**A novel one-pot pseudo-five-component condensation reaction towards bifunctional diazepine-tetrazole containing compounds: synthesis of 1H-tetrazolyl-1H-1,4-diazepine-2,3-dicarbonitriles and 1H-tetrazolyl-benzo[b][1,4]diazepines**

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**Abstract** A novel and efficient method has been developed for the one-pot synthesis of bifunctional diazepine-tetrazole containing compounds. 1H-Tetrazolyl-1H-1,4-diazepine-2,3-dicarbonitrile and 1H-tetrazolyl-benzo[b][1,4]diazepine derivatives were synthesized in good yields using 2,3-diaminomaleonitrile or an aromatic diamine, ketones, trimethylsilyl azide, and an isocyanide in the presence of p-toluenesulfonic acid as a catalyst in methanol at room temperature.

**Keywords** 1H-Tetrazolyl-1H-1,4-diazepine-2,3-dicarbonitrile · 1H-Tetrazolyl-benzo[b][1,4]diazepine · Trimethylsilyl azide · Multicomponent reaction · MCR · Isocyanide

**Introduction**

Benzodiazepine compounds such as diazepam I, 2,3,4,5-tetrahydro-1H-1,5-benzodiazepines II, and peptide hormones III have a variety of pharmaceutical properties including anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant, amnestic, diabetic nephropathy or glomerulosclerosis, and peptide hormones properties [1–3]. Because of these properties, various synthetic methods have been reported by different research groups for the synthesis of benzodiazepines (Fig. 1) [4].

Tetrazoles have received significant attention because of their biological activities. This moiety is a bioisostere for carboxylic acid which does not show acidic properties [5]. It is reported that using a tetrazole instead of a carboxylic acid the toxicity of a drug could be reduced [6]. Some examples include losartan IV, angiotensin II antagonist, pentylenetetrazole (PTZ) V, and tetrazole VI (Fig. 2) [7].

Synthesis of complex and biologically relevant molecules could be done via multicomponent reactions (MCRs). MCRs are very useful methods because of properties such as atom economy, convergent character, operational simplicity, and the structural diversity. These properties make this procedure very useful for the discovery and optimization of processes in the pharmaceutical industry [8]. By simply varying each component in multicomponent method, especially isocyanide-based MCRs (IMCRs), large libraries of organic molecules can be synthesized. 1,4-Benzodiazepine and tetrazole derivatives can be synthesized via MCRs approach, as well [9,10].

**Results and discussions**

In view of our current interest in IMCRs of diamines [11–17] and potential use of 1,4-benzodiazepines and tetrazoles, herein we wish to report two hitherto unknown IMCRs which afford 1H-tetrazolyl-1H-1,4-diazepine-2,3-dicarbonitriles 6a–g and 1H-tetrazolyl-benzo[b][1,4]diazepines 7a–i with regiochemical control via a condensation reaction between 2,3-diaminomaleonitrile 1 or o-phenylenediamines 2, ketones 3, isocyanides 4, and TMSN₃ 5, respectively (Scheme 1). To the best of our knowledge, this is the first report of the synthesis of 1H-tetrazolyl-1H-1,4-diazepine-2,3-dicarbonitrile and 1H-tetrazolyl-benzo[b][1,4]diazepine derivatives using IMCRs, and these new reactions open an
important field for the use of MCRs in heterocyclic synthesis. These routes permit us to introduce a high degree of molecular diversity under mild reaction conditions, including substitution and scaffold diversity. A potential large number of derivatives could be rapidly synthesized in high purity and yield by using this method.

In a model reaction, 2,3-diaminomaleonitrile and acetone were stirred in the presence of a catalytic amount of $p$-toluenesulfonic acid in methanol at room temperature. The progress of the reaction was monitored by TLC. After 4 h, trimethylsilyl azide and cyclohexyl isocyanide were added to the reaction mixture and stirring was continued for 6 h. After reaction completion (monitored by TLC method), an aqueous workup afforded 5-((1-cyclohexyl-1-$H$)-1,4-diazepol-2,3-dicarbonitriles 6a–g in 75–90% yield.

To identify the best reaction conditions, 2,3-diaminomaleonitrile, cyclohexanone, cyclohexyl isocyanide, and either sodium azide or trimethylsilyl azide in the presence of $p$-TsOH·H$_2$O in various organic solvents and water were allowed to react at room temperature. As it can be seen from Table 1, methanol and trimethylsilyl azide are the best solvent and reactant, respectively, for the synthesis of compound 6c based on yield and reaction time. It is important to underline that the second step of the reaction either did not occur or that the reaction yield decreased in other solvents, even using trimethylsilyl azide as a reactant.

Table 1 Optimization of the tetrazole formation

<table>
<thead>
<tr>
<th>Solvents/ Azide</th>
<th>Time</th>
<th>Yields 11 %</th>
<th>Yields 6c %</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$O/NaN$_3$</td>
<td>24 h</td>
<td>85</td>
<td>-</td>
</tr>
<tr>
<td>H$_2$O/TMSN$_3$</td>
<td>24 h</td>
<td>85</td>
<td>-</td>
</tr>
<tr>
<td>CH$_3$Cl/NaN$_3$</td>
<td>24 h</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>CH$_3$Cl/TMSN$_3$</td>
<td>24 h</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>CH$_3$CN/NaN$_3$</td>
<td>24 h</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>CH$_3$CN/TMSN$_3$</td>
<td>24 h</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>EtOH/NaN$_3$</td>
<td>24 h</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>EtOH / TMSN$_3$</td>
<td>24 h</td>
<td>94</td>
<td>10</td>
</tr>
<tr>
<td>MeOH/NaN$_3$</td>
<td>24 h</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>MeOH/ TMSN$_3$</td>
<td>10 h</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>

In light of the success of the above reaction, we explored the scope of this method by varying the isocyanides and ketones component. The reaction proceeds very cleanly at room temperature and no undesirable side reactions were observed. Representative products 6a–g are shown in Fig. 3.

The structures of compounds 6a–g were elucidated from their IR, mass spectrometry, $^1$H NMR and $^{13}$C NMR spectra. For example, the $^1$H NMR spectrum of 6a exhibited a multiplet for the cyclohexyl ring, three methyl groups and one CH moiety at $\delta = 1.00$–2.10. One ABq for CH$_2$ at $\delta = 2.79$, a multiplet at $\delta = 4.75$ for CH-NH of cyclohexyl, two singlets at $\delta = 5.75$ and $\delta = 6.78$ for NH groups. The $^1$H-decoupled $^{13}$C NMR spectrum of 6a showed 16-distinct resonances in agreement with the proposed structure. The mass spectra of these compounds displayed molecular ion peaks at the appropriate $m/z$ values.

Finally, the structure of 6c was confirmed unambiguously by single-crystal X-ray analysis (Fig. 4).