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Energy efficient and greener synthesis of pharmacologically important thio-moieties

NEERAJANA VASHISHTHA

Chemistry Department, Shyam Sunder Memorial P. G. College,
Chandausi, District Moradabad (India).

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ABSTRACT

In the field of medicine the importance of thiosemicarbazides is well known. –N=C=S group possessing thiosemicarbazides the have been known to show pronounced biological activites. In this paper, we propose the synthesis of title compounds by the condensation of 3,4-dichloro and 2,4-dimethoxy malonamic acid hydrazides with substituted phenyl isothiocyanates under microwave irradiation. The synthesized compounds were subjected to antibacterial screenings.

Key words: Synthesis, thiosemicarbazides, microwave irradiation, antibacterial screenings.

INTRODUCTION

The synthesis of thiosemicarbazides has been the area of extensive research since decades especially while investigating compounds to be potential pharmacological candidates. –N=C=S group possessing thiosemicarbazides the have been known to show pronounced biological activites. Thiosemicarbazides have shown unique spectrum of anticonvulsant[1], antifungal[2], plant growth promoting[3], antibacterial[4], anti-tubercular[5] properties. Microwave Assisted Organic Synthesis (MAOS) serve as one of the greener methodologies in organic synthesis. It has become increasingly important in performing chemical transformations in minutes instead of hours by conventional methods. Rapid reactions, high yields and the use of inexpensive reagents under microwave irradiation are attractive features of this protocol.

Under the framework of "MAOS" we propose to present a very simple, fast and ecofriendly procedure where the reaction of substituted isothiocyanate with substituted acid hydrazides leads for the synthesis of some thiosemicarbazides. The synthesized compounds were evaluated for anti bacterial activity against *S. aureus* and *E. coli.*

Table 1: Antibacterial activity of the compounds 1-12; Key to symbols: Resistance = R; slightly active = + (inhibition zone 6-9mm); moderately active

S. No	1	2	3	4	5	6	7	8	9	10	11	12	Streptomycin
E.coli	R	+	++	+	++	+++	+	R	+	R	+	++	+++
S. aureus	R	+	+	R	+	++	R	R	+	+	++	+++	+++

= + + (inhibition zone 9-12 mm); highly active = + + + (inhibition zone> 12 mm)

Table 1: Thiosemicarbazides obtained by the condensation of N-(3,4-Dichloro) phenyl malonamic acid hydrazide with different phenyl isothiocyanates

S. No	R_1	Mol. Formula	m.p (°C)	% Yield Heating	% Yield MWI	% C Found (Calc.)	% H Found (Calc.)	% N Found (Calc.)	% S Found (Calc.)
1.	H	$C_{16}H_{14}O_2N_4SCl_2$	124	55.63	59.44	-	-	14.23 (14.11)	7.92 (8.06)
2.	3- CH_3	$C_{17}H_{16}O_2N_4SCl_2$	158	59.42	62.95	49.81 (49.64)	3.79 (3.89)	13.71 (13.63)	7.70 (7.79)
3.	4-CH_3	$C_{17}H_{16}O_2N_4SCl_2$	168	61.36	63.57	-	-	13.69 (13.63)	7.72 (7.79)
4.	3,4- $(CH_3)_2$	$C_{18}H_{18}O_2N_4SCl_2$	120	56.79	61.06	-	-	13.23 (13.18)	7.57 (7.53)
5.	4-Br	$C_{16}H_{13}O_2N_4SBrCl_2$	115	63.68	67.83	-	-	11.80 (11.76)	6.68 (6.72)
6.	4-F	$C_{16}H_{13}O_2N_4SFCl_2$	171	54.31	60.53	-	-	13.41 (13.49)	7.78 (7.71)

Table 2: Thiosemicarbazides obtained by the condensation of N-(2,5-Dimethoxy) phenyl malonamic acid hydrazide with different phenyl isothiocyanates

S. No	R_1	Mol. Formula	m.p (°C)	% Yield Heating	% Yield MWI	% C Found (Calc.)	% H Found (Calc.)	% N Found (Calc.)	% S Found (Calc.)
7.	H	$C_{18}H_{20}O_4N_4S$	1140	58.45	62.43	-	-	14.51 (14.43)	8.16 (8.24)
8.	3- CH_3	$C_{19}H_{22}O_4N_4S$	155	65.32	69.81	56.98 (56.72)	5.44 (5.47)	13.99 (13.93)	7.92 (7.96)
9.	4-CH_3	$C_{19}H_{22}O_4N_4S$	170	67.58	71.37	-	-	13.97 (13.93)	7.93 (7.96)
10.	3,4- $(CH_3)_2$	$C_{20}H_{24}O_4N_4S$	157	61.39	64.85	-	-	13.50 (13.46)	7.65 (7.69)
11.	4-Br	$C_{18}H_{19}O_2N_4SBr$	146	67.84	70.36	-	-	12.10 (11.99)	6.74 (6.85)
12.	4-F	$C_{18}H_{19}O_2N_4SF$	178	60.05	63.27	-	-	13.86 (13.79)	7.95 (7.88)

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purities of the compounds were checked on silica-gel-coated Al plates (Merck). ^{1}H-NMR spectra was measured on Advance Bruker DRX-300 using solution in hexadeuterio dimethyl sulfoxide (DMSO) with trimethyl silane(TMS) as the internal standard , chemical shifts are given in δ (ppm). Elemental analysis was performed on Elementor Vario EL III at C.D.R.I., Lucknow.

IR spectra were recorded in KBr on a Perkin Elmer Spectrum RX-1 FT-IR spectrophotometer. Microwave irradiations were carried out in an IFB domestic microwave oven. All chemicals were of analytical grade.

General procedure

Method A(Heating)

Substituted malonamic acid hydrazide (5mmol) and stirred solution of substituted phenyl isothiocyanates (5mmol) in ethanol (10 mL) was refluxed for 3 hrs, and then filtered to give the corresponding thiosemicarbazide which was recrystallized from ethanol[6-7].

Method B (Microwave irradiation)

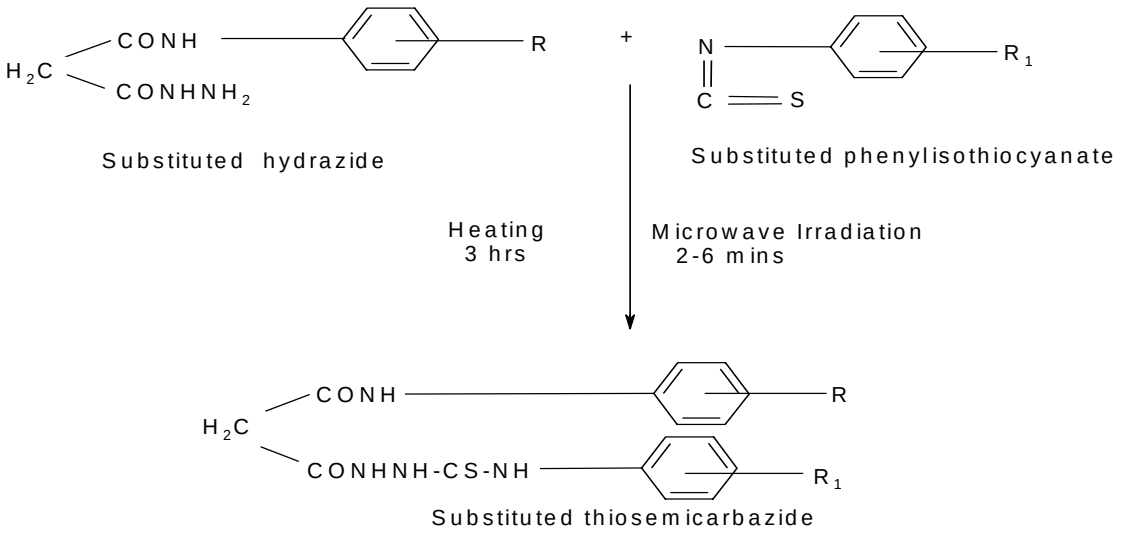
Substituted malonamic acid hydrazide (5mmol), ethanol (5-8 drops) and substituted phenyl isothiocyanate (5mmol) were irradiated in microwave for 2-6 mins. Solid obtained was purified by recrystallization from hot ethanol.

Antibacterial activity

The synthesized compounds (1-12) were screened for antibacterial activity against *S. aureus*

Table 3: Spectral data of the compounds

S. No	I.R (cm^{-1})	H^1 N.M.R (δ ppm)	MS: m/z =
1.	(N-H)-3424, Ar-H(C-H)-3029, -CH_2 (C-H)-2874, (N-C=O)-1540, (C=S)-1331, (N-N)-1220.	2.50 (DMSO), 3.32 (s,2H, CH_2), 4.56 (s,1H, NH), 6.46-7.84 (m, 8H, Ar-H), 8.32(s,1H, CONH), 8.49 (s, 1H, CONH).	397.5 [M+]
2.	(N-H)-3430, Ar-H(C-H)-3038, -CH_2 (C-H)-2879, (N-C=O)-1535, (C=S)-1339, (N-N)-1225.	2.51 (DMSO), 2.68 (s, 3H, CH_3), 3.45 (s,2H, CH_2), 4.83(s,1H, NH), 6.38-7.78 (m, 7H, Ar-H), 8.20(s,1H, CONH), 8.81 (s, 1H, CONH).	411 [M+]
3.	(N-H)-3436, Ar-H(C-H)-3032, -CH_2 (C-H)-2899, (N-C=O)-1538, (C=S)-1336, (N-N)-1220.	2.50 (DMSO), 2.79 (s, 3H, CH_3), 3.50 (s,2H, CH_2), 4.96(s,1H, NH), 6.32-7.90 (m, 7H, Ar-H), 8.16(s,1H, CONH), 8.92 (s, 1H, CONH).	411 [M+]
10.	(N-H)-3442, Ar-H(C-H)-3039, -CH_2 (C-H)-2907, (N-C=O)-1545, (C=S)-1341, (N-N)-1222	2.50 (DMSO), 2.62 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.52 (s,2H, CH_2), 4.93 (s,1H, NH), 6.28-7.82 (m, 7H, Ar-H), 8.31(s,1H, CONH), 8.94 (s, 1H, CONH)	416.5 [M+]
11.	(N-H)-3431, Ar-H(C-H)-3030, -CH_2 (C-H)-2918, (N-C=O)-1539, (C=S)-1337, (N-N)-1221	2.51 (DMSO), 3.31 (s, 2H, CH_2), 3.92 (s, 6H, OCH_3), 5.20 (s,1H, NH), 6.38-7.50 (m, 7H, Ar-H), 8.32(s,1H, CONH), 9.12 (s, 1H, CONH)	467 [M+]
12.	(N-H)-3428, Ar-H(C-H)-3040, -CH_2 (C-H)-2926, (N-C=O)-1541, (C=S)-1339, (N-N)-1219	2.50 (DMSO), 3.50 (s,2H, CH_2), 3.82 (s, 6H, OCH_3), 4.63 (s,1H, NH), 6.30-7.70 (m, 7H, Ar-H), 8.30(s,1H, CONH), 9.12 (s, 1H, CONH).	406.5 [M+]



and *E. coli* adopting disc diffusion technique[8] at concentration of 100µg/ml. Compounds have shown moderate to good antibacterial activity.

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