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Comproportionation based Cu(I) catalyzed [3+2] cycloaddition of nitriles and sodium azide

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Abstract: A simple and convenient procedure for synthesis of 5-substituted 1H-tetrazoles using various nitriles and sodium azide in the presence of a catalytic amount of Cu-powder and anhydrous CuSO 4 in DMF solvent in good to high yields is reported. The reaction plausibly proceeds involving active Cu(I) catalyst which is formed due to comproportionation of the Cu(II)/Cu(0) couple and in situ formation of a Cu(I) azide species. Process safety RC (reaction calorimetry) study was also performed to understand the exothermicity during the reaction.

Keywords: Cu(I) catalyst, cycloaddition, tetrazole, azide

Introduction

Tetrazole is an impressive functionality with diverse applications in medicinal chemistry. [1] Interest in tetrazole chemistry is found to be extremely important due to the fact that it acts as stable carboxylic acid surrogate that offers superior pharmacokinetic profile to the parent molecule. [2] Such an advancement led to the discovery of angiotensin II antagonists. [3] This functionality has also been frequently exploited as lipophilic spacers, ligands, precursors of a variety of nitrogen containing heterocycles in coordination chemistry [4 & 5] and in material sciences including photography, information recording systems, and explosives. [6] Most widely practiced synthesis of 5-substituted 1H-tetrazoles is [3+2] cycloaddition reaction involving nitriles and azides. A number of synthetic protocols with variations are precedent. [6] In most instances, sodium azide (NaN₃) has been used as an inorganic azide source in combination with ammonium halides (Cl⁻ and Br⁻) as an additive employing dipolar...
aprotic solvents.\textsuperscript{[6&7]} In some cases, Brønsted\textsuperscript{8} or Lewis acids,\textsuperscript{[9]} or stoichiometric amounts of Zn(II) salts\textsuperscript{[10]} have been reported as suitable additives to afford the desired azide–nitrite addition process. As an alternative to inorganic azide salts, trimethylsilyl,\textsuperscript{[11]} trialkyltin\textsuperscript{[12]} and organoaluminum azides\textsuperscript{[13]} have been introduced as comparatively safer azide sources and these have the advantage of being soluble in organic solvents. Unfortunately, with very few exceptions, all of these methods require longer reaction times in combination with higher reaction temperatures.

Heterogeneous catalysis is a very attractive strategy as it allows the production and easy separation of large quantities of products with the use of catalyst. Recently, several heterogeneous catalytic systems were reported, for example, nanocrystalline ZnO,\textsuperscript{[14a]} Zn/Al hydrotalcite,\textsuperscript{[14b]} Zn hydroxyapatite,\textsuperscript{[14c]} Cu-Zn alloy,\textsuperscript{[14d]} and Cu$_2$O.\textsuperscript{[15a]} tungstate salts\textsuperscript{[16]} as catalysts, mesoporous ZnS nanospheres,\textsuperscript{[17]} reusable catalyst CuFe$_2$O$_4$ nanoparticles,\textsuperscript{[18]} CoY Zeolite,\textsuperscript{[19]} montmorillonite K-10,\textsuperscript{[20]} and Fe (HSO$_4$)$_3$;\textsuperscript{[21]} InCl$_3$;\textsuperscript{[22]} and Phosphomolybdic acid (H$_3$Mo$_{12}$O$_{40}$P)$_3$;\textsuperscript{[23]} have been reported as catalyst for the synthesis of 5-substituted 1H-tetrazoles. Organic azides e.g. triethyl ammonium azide\textsuperscript{24} and NaN$_3$ in the presence of the acidic resin amberlyst-15,\textsuperscript{25a} Recently, AgNO$_3$, DMAP acetate,\textsuperscript{25b} have also been reported to achieve similar cycloaddition reaction.

The development of a catalytic synthetic method for the preparation of tetrazole molecules still remains a fascinating research area. Reports for synthesis of triazoles using Cu(I) species are well documented.\textsuperscript{[28]} The utilization of Cu(I) species for synthesis of tertazoles gaining significant interest. Herein we utilized precedent comproportionation based strategy to prepare Cu(I) species in situ by using Cu(0) and Cu$_2$O.\textsuperscript{[29&30]} Considering this approach we attempted the synthesis of 5-substituted 1H-tetrazoles 2 by using the catalytic potential of Cu-powder [Cu(0)] and anhydrous CuSO$_4$ via [3+2] cycloaddition reaction involving the corresponding nitriles 1 and sodium azide in DMF solvent (Scheme 1).

**Results and Discussion**

Initially, we focused on the synthesis of API (active pharmaceutical ingredients) related tetrazole intermediates like valsartan intermediate 2a and irbesartan 2b by using different catalytic systems. Substrate 1a was selected for the model studies to examine the catalytic potential of different systems (Table 1). First set of reaction was conducted using Cu and CuSO$_4$ individually in presence of DMF solvent and NaN$_3$ as azide source (entry 1 and 2, Table 1). We did not obtain promising results hence we adopted the reported conditions,\textsuperscript{[15a, 15b & 27]} for the synthesis of valsartan intermediate 2a, (Table 1; entries 5, 6 and 7.), and observed less yields and low ee\%.

**Table 1. Optimization of reaction conditions for synthesis of 5-substituted 1H-tetrazoles.\textsuperscript{a}**

\textsuperscript{a}Reaction conditions: 1a (2.46 mmol), metal catalysts each (10 mol%), NaN$_3$ (3.69 mmol), TMSN$_3$ (3.69 mmol), Solvent (10 mL) at 123±2 °C; \textsuperscript{b}Isolated yields; \textsuperscript{c} Determined by chiral HPLC; NA-analysis not performed.
We made efforts to understand the importance of solubility on reaction progress. We examined this by performing cycloaddition reaction between \( \text{1a} \) and \( \text{NaN}_3 \), to obtain tetrazole \( \text{2a} \) (Table 1) in different solvents e.g. DMF and DMSO. Among these two solvents, DMF along with 1.5 equivalent of \( \text{NaN}_3 \), 10 mol% Cu-powder and 10 mol% of anhydrous \( \text{CuSO}_4 \) afforded the product in good yields (85%) with 88% \( \text{ee} \) at 123±2 °C in 17 h and the results are summarized in Table 1.

Based on this promising result, we started investigating the catalytic potential of above mentioned catalytic system for the synthesis of aromatic and alkyl tetrazoles.

In order to establish its generality for broader application of this method, we selected a variety of structurally divergent nitriles 1 to understand the scope of the Cu(I) catalyzed/promoted [3+2] cycloaddition to form 5-substituted 1H-tetrazole with Cu(0) powder (10mol%) with anhydrous \( \text{CuSO}_4 \) (10 mol%), the results are presented in Table 2. The reactions of the aryl nitrile, bearing electron donating substituent in \text{para} position and ortho position of aromatic ring, afforded the corresponding tetrazole in similar yields when compared with electron withdrawing substituent (Table 2). Benzyl nitriles containing \text{p-}, \text{o-}, \text{m-methoxy group also offered the tetrazoles 2j, 2k and 2l in moderate to high yields and alkyl nitriles offered corresponding tetrazole 2o in lower yields. On the other hand this method has proven to be noteworthy when compared with the reported methods\cite{27} for synthesis of sterically hindered structures like sartans (Table 2, entries: 2a, 2b, and 2c).

### Process Safety Studies

Since the literature on hazards associated with the process to synthesize 2 is unavailable therefore reaction calorimetry (RC) studies were performed for the synthesis of tetrazoles 2 (Figure 2, 3, 4 and 5). Based on this study, it was possible to recommend process change in operation during scale-up.

The reaction of \( \text{1d} \) (85.36 mmol) with \( \text{NaN}_3 \) (128.0 mmol) in the presence of Cu-powder (10 mol%) and \( \text{CuSO}_4 \) (10 mol%), in DMF (100 mL) was studied for heat of reaction and adiabatic temperature rise by using calorimeter equipped with 4-blade propeller agitator having 0.06 m diameter with 300 rpm. Comparison of the batch temperature profile inside the reactor (Tr) with the reactor jacket temperature profile (Tj) in isothermal mode revealed that the reaction was instantaneous with insignificant heat evolution. We studied the heat evolution from 33 °C to 123 °C at a rate of 0.5 °C /min.

The reaction mass temperature was elevated to 134.44 °C from 123 °C which was evident from the insignificant deviation between Tr and Tj.

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### Table 1: Reaction Conditions and Results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper source</th>
<th>Azide source</th>
<th>Solvent</th>
<th>Yield (%) ( ^* )</th>
<th>Time/h</th>
<th>( \text{ee} ) (%) ( ^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(0)</td>
<td>( \text{NaN}_3 )</td>
<td>DMF</td>
<td>40</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>( \text{CuSO}_4 )</td>
<td>( \text{NaN}_3 )</td>
<td>DMF</td>
<td>35</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Cu(0)+( \text{CuSO}_4 )</td>
<td>( \text{NaN}_3 )</td>
<td>DMF</td>
<td>85 (15a, c)</td>
<td>17</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Cu(0)+( \text{CuSO}_4 )</td>
<td>( \text{NaN}_3 )</td>
<td>DMSO</td>
<td>80</td>
<td>17</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>CuO</td>
<td>( \text{TMSN}_3 ) [15a, c]</td>
<td>DMF/MeOH</td>
<td>55</td>
<td>24</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>CuO</td>
<td>( \text{NaN}_3 ) [15b]</td>
<td>DMF</td>
<td>45</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>CuSO(_2)(\cdot)(\text{SH}_2)(\text{O} )</td>
<td>( \text{NaN}_3 ) [27]</td>
<td>DMSO</td>
<td>65</td>
<td>24</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>( \text{Cu}_2)(\text{O} )</td>
<td>( \text{NaN}_3 )</td>
<td>DMF</td>
<td>38</td>
<td>24</td>
<td>NA</td>
</tr>
</tbody>
</table>
For 10 g of 1d, the heat of reaction/process (H_r) for the batch size taken in RC1e indicates that the estimated adiabatic temperature rise was 11.4 °C. [31]

Likewise, during the maintenance at 123 °C from 3h, the adiabatic temperature rise was observed to be 6.49 °C (see supporting). Based on this it was concluded that the generation of CuN_3 from Cu(0) and CuSO_4, followed by tetrazole formation is slightly exothermic in nature over formation of 2.

Therefore, an impetus was given to ensure the rate of heat was controlled throughout the course of the reaction and efficient jacket cooling was recommended. RC experiment involving RSD (Rapid Screening Device) indicated the degree of explosivity which was found to be violent at >250 °C (see supporting). As a result, we were limited to conduct all our experiments featured in the work at 123±2 °C only. Moreover, RC studies indicate that this chemistry/process as such is safe to practice.

Mechanistically, based on the precededent literature [15a,15c,28,30] it is understood that, in situ generation of Cu(I) by comproportionation of Cu(0) and CuSO_4 may lead to cyclo addition. The Cu(I) reacts with NaN_3 to produce the CuN_3 (at any given point of time CuN_3 will not be left unreacted as we understood that the rate of cycloaddition event is much faster than comproportionation; therefore the safety concerns associated with CuN_3 can be well estimated). Thus, resulting CuN_3 reacts with the C≡N bond of nitrile by [3+2] cycloaddition to generate the intermediate C-2 via C-1 complex. Transmetalation of Cu with sodium in intermediate C-2 was achieved by using NaN_3 as shown in Figure 1. To support this mechanism, the reaction of 1 with NaN_3 in DMF was conducted and we found that the reaction did not proceed at all in the absence of the Cu/CuSO_4 catalyst [15a,15c].

**Figure 1.** A plausible mechanism for the formation of 5-substituted 1H-tetrazole.

In conclusion, we have developed a comproportionation based Cu(I) catalyzed/promoted efficient cycloaddition reaction involving an array of diverse nitriles and azide to obtain pharmaceutically relevant molecules. This method has advantage over the use of isolated CuN_3 in cycloaddition reactions which is not safe to handle.

**General procedure for the synthesis of tetrazole 2**

The procedure for the synthesis of the tetrazole 2 is representative. A mixture of nitrile 1d (8.53 mmol, 1.0 equiv), sodium azide (12.8 mmol, 1.5 equiv), Cu-powder (10 mol%), anhydrous CuSO_4 (10 mol%) and DMF (10 mL) was taken in a round–bottom flask and stirred at 123±2 °C until complete conversion of the starting material, which was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted the reaction mass with water (20 mL) at 25-35 °C. The reaction mass containing excess metal azide traces was safely decomposed by adding sodium nitrite (6.4 mmol) and 5N aqueous hydrochloric acid (50 mL) at 5-10 °C, and the unwanted salts were removed by filtration through celite and the filtrate was treated with ethyl acetate (2x50 mL). The resultant organic
RC1e study

**Figure 2.** RC study graphical representation. Comparison of the batch temperature profile inside the reactor (Tr) with the reactor jacket temperature profile (Tj) in isothermal mode.

**Figure 3.** Maintenance at 123 °C (123±2°C ≈ 123 °C) for 3h represents the adiabatic temperature rise.
Rapid Screening Device Data

Figure 4. Temperature difference as a function of reference temperature (RSD data). [RC experiment involving RSD (Rapid Screening Device) indicated the degree of explosivity which was found to violent at 250 °C.]

Figure 5. Pressure difference as a function of reference temperature (RSD data).
Table 2 Cu(0)/Cu(II)-catalyzed synthesis of 5-substituted 1H-tetrazoles 2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time/h</th>
<th>Yield (%)</th>
</tr>
</thead>
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<td><img src="image" alt="2b" /></td>
<td>17</td>
<td>78(^a)</td>
</tr>
<tr>
<td>2</td>
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<td>16</td>
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</tr>
<tr>
<td>5</td>
<td><img src="image" alt="2f" /></td>
<td>1.5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="2g" /></td>
<td>1.5</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Yield</td>
<td>Notes</td>
</tr>
<tr>
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<td>-----------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Chemical Structure 2h" /></td>
<td>1.0</td>
<td>95</td>
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<td>92</td>
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<td>14</td>
<td><img src="image" alt="Chemical Structure 2o" /></td>
<td>5</td>
<td>50</td>
</tr>
</tbody>
</table>

*Reaction conditions: Reactions were carried out on a 1.0 g scale of 1 with NaN₃ (1.5 equiv) in the presence of Cu(0) (10 mol%) and CuSO₄ (10 mol%) in DMF (10 mL) at 123±2°C; Isolated yields; yield after column purification.*
layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layer was washed with 10 % aq. NaCl solution (2x50 mL) and dried over anhydrous Na$_2$SO$_4$ and concentrated to give a crude product, which was isolated using chilled water after 3-4 h maintenance, and eventually filtered off to give desired product 2 (b-n). Whereas compound 2a and 2o were isolated by dissolving the reaction mass in ethyl acetate and hexane (1:9) and the solution was maintained for 3 h at 0-5 °C to obtain the product. 

(S)-Methyl N-((2'-((1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-N-pentanoyl-L-valinate (2a) 
Pale-yellow solid (Yield: 85%). FT-IR (KBr) $3451, 2962, 2933, 2873, 2743, 1739, 1617, 1467, 1206$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): (major rotamer) $\delta$ 8.00-7.05 (m, 8H), 4.94-4.89 (2H, m), 4.29-4.25 (d, $J = 15.5$ Hz, 1H), 3.47 (s, 3H), 2.61-2.17 (m, 3H), 1.42-1.23 (m, 4H), 0.99-0.82 (m, 9H). (minor rotamer) $\delta$ 8.00-7.05 (m, 8H), 4.68-4.57 (2H, m), 4.08-4.05 (d, $J = 15.5$ Hz, 1H), 3.41 (s, 3H), 2.61-2.17 (m, 3H), 1.42-1.23 (m, 4H), 0.99-0.82 (m, 9H); $^{13}$C NMR (400 MHz, CDCl$_3$): (major rotamer): $\delta$ 174.9, 171.3, 154.8, 141.0, 137.9, 136.9, 131.1, 130.8, 129.4, 128.0, 127.3, 126.0, 123.1, 66.0, 52.9, 48.0, 33.4, 27.7, 27.5, 26.9, 22.4, 19.8, 18.7, 13.8. (minor rotamer) $\delta$ 174.8, 170.3, 155.3, 137.7, 131.1, 130.7, 129.0, 128.0, 122.8, 61.7, 51.9, 45.6, 33.4, 27.7, 27.3, 22.4, 19.8, 18.6; EI-Mass: $m/z$ 450.4 [M+H$^+$].

3-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (Irbesartan) (2b) 
White solid (Yield: 78 %). FT-IR (KBr) $3434.3, 2959.6, 2871.5, 2437.8, 1731.6, 1618.1, 1405.9, 756.2$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $7.69$(m, 2H), $7.59$(m, 2H), $7.09$(s, 4H), $4.69$(s, 2H), $2.31$(t, $J = 7.36$ Hz, 2H), $1.8-1.68$(m, 7H), $1.67-1.65$(t, $J = 8.52$ Hz, 2H), $1.4-1.5(q, J = 7.6$ Hz, 2H), $1.28-1.23$(m, 2H), $0.78$(t, $J = 14.68$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO): $\delta 186.1, 161.6, 155.5, 141.5, 138.8, 136.8, 131.5, 131.0, 129.7, 128.3, 126.7, 123.9, 76.3, 42.7, 37.3, 27.9, 27.0, 25.9, 22.0, 14.1; EI-Mass: $m/z$ 429 [M+H$^+$].

5-(4'-Methylbiphenyl-2-yl)-1H-tetrazole (2c) 
White solid (Yield: 85 %). FT-IR (KBr) 3430.1, 2981.5, 2901.4, 2717.4, 2610.0, 1776.3, 1601, 1566.3, 1480, 1250.7, 753.6 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO): $\delta 155.1$(br), 141.5, 136.8, 136.3, 131.1, 130.6, 130.5, 128.9, 128.6, 127.5, 123.4, 20.6; EI-Mass: $m/z$ 237 [M+H$^+$].

5-(p-Tolyl-1H-tetrazole (2d) 
White solid (Yield: 95 %). FT-IR (KBr) 2688.8, 2543.5, 1887.1, 1615.6, 1572.9, 1499.3, 1160.8, 1052.5, 987.3, 821.740.0 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO): $\delta 7.93$(d, $J = 8.04 H, z2H), 7.44(d, $J = 7.8$ Hz, 2H), 2.40(s, 3H); $^{13}$C NMR (100 MHz, DMSO): $\delta$ 155.1, 141.2, 129.9, 126.9, 121.4, 21.0; EI-Mass: $m/z$ 161 [M+H$^+$].

5-(3-Nitrophenyl)-1H-tetrazole (2g) 
Pale-yellow solid (Yield: 90%). FT-IR (KBr) 3392, 3079.8, 2630.8, 1656.5, 1527.6, 1346.7,
1015.1, 735.2 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ8.85 (s, 1H), 8.49 (d, J = 7.81 Hz, 1H), 8.44 (d, J = 9.76 Hz, 1H), 7.93 (t, J = 8.01 Hz, 1H); ¹³C NMR (100 MHz, DMSO): δ153.8, 148.2, 133.7, 132.4, 131.6, 124.9, 119.3; EI-Mass: m/z 190 [M-H].

5-(3,5-Dinitrophenyl)-1H-tetrazole (2h)
Pale-yellow solid (Yield: 95%). FT-IR (KBr) 3415.1, 3098.2, 2882.8, 2739.4, 1537.4, 1348.9, 1088.3, 918.7, 722.5 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ8.85 (s, 1H), 8.49 (d, J = 7.81 Hz, 1H), 8.44 (d, J = 9.76 Hz, 1H), 7.93 (t, J = 8.01 Hz, 1H); ¹³C NMR (100 MHz, DMSO): δ153.8, 148.2, 133.7, 132.4, 131.6, 124.9, 119.3; EI-Mass: m/z 190 [M-H].

5-(Naphthalen-2-yl)-1H-tetrazole (2i)
White solid (Yield: 92 %) FT-IR (KBr) 3056.4, 2750.7, 2627.9, 1564.7, 1414.6, 1077.5, 1012.9, 913.3, 760.4 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ9.16 (s, 2H), 8.97 (s, 1H); ¹³C NMR (100 MHz, DMSO): δ154.8, 148.7, 127.9, 126.8, 120.2; EI-Mass: m/z 235 [M-H]-.

5-(4-Methoxybenzyl)-1H-tetrazole (2j)
Pale-brown solid (Yield: 80 %). FT-IR (KBr) 2961.8, 2839.9, 2721.6, 1608.5, 1511.4, 1247.9, 1174.2, 1051.9, 1028.1, 841, 831, 753 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ16.24 (br, 1H), 7.20 (d, J = 8.56 Hz, 2H), 6.90 (d, J = 8.56 Hz, 2H), 4.20 (s, 2H), 3.72 (s, 3H); ¹³C NMR (100 MHz, DMSO): δ158.7, 130.2, 128.2, 114.6, 114.3, 55.5, 28.5; EI-Mass: m/z 191 [M-H]+.

5-(2-Methoxybenzyl)-1H-tetrazole (2k)
Pale-brown solid (Yield: 75 %). FT-IR (KBr) 3056.4, 2750.7, 2627.9, 1564.7, 1414.6, 1077.5, 1012.9, 913.3, 760.4 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ8.85 (s, 1H), 8.49 (d, J = 7.81 Hz, 1H), 8.44 (d, J = 9.76 Hz, 1H), 7.93 (t, J = 8.01 Hz, 1H); ¹³C NMR (100 MHz, DMSO): δ153.8, 148.2, 133.7, 132.4, 131.6, 124.9, 119.3; EI-Mass: m/z 190 [M-H].

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Reference and notes
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