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Microwave assisted synthesis and photochemical reactions of 3-(amine dithiocarbamyl) phthalides

K. P. Srivastava*, Sweta Singh and Harimohan Kumar

Department of Chemistry, Ganga Singh College, Chhapra-841 301, Bihar, INDIA

ABSTRACT

An efficient and environmentally benign exclusive method of synthesis of 3-(amine dithiocarbamyl) phthalides has been developed using reaction of 3-chlorophthalide with amine dithiocarbamate effectively in an aqueous medium with excellent yields under microwave irradiation. The results were compared with conventional methods. All the ecofriendly synthesized 3-(amine dithiocarbamyl) phthalides were characterized by analytical and spectral methods. The photochemical decomposition of 3-(amine dithiocarbamyl) phthalides yielded meso-3, 3'- dihydrobiphthalide as the only isolable product. The mechanisms of the green synthesis and photochemical reactions have also been studied.

Keywords: Green synthesis, microwave irradiation, photochemical reactions, 3-(amine dithiocarbamyl) phthalides, meso-3, 3'- dihydrobiphthalide

INTRODUCTION

Synthesis of new chemical entities is major bottleneck in drug discovery. Conventional methods for various chemical syntheses are very well documented and practiced. The methods for synthesis (Heating process) of organic compounds has continuously modified from the decade. In 1855, Robert Bunsen invented the burner which acts as energy source for heating a reaction vessel; this was later superseded by isothermal, oil bath or hot plate, but the drawback of heating, though method remains the same. Microwave Assisted Organic Synthesis (MAOS), which has developed in recent years, has been considered superior to traditional heating.

Microwave assisted organic synthesis [1-6](MAOS) has emerged as a new "lead" in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product. Now day's technique is considered as an important approach toward green chemistry, because this technique is more environmentally friendly. This technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/reagents lead to environmental pollution. This growth of green chemistry [7] holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Due to its ability to

couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.

In continuation of environmental friendly synthesis and photochemical reactions of various organic compounds [8-10], here we have present the microwave assisted synthesis and photochemical reactions of 3-(amine dithiocarbamyl) phthalides.

MATERIALS AND METHODS

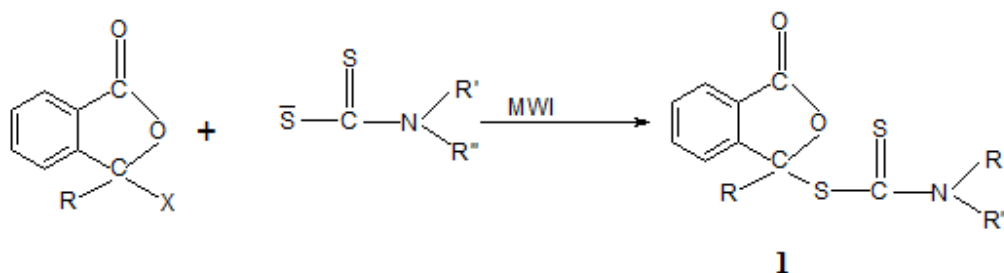
Materials and Techniques

All starting reagents were purchased from commercial sources and used without further purification. 3-chlorophthalide, 3-bromophthalide, dimethylamine dithiocarbamate, diethylamine dithiocarbamate, pyrrolidine dithiocarbamate, piperidine dithiocarbamate, etc. were prepared by reported standard procedures [11-14].

The microwave irradiations were performed using a commercial / kitchen microwave oven model BMO: 700T (BPL- make). All irradiation experiments were carried out using a non-rotating annular photochemical reactor. All melting points were determined on a melting point apparatus and are uncorrected. Infrared (KBr) spectra were recorded on a Perkin-Elmer, Model-137 infrared spectrophotometer and UV spectra were determined on a Beckmann-DB spectrophotometer. NMR spectra were recorded on a Bruker Varian-300 MHz NMR spectrometer in CDCl₃ with TMS as an internal standard. The chemical shifts are expressed in δ -scale downfield from TMS and proton signals are indicated as *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet. The TLC was run on silica gel plates using acetone-benzene (1:3) as the irrigant. All compounds were analysed satisfactorily for C, H, S and N using Carl-Ebra 1106 elemental analyser in micro analytical laboratory.

(a) Synthesis of 3-amine dithiocarbamylphthalides

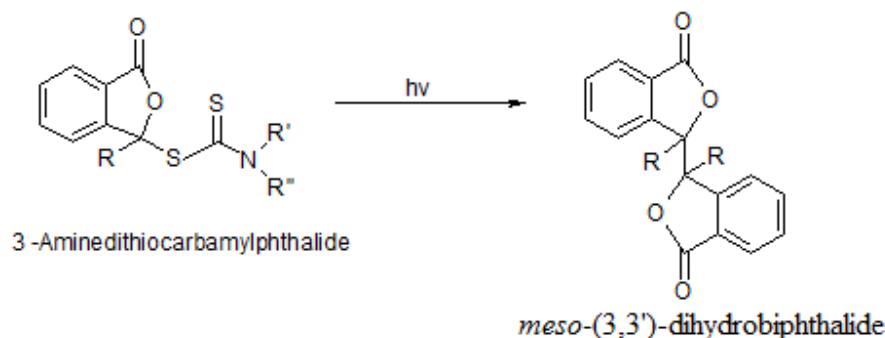
A solution of 3-chlorophthalide in acetone, maintained around 298K was gradually added to amine dithiocarbamate in small portions and with constant stirring in microwave oven. After removal of the solvent from the reaction mixture, the residue was treated with excess of water to remove any unchanged amine dithiocarbamate and recrystallized from a mixture (1:1) of ethanol and methylene chloride to give 3-(Amine Dithiocarbamyl) Phthalides (**1**)(scheme-1).



Scheme-1: Synthesis of 3-(amine dithiocarbamyl) phthalides

(b) Photolysis of 3-amine dithiocarbamyl phthalides

A typical solution of 3-amine dithiocarbamyl phthalides in benzene was irradiated for one hour, at room temperature. The removal of the solvent under vacuum gave a product which on recrystallization from acetic acid gave *meso*-3,3'- dihydrobipthalide, m.p. 543K.



Scheme-2: Photolysis of 3-amine dithiocarbamyl phthalides

ANALYTICAL RESULTS AND SPECTRAL DATA**Analytical and Spectral Characterisation of 3-(Dimethylamine dithiocarbamyl) phthalide (1a):****Molecular Formula:** C₁₁H₁₁O₂NS₂; **Molecular Mass:** 253u

Analytical Data: calculated:	%C = 50.00	%H = 04.54	%N = 05.78	%S = 25.29
Found:	50.15	04.50	05.55	25.30

IR Spectrum (KBr) [ν_{\max}] = 1750cm⁻¹ (C=O group).UV Spectrum (CH₂Cl₂) [λ_{\max}] = 282nm, (ϵ , 11,850) and 340nm, (ϵ , 60).

Analytical Data: calculated:	%C = 55.51	%H = 05.33	%N = 04.98	%S = 22.77
Found:	55.35	05.20	05.15	22.70

IR Spectrum (KBr) [ν_{\max}] = 1760cm⁻¹ (C=O group).UV Spectrum (CH₂Cl₂) [λ_{\max}] = 284nm, (ϵ , 11,350) and 340nm, (ϵ , 120).**Analytical and Spectral Characterisation of 3-(Diethylamine dithiocarbamyl) phthalide (1b):****Molecular Formula:** C₁₃H₁₅O₂NS₂; **Molecular Mass:** 281u

Found:	52.75	04.45	4.55	21.80
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IR Spectrum (KBr) [ν_{\max}] = 1750cm⁻¹ (C=O group).UV Spectrum (CH₂Cl₂) [λ_{\max}] = 288 nm, (ϵ , 14,800) and 350nm, (ϵ , 130).**Analytical and Spectral Characterisation of 3-(Pyrrolidine dithiocarbamyl) phthalide (1c):****Molecular Formula:** C₁₃H₁₃O₂NS₂; **Molecular Mass:** 279u

Analytical Data: calculated:	%C = 55.91	%H = 04.65	%N = 05.00	%S = 22.94
Found:	56.15	04.50	05.05	22.90

IR Spectrum (KBr) [ν_{\max}] = 1750cm⁻¹ (C=O group).UV Spectrum (CH₂Cl₂) [λ_{\max}] = 284nm, (ϵ , 13,150) and 334nm, (ϵ , 100).**Analytical and Spectral Characterisation of 3-(Piperidine dithiocarbamyl) phthalide (1d):****Molecular Formula:** C₁₄H₄O₂NS₂; **Molecular Mass:** 282u

Analytical Data: calculated:	%C = 57.33	%H = 05.11	%N = 04.77	%S = 22.69
Found:	57.50	05.20	04.65	22.50

IR Spectrum (KBr) [ν_{\max}] = 1750cm⁻¹ (C=O group).UV Spectrum (CH₂Cl₂) [λ_{\max}] = 286nm, (ϵ , 16,650) and 340nm, (ϵ , 100).

Analytical and Spectral Characterisation of 3-(Morpholine dithiocarbamyl) phthalide (1e):**Molecular Formula:** C₁₃H₁₃O₂NS₂; **Molecular Mass:** 295u**Analytical Data:** calculated: %C = 52.88 %H = 04.40 %N = 04.74 %S = 21.69**DISCUSSION**

Our main objective was to examine the reactions of 3-chlorophthalide, 3-chloro-3-phenylphthalide and 3-bromophthalide with different amine dithiocarbamates with a view to studying the nature of the products formed in these microwave irradiated reactions.

The reaction of 3-chlorophthalide with dimethylamine di-thiocarbamate, for example, gave a 92% yield of a product 459K and identified as 3-(dimethylamine dithiocarbamyl) phthalide (**1a**), based on analytical results and spectral data. The IR spectrum of **1a** showed an absorption band at 1750 cm characteristic of a Y-carbonyl group. The UV spectrum of **1a** showed an absorption maximum at 340 nm (ϵ , 90), characteristic of unsymmetrical phthalic amine dithiocarbamic anhydrides [15].

The NMR spectrum of **1a** (**Figure-1**) showed a multiplet centered around 7.95 ppm (5H) due to the four aromatic protons and the tertiary proton attached to the 3-carbon of the phthalide nucleus. In addition, the spectrum showed two singlets at 3.42 ppm (3H) and 3.63 ppm (3H), respectively, due to the two methyl groups of the dithiocarbamate group.

The magnetic inequivalence of these two methyl groups is attributed to the restricted rotation about the C-N bond in **1a**, similar to the restricted rotation that is observed in amides [16-25].

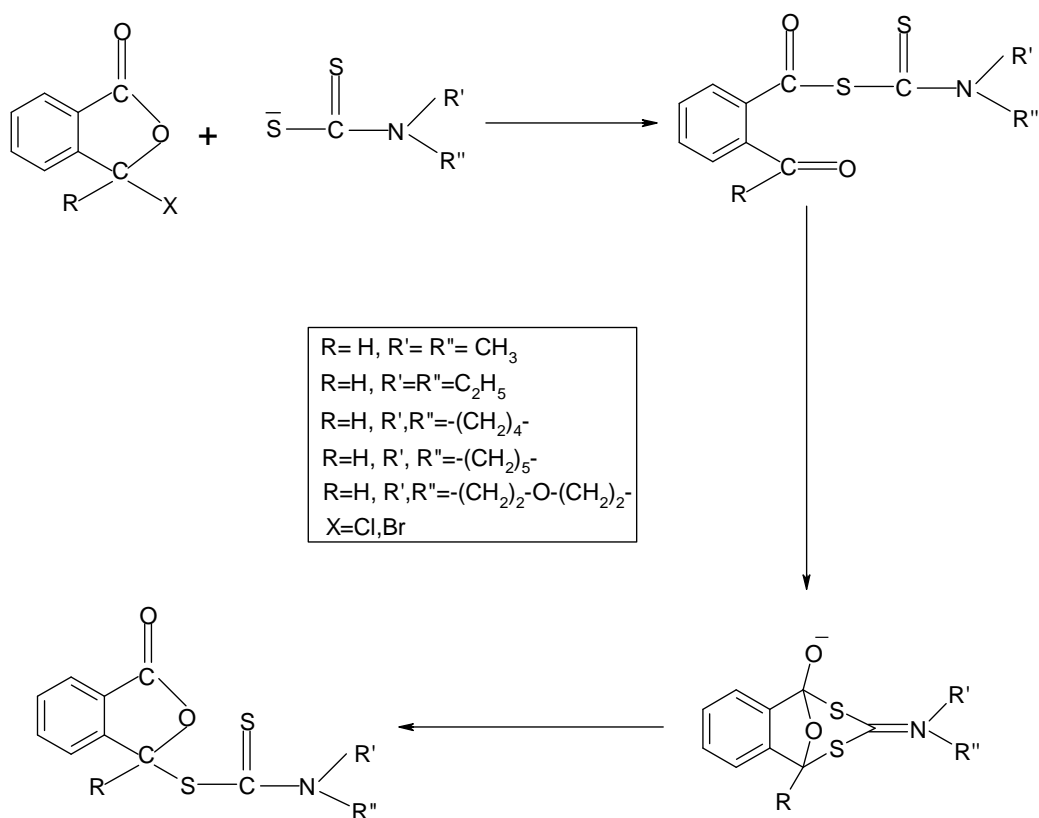
Further, it was observed that the two separate peaks appearing at 3.42 ppm and 3.63 ppm coalesced to a single broad peak at 3.5 ppm, when the NMR spectrum was determined at 333K. As in the case of the reaction of 3-chlorophthalide with potassium O-ethyl xanthate, a freshly mixed solution of 3-chlorophthalide and dimethylamine dithiocarbamate showed an absorption maximum at 394 nm (ϵ , 100), characteristic of the -CO-S-CS- chromophore [26-29].

Further, it was observed that the absorption band at 394 nm disappeared on keeping the solution at room temperature for a couple of hours and a new absorption maximum at 340 nm (ϵ , 90), characteristic of amine dithiocarbamylphthalides, was observed [30-31].

The initial appearance of the absorption maximum at 394 nm is attributed to the formation of the unstable benzoic dithiocarbamic anhydride intermediate which then rapidly rearranges to **1a** through the bicycle-[3,2,1]-transition state, as shown in **scheme-3**. Similarly, the reaction of pyrrolidine dithiocarbamate with 3-chlorophthalide gave rise to a 78% yield of 3-(pyrrolidine dithiocarbamyl) phthalide (**1e**).

Table-1: Comparison of % yield of synthesized compounds

Compound	m.p. (in K)	% Yield	
		Classical method	Green method
1a	460	72	87
1b	395	75	93
1c	449	64	80
1d	389	67	85
1e	441	73	92



Scheme-3: Mechanism of synthesis of 3-(amine dithiocarbamyl) phthalides

Similarly, the reactions of 3-bromophthalide with diethylamine dithiocarbamate, pyrrolidine dithiocarbamate, piperidine dithiocarbamate and morpholine dithiocarbamate gave the corresponding 3-amine dithiocarbamyl phthalides, 4b-e in yields ranging between 78% and 93% (**table-1**).

The C-S type of bond fission occurring in the photolysis of acyl and aroyl xanthates has also been postulated in the photolysis of dithiocarbamic anhydrides [32].

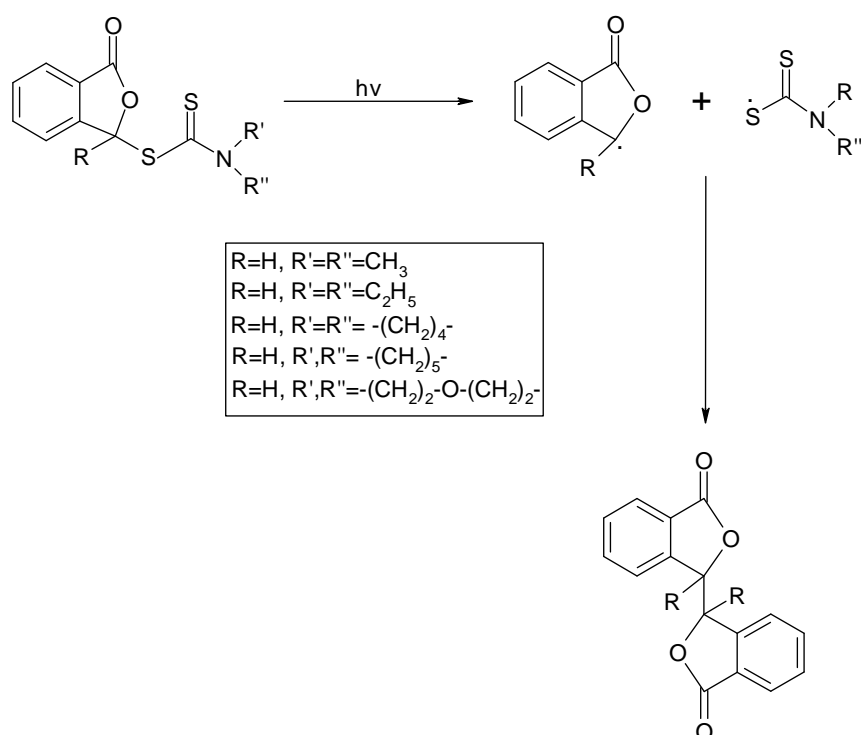
During the course of the present investigation we have examined the photochemical transformations of several amine dithiocarbamyl phthalides with a view to studying the nature of the products formed in these reactions. Photolysis of a benzene solution of 3-(dimethylamine dithiocarbamyl) phthalide (**1a**), for example, gave a 27% yield of *meso*-3,3'-dihydrobipthalide, as the only isolable product.

Similarly, the photolysis of 3-(diethylamine dithiocarbamyl) phthalide (**1b**), 3-(pyrrolidine dithiocarbamyl) phthalide (**1c**), 3-(piperidine dithiocarbamyl) phthalide (**1d**) and 3-(morpholine dithiocarbamyl) phthalide (**1e**) gave *meso*-3,3'-dihydrobipthalide, in each case, and in yields ranging between 25-50% (**table-2**).

The formation of 3,3'-dihydrobipthalide in the photolysis of 3-(amine dithiocarbamyl) phthalides (**1a-e**) may be rationalized in terms of the initial C-S bond fission leading to the generation of the phthalide radicals, through reaction paths similar to those indicated in **scheme-4**.

Table-2: The % yield of photolysed compounds

Compound	% Yield
1a	27
1b	40
1c	25
1d	27
1e	25



Scheme-4: Mechanism of photolysis of 3-(amine dithiocarbamyl) phthalides

CONCLUSION

In the present protocol we observed better yields in a shorter period compared to the conventional methods. In conclusion, we have described here an efficient and environmentally benign synthesis of 3-(amine dithiocarbamyl) phthalides and their photochemical reactions under microwave irradiation which is simple, mild and ecofriendly from green chemistry point of view. The photochemical decomposition of 3-(amine dithiocarbamyl) phthalides yielded *meso*-3, 3'- dihydrobipthalide as the only isolable product. The mechanisms of the green synthesis and photochemical reactions have also been presented.

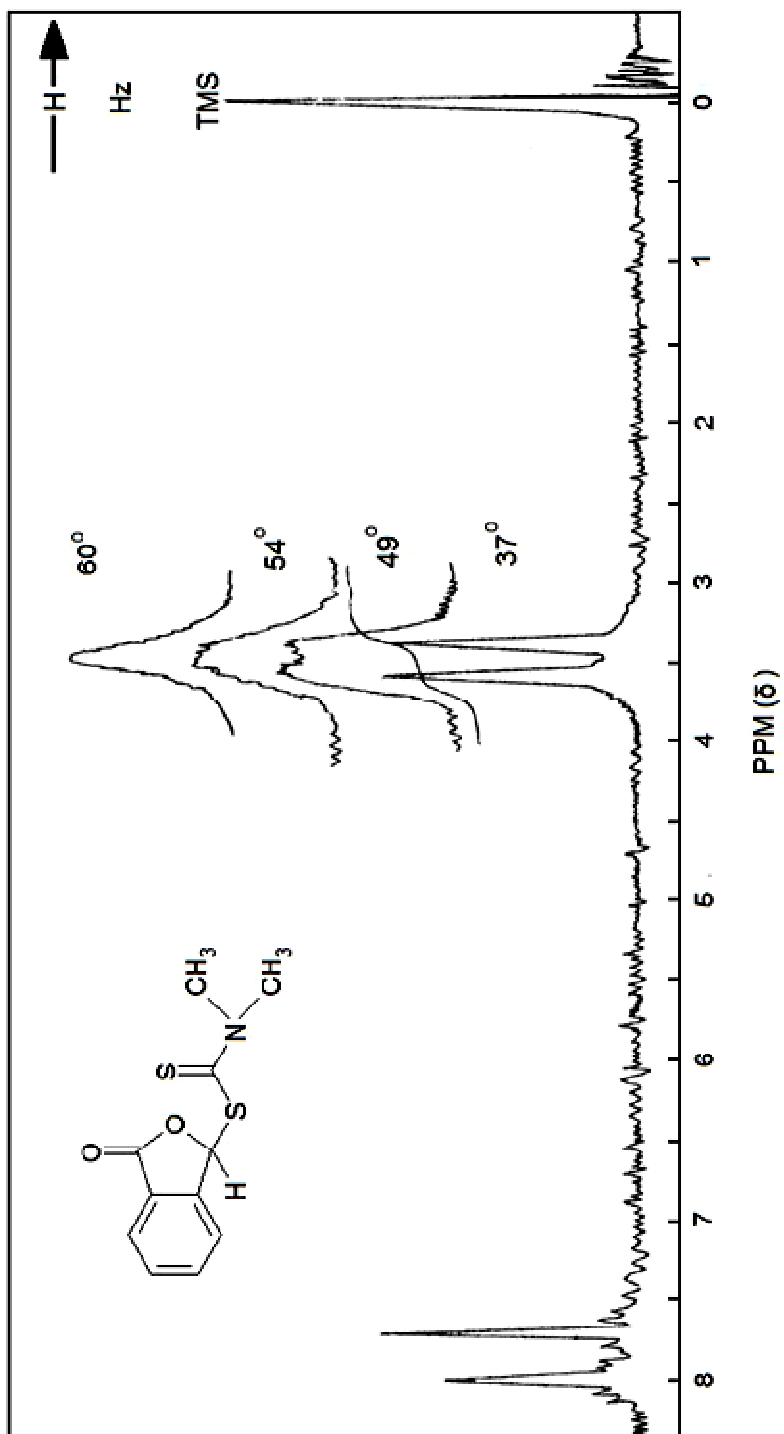


Figure-1: NMR spectrum of 3-(dimethylamine dithiocarbamyl) phthalide (1a)

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