.01m), which immediately afforded the compound **2b** (yield = 75%), which was confirmed by m. p, mixture m.p and super imposable IR with that obtained from the irradiation of 1b in CH_3CN/2M NaOH condition.

N-Benzyl-N', N'-dimethyl thiourea: (2c)

An acetonitrile (150ml) solution of thiourea 1c (0.23g, 0.001m) containing 2M NaOH (30ml), was flushed with nitrogen for 1 h and irradiated in a thin film reactor for 2.5 h. Usual work gave up the thiourea2c. Yield: 0.16g (80%). M.P: 93-95 ^{0}C. IR (KBr): 3259, 2927, 1542, 1446, 1377 cm^{-1}. ^{1}H-NMR: δ3.2 (s, 6H, N(CH$_3$)$_2$), 4.85 (d, 2H, *J* = 5.47Hz, N-CH$_2$), 5.85 (s, 1H,NH), 7.2-7.4 (m, Ar-H, 5H). (CDCl$_3$, 400MHz).^{13}C-NMR: δ40.54 (CH$_3$), 50.16 (CH$_3$), 127.51, 128.46, 128.67, 129.37 (all CH), 138.13, 181.92 (C=S). MS, m/z:194, 178, 162, 148, 120, 106, 92, 91, 77. The authentic sample of **2c**(70% yield) was prepared by the reaction of benzyl isothiocyanate (1.288g, 0.007m) with dimethylamine (0.32g, 0.007m) and compared with the photochemical product and confirmed by m.p, mixture m.p and super imposable IR spectrum.

N-Benzyl-N', N'-diethyl thiourea: (2d)

An acetonitrile (150ml) solution of thiourea 1d (0.26g, 0.001m) containing 2M NaOH (30ml), was flushed with nitrogen for 1 h and irradiated in a thin film reactor for 2.5 h. Usual work gave up the thiourea 2d. Yield: 0.19g (70%). M.P.: 110-112^{0}C. IR (KBr): 3237, 2917, 1642, 1432, 1381 cm^{-1}. ^{1}H-NMR: δ 3.7(t, 2H, CH$_2$), 1.6(q, 3H, CH$_3$), δ4.75 (d, 2H, J= 5.74Hz, N-CH$_2$), 5.9 (s, 1H, NH), 7.2-7.6 (m, Ar-H, 5H). ^{13}C-NMR: δ41.25 (CH$_3$), 49.25 (CH$_2$), 51.25 (N-CH$_2$), 128.46, 128.76, 129.33, 139.13, 182.29 (C=S).MS, m/z:193,150,106,92,91,77. The authentic sample of 2d (70% yield) was prepared by the reaction of benzyl isothiocyanate (1.288g, 0.007m) with dimethylamine (0.32g, 0.007m) and compared with the photochemical product and confirmed by m.p, mixture m.p and super imposable IR spectrum.

N, N'-Di-(2-chlorobenzyl) urea: (2e)

Irradiation of the thiourea1e (0.33g, 0.001m) in acetonitrile solution, containing 2M NaOH, in thin film reactor furnished the urea 2e. Yield: 0.137g (50%). M.P.: 225-227 ^{0}C. IR (KBr): 3237, 1640, 1554, 1432, 1300 cm^{-1}. ^{1}H-NMR: δ4.3 (s, 4H, CH$_2$), 6.4 (s, 2H,NH), 7.2-7.3 (m, 8H, Ar-H), 7.9 (s, 1H, C$_3$-H). (CDCl$_3$, 400 MHz). ^{13}C-NMR: δ41.16 (CH$_2$), 126.79, 128.11, 128.85, 128.94 (all CH), 132.43, 137.62 (all C), 158.16 (C=O). MS, m/z : 273, 275, 183, 148, 140, 142, 125, 127, 90. To the thiourea 1d (1g, 0.003m) in hydrogen peroxide solution at 0^{0}C, sodium hydroxide was added and stirred for 2 hours, which furnished the urea 2e (0.75g, 85%) which was compared with the TLC, m.p., mixture m.p, and super imposable IR of the product obtained under the above photolytic condition.

N,N'-Di-2-(bromobenzyl)-urea: (2f)

An acetonitrile (150ml) solution of thiourea 1f (0.26g, 0.001m) containing 2M NaOH (30ml), was flushed with nitrogen for 1 h and irradiated in a thin film reactor for 2.5 h. Usual work gave up the urea 2f.Yield: 0.213g (60%). M.P:182-183^{0}C.^{1}H-NMR: δ4.2 (s, 4H, CH$_2$), 6.7 (s, 2H, NH(, 7.2-7.4 (m, 8H, Ar-H). ^{13}C-NMR: δ42.25 (CH$_{2),}$ 128.19, 128.91, 128.92, 132.45, 138.65, 159.16(C=O).MS,m/z:483,485,393,303,318,303,275,183,140,125,127,90. The authentic sample of 2e (75%, yield) prepared by the reaction of thiourea 2e and hydrogen peroxide by the usual workup and compared with TLC, m.p., mixture m.p, and super imposable IR of the product obtained under the above photolytic condition.

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