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A copper-benzotriazole based coordination polymer catalyzes the efficient one-pot synthesis of (N’-substituted)-hydrazo-4-aryl-1,4-dihydropyridines from azines

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Abstract. A series of new (N’-substituted)-hydrazo-4-aryl-1,4-dihydropyridines were successfully synthesized via a facile one-pot catalytic pathway utilizing azines and propiolate esters as starting materials and 1D Cu benzotriazoles based coordination polymer as catalyst. In the absence of catalyst, the corresponding 5-substituted 4,5-dihydro pyrazoles were formed in moderate to high yields. Fine-tuning the catalysts allowed us to gain more insights regarding the plausible reaction mechanism.

Keywords: catalysis; copper; azine;1,4-dihydropyridines; coordination polymer

Introduction

Azines (aldazines and ketazines), 1 are a class of compounds with interesting chemical properties that undergo a wide variety of chemical processes (i.e. redox, cycloadditions, criss-cross reactions)2-4 to yield hydrazones, pyrazoles, purines or pyrimidines (Scheme 1). Aldazines, as conjugated diene, undergo [1,3]-cycloaddition with electron poor unsaturated molecules, providing an efficient route towards 1,5-diazabicyclooctanes through the known criss-cross reaction. 5 In view of the importance of the synthesis of 1,4-dihydropyridines (1,4-DHPs), the metal-catalyzed process has received considerable attention. 6,7,10,11 1,4-DHPs and their derivatives, are an important class of biologically active organic compounds, i.e. the calcium channel blocker, amlodipine.7-9 Moreover, symmetrical N’-substituted-hydrazo-4-aryl-1,4-DHPs (HA-1,4-DHPs), are new heterocycles in nature with probably wide-ranging biological activity.10,11 Methodologies including Hantzsch,12 multicomponent,5,6,13 cycloaddition,14-16 or C-C coupling reactions,17 are used for the synthesis of 1,4-DHPs derivatives (see Supporting Information, Scheme S1). A series of organocatalytic procedures have been used for such reaction,18-21 these however exhibit major drawbacks such as the high cost of the reagents, the high temperature and tedious work up.

Coordination polymers (CPs) are a class of compounds containing repeating coordination entities extending in 1, 2 or 3 dimensions. 22 that have received considerable attention due to their applications in gas adsorption, catalysis, drug delivery, separation, and imaging.23 Especially in catalysis, in contrast to the porous well-structured three dimensional CPs (known as metal organic frameworks MOFs), that retain their structural integrity during a catalytic reaction, one dimensional (1D) CPs have been far less studied.24-26 However, their easy synthesis and the possibility for tuning make them very promising candidates for catalysis.

Combining our research interests on the synthesis of simple biologically active compounds, 27-29 and the coordination chemistry of benzotriazole based organic ligands, 30,31 we report herein a new one-pot synthesis, under mild conditions, of a series of HA-1,4-DHPs based on Cu-catalyzed reactions between symmetrical electron rich aldazines and alkylpropiolate (Scheme 1). To the best of our knowledge, the synthesis of substituted symmetrical HA-1,4-DHPs using aryl aldazines and propiolates as starting materials, is an unknown chemical transformation.
**Results and Discussion**

The present catalytic protocol arose during the study of the title reaction using 1,2-bis ((E)-4-methylbenzylidene) hydrazine (1) and ethyl propiolate, in the presence of different copper salts Cu(ClO₄)₂, Cu(NO₃)₂, Cu(ONO)₂, CuCl₂, CuSO₄, [Cu(PPh₃)₃(MeCN)]ClO₄ (see Supporting Information for synthesis) and the following [Cu(II)(L)₂(MeCN)₂]·2(ClO₄)·2MeCN (2), [Cu(II)(L)₂(NO₃)₂] (3) and [Zn(L)₂(H₂O)₂]·2(ClO₄)·2MeCN (4) CPs, where L is 1-(2-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)benzyl)-1H-benzo[d][1,2,3]triazole. Metal salts were used with no further purification, whereas compounds 2–4 were characterized with IR, NMR, UV-Vis, ESI-MS, TGA (see Supporting Information) and single crystal X-Ray diffraction. Compound 2 consists of a Cu(II) center, possessing a slightly distorted octahedral geometry, coordinated to four nitrogen atoms belonging to four different organic ligands (equatorial positions) and two acetonitrile solvent molecules (axial positions). The structure extends to one dimension along the a axis, forming a 1D CP (Figure 1). Compound 4 is isostructural to 2; the two coordinating acetonitrile moieties are replaced by H₂O molecules (see Supporting Information, Figure S2). In compound 3, the asymmetric unit consists of a Cu(II) center, one organic ligand molecule, two nitrate anions and one acetonitrile solvent molecule (see Supporting Information, Figure S3). The Cu(II) center has a coordination environment of [N₂O₅] and possesses a pseudo octahedral geometry. A dimeric Cu(II) unit is formed via the chelating and bridging nitrate moieties and the structure extends in two dimensions along the b plane. The relevant N-Cu-O bond angles range from 85.32(4)° to 95.66(4)°. As for the relevant bond lengths, the mean Cu-N distances are 1.9849(6) and 1.9916(6) Å, while the Cu-O distances range from 1.9813(6) to 2.6587(6) Å.

The initial experiments with copper salts, 0.1 mmol of 1, ethyl propiolate (2 eq. based on the amount of 1) in MeOH under reflux for 24h (Table 1, entries 1-6), show almost quantitative consumption of 1 with the corresponding 4-methylbenzaldehyde (1e) to produced as the major or only product, along with a mixture of unidentified products. Aldehyde is the product formed through a hydrolysis pathway or an oxidation reaction between the starting aldazine with molecular oxygen. Indeed, aldehyde 1c was formed as the only product, when oxygen saturated methanolic solution of 1 was used under the same catalytic conditions (result not shown). In the absence of catalyst, except aldehyde 1c that was formed in 35% relative yield, a significant amount (30%) of the 5-(p-tolyl)-4,5-dihydro-1H-pyrazole-4-carboxylate derivative (1b) was isolated (Table 1, entry 8). To the best of our knowledge, this transformation has never been reported before under the present reaction conditions, however, the average relative pyrazole yields are in the range of 5-30% (see Supporting Information, Table S1). When we employed L as catalyst, formation of 1b with lower conversion and yield was observed (Table 1, entry 9). Astonishingly, incorporating 2 (2 mol%) as the catalyst under similar conditions, the corresponding 1a was formed in 65% yield, determined by ¹H NMR (Table 1, entry 10). On the contrary, the use of 3 gives no conversion (Table 1, entry 11), whereas the use of 4 yields 1b (Table 1, entry 12). These results clearly indicate that a clean and selective transformation of 1 to 1a takes place only in the presence of 2. For comparison, a mixture of Cu(ClO₄)₂ (2 mol%) and L (4mol%) was found to catalyze the formation of 1a in lower yield 14% (Table 1, entry 7), however, in the absence of L no formation of 1a was observed (Table 1, entry 1). The latter indicates a significant ligand-effect that probably plays a crucial role to the catalytic reaction mechanism (see below in the mechanistic part).

Among the solvents studied, high conversion of 1 was observed using methanol and less in EtOH, however, in non protic polar solvents, such as DMF, CH₃CN, acetone, DCE or THF, the C-C coupling product, diethyl hexa-2,4-diyne-dioate, was only observed (see Supporting Information, Table S2). In contrary, using H₂O as reaction solvent or co-solvent,
no formation of 1a was observed. However, under dry methanolic solution (over 3A molecular sieves) no significant increase of the relative yield of 1a was observed (see Supporting Information, Table S2). In addition, using higher loadings of 2 or the ethyl propiolate, the corresponding hydrolytation product ethyl (Z)-3-methoxyacrylate was observed as the major product (see Supporting Information, Table S3). When a similar reaction is performed at room temperature, then 1 remains intact, however under microwave irradiation the formation of the ethyl (Z)-3-methoxyacrylate is only observed (see Supporting Information, Table S3). Finally, in the presence of several other alkyl or aryl alkynes (i.e. DMAD, phenyl acetylene, propargyl bromide, propargyl alcohol and crotyl ester), no formation of the corresponding HA-1,4-DHP derivative was observed (see Supporting Information, Table S4).

Table 1. Transformation of aldazine (1) in HA-1,4-DHPs derivative (1a) using various catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst[a]</th>
<th>Conv.[b]</th>
<th>1a[c]</th>
<th>1b[d]</th>
<th>1c[d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[4]</td>
<td>Cu(ClO4)2</td>
<td>98%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2[4]</td>
<td>Cu(NO3)2</td>
<td>54%</td>
<td>-</td>
<td>-</td>
<td>31%</td>
</tr>
<tr>
<td>3[4]</td>
<td>Cu(OAc)2</td>
<td>42%</td>
<td>-</td>
<td>-</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>CuCl2</td>
<td>&gt;99%</td>
<td>-</td>
<td>-</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>5</td>
<td>CuSO4</td>
<td>&gt;99%</td>
<td>-</td>
<td>-</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>6</td>
<td>Cu(PPh3)2</td>
<td>N.r.[i]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7[4]</td>
<td>(MeCN)2ClO4</td>
<td>99%</td>
<td>14%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>No catalyst</td>
<td>65%</td>
<td>-</td>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>9</td>
<td>L</td>
<td>25%</td>
<td>-</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>&gt;99%</td>
<td>65%</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>N.r.[i]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>52%</td>
<td>-</td>
<td>25%</td>
<td>27%</td>
</tr>
</tbody>
</table>

[a] 1 (0.1 mmol), ethyl propiolate (0.2 mmol) and 3 mg of the solid catalysts. [b] Based on the consumption of 1 determined by 1H NMR. [c] Relative yields based on 1H NMR analysis from the integration of the corresponding proton shifts. [d] A mixture of unidentified products was observed by 1H NMR. [e] Five equivalents of benzo[d]thiazole (3mg) was added into the reaction mixture. [f] No reaction.

To study the limitation of the above catalytic procedure, a series of substituted azines (1 and 5-13) were examined. Figure 2 summarizes the results obtained using catalyst 2 as catalyst. In all cases the corresponding HA-1,4-DHPs derivatives (1a and 5a-13a (R=Et) and 14a-18a (R=Me)) were formed with good isolated yields (ca. 44-68%). It is worth noting that electron rich aromatic azines (1 and 5-8) are transformed to the corresponding HA-1,4-DHPs derivatives (1a and 5a-8a), with higher yields (44%-68%) within 24h, compared to the electron deficient azine (11, X=CF3) in which negligible yield (<5%) was observed within 48 h. Remarkably, no reaction was observed when para-nitrosubstituted azine 12 was used as substrate. In addition, the use of methyl propiolate instead of ethyl propiolate gave similar conversions and isolated yields of the corresponding HA-1,4-DHPs derivatives compared to the corresponding ethyl propiolate (Figure 2, 14a – 18a).

It is worth noting that, heterocyclic substituted azines 20 (2-thiophenyl) and 21 (2-furyl), under the present catalytic conditions gives the corresponding dihydroxypyridines 20a and 21a in ca.10% and 67% isolated yield, respectively. Subsequently, naphthyl substituted azine 22a shows lower activity, with the corresponding product formed in negligible yield (<5%), see Figure 2. All the products were determined by 1H NMR spectroscopy, whereas 7a, 8a, 9a and 16a were additionally characterized with single X-Ray diffraction (see Supporting Information, Figure S11).
Regarding the mechanism of the title reaction, we observed the following:

a) For azines bearing electron donating groups such as 1 (4-Me), 5 (4-MeO), 6 (3-MeO), 7 (3,4-diMeO) and 8 (2,5-diMe) a five times faster reaction was observed than the corresponding reaction of azine 10 (4-H). On the other hand, azines 11 (4-Cl), 12 (4-NO₂) remain intact. This first observation implies that an initial complex between the azine and the CuII-catalyst is formed, followed by a single electron transfer (SET) process forming the active species CuI_L2Y (Scheme 2).

In this context, addition of a small amount (10 mol%, based on 1) of an electron donor molecule (e.g. trimethoxybenzene, TMB) with oxidation potential less than that of azines (E_{1/2}OH, 3-MeO), 33 retards the reaction process (see Supporting Information, Table S3).

b) Based on the azines ability to donate electrons via lone pairs of the N atom or the C=N p-orbital electrons, 1 it is known that they show versatile properties of coordination in binding to metal centers, such as CuII or FeIII, especially when the aromatic ring of the azine contains a hydroxyl group in the ortho position. 34 Indeed, under our catalytic conditions, azine 13 (2-OH, 3-MeO), shows no reactivity towards the synthesis of 13a, probably through the in-situ azine-CuII-catalyst coordination effect (see Figure 2 and Figure S12 in Supporting Information).

c) The reaction of 4-methylbenzaldehyde (1c), ethyl propiolate and 2 in methanol yielded a mixture of unidentified products as confirmed by 1H NMR (see Supporting Information, Figure S13). In the case of the hetero-azine 19, which bears two different substituent’s in the para-positions of the aromatic rings (MeO and Cl), both HA-1,4-DHP derivatives 19a and 19a’ were formed in a ratio of 2:1, as determined by 1H NMR and LC-MS (see Supporting Information, Figures S14-S16). These results indicate that the azines do not dissociate during our catalytic reactions. Therefore, our catalytic procedure follows probably a different mechanistic pathway compared to the common proposed multi component reaction (MCR) or Lewis-acid catalyzed processes. 35, 36 In addition, using the (Z)-3-methoxycrotyl (a common starting material for the above literature studies) instead of the propiolate ester, and under the same catalytic conditions, the desired 1,4-dihydropyridine product was not observed (see Supporting Information, Table S4).

d) In our attempts to recover the catalyst we isolated and characterized via single crystal X-Ray crystallography a yellow solid material formulated [Cu/LCI] (2i) corresponding to a 1D CP (see Supporting Information, Figure S4). This indicates that ClO₄⁻ converts to Cl⁻ and CuII to CuI. 37, 38 Therefore, we envisage that at a certain point, transformation of perchlorate to chloride occurs, which in turn starts to coordinate to CuI centres, transforming the catalyst to 2i (Scheme 2). In addition, under new catalytic cyclic 2i was found to be inactive. This result indicates a low value of turn over number (TON) of the present catalytic system 2, with a max number of ca. 55.

Based on the above experimental results we propose a possible reaction mechanism (Scheme 2). Azine (Y) initially coordinates to the catalyst CuII_L2 forming a new catalytic intermediate CuI_L2Y (Scheme 2). ESI-MS and UV-Vis studies in methanolic solutions indicate that CuII in 2 retains the octahedral geometry and coordinates to four N atoms of four different L ligands; a similar pattern was observed for the isostructural Zn analogue 4. In addition, CuII, in the catalytically inactive compound 3, retains its geometry but coordinates to two N atoms belonging to two ligands L. 36 In sequence, a single electron transfer (SET) occurs from the electron rich azine to the CuII_L2Y, yielding the active reduced form; CuI_L2Y. This active specie is responsible for the first catalytic pathway which contains the simultaneously propiolate complexes and the proton release by the presence of the perchlorate anion forming the corresponding CuI-acetylidyde intermediate (CuI_L2Y'). Then, CuI_L2Y' undergoes a cyclization process, forming the unusual five-membered CuIII-metallacycle intermediate I (path A, Scheme 2). Similar intermediate is been supported by previous theoretical study on the copper-catalyzed synthesis of azoles. 37 This hypothesis found support from related literature on Cu-benzotriazole catalyzed electrophilic cyclization of N-arylmines, 38 as well as Cu-catalyzed synthesis of isoquinoline derivatives or other heteroarenes. 39-41
Subsequently, a reductive single cleavage (ring contraction) leads to the common intermediate II, which after proteolysis releases the cyclo-compound dihydroazete III, followed by simultaneously conrotatory ring opening, yielding the corresponding diene which in turn reacts in situ with a second molecule of propiolate via a [4+2], giving the desired product dihdropropydride derivative (HA-1,4-DHPs).

In contrast, pathway B that contains the cyclization process without any ligand replacement or azine binding effect cannot be excluded (path B, Scheme 2). It is worth noting that during the catalytic process a white powder was formed, that was found to be ligand L (confirmed by IR and NMR). In addition, a possible reductive elimination pathway from intermediate I, leads to the CuL complex which react with Cl\textsuperscript{−} to form the inactive specie CuLCl\textsuperscript{2} (Scheme 2).

In parallel and under non catalytic conditions, only pyrazole products were formed, through a stepwise mechanism contains a known criss-cross reaction ([3+2] cycloaddition) between the azine and the triple bond of propiolate, at a first step. After that, a nucleophilic addition and hydrolysis take place simultaneously (or with the opposite turn) forming the corresponding 5-substituted-4,5-dihydro pyrazoles, as shown in Figure S17 of the Supporting Information, accompanying with an equimolar amount of the corresponding X-substituted benzaldheydes as the product from the hydrolysis pathway. It is worth noting that X-substituted benzylaldehyde were also formed through an oxidative pathway form the initial azine (result not shown). Indeed, using molecular oxygen (O\textsubscript{2}) saturated methanolic solution and under the present catalytic conditions (I, ethylpropiolate and 2 as catalyst) the corresponding aldehyde 1e was observed as the only product (see Supporting Information, Table S3).

Conclusion

In conclusion, the current work exemplifies the unique nature of the Cu-benzotiazole one-dimensional coordination polymer as a catalyst in the efficient synthesis of (N'-substituted)-hydrazo-4-aryl-1,4-dihydropyridines (HA-1,4-DHPs). A series of substituted HA-1,4-DHPs we formed in good isolated yields; however, fine tuning the catalyst we were able to obtain useful information about the mechanism. From the mechanistic point of view, a hydrazine coordination initial step following by a SET pathway and a cyclization process forming a five-membered CuIII-metalacycle intermediate, constitutes the basic catalytic procedures in the title reaction. The herein Cu-catalyzed process is advantageous because of its possible wide use towards the synthesis of different heterocyclic organic molecules and because of its unique mechanistic understanding. Future efforts of our group will concentrate on improving the catalytic behavior of 2 and its application towards other chemical transformations.

Experimental Section

General

The aromatic aldehydes used as starting materials for the synthesis of aryl hydrazines were of high purity and commercially available from Aldrich. Aryl hydrazines were synthesized via the reaction between the corresponding aldehydes and hydrazine. Cu(ClO\textsubscript{4})\textsubscript{2}, Cu(NO\textsubscript{3})\textsubscript{2}, Cu(OAc)\textsubscript{2}, CuCl\textsubscript{2}, CuSO\textsubscript{4} and all the solvents were purchased from Sigma-Aldrich.

Cu-Catalyst (2) preparation

Synthetic Protocol.0.24 mmol (0.082 g) of L were dissolved in 10 ml MeCN while stirring to produce a colorless solution. A solution containing 0.48 mmol (0.178 g) of Cu(ClO\textsubscript{4})\textsubscript{2}·6H\textsubscript{2}O in MeCN (7.5 ml) was slowly added. The resulting green solution was filtered, then stored at room temperature. High quality green crystals were obtained after 3 days. Yield: 49% (based on Cu). For Ca\textsubscript{6}H\textsubscript{4}Cl\textsubscript{2}CuN\textsubscript{14}SO\textsubscript{4} (M\textsubscript{w}=1059.37 g/mol) crystal data see Supporting Information.

General Cu-Catalyzed Reactions

Into a sealed tube containing the azine (0.2 mmol) and methanol (1 ml), 0.4 mmol of ethylpropiolate and 3 mg of the corresponding catalyst (2 mol% Cu) were added. The reaction mixture was vigorously stirred at 70 °C for selected time and then reaction process was monitored by thin layer chromatography (TLC). After completion, the slurry was filtered and the filtrate was then evaporated under vacuum to give a mixture containing the corresponding HA-1,4-DHPs. Further purification with column chromatography afforded the HA-1,4-DHPs in pure form (see Supporting Information). Product analysis was conducted by \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopy (Bruker AM 300 and Agilent AM 500). Identification of the products was realized by comparing the NMR spectra data with those of the commercially available pure substances. Mass spectra were determined on an LCMS-2010 EV Instrument (Shimadzu) under Electrospray Ionization (ESI) conditions.

Acknowledgements

Financial support by the A.U.TH Research Committee (KA 89309) is kindly acknowledged. I.N.L. and M.K. acknowledged the sponsorship of the Short Term Scientific Mission from COST action CM1201. We thank Dr. Nikolaos Tsourapas (University of Sussex) for preliminary CV data of compound 2. We thank the EPSRC UK National Crystallography Service at the University of Southampton for the collection of the crystallographic data for compounds 2a, 7a and 16a.

References
preliminary experiments due to low solubility. Preliminary experiments showed a quasi-reversible behaviour, but 2 does remain intact as confirmed by UV-Vis and ESI-MS (see Supporting Information).
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