Indian Journal of Chemistry
Vol. 45B, December 2006, pp. 2776-2780

Note

Conventional and ultrasound mediated synthesis of some thiadiazoles, triazoles and oxadiazoles

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Received 13 May 2005; accepted (revised) 26 September 2006

Acid hydrazide **1** when treated with aryl isothiocyanates gives the compounds **2.** These compounds **2** on ultrasound irradiation in acidic medium give compounds **3** i.e. thiadiazoles and in basic medium gives compounds **4** i.e. triazoles. These compounds **2** on treatment with I_2/KI and NaOH resulted in compounds **5** i.e. oxadiazoles. These compounds are synthesized by conventional method as well as ultra sound irradiation method.

Keywords: Acid hydrazide, ultrasound irradiation, thiadiazoles, triazoles, oxadiazoles

IPC Code: Int.Cl.[8] C 07 D

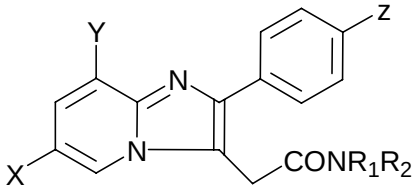
Literature survey indicates that thiosemicarbazide are found to be associated with antibacterial[1], antifungal[2], herbicidal[3], antiacetyl cholinesterase[4] and antituburcular[5] activities. Compounds containing 1,3,4-thiadiazole nucleus have been reported to a variety of biological activities like fungitoxic[6], CNS stimulant[7], anticholinergic[8], hypoglycemia[9] and anticonvulsant[10,11]. Some of the thiadiazole derivatives are found to be associated with spasmolytic activites[12] and anti-inflammatory activities[12]. Triazoles are known for their fungicidal[13], pesticidal[14], tranquiliser and sedative[15] properties. They express antifungal[16], bactericidal[16,17], anxiolytic[18,19], anticonvulsant[20] or herbicidal[21] activities or can act as antidepressants[22]. Several oxadiazoles and thiadiazoles also exhibit antitubercular[23], antifungal and herbicidal[24] properties.

The advantageous use of ultrasound irradiation technique for activating various reactions is well documented in the literature such as synthesis of azoles and diazenes[25], reformatsky reaction[26], oxidation of substrates like hydroquinones[27], conversion of nitro compounds to carbamates[28], pinacol coupling[29], Ullmann condensation[30], Suzuki cross-coupling[31] etc.

γ- Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS of vertebrates. The three types of GABA receptors denoted $GABA_A$, $GABA_B$ and $GABA_C$, have so far been characterized. The most abundant $GABA_A$ receptors are ligand-gated chloride ion channels and are characterized by the presence of several allosteric modulatory sites that regulates GABA affinity[32,33]. These sites include distinct ones for barbiturates, benzodiazepines (BZs), neurosteroids and ethanol. Molecular biological studies have demonstrated that several receptor subunits (α_1- α_6, β_1- β_3, γ_1- γ_3, δ) combine to form the $GAGA_A$ receptor complex[34]. Of the chemical classes which have binding sites on this macromolecular ionophore, the benzodiazepines are the most widely studied. Although the exact nature of the BZ/chloride ionophore receptor complex remains to be established, expression of α, β and γ subunits results in a channel assembly that favor ligands of the BZ receptor complex. Using classical BZ_1/BZ_2 nomenclature[35,36], the Bz_1 receptors are probably formed by the combination of subunits $\alpha_1\beta_2\gamma_2$, whereas a mixture of subunits α_2-, α_3- and α_5 $\beta_2\gamma_2$ represents BZ_2 receptors[37,38]. The third type, namely the BZ_3 receptors, constitute the "peripheral" receptors since they have been identified in the brain as well as in a wide range of peripheral tissues; their subcellular location has been reported to be mainly mitochondrial[39-41], and hence, this receptor is also termed "mitochondrial benzodiazepine receptor"[42]. Although the pharmacological role of the BZ_3 receptors remains fully clarified, some evidence indicates their involvement in important cellular functions such as the production of neurosteroids[42].

Among the known ligands, the N,N-dialkyl-2-phenylacetamidoimidazo[1,2-α]pyridines **A** (Alpidem) and **B** (Zolpidem) showed both high affinity and selectivity towards non-BZ_2 receptors[43]. Thus, Alpidem has high affinity for BZ_1 and BZ_3 sites while

zolpidem possesses high affinity for BZ_1 but neither for BZ_2 nor peripheral sites.



A = Alpidem X = Z = Cl; Y = H; $R_1 = R_2 = C_3H_7$
B = Zolpidem X = Z = CH_3; Y = H; $R_1 = R_2 = CH_3$

Biological activities associated with zolpidem moiety, triazoles, oxadiazoles and thiadiazoles and advantages of sonochemical synthesis prompted us to prepare some triazoles, oxadiazoles and thiadiazoles with zolpidem nucleus by sonochemical method.

In present work Acid hydrazide **1** when treated with aryl isothiocyanates gave the compounds **2.** These compounds **2** on in acidic medium gave compounds **3** i.e. thiadiazoles and in basic medium gave compounds **4** i.e. triazoles. These compounds **2** on treatment with I_2/KI and NaOH gave compounds **5** i.e. oxadiazoles **Scheme I**. These compounds are synthesized by conventional method as well as ultra sound irradiation method.

Results of conventional and ultrasonic methods indicates that ultrasound mediated synthesis is more superior to conventional method, as time required for completion of reaction is very less, yields are better and reaction can be carried out at room temperature for the synthesis of these compounds.

Experimental Section

All the recorded melting points were determined in open capillary tubes and are uncorrected. I.R. spectra were recorded on a Perkin-Elmer FTIR spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrophotometer in DMSO as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. Mass spectra were obtained by Finnigan mass spectrometer. Experiment under ultrasound irradiation was carried out in ultrasonic cleaner model EN-20U-S manufactured by ENERTECH ELECTRONICS PVT.LTD, Mumbai, India having maximum power output of 100W and 33 KHz operating frequency.

1-(2-(6-Methyl-2-*p*-tolyl-l*H*-imidazo[1,2-*a*]pyridin-3-yl)acetyl-4-phenyl thiosemicarbazides (2a-j) General procedure:

By conventional method

Acid hydrazide (0.01 mole) and phenyl isothiocyanate (0.01 mole) were taken in ethanol (15 mL) and the reaction mixture was heated under reflux for 60 min. After completion of reaction, (monitored by TLC) the contents were cooled to room temperature and the white product obtained was separated by filtration. The formation of compounds **2** was confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the **Table I**.

By ultrasonic irradiation

Equimolar quantities (0.01 mole) of acid hydrazide **1** and phenyl isothiocyanate were taken in 100 mL RBF with 15 mL ethanol and the reaction mixture was subjected to ultrasonic irradiation for 15-20 min at room temperature. The white product obtained was separated by filtration. The formation of compounds **2** was confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the **Table I**.

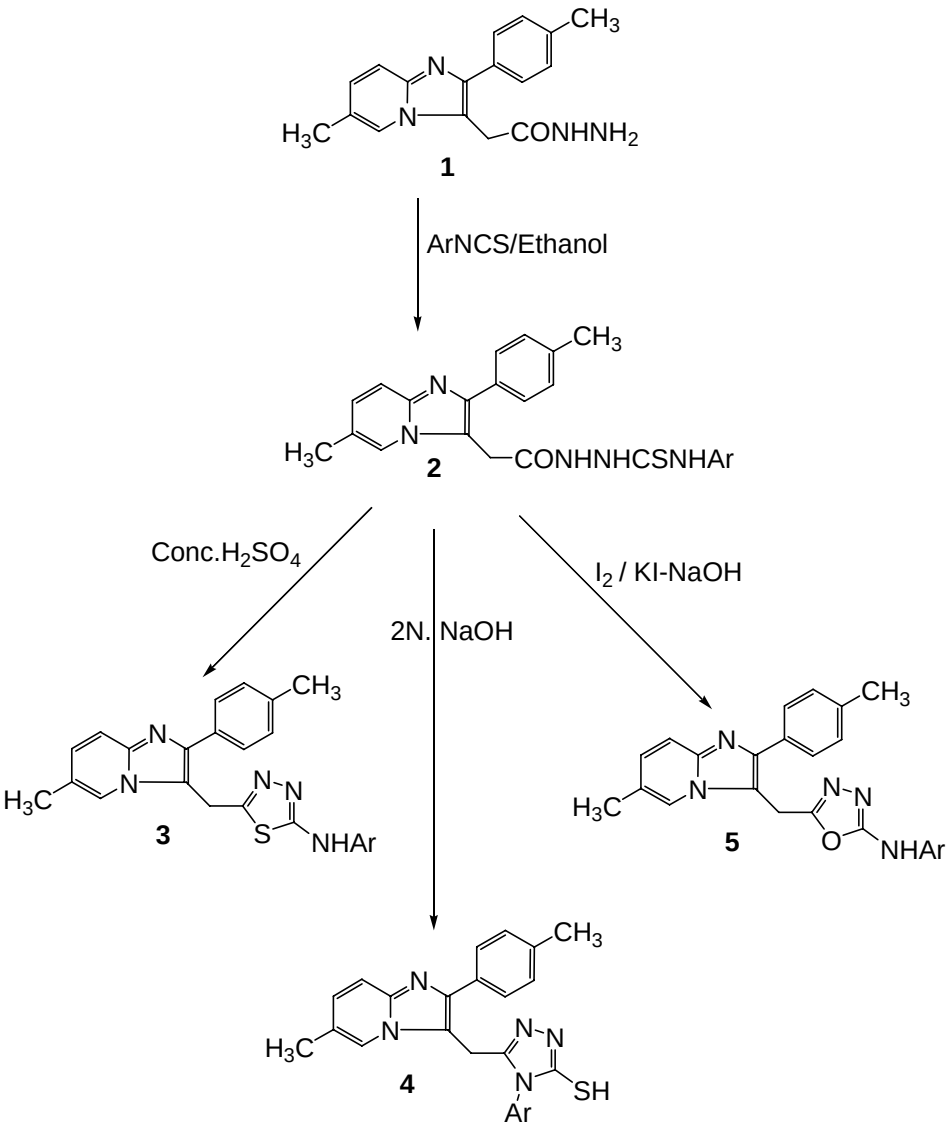
Compound **2c**: IR: 3400 to 3183 (-N-H), 1676 (–C=O), 1590 (-C=N), 1538 cm^{-1} (–C=S); ^{1}H NMR: δ 2.35 (s, 3H), 2.49 (s, 3H), 4.07 (s, 2H), 7.10 to 8.16 (m, 11H), 10.43 (s, 1H), 9.81 (s, 2H); Mass: M^+ 509.

Compound **2f**: IR: 3371 to 3215 (-N-H), 1678 (–C=O), 1601 (-C=N), 1228 cm^{-1} (–C=S); ^{1}H NMR: δ 2.29 (s, 3H), 2.33 (s, 3H), 3.38 (s, 3H), 4.07 (s, 2H), 6.91 to 7.69 (m, 11H), 9.22 (s, 1H), 9.77 (s, 1H), 10.52 (s, 1H); Mass: M^+ 443.

Compound **2g**: IR: 3183 b s (-N-H), 1676 (–C=O), 1590 (-C=N), 1243 cm^{-1} (–C=S); ^{1}H NMR: δ 2.31 (s, 3H), 2.49 (s, 3H), 4.07 (s, 2H), 7.01 to 7.74 (m, 12H), 8.16 (s, 1H), 9.81 (s, 1H), 10.43 (s, 1H); Mass: M^+ 429.

5-(6-Methyl-2-*p*-tolyl-l*H*-imidazo[1,2-*a*]pyridine-3-yl)methyl-N-phenyl-1,3,4-thiadiazol-2-amine (3a-g) General procedure:
By conventional method

Thiosemicarbazide **2** (0.005 mole) and concentrated sulphuric acid (5 mL) were taken in a beaker (50 mL) and the reaction mixture was kept at room temperature for 2.5 hr. The reaction mixture was then poured over ice water. The product was separated by filtration and crystallized with DMF to afford the title compounds **3**. The formation of



Scheme I

compounds **3** was confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the **Table I**.

By ultrasonic irradiation

Thiosemicarbazide **2** (0.005 mole) and concentrated sulphuric acid (5 mL) were taken in a beaker (50 mL) and the reaction mixture was subjected to ultrasonic irradiated for 20-25 min at room temperature. Progress of reaction was monitored by TLC. The reaction mixture was then poured over ice water. Product was separated by filtration and crystallized with DMF to afford the title compounds **3**. The formation of compounds **3** was confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the **Table I**.

Compound **3e**: IR: 3424 (-N-H), 1615 (-C=N), 1513(aromatic), 757 cm^{-1} (C-S); ^{1}H NMR: δ 2.23 (s, 3H), 2.39 (s, 3H), 2.41 (s, 3H), 4.84 (s,2H), 7.10 to 8.62 (m, 11H), 10.10(s, 1H); Mass: M^+ 425.

Compound **3f**: IR: 3423 (-N-H), 1655 (-C=N), 1615 &1613(aromatic), 760 cm^{-1} (C-S); ^{1}H NMR: δ 2.23 (s, 3H), 2.39 (s, 3H), 2.41 (s, 3H), 4.84 (s,2H), 7.10 to 8.62 (m, 11H), 10.20(s, 1H); Mass: M^+ 425.

5-[(6-Methyl-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine-3-yl)methyl-4-phenyl-4*H*-1,2,4-triazole-3-thiol (4a-g). General procedure:

By conventional method

Thiosemicarbazide **2** (0.005 mole) and 10 mL of 2*N* sodium hydroxide solution were taken in 100 mL RBF and the reaction mixture was heated under mild

Table I — Characterization data of the synthesized compounds

Compd. No.	Ar	Ultra sound method			Conventional method	
		Time (min)	Yield (%)	m.p. (°C)	Time (min)	Yield (%)
2a	2-Methoxy phenyl	20	89	204	60	68
2b	4-Methoxy phenyl	20	84	216	60	62
2c	4-Bromo phenyl	18	73	196	60	64
2d	3-Methyl phenyl	17	77	184	60	58
2e	2-Methyl phenyl	18	86	210	60	60
2f	4-Methyl phenyl	20	87	218	60	61
2g	Phenyl	28	81	204	60	64
2h	3-Chloro phenyl	20	86	223	60	62
2i	4-Chloro phenyl	20	85	222	60	67
2j	3-Methoxy phenyl	20	84	202	60	66
3a	2-Methoxy phenyl	25	88	298	150	58
3b	4-Methoxy phenyl	20	85	278	150	63
3c	4-Bromo phenyl	22	83	182	150	69
3d	3-Methyl phenyl	20	80	298	150	66
3e	2-Methyl phenyl	24	84	216	150	64
3f	4-Methyl phenyl	22	76	206	150	62
3g	Phenyl	20	87	254	150	65
4a	2-Methoxy phenyl	30	71	232	90	68
4b	4-Methoxy phenyl	35	76	220	90	66
4c	4-Bromo phenyl	33	70	210	90	62
4d	3-Methyl phenyl	34	68	214	90	64
4e	2-Methyl phenyl	35	79	258	90	65
4f	4-Methyl phenyl	30	77	230	90	63
4g	Phenyl	35	80	220	90	64
5a	3-Chloro phenyl	--	--	280	270	56
5b	4-Methyl phenyl	--	--	267	270	60
5c	2-Methoxy phenyl	--	--	230	270	58
5d	2-Methyl phenyl	--	--	230	270	61
5e	4-Methoxy phenyl	--	--	250	270	58
5f	3-Methoxy phenyl	--	--	243	270	54
5g	4-Chloro phenyl	--	--	278	270	45

reflux for 1.5 hr. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured over ice water and acidified with dilute hydrochloric acid. Product was separated by filtration and crystallized with DMF/water to afford the title compounds **4**. The formation of compounds **4** was confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the **Table I**.

By ultrasonic irradiation

Thiosemicarbazide **2** (0.005 mole) and 10 mL of 2*N* sodium hydroxide solution was taken in a beaker (50 mL) and the reaction mixture was subjected to ultrasonic irradiated for 30-35 min at room temperature. Progress of reaction was monitored by TLC. The reaction mixture was then poured over ice water and acidified with dilute hydrochloric acid. Product was separated by filtration and crystallized with DMF/water to afford the title compounds **4**. The formation of compounds **3** confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the **Table I**.

Compound **4a**: IR: 3039 (=C-H), 1662 (-C=N), 1583 & 1506 cm^{-1} (aromatic);

^{1}H NMR: δ 2.31 (s, 3H), 2.35 (s, 3H), 3.55 (s, 3H), 4.10 (s, 2H), 6.8 to 7.9 (m, 12H); Mass: M^+ 441.

Compound **4f**: IR: 3050 (=C-H), 1678 (-C=N), 1601 & 1504 cm^{-1} (aromatic);

^{1}H NMR: δ 2.29 (s, 3H), 2.34 (s, 3H), 3.78 (s, 3H), 4.07 (s, 2H), 6.91 to 8.15 (m, 11H), 10.52 (s, 1H); Mass: M^+ 425.

5-(6-Methyl-2-*p*-tolyl-l*H*-imidazo[1,2-*a*]pyridine-3-yl)methyl-N-phenyl-1,3,4-oxadiazol-2-amine (5a-g)

General procedure:

Thiosemicarbazide **2** (0.002 mole) was dissolved in 20 mL ethanol. To this reaction mixture 500 mg I_2 and 640 mg KI (in 20 mL H_2O) was added with 4*N* NaOH 2 mL and the reaction mixture was heated under mild reflux for 4.5 hr. Progress of reaction was monitored by TLC. Then from reaction mixture around 50% solvent was removed by distillation. The reaction mixture was cooled and the product obtained was separated by filtration and crystallized with alcohol to afford the title compounds **5**. The formation of compounds **5** was confirmed by spectral and analytical data. Their characterization data is given in the **Table I**.

Compound **5e**: IR: 3028 (=C-H), 1635 (-C=N), 1571 & 1512 cm^{-1} (aromatic); ^{1}H NMR: δ 2.35 (s, 3H), 2.38 (s, 3H), 3.70 (s, 3H), 4.22 (s, 2H), 6.75 to 7.95 (m, 11H), 9.60 (s, 1H); Mass: M^+ 425.

Acknowledgement

Authors are thankful to the Principal, Dr. G. T. Sangale, SSGM College, Kopargaon, Ahmednagar for constant encouragement and providing necessary facilities.

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