New Synthesis of Perhydrotriazolotriazoles Catalyzed by TiCl$_4$ under Ambient Conditions

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ABSTRACT. Aromatic 2,3-diazabuta-1,3-dienes in glacial acetic acid with isothiocyanate in the presence of catalyst TiCl$_4$ at room temperature produced via criss-cross cycloaddition reactions the corresponding perhydro[1,2,4]triazolo[1,2-a][1,2,4]triazole-1,5-dithiones in relatively high yields and short reaction time.

Key words: Criss cross cycloaddition, Azine, Catalyst, Perhydrotriazolotriazole

INTRODUCTION

1, 3-Dipolar cycloaddition reactions are fundamental processes in organic chemistry, and their asymmetric version offers a powerful and reliable synthetic methodology to access five-membered heterocyclic rings in regio-and stereocontrolled fashion. Criss-cross cycloaddition was described in 1917 as intermolecular reaction of benzaldazine with 2 equiv of thiocyanate affording a heterocyclic compound having two fused five-membered ring. Criss-cross cycloaddition may be classified as a special type of [3+2] cycloaddition or 1, 3-Dipolar cycloaddition, respectively. The formation of their products was explained in 1963 by Huisgen as a success of two successive 1, 3-Dipolar cycloadditions. This assumption was proved in 1973 when as Table 1, 3-Dipole was identified by X-ray crystallographic analysis. The 1, 3-Dipolar aldazine or ketazine are actually 1, 3-Heterodienes and have double 1, 3-Dipolar sites (Scheme 1).

These acyclic 1, 3-Heterodienes adopt the s-trans conformation due to steric interactions of the alkyl or aryl substations. This conformation does not undergoes the [4+2] cycloaddition known as the Diels-Alder reaction. Azines as heterodiene reacted with two equiv of dipolarophiles, such as thiocyanate, in [3+2] cycloaddition reactions and gave Perhydrotriazolotriazole derivatives.

Meantime, it was found that this kind of compounds possesses many kinds of biological activities such as fungicidal, bactericidal, analgesics, anxiolytic and anti-inflammatory.

RESULTS AND DISCUSSION

Main recent papers describing synthesis of perhydrotriazolotriazoles by classical method, but this method has defects such as long reaction times and low yield. Herein we report a facial and efficient method for the synthesis perhydrotriazolotriazoles catalyzed by TiCl$_4$. In an initial study, for examination of the catalytic activity of different catalysts such as BF$_3$, VCl$_5$, WCl$_6$, AlCl$_3$, ZrCl$_4$, SbCl$_5$, Al$_2$O$_3$-P$_2$O$_5$, and TiCl$_4$, in this cycloaddition reaction, benzaldazine was first reacted with potassium isothiocyanate in CH$_3$CN (10 mL) in the presence of each catalysts (0.2 equiv.) separately. In the course of this study we found that TiCl$_4$ was the most effective catalyst in term of yield of the perhydrotriazolotriazoles (98%) while other catalysts formed the product with the yields of 46-88% (Table 1). In the absence of catalyst, the yield of the product was found to be very low (Table 2). All the products were char-
characterized by NMR, IR and elemental analyses. The presence of signal at 1247-1293 cm\(^{-1}\) in IR spectra and 10.21-11.51 ppm in \(^1\)H NMR spectra, due to NH related to the fused five membered rings.

**CONCLUSION**

This work demonstrates a novel and highly efficient methodology for the synthesis of perhydrotriazolotriazoles from two successive 1, 3-Dipolar cycloaddition of azine derivatives and potassium isothiocyanate through TiCl\(_4\) catalyzed at room temperature. In addition of efficiency and simplicity, this protocol provides a fast and low cost procedure for the synthesis of these products.

**EXPERIMENTAL**

**Instrumentation**

Thin layer chromatography (TLC) was performed to monitor the reaction progress and purity of products. Melting points were measured using an electro thermal MK3 apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer FT-IR 550 spectrometer in KBr pellets and reported in cm\(^{-1}\). NMR spectra were measured on a Bruker DRX 400 MHz spectrometer in DMSO-d6 with chemical shift (\(\delta\)) given in ppm relative to TMS as internal standard. The element analysis (C, H, N) were obtained from a Carlo ERBA model EA 1108 analyzer carried out on Perkin-Elmer 240 c analyzers.

**Reagents**

All reactions were carried out at room temperature. Solvents and chemicals were purchased from Merck and used without prior purification. The compounds were prepared following reported procedure.

**Recommended procedure**

To mixture of KSCN (2.5 g, 0.0257 mol), CH\(_3\)CN (10 mL) and aldazine (0.0128 mol) was added TiCl\(_4\) and the reaction mixture was stirred at room temperature for 20 min. the progress of the reaction was followed by TLC. After completion of the reaction, the suspension was poured in H\(_2\)O (200 mL) and the mixture was concentrated in vacuo to remove the solvent. The resulting solid was washed successively with water. After dried in vacuum the product was obtained with enough purity for spectral analysis (Scheme 2).

![Scheme 2](image)

**Table 1. Synthesis of perhydrotriazolotriazole (3a) in the presence of different catalysts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF(_3)</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>VCl(_3)</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>WCl(_6)</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>AlCl(_3)</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>ZrCl(_4)</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>SbCl(_5)</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>TiCl(_4)</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>Al(_2)O(3)-P(_2)O(_5)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)Yields refer to the pure isolated product.

**Table 2. Synthesis of perhydrotriazolotriazoles in CH\(_3\)CN in the presence of catalyst TiCl\(_4\) at room temperature (Method A) and in the absence of catalyst TiCl\(_4\) (Method B)**

<table>
<thead>
<tr>
<th>Product(^a)</th>
<th>R</th>
<th>R(_1)</th>
<th>Min(time)/Yield%(^b) (Method A)</th>
<th>Min(time)/Yield%(^b) (Method B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C(_6)H(_5)</td>
<td>H</td>
<td>21/97</td>
<td>105/91</td>
</tr>
<tr>
<td>3b</td>
<td>4-Cl C(_6)H(_5)</td>
<td>H</td>
<td>15/91</td>
<td>60/79</td>
</tr>
<tr>
<td>3c</td>
<td>3-Cl C(_6)H(_5)</td>
<td>H</td>
<td>20/89</td>
<td>120/75</td>
</tr>
<tr>
<td>N.R</td>
<td>4-O(Me)C(_6)H(_5)</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3d</td>
<td>3-Br C(_6)H(_5)</td>
<td>H</td>
<td>20/90</td>
<td>100/80</td>
</tr>
<tr>
<td>3e</td>
<td>C(_6)H(_5)</td>
<td>Me</td>
<td>38/76</td>
<td>120/65</td>
</tr>
<tr>
<td>N.R</td>
<td>4-O(H)C(_6)H(_5)</td>
<td>Me</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3f</td>
<td>3-Me C(_6)H(_5)</td>
<td>Me</td>
<td>40/79</td>
<td>180/68</td>
</tr>
</tbody>
</table>

\(^a\)All products were characterized by \(^1\)H NMR, \(^{13}\)C NMR, IR and element analysis.

\(^b\)Isolated yields
Tetrahydro-3, 7-diphenyl-[1,2,4] triazole [1,2-a][1,2,4] triazole-1,5-dithione (3a, C₁₆H₁₃N₄S₂)

Yield: (97%) 3a. M.p.: 187-188 °C; Rₛ/(ethyl acetate/n-Hexane) (3/7)=0.51; ¹H NMR (400 MHz, DMSO): δ= 6.82 (s, 2H, CH), 7.39 (t, 2H, CH), 7.41 (t, 2H, CH), 7.45 (t, 2H, CH), 11.42 (s, 2H, NH) ppm; ¹³C NMR (100 MHz, DMSO): δ=73.02 (CH), 124.88 (CH), 127.15 (CH), 128.31 (CH), 128.39 (CH), 131.22 (CH), 132.61 (CH), 136.45 (CH), 184.00 (C), ppm; IR (KBr): ν=3415, 1500, 1252 cm⁻¹

3,7-Bis(3-chlorophenyl)-tetrahydro-[1,2,4]triazolo [1,2-a][1,2,4]triazole-1,5-dithione (3b, C₁₆H₁₂N₄S₂Cl₂)

Yield: (91%) 3b. M.p.: 198-200 °C; Rₛ/(ethyl acetate/n-Hexane) (3/7)=0.32; ¹H NMR (400 MHz, DMSO): δ= 6.85 (s, 1H, CH), 7.39 (dd, 1H, CH), 7.51 (dd, 1H, CH), 11.48 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, DMSO): δ=75.50 (CH), 128.41 (CH), 128.80 (CH), 138.21 (C), 142.42 (C), 179.41 (C), ppm; IR (KBr): ν=3405, 1588, 1291 cm⁻¹

3,7-Bis(3-chlorophenyl)-tetrahydro-[1,2,4]triazolo [1,2-a][1,2,4]triazole-1,5-dithione (3c, C₁₆H₁₂N₄S₂Cl₂)

Yield: (98%) 3c. M.p.: 194-195 °C; Rₛ/(ethyl acetate/n-Hexane) (3/7)=0.31; ¹H NMR (400 MHz, DMSO): δ= 6.89 (s, 2H, CH), 7.16 (dd, 2H, CH), 7.37 (dd, 2H, CH), 7.42 (dd, 2H, CH), 7.49 (dd, 2H, CH), 11.50 (s, 2H, NH) ppm; ¹³C NMR (100 MHz, DMSO): δ=76.62 (CH), 124.88 (CH), 128.39 (CH), 128.12 (CH), 131.45 (C), 184.47 (C), ppm; IR (KBr): ν=3401, 1490, 1248 cm⁻¹

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REFERENCES