Synthesis of 8-(Substituted-2,4-Dithiabiureto)-1-Methyl-6-Phenyl-4H-[1,2,4] Triazolo[4,3-A] [1,4] Benzodiazepines

Keywords: Various isothiocyanate, 8-(substituted-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4] benzodiazepines, 50% acetone-ethanol

ABSTRACT

Recently in this laboratory convenient method for synthesis of 8-(substituted-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4] benzodiazepines [VA(a-h)] was developed. The interactions of 8-thiocarbamido-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4] benzodiazepine [IIIa(a)] with various isothiocyanates (IVA-h) in 50% acetone-ethanol medium were carried out on water bath to synthesized [VA(a-h)] respectively. The structures of the synthesized compounds were justified on the basis of chemical characteristics, elemental analysis and spectral studies.
INTRODUCTION

Benzodiazepine nucleus is useful nucleus in the case of liposome in a potent carrier for targeted doxorubicin having high affinity for sigma receptor and used for the treatment of human malignancies including human prostate cancer cells. 1,4-Benzodiazepinedione has been reported as potent antagonist’s interaction in vitro and in cell-based assays and also proved that they possess anti-conversant, anxiolytic, anti-tumor properties. It is effective against cholecystokinin receptor (CCK), opiate receptor and platelet glycoprotein antagonists. Many derivatives of benzodiazepines are widely used as sedative, anti-depressive, anti-inflammatory and hypnotic agents. It is also used as dyes for acrylic fibers. Recently new series of 1,2,4-thiadiazoles, 1,3,5-thiadiazines and 1,3,5-dithiazines were synthesized by exploring the synthetic applications of -thiocarbamido, -amino, -halo, -cyano, etc. and their antimicrobial, antifungal, antibacterial, analgesic physiochemical parameters were studied. Benzodiazepine, dithiobiurets and their derivatives showed agricultural, medicinal, biological, pharmaceutical, industrial significances and applications. By considering all these facts this research scheme was designed.

The main objective of the work is to synthesize a novel series of 8-(substituted-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepines[VA(a-h)]. These were synthesized by the interactions of 8-thiocarbamido-1-methyl-6-phenyl-4H-[1,2,4] triazolo[4,3-a][1,4]benzodiazepine [III(a)] with various thioureas (IIa-e) in 50% acetone-ethanol medium, Scheme-I.

Where, R= -methyl, -ethyl, -t-butyl, -phenyl, p-chlorophenyl, -o-tolyl.
Scheme-I
1) 8-(Phenyl-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine [VA(a)]

A reaction mixture of 8-thiocarbamido-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4] benzodiazepine [IIIA(a)] and phenyl isothiocyanate (IVa) in 1:1 molar proportion were refluxed in 50% acetone-ethanol medium for 4 hours on water bath, ivory coloured crystals were separated out, they were filtered and dried at room conditions. Recrystallised from aqueous ethanol. Yield 95 %, m.p. 247°C. The formation of [VA(a)] is depicted below,

Properties of [VA(a)]

It is brown colour crystalline solid having melting point 247°C. It gave positive test for nitrogen and sulphur. It was desulphurized by alkaline plumbite solution which clearly indicate the presence of C=S group. It was soluble in water, ethanol, DMSO-d₆ while insoluble in carbon tetrachloride, chloroform, benzene, petroleum ether. It formed picrate having melting point 209°C. **Elemental analysis:** [C: 61.70% (found), 62.11% (calculated)], [H: 03.12% (found), 4.34% (calculated)], [N: 19.20% (found), 20.28% (calculated)], [S: 12.20% (found), 13.25% (calculated)], **IR Spectrum:** The IR spectrum was carried out in KBr-pellets. The important absorptions are correlated as (cm⁻¹) 3390.86 N–H stretching, 2891.30 C-H stretching, 1614.42 N=C-N stretching, 1562.34 N-C=S stretching, 1087.34 C-N stretching. **NMR Spectrum:** The NMR spectrum was carried out in DMSO-d₆ and CDCl₃ This spectrum distinctly displayed the signals due to Ar-H protons at δ 9.6496-6.8132 ppm, -NH proton at δ 3.4327 ppm, -CH₂ protons at δ 2.6265-2.1202 ppm, -CH₃ protons at δ 1.2435 ppm.
Similarly, 8-thiocarbamido-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine [III(a)] interact with ethylisothiocyanate (IVb) methylisothiocyanate (IVc) tert-butylisothiocyanate (IVd) p-chlorophenylisothiocyanate (IVe) p-tolylisothiocyanate (IVf) to form 8-(ethyl-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4] benzodiazepine [VA(b)], 8-(methyl-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4] triazolo [4,3-a][1,4] benzodiazepine [VA(c)], 8-(tertbutyl-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4] triazolo[4,3-a][1,4]benzodiazepine [VA(d)], 8-(p-chlorophenylthiabiureto)-1-methyl-6-phenyl -4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine [VA(e)], 8-(p-tolyl-2,4-dithiabiureto)-1-methyl -6-phenyl-4H-[1,2,4]triazolo [4,3-a] [1,4] benzodiazepine [VA(f)], respectively by the above mentioned method and enlisted in Table No. I

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>8-(Substituted)-2,4-dithiabiureto)-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine[VA(c-h)].</th>
<th>Yield (%)</th>
<th>M.P. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>8-(Ethyl)---------------------------------------------------------benzodiazepine [VA(b)]</td>
<td>96</td>
<td>214</td>
</tr>
<tr>
<td>2.</td>
<td>8-(Methyl)--------------------------------------------------------benzodiazepine [VA(c)]</td>
<td>94</td>
<td>237</td>
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<tr>
<td>3.</td>
<td>8-(Tertbutyl)------------------------------------------------------benzodiazepine [VA(d)]</td>
<td>86</td>
<td>173</td>
</tr>
<tr>
<td>4.</td>
<td>8-(p-Chlorophenyl)----------------------------------benzodiazepine[VA(e)]</td>
<td>88</td>
<td>201</td>
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<tr>
<td>5.</td>
<td>8-(p-Tolyl)--------------------------------------------------------- benzodiazepine [VA(f)]</td>
<td>92</td>
<td>262</td>
</tr>
</tbody>
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REFERENCES