MICROWAVE ASSISTED ONE POT SYNTHESIS OF HYDRAZINYL THIAZOLE DERIVATIVES UNDER SOLVENT AND CATALYST FREE CONDITION

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Abstract: A rapid synthesis of hydrazinyl thiazoles under solvent and catalyst free condition is reported within 30 s. 2-hydroxy naphthaldehyde thiosemicarbazone, thiosemicarbazide and substituted phenacyl bromide were used. This is an environmentally benign microwave assisted and efficient method for rapid synthesis of hydrazinyl thiazoles.

***Index Terms*: Thiazole, thiosemicarbazide, phenacyl bromide, microwave.**

I.INTRODUCTION

In the recent years thiazoles and their derivatives have attracted medicinal chemists because of their biological properties and their application found in drug development for the treatment of allergies [1], hypertension [2], inflammation [3], schizophrenia [4], antibacterial [5], HIV infections [6],hypnotics [7], and more recently for treatment of pain [8],as fibrinogen receptor antagonist with antithrombotic activity [9], and as new inhibitors of bacterial DNA gyrase B. [10]. In the proposed investigation the compounds to be synthesized contain a thiazole moiety in the total heterocyclic system. There are many examples of biologically active thiazoles which showed very interesting pharmacological properties such as anti-inflammatory, anti-hypertensive, antibacterial and anti HIV infectious etc. Amino thiazoles are known to be ligands of estrogen receptors [11], as well as novel class of adenosine receptor antagonists [12], moreover organic compounds containing thiazole nucleus are found to possess high second order hyper polarizability [13–16]. In view of the importance of thiazoles and their derivatives several methods for the synthesis of thiazole derivatives were developed [17,18]. However in spite of their potential utility many of these reported methods suffer from drawbacks such as harsh reaction conditions, wastage of solvents and catalyst which have to be recovered, treated and disposed. Microwave assisted organic reactions using dry media have attracted much interest because of the simplicity in operation, greater compounds. Thus it was thought worthwhile to synthesize the thiazole derivatives using green route that is the microwave organic reaction enhancement method (MORE). In this context the present investigation leads to the microwave assisted one pot synthesis of not yet synthesized newer heterocyclic moiety with thiazole nucleus.

II. EXPERIMENTAL

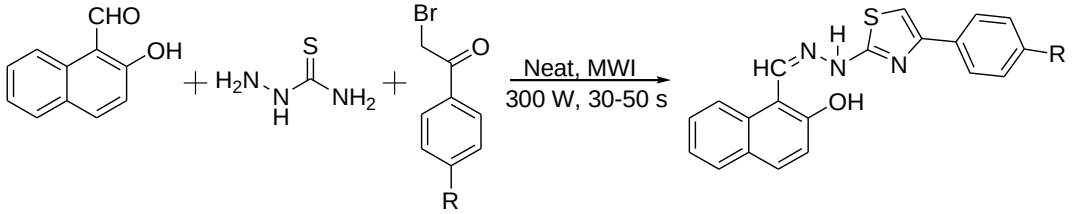
2.1. Instruments

The IR spectrum was recorded in an AVATAR-330 FT-IR spectrophotometer and only noteworthy absorption levels (reciprocal centimeters) were listed. 1H NMR spectra were recorded at 400 and 500 MHz on a Bruker AMX 400 and 500 MHz spectrophotometer using CDCl3 or DMSO-d6 as solvent and TMS as the internal standard. 13C NMR spectra were recorded at 100 and 125 MHz on a Bruker AMX 400 and 500 MHz spectrophotometer using CDCl3 or DMSO-d6 as the solvent. HRMS (ESI) was carried out in a Bruker Maxis instrument in the School of Chemistry, University of Hyderabad. Elemental analyses (CHN) were recorded on a Thermo Finnigan Flash EA 1112 analyzer at the School of Chemistry, University of Hyderabad. Routine monitoring of the reactions was performed by TLC, using silica gel plates (Merck 60 F254) and compounds were visualized with a UV light at 254 nm.

2.2 Synthesis

2.2..1. (Z)-1-((2-(4-phenylthiazol-2-yl)hydrazono) methyl)naphthalen-2-ols (I and II)

Equimolar mixture of 2–hydroxy naphthaldehyde (0.1 mmol), thiosemicarbazide (0.1 mmol) and substituted phenacyl bromide (0.1 mmol) were mixed and subjected to microwave irradiation for 30–50 s at a heating rate of 300 W. Scheme 1. For the two compounds IR, ^{1}H NMR and ^{13}C NMR spectra have been recorded.



Scheme 1

Table 1 Microwave-assisted neat synthesis of hydrazinyl thiazoles

Compounds	R	Time (s)	Yield %
I	OCH_3	10	80
II	NO_2	20	70

III. Results and discussion

One pot processes are very attractive and sustainable in modern synthetic organic chemistry. A greener and more facile procedure for the synthesis of hydrazinyl thiazoles was developed from readily available 2-hydroxy Naphthaldehyde thiosemicarbazide and substituted phenacyl bromide .The eco-friendly attributes of this process are solvent and catalyst free conditions. The reaction protocol includes advantages of short reaction time and easy work-up or purification step and the high purity of product. Hence we examined the reaction of acetophenones with thiosemicarbazide and substituted phenacyl bromide under different conditions using MW activation; we found that the best result was obtained when the reaction mixture was irradiated at a power level of 300 W for 30–175 s and 400 W for 50–120 s. Table 1. Here we found that the reaction of phenacyl bromide having the electron donating methoxy group was rapid compared to that one having electron withdrawing group and also high yield of the product was obtained when there is the electron donating group inthe para position. Types of spectrum recorded for the synthesized compounds I and II are shown in Table 2

Table 2: Types of spectrum recorded for the synthesized compounds (I **and** II)

Compounds	IR	^{1}H NMR	^{13}C NMR	Mass	CHN Analysis
I	√	√	√	√	√
II	√	√	√	√	√

3.1.1. Spectral analysis of compounds (I and II)

Compounds I and II are derived from 2–hydroxy naphthaldehyde. In the ^{1}H NMR spectrum of compound I and II there is a peak at around 10.83 ppm due to the hydroxy group in naphthyl ring. The signal observed at 13.0 ppm is due to NH proton. The singlet observed at 9.13 ppm is due to the azomethane (CH=N) proton. The spectral characterization is carried out in a similar manner as carried out for all the compounds as discussed in above.

Table 3: ^{1}H Chemical shifts of compounds (I and II) [δ (ppm)]

Compounds	H–5	OCH_3	Aromatic protons	CH=N	NH	OH
1	6.64	3.90	6.98–8.37	9.36	13.17	10.83
2	6.98	–	7.04–8.88	8.92	–	9.02

Table 4: ^{13}C Chemical shifts of compounds (I and II) [δ (ppm)]

Compounds	OCH_3	C–5	CH=N	C=N (C–2)	Aromatic carbons
I	55.3	106.6	156.9	164.4	110.5–132.3
II	–	106.4	156.9	168.5	110.6–148.7

The physical data and results of elemental analysis are given in Tables 5and 6. There is an excellent agreement between the experimental and calculated values for the percentages of carbon, hydrogen and nitrogen.

Table 5: Analytical and spectral data of *(E)–3–((2–(4–(4–methoxyphenyl) thiazol–2–yl)hydrazono) methyl)naphthalen–2–ol* (I)

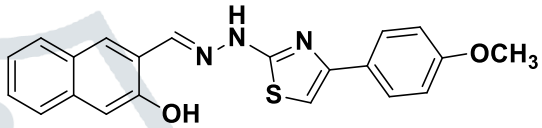
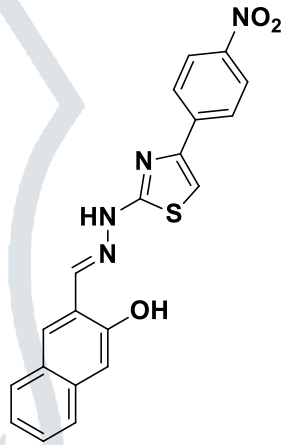
M.F.: $C_{21}H_{17}N_3O_2S$	**m.p. (°C):** 113–115	**Yield (%):** 80	**Structure**
IR (KBr, cm^{-1}); **1629 (C=N), 2926 (C–H stretching), 3451 (N–H stretching)**			
^1H NMR (DMSO–d_6, ppm); **δ: 3.90 (OCH_3), 6.64 (s, CH thiazole), 6.98–7.00 (d, ArH), 7.14–7.16 (d, ArH), 7.20–7.22 (d, ArH), 7.40–7.46 (m, ArH), 7.66–7.68 (S, ArH), 7.79–7.81 (d, ArH), 7.87–7.89 (d, ArH), 7.98 (s, ArH), 8.01–8.04 (t, ArH), 8.35–8.37 (d, ArH). 9.36 (CH=N), 10.83 (OH), 13.17 (NH)**			
^{13}C NMR (DMSO–d_6, ppm); **δ: 55.3, 106.6, 110.5, 114.4, 118.7, 123.9, 127.4, 127.7, 128.1, 128.6, 129.1, 129.2, 131.5, 132.3, 156.9, 164.4**			
Mass: **Calculated. 375; found. 374 $(M-H)^+$**			
CHN Analysis: **Anal. Calcd. (%) for: C, 67.18; H, 4.56; N, 11.19; found (%): C, 67.20; H, 4.57; N, 11.21**			

Table 6 Analytical and spectral data of (E)–3–((2–(4–(4–nitrophenyl)thiazol–2–yl)hydrazono)methyl) naphthalen–2–ol (II)

M.F.: $C_{20}H_{14}N_4O_3S$	**m.p. (°C):** 151–153	**Yield (%):** 75	**Structure**
IR (KBr, cm^{-1}); **1624 (C=N), 2921 (C–H stretching), 3430 (N–H stretching)**			
^1H NMR (DMSO–d_6, ppm); **δ: 6.98 (s, CH, thiazole), 7.04 (s, ArH), 7.17 (s, ArH), 7.23–7.39 (m, ArH), 7.41–7.49 (t, ArH), 7.57–7.60 (m, ArH), 7.72 (s, ArH), 7.86–7.88 (d, ArH), 8.15–8.17 (d, ArH), 8.25–8.27 (d, ArH), 8.32–34 (d, ArH), 8.39–8.40 (d, ArH), 8.46–8.48 (d, ArH), 8.70–8.73 (d, ArH), 8.77–8.79 (m, ArH), 8.86–8.88 (d, ArH), 8.92 (s, ArH), 9.02 (CH=N)**			
^{13}C NMR (DMSO–d_6, ppm); **δ: 106.4, 110.6, 118.5, 118.7, 120.4, 122.5, 123.6, 123.9, 128.1, 128.6, 129.2, 130.7, 131.5, 132.1, 132.4, 141.8, 148.78, 156.9, 168.5**			
Mass: **Calculated. 390; found. 391$(M+H)^+$**			
CHN Analysis: **Anal. Calcd. (%) for: C, 61.53; H, 3.61; N, 14.35; found (%): C, 61.50; H, 3.64; N, 14.40**			

3.1.6. Antimicrobial studies

The zone of inhibition (mm) of compounds Iand II against all tested microorganisms are given in the Table 7.

Table 7 Antibacterial activity of compounds (I and II) by disc diffusion method

Microorganism	Zone of inhibition (mm)		
	Amikacin	Compounds	
		I	II
S. typhi	**0.8**	**1.1**	**1.3**
S. aureus	**1.0**	**0.9**	**1.1**
E. coli	**2.0**	**1.0**	**1.4**
K. pneumoniae	**1.5**	**1.1**	**1.2**
P.seudomonas	**2.6**	**1.0**	**1.3**

The compounds I and II are tested for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, salmonella typhi* and *Pseudomonas*.

From the zone of inhibition Table 7. It is clear that the compound I and II show very good activity against *Salmonella typhi* and *Staphylococcus aureus* when compared to the standard. The zone of inhibition (mm) of compounds Iand II against all tested fungal strains are given in the Table 8.

Table 8. Antifungal activity of compounds I and II by disc diffusion method.

Micro organism	Zone of inhibition (mm)		
	Amphotericin B	Compounds	
		I	**II**
A. flavus	**1.6**	**1.0**	**1.4**
C.albicans	**1.2**	**0.9**	**1.1**
A.fumigatus	**1.6**	**1.2**	**1.5**
A. niger	**1.5**	**0.8**	**1.3**

From the zone of inhibition of tested compounds I and II it is inferred that they show very good activity against *Aspergillus niger* compared to the standard but they show very less activity 46 against all other fungal strains when compared to the standard *amphotericin B.*

It is clear that both the compounds exhibit excellent activity compared to the standard *Amikacin* and *Amphotoricin B* Especially the NO_2 substituted compound II is found to be more potent and exhibits an enhanced activity than *Amikacin* and *Amphotoricin* than the compound I II shows very better activity than I. The decreased activity of the compounds I compared II may be due to the presence of substituent (OCH_3) in the *para* position of the phenyl ring.

The compound I having the methoxy substituents on the para position of the phenyl rings not only shows similar activity but also demonstrated a poor activity against the germ *Staphylococcus aureus* when compared to the standard. This might be due to the presence of electron donating (methoxy) substituents in the phenyl rings.

IV. Conclusion

In summary we have developed a novel and convenient method for the synthesis of a series of heterocyclic compounds possessing biologically potent thiazole nucleus with good to excellent yield and purity.

References

[1] K.D. Hargrave, F.K. Hess, J.T. Oliver, J. Med. Chem. 26 (1983)1158–1163.
[2] (a) S. Bondock, W. Khalifa, A.A. Fadda, Eur. J. Med. Chem. 42(2007) 948–954;
(b) B.A. Steinbaugh, B.L. Batley, C.A. Painchaud, S.T.Rapundalo, B.M. Michniewicz, S.C.J. Olson, J. Med. Chem.35 (1992) 2562–2572.
[3] P.K. Sharma, S.N. Sawnhney, A. Gupta, G.B. Singh, S. Bani,Indian. J. Chem. 37B (1998) 376–381.
[4] J.C. Jaen, L.D. Wise, B.W. Caprathe, H. Tecle, S. Bergmeier,C.C. Humblet, T.G. Heffner, L.T. Meltzner, T.A. Pugsley, J.
Med. Chem. 33 (1990) 311–317.
[5] K. Tsuji, H. Ishikawa, Bioorg. Med. Chem. Lett. 4 (1994) 1601–1606.
[6] F.W. Bell, A.S. Cantrell, M. Hogberg, S.R. Jaskunas, N.G. Johansson, C.L. Jordon, P. Pranc, C. Sahlberg, R.J. Ternansky,R.T. Vasileff, L. Vrang, S.J. West, H. Zhang, X.X. Zhou, J.Med. Chem. 38 (1995) 4929–4936.
[7] N. Ergenc, G. Capan, N.S. Gu¨ nay, S. O¨ zkirimli, M. Gu¨ ngo¨ r, S.O¨zbey, E. Kendi, Arch. Pharm. Pharm. Med. Chem. 332 (1999)343–347.
[8] J.S. Carter, S. Kramer, J.J. Talley, T. Penning, P. Collins, M.J.Graneto, K. Seibert, C. Koboldt, J. Masferrer, B. Zweifel,Bioorg. Med. Chem. Lett. 9 (1999) 1171–1174.
[9] A. Badorc, M.F. Bordes, P. Cointet, P. Savi, A. Bernat, A. Lale, M. Petitou, J.P. Maffrand, J.M. Herbert, J. Med. Chem. 40(1997) 3393–3401.
[10] J. Rudolph, H. Theis, R. Hanke, R. Endermann, L. Johannsen, F.U. Geschke, J. Med. Chem. 44 (2001) 619–626.
[11] B.A. Fink, D.S. Mortensen, S.R. Stauffer, Z.D. Aron, J.A. Katzenellenbogen, Chem. Biol. 6 (1999) 205–219.
[12] J.E. Van Muijlwijk-Koezen, H. Timmerman, R.C. Vollinga, J.F. VonDrabbeKunzel, M. DeGroote, S. Visser, A.P. Ijzerman, J.Med. Chem. 44 (2001) 749–762.
[13] H.L. Chang, H.L. Lin, Y.C. Wang, S.A. Dai, W.C. Su, R. Jeng, J. Polym. 48 (2007) 2046–2055.
[14] T. Baehr-Jones, M. Hochberg Guangxi Wang, R. Lawson, Y. Liao, P.A. Sullivan, L. Dalton, A.K.Y. Jen, A. Scherer, Optics Express 13 (14) (2005) 5216–5226.
[15] Y. Cui, H. Ren, J. Yu, Z. Wang, G. Qian, Dyes Pigm. 81 (2009) 53–57.
[16] F.X. Qiu, Y.M. Zhou, J.Z. Liu, X.P. Zhang, Dyes. Pigm. 71 (2006) 37–42.
[17] B.R. Vaddula, R.S. Varma, J. Leazer, Tetrahedron Lett. 54 (2013) 1538–1541.
[18] Q.P. Nguyen, T.H. Kim, Tetrahedron 69 (2013) 4938–4943. Synthesis of hydrazinyl thiazole derivatives