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

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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 I₂/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

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Literature survey indicates that thiosemicarbazide are found to be associated with antibacterial1, antifungal2, herbicidal3, antiacetyl cholinesterase4 and antitubercular5 activities. Compounds containing 1,3,4-thiadiazole nucleus have been reported to a variety of biological activities like fungitoxic6, CNS stimulant7, anticholinergic8, hypoglycemia9 and anticonvulsant10,11. These compounds are synthesized by conventional method as well as ultrasound irradiation method.

Note

γ - Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS of vertebrates. The three types of GABA receptors denoted GABAₐ, GABAₐ and GABAₐC, have so far been characterized. The most abundant GABAₐ receptors are ligand-gated chloride ion channels and are characterized by the presence of several allosteric modulatory sites that regulates GABA affinity32,33. These sites include distinct ones for barbiturates, benzodiazepines (BZs), neurosteroids and ethanol. Molecular biological studies have demonstrated that several receptor subunits (α₁- α₆, β₁- β₃, γ₁- γ₃, δ) combine to form the GABAₐ receptor complex34. 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 favors ligands of the BZ receptor complex. Using classical BZ₁/BZ₂ nomenclature35,36, the BZ₁ receptors are probably formed by the combination of subunits α₁β₂γ₂, whereas a mixture of subunits α₂-α₃- and α₅β₂γ₂ represents BZ₂ receptors37,38. The third type, namely the BZ₃ 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 mitochondrial39,41, and hence, this receptor is also termed “mitochondrial benzodiazepine receptor”42. Although the pharmacological role of the BZ₃ receptors remains fully clarified, some evidence indicates their involvement in important cellular functions such as the production of neurosteroids42.

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-BZ₂ receptors43. Thus, Alpidem has high affinity for BZ₁ and BZ₃ sites while...
zolpidem possesses high affinity for BZ$_1$ but neither for BZ$_2$ nor peripheral sites.

\[
\begin{array}{c}
\text{A = Alpidem } X = Z = \text{Cl}; \ Y = \text{H}; \ R_1 = R_2 = \text{C}_3\text{H}_7 \\
\text{B = Zolpidem } X = Z = \text{CH}_3; \ Y = \text{H}; \ R_1 = R_2 = \text{CH}_3
\end{array}
\]

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 ultrasound 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 $\delta$ 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-(6-Methyl-2-p-tolyl-1H-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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR:</th>
<th>$^1$H NMR:</th>
<th>Mass:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2c</td>
<td>$\delta$ 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);</td>
<td>M$^+$ 509.</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>$\delta$ 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);</td>
<td>M$^+$ 443.</td>
<td></td>
</tr>
<tr>
<td>2g</td>
<td>$\delta$ 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);</td>
<td>M$^+$ 429.</td>
<td></td>
</tr>
</tbody>
</table>

5-(6-Methyl-2-p-tolyl-1H-imidazo[1,2-a]pyridin-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
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.

### Scheme I

**Compound 3e:** IR: 3424 (-N-H), 1615 (-C=N), 1513 (aromatic), 757 cm⁻¹ (C-S); ¹H 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); ¹H 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-tolyH-imidazo[1,2-a]pyridine-3-yl)methyl-4-phenyl-4H-1,2,4-triazole-3-thiol (4a-g). General procedure:**

**By conventional method**

Thiosemicarbazide 2 (0.005 mole) and 10 mL of 2N sodium hydroxide solution were taken in 100 mL RBF and the reaction mixture was heated under mild
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 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 (s=C-H), 1662 (s=C=N), 1583 & 1506 cm$^{-1}$ (aromatic); $^1$H NMR: $\delta$ 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 (s=C-H), 1678 (s=C=N), 1601 & 1504 cm$^{-1}$ (aromatic); $^1$H NMR: $\delta$ 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-1H-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$_2$O) was added with 4N 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 (s=C-H), 1635 & 1512 cm$^{-1}$ (aromatic); $^1$H NMR: $\delta$ 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.

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References