IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
February 2015 Vol.:2, Issue:3

Efficient, Eco friendly and catalyst free synthesis of 1-[2-(4-substituted-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide in PEG 400 medium

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ISSN 2349-7203
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Submission: 22 January 2015
Accepted: 2 February 2015
Published: 25 February 2015

Keywords: Thiocarbamide, PEG 400, environmentally benign, Efficient, high yield, cost effective, Thiourea

ABSTRACT

Efficient synthesis of 1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (5a) and other different 1-[2-(4-substituted-1-hydroxynaphthalen-2-yl) -2 oxoethyl] thiocarbamide (5) derivative of thiocarbamide in high yield were carried out by interaction of, a mixture of 2-bromo-1-(4-bromo-1-hydroxynaphthalen-2-yl) ethanone (3a) and 2-bromo-1-(4-substituted-1-hydroxynaphthalen-2-yl) ethanone (3) with thiourea (4) and phenyl thiourea (4a) in an environmentally benign easily available and cost effective solvent medium such as PEG 400 without using any catalyst below room temperature at 0-5^{0}C . Structure of all the synthesized compounds have been characterized by C, H, N elemental analysis, IR and ^{1}H NMR spectral analysis.

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INTRODUCTION

Thiocarbamides are the nitrogen and sulphur containing organic compounds. The compounds containing nitrogen and sulphur are pharmaceutically and biologically active. Thiocarbamides and their derivatives showed remarkable tuberculostatic activity and are used by medicinal practitioners[1-11]. Thiocarbamide group is present in a variety of natural and synthetic compounds with interesting biological or chemical properties, and therefore has been known for its important medicinal activity[12-14]. A number of derivatives of thiocarbamides have been also reported to exhibit marked antibacterial and fungicidal activity[15-24]. These derivatives contain the –N=C=S group, is a characteristic of many well known compounds which show toxicity to fungi[25], significant insecticidal activity has also been reported for these compounds. These compounds are having numerous chemical and biological applications such as Anesthetic and Antiviral[26-30]. Derivatives of N-aryl- or N-heteroarylthioureas are known as potential inhibitors of HIV-1 Reverse Transcriptase and related viruses, antihyperthyroid drugs, anti-inflammatory and analgesic agents, acaricides, as well as for their wide spectrum of anthelmintics activity[31-36]. In recent literature, it was observed that the synthesis of thiocarbamide was carried out by using various substrates[37-42]. But most of the methods employed for synthesis of thiocarbamide are suffered from various drawbacks such as use of hazardous catalyst and solvent medium that may harm to environment and human being. Also the time required for completion of reactions are very long, so it is necessary to develop new alternative path for synthesis of title compound by avoiding the hazardous catalyst, solvent medium and minimizing the reaction time. Considering these facts in our present research work, we developed a new reaction condition by using eco-friendly solvent medium such as Polyethylene glycol-400 and without using any catalyst. Hence, it was thought interesting to investigate reactions of 2-bromo-1-(4-substituted-1-hydroxynaphthalen-2-yl) ethanone (3) with different thioureas (4) to synthesize 1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (5).

With above aim and objectives the interactions of 2-bromo-1-(4-substituted-1-hydroxynaphthalen-2-yl) ethanone (3) with different thioureas (5) in presence of PEG-400 medium were investigated (Scheme-1).

MATERIALS AND METHODS

Experimental

All chemicals used were of AR grade. The melting points of all the synthesized compounds were recorded using hot paraffin bath. The Carbon and Hydrogen analysis was carried out on Carlo-Ebra 1106 analyser. Nitrogen estimation was carried out on Colman-N-analyzer-29. Merck, pre-coated Silica gel 60 F254 (Aluminum sheets) plates were used for analytical TLC. IR spectra were recorded on FTIR spectrophotometer. 1 H NMR spectra were recorded (in $CDCl_3$) on 500 MHz spectrometer using TMS as an internal standard.

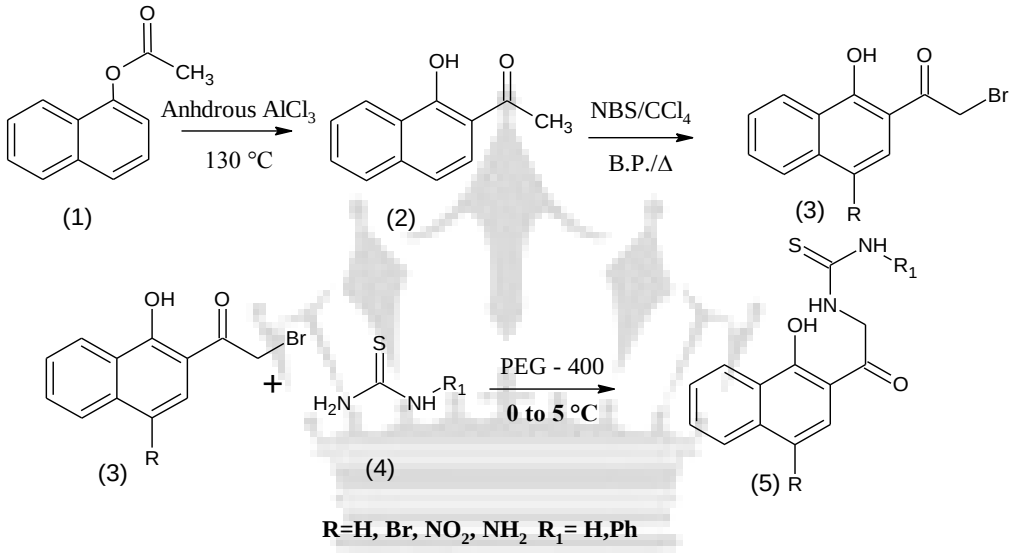

Figure 1. (Scheme – 1)

General Procedure for synthesis of 1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (5a)

1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (5a) was prepared by, a mixture of 2-bromo-1-(4-bromo-1-hydroxynaphthalen-2-yl)ethanone (3a) (1 gm, 3.6 mmol), thiourea (4) (0.29 gm, 3.6 mmol) in 20 ml of PEG 400 was stirred at 0-5^{0}C temperature on magnetic stirrer until 5-6 minutes. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate: hexane = 20:80). On completion of the reaction, the reaction mixture was poured into crushed ice then neutralized the reaction mixture by dilute sodium hydroxide solution to obtain the product. The precipitated product was filtered and dried. The

product was pure enough (single spot on TLC) for all practical purposes. However, for characterization purposes, it was further purified by column chromatography.

The yield of the dried crude product was found to be 0.96 g (96 %).

Melting Point - 119^{o}C

Colour of compound (5a) - Yellow Crystalline solid

IR (KBr, cm^{-1}): 3432.67 cm^{-1}, 3232.11 cm^{-1}, 3351.68 cm^{-1}, 1604.48 cm^{-1}, 1569.77 cm^{-1}, 1199.51 cm^{-1}, 1307.50 cm^{-1}, 1014.37 cm^{-1}, and 748.25 cm^{-1}

^{1}H NMR (500 MHz, CdCl3): δ 1.64 (s, 2H, -CH_2), δ 2.17 (s, 2H, -NH), δ 2.86 (s, 1H, OH), δ 7.13-8.09 (m, 5H,-$C_{10}H_5$)

Elemental Analysis of $C_{13}H_{11}BrN_2O_2S$:

% Found: - C, 45.98%; H, 3.33%; Br, 23.46%; N, 8.18%; S, 9.60%

% Calculated: - C, 46.03%; H, 3.27%; Br, 23.56%; N, 8.20%; S, 9.45%

General Procedure for synthesis of 1-[2-(4-nitro-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (5b)

1-[2-(4-nitro-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (6b) was prepared by, a mixture of 2-bromo-1-(4-nitro-1-hydroxynaphthalen-2-yl)ethanone (4) (1 gm, 3.6 mmol), thiourea (5) (0.29 gm, 3.6 mmol) in 20 ml of PEG 400 was stirred at 0-5^{0}C temperature on magnetic stirrer until 5 minutes. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate: hexane = 20:80). On completion of the reaction, the reaction mixture was poured into crushed ice, and then neutralized the reaction mixture by dilute sodium hydroxide solution to obtain the product. The precipitated product was filtered and dried. The product was pure enough (single spot on TLC) for all practical purposes. However, for characterization purposes, it was further purified by column chromatography.

The yield of the dried product was found to be 0.86 g (86%).

Melting Point – 187^{0}C

Colour of compound (5b) - Yellow orange solid

IR (KBr, cm^{-1}): 3590.81 cm^{-1}, 3243.68 cm^{-1}, 3367.10 cm^{-1} &3316.96 cm^{-1}, 1654.62 cm^{-1}, 1608.34 cm^{-1}, 1531.77 cm^{-1}, 1357.64 cm^{-1}, 1280.50 cm^{-1},1018.37 cm^{-1} and 736 cm^{-1}

^{1}H NMR (500 MHz, CdCl3): δ 1.25 (s, 2H, -NH_2), δ 2.69 (s, 2H, HN-CH_2), δ 2.76 (d, 3H-CH_2-NH) 6.81 (s, 1H,OH), δ 7.46-8.50 (m,5H,-$C_{10}H_5$)

Elemental Analysis of $C_{13}H_{12}N_3O_4S$:-

% Found:-C, 51.21%; H, 3.64%; N, 13.80%; S,10.39%

% Calculated:- C, 51.14%; H, 3.63%; N,13.76%; S, 10.50%

General Procedure for synthesis of 1-[2-(4-amino-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (5c)

1-[2-(4-amino-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (5c) was prepared by, a mixture of 2-bromo-1-(4-amino-1-hydroxynaphthalen-2-yl)ethanone (3c) (1gm, 3.6 mmol), thiourea (4) (0.29 gm, 3.6 mmol) in 20 ml of PEG 400 was stirred at 0-5^{0}C temperature on magnetic stirrer until 10 minutes. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate: hexane = 20:80). On completion of the reaction, the reaction mixture was poured into crushed ice and then neutralized the reaction mixture by dilute sodium hydroxide solution to obtain the product. The precipitated product was filtered and dried. The product was pure enough (single spot on TLC) for all practical purposes. The product was recrystallized by hot ethanol. However, for characterization purposes, it was further purified by column chromatography.

The yield of the dried product was found to be 0.86 g (86%).

Melting Point - 272^{o}C

Colour of compound (5c) - Light brown Crystalline solid

IR (KBr, cm^{-1}): 3517.52cm^{-1}, 3424.96 cm^{-1} and 3351.68 cm^{-1}, 3232.11 cm^{-1}, 1616.08 cm^{-1}, 1509.77 cm^{-1} 1307.50 cm^{-1}, 1241.93 cm^{-1}, 1018.23 cm^{-1} and 748.25 cm^{-1}

^{1}H NMR (500 MHz, CdCl3): δ 2.17 (s, 2H, NH_2), δ 2.88 (s, 2H, -CH_2), δ 2.69 (s, 1H, -NH), δ 2.95 (s, 1H, OH), δ 7.04-8.50 (m, 5H,-$C_{10}H_5$)

Elemental Analysis of $C_{13}H_{12}N_2OS$:

% Found:-C, 56.92%; H, 5.03%; N, 15.43%; S, 11.10%

% Calculated: - C, 56.71%; H, 4.76%; N, 15.26%; S, 11.65%

RESULTS AND DISCUSSION

To study the Synthesis of 1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (5a) from 2-bromo-1-(4-bromo-1-hydroxynaphthalen-2-yl)ethanone (3a) and thiourea (4) in proper way, to reduce time duration of reaction and for maintaining green chemistry parameters

and to develop new reaction conditions, the reactions were also carried out in other different solvent medium and the time required for completion of reactions were noted, it was observed that the time required for completion of reaction in other than PEG 400 medium were in between 50 to 60 minutes. As well as the quantity of solvent medium required were large but when we use such solvent as a medium in any reaction these solvent medium show adverse effect. They are very hazardous to our delicate environment and human health, after carrying the reactions in various other solvent mediums, it was observed that the time required for completion of the reaction in Polyethylene glycol 400 medium was reduced and the quantity of solvent required were also less as compared to the other solvent medium as well as yield is also increased as shown in Table 1.

Table 1. Reaction of 2-bromo-1-(4-bromo-1-hydroxynaphthalen-2-yl)ethanone (3a) and thiourea (4) in various solvent medium.

Sr. No.	Medium	Quantity of medium (ml)	Time Duration in Min.	Yield (%)	M.P. (^{0}C)
1.	Acetone	30	10	55	119
2.	Ethanol	30	30	60	118
3.	DMF	40	60	65	120
4.	PEG-400	20	05	96	119
5.	Ethanol-Acetone	30	20	76	119
6.	Iso propyl alcohol	40	50	55	121

From above results, it was clear that the PEG 400 medium produces the product in good yield in a short period of time, the quantity required is also less among all the reactions performed using hazardous solvent conditions. If the reaction is performed in PEG 400 medium, green chemistry will be maintained. Hence author was interested to reduce time span and quantity of solvent used as medium and also to increase yield as well as to maintain eco-friendly reactions. Physical study and mechanisms were not studied during reactions.

Interactions of different 2-bromo-1-(4-substituted-1-hydroxynaphthalen-2-yl)ethanone (3) and thioureas(4) in Polyethylene glycol 400 medium were carried out and the time required for completion of reactions were noted, it was observed that all the reactions were completed within 5 to 15 Minutes. To reduce time duration of reaction, maintain green chemistry parameters and

develop new reaction conditions, the reactions were carried out in Polyethylene glycol 400 medium. It was observed that time duration of the reactions were reduced, the quantity of medium required is also reduced and yield of the product were better. If the reaction is performed in Polyethylene glycol 400, green chemistry will be maintained. Hence author is interested to develop new methodology that does not harm environment, human health and to maintain eco-friendly reaction conditions.

Similarly, synthesis of 1-[2-(1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (5d), 1-[2-(1 hydroxynaphthalen-2-yl)-2-oxoethyl]-3-phenylthiocarbamide (5e), 1-[2-(2-hydroxynaphthalen-1-yl)-2-oxoethyl]thiocarbamide (5f), 1-[2-(6-bromo-2-hydroxynaphthalen-1-yl)-2-oxoethyl] thiocarbamide (5g), 1-[2-(2-hydroxy-6-nitronaphthalen-1-yl)-2-oxoethyl] thiocarbamide (5h), 1-[2-(naphthalen-2-yl)-2-oxoethyl]thiocarbamide (5i), 1-(2-oxo-2-phenylethyl)thiocarbamide (5j) were prepared by the interaction of 2-bromo-1-(1-hydroxynaphthalen-2-yl)ethanone (3d) with thiourea (4) and Phenylthiourea (4a) in PEG 400 medium, 2-bromo-1-(2-hydroxynaphthalen-1-yl)ethanone (3e), 2-bromo-1-(6-bromo-2-hydroxynaphthalen-1-yl)ethanone (3f), 2-bromo-1-(2-hydroxy-6-nitronaphthalen-1-yl)ethanone (3g) 2-bromo-1-(naphthalen-2-yl)ethanone (3h) and 2-bromo-1-phenylethanone (3i) with thiourea (5) respectively by above mentioned method which are listed in Table 2.

Table 2. Synthesis of seven different 1-[2-(4-substituted-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide in PEG 400 medium

Sr. No.	Expt. No.	Compound synthesized	Yield %	M.P ^{0}C	Colour
1	4	1-[2-(1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (5d)	73	114	Yellow
2	5	1-[2-(1 hydroxynaphthalen-2-yl)-2-oxoethyl]-3-phenylthiocarbamide (5e)	65	132	Yellow Brown
3	6	1-[2-(2-hydroxynaphthalen-1-yl)-2-oxoethyl]thiocarbamide(5f)	60	59	Light Brown
4	7	1-[2-(6-bromo-2-hydroxynaphthalen-1-yl)-2-oxoethyl] thiocarbamide (5g)	80	154	Yellow
5	8	1-[2-(2-hydroxy-6-nitronaphthalen-1-yl)-2-oxoethyl] thiocarbamide (5h)	90	189	Yellow
5	9	1-[2-(naphthalen-2-yl)-2-oxoethyl]thiocarbamide (5i)	85	283	Yellow solid
6	10	1-(2-oxo-2-phenylethyl)thiocarbamide (5j)	91	116	Yellow

CONCLUSION

Synthesis of thiocarbamide has wide scope due to its varied application in pharmaceutics. Its varied role in biological and pharmaceutical science creates more interest among the scientist and research scholar for its synthesis as it possesses antimicrobial properties against various microbes. PEG 400 (Polyethylene glycol 400) is easily available, water soluble and environmentally benign solvent medium. Therefore the work up of the reaction becomes easy. Most of the chemicals are soluble in the PEG 400 medium as well as it does not decompose easily. Due to solubility of PEG 400 in water the product can be isolated by simple filtration method without applying the tedious processes such as liquid-liquid extraction or distillation process. In the liquid-liquid extraction of product most of the solvent are wasted and the method becomes costly. Also the PEG 400 medium does not show any adverse effect on environment and human health. This work may increase interest among the researchers and inspire them about the use of PEG-400 as a solvent medium in various organic transformations.

ACKNOWLEDGMENT

Authors are thankful to the services from Pune University for NMR and Dahiwadi College, Dahiwadi for IR spectra. Author also thank to the Principal, Sharadchandra Pawar Mahavidyalaya, Lonand and Principal, B. B. Arts, N.B. Commerce and B. P. Science College, Digras, Dist. Yavatmal for providing the necessary laboratory facilities.

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