Copper malonamide complexes and their use in azide-alkyne cycloaddition reactions

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We report a rare example of the malonamide functionality being used as a ligand in copper catalysis. We have ligated a homologous series of these O,O-chelating architectures to copper, investigated their structure and exploited them in azide-alkyne cycloaddition reactions for the step-growth synthesis of oligo(triazoles) and in the synthesis of small organic azoles.

Introduction

The development of new ligands is an important undertaking in synthetic chemistry, providing access to untapped facets of classical coordination chemistry and providing us with the opportunity to enhance known catalytic transformations or even to develop entirely new catalytic processes. The malonamide motif is known to act as an O,O-chelating ligand for Cu(II), and we extended the reactivity of malonamides to include the step growth synthesis of polymalonates. As a consequence we were intrigued by the further potential of the malonamide motif and whether its novel use as a ligand could be developed for important catalytic transformations. To the best of our knowledge this class of simple copper (II) O,O-chelate have never been used in a catalytic process; this is somewhat surprising given the levels of steric and electronic variance that can be achieved along with the flexibility to ligate as a neutral donor or as an ionic donor (analogous to the ubiquitous acac motif). The tuneable nature of this pro-ligand makes it ideal for catalysis. We herein report our initial results in this area, where Cu(I) malonamide complexes have been synthesised and their catalytic competency in azide-alkyne cycloaddition reactions studied, both for the synthesis of small organic triazoles and in the step growth cycloaddition synthesis of oligo(triazoles).

The azide-alkyne cycloaddition reaction (or Huisgen 1,3-dipolar cycloaddition reaction) is undoubtedly of universal importance, being exploited under exacting ‘click’ conditions in the synthesis of small organic motifs, with 1,4-regioselectivity being observed preferentially using copper catalysts. The utility of this reaction is further highlighted in the synthesis of poly(triazoles) for use in polymer chemistry and materials science. The transformation has also found applications in medicinal chemistry and biochemistry. Given the prevalence and importance of this transformation, we opted to test the potential of our new complexes in these cycloadditions.

Results and discussion

We initiated our research by synthesising a small library of pro-ligands with a range of steric and electronic properties. This was achieved in generally good yields (up to 56%) and on a large scale (up to 0.1 mol). Two principal routes can be used; due to steric hindrance, 1 can only be accessed using Mukaiyama’s reagent to couple malonic acid to disopropylamine whereas synthesis of 2 to 4 is possible using aminolysis by reacting dimethylmalonate with the appropriate amine.

Reaction of the pro-ligands with [Cu(MeCN)]_2BF_4 gives the desired Cu(I) complexes (1-Cu to 3-Cu) in high yield as lilac solids. These solids are air stable in the solid state for several days but become air-sensitive when suspended in solvent or with prolonged exposure to moisture in the atmosphere. No copper complex was isolated. This is presumably due to steric hindrance limiting product formation, reflecting the poor yield obtained when preparing the pro-ligand, 4. Elemental analysis of 1-Cu, 2-Cu and 3-Cu indicates the presence of one MeCN per metal centre. The Cu(I) complexes (1-Cu to 3-Cu) are insoluble in standard deuterated solvents and thus the chemical composition is proven by elemental analysis and by controlled oxidation to the Cu(II) congener.
(5, 6 and 7 respectively) by exposure to air and then recrystallisation in CH\textsubscript{2}Cl\textsubscript{2}/pentane or THF/pentane to yield the requisite Cu(II) malonamide complexes. Conversion from Cu(I) to the pale blue-turquoise Cu(II) complexes occurs in moderate yield (11 to 47%), where the yield is limited to 50% due to sequestration of an extra BF\textsubscript{4} anion to allow oxidation. Presumably the remaining copper disproportionates into Cu(0), similar to observations made by Lei and co-workers on the disproportionation of Cu(I) β-keto enolate analogues.\(^9\)

\[ \text{Cu(MeCN)}_2\text{BF}_4 \rightarrow \text{Cu}^{\text{II}}(\text{malonamide})_2(\text{NMe}_2)_x \text{BF}_4 \]

Scheme 2. Synthesis of Cu(I) complexes 1-Cu to 3-Cu.

Complex 5\(^{10}\) exists in a square pyramid geometry in the solid state. Crystallisation in hydrous solvent allows ligation of H\textsubscript{2}O to the metal centre, which is subsequently able to hydrogen bond to both BF\textsubscript{4} counterions. An interesting feature of this Cu(II) complex is the ring-puckering at C9, which is not observed at C1; this ring maintains an almost planar geometry around the metal-centre. Ring puckering at C9 results in a narrow C10-C9-C10 bond angle (112.3(3)°) and widening of the O2-Cu-O2 angle (92.47(7)°) compared to the planar ring which exhibits an angle of 118.2(3)° around C1 and a close to right-angle connectivity for O1-Cu-O1 (89.28(7)°).

With our Cu(II) malonamide complexes, 1-Cu, 2-Cu and 3-Cu in hand we began to explore their synthetic utility as catalysts in the azide-alkyne cycloaddition reaction. We started our investigation in this area by comparing the reactivity of 1-Cu, 2-Cu and 3-Cu in the azide-alkyne cycloaddition of phenylacetylene and benzylazide (Table 1). The control experiments gave very poor yields of cycloaddition product (compare Entries 1 to 4). With 2.5 mol% loading of pre-catalyst 1-Cu we observe 87% spectroscopic yield of the cycloaddition product (8a) after one hour at RT. This is modest in comparison to other 1,3-dipolar cycloaddition reactions under neat conditions,\(^4\) where state-of-the-art examples using a Cu(I) complex as the pre-catalyst include, but are not limited to, highly active NHC systems developed by Nolan,\(^12\) Sarkar’s abnormal NHC systems\(^13\) and Díez-González’s phosphine-based pre-catalyst.\(^14\) Using 1-Cu as the pre-catalyst, the reaction has an initial turnover frequency of 167 h\(^{-1}\) for the first five minutes of the reaction, which drops to 60 h\(^{-1}\) after 25 minutes and after 40 minutes the reaction is incredibly sluggish, with little turnover observed. Reaction monitoring under an inert atmosphere in C\textsubscript{6}D\textsubscript{6} for ease of NMR studies shows that the reaction is much slower in this solvent (only 10% complete after 1 h at RT using 2.5 mol% 1-Cu). Stirring is also vital for the reaction to proceed; in an NMR tube saturation kinetics are observed when the catalyst loading is increased to 3.75 mol%.

When the benzyl adduct 2-Cu is used in neat conditions, only 55% spectroscopic yield is obtained and 43% with the aniline-derived complex, 3-Cu (Table 1, Entries 5 and 6). Pleasingly, the reaction can also be carried out on water (Entry 7) and \textit{in situ} catalyst preparation continues to give modest yield of product (Entry 8). \textit{In situ} reduction of the air-stable Cu(II) congenor, 5, using sodium ascorbate\(^15\) gives 21% 8a after 1 h at RT and 69% after 4 h at RT (Entry 9), thus offering a viable alternative to the air-sensitive handling conditions required when using the Cu(II) pre-catalysts.
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### Conclusions

In summary, we have presented initial investigations into the use of the malonamide motif as a neutral ligand in Cu(I) catalysis. The complexes prepared prove to be competent pre-catalysts for the synthesis of triazoles using azide-alkyne cycloaddition methodology. The Cu(I) complexes are readily oxidised in hydrous solvent to furnish the Cu(II) analogues in good yield. Catalysis with the Cu(II) complexes has also been extended to include preliminary studies in oligo(azide-alkyne) cycloadditions, with the pre-polymers prepared demonstrating good thermal stability and in one case a high Tg of 80.1 °C is observed. Overall, we have demonstrated that the malonamide is a good ligand for copper catalysis and hints at the potential of this ligand in other transformations, where we envisage that it could be further exploited as neutral donor or developed as even with prolonged heating at 60 °C. No reaction is observed with the internal alkyne methyl-2-butynoate, however, dimethylacetylene dicarboxylate does give good yield of the corresponding triazole after 1 h at RT. It should be noted that this transformation is in fact not a catalytic one and the cycloaddition occurs readily at RT catalyst-free (Scheme 3). In the presence of 2.5 mol% 1-Cu, 73% 9a and 61% 9b is obtained.

Finally the competency of 1-Cu at catalysing the polymerisation of diazides and diynes was explored (Table 2). The oligomeric pre-polymers are insoluble in organic solvents but DSC analysis shows that both products have good thermal stability, where 10b has a Tg of 80.1 °C and a Tm of 248.4 °C. In comparison 10a has a much reduced Tg (18.1 °C), but this is contrasted by a high Tm of 283.2 °C. Analysis by MALDI-ToF indicates both products form pre-polymer with very similar molecular weights (1,800 gmol$^{-1}$). This is the first time these oligo(triazole) structures have been reported and we are currently investigating the potential of high molecular weight polymer synthesis through vacuum condensation and subsequent post-polymerisation functionalisation.

![Scheme 3. Cycloaddition of internal alkyne dimethylacetylene dicarboxylate. Reaction conditions: azide (0.5 mmol), alkyne (0.5 mmol), RT, 1 h, N2.](image)

**Table 1. Optimisation of azide-alkyne cycloaddition.**

| Entry | Pre-catalyst | Conditions | Spec. Yield | Spec. Yield
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu-free</td>
<td>-</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cu(MeCN)BF$_4$</td>
<td>2.5 mol%</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>5 mol%</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1-Cu</td>
<td>2.5 mol%</td>
<td>87 (84)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2-Cu</td>
<td>2.5 mol%</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3-Cu</td>
<td>2.5 mol%, H$_2$O</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1-Cu</td>
<td>2.5 mol%</td>
<td>5 mol%, 1.25 mol% [Cu]</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>1 + Cu(MeCN)BF$_4$</td>
<td>5 mol%</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5 + Na ascorbate</td>
<td>2.5 mol% [Cu]</td>
<td>15, 69</td>
<td></td>
</tr>
</tbody>
</table>

General reaction conditions: benzyl azide (63 μL, 0.5 mmol), phenylacetylene (50 μL, 0.5 mmol), 1 h, RT, N$_2$. *Determined by $^1$H NMR spectroscopy using 1,2-DCE as an analytical standard (isolated yield shown in brackets). *Degasmed H$_2$O, performed under N$_2$, 4 h, RT.

Using pre-catalyst 1-Cu, a range of alkynes are tolerated in this transformation (Figure 3) including propiolates (8c and 8d), nitriles (8f), unactivated alkynes (8g) and halo-substituted alkynes (8h). The azide coupling partner can also be varied (8i, 8j, 8k and 8l) and all reactions can still be undertaken at RT with only a modest increase in reaction time necessary in some cases. Synthesis of 8c and 8k can be achieved thermally in the absence of 1-Cu; heating at 70 °C for 1 h gives 68% and 21% of 8c and 8k respectively. However, no reaction is observed in the absence of a catalyst after 3 h at RT.

![Fig. 3. Substrate scope for azide-alkyne cycloaddition reaction using complex 1-Cu. Reaction conditions: azide (0.5 mmol), alkyne (0.5 mmol), 1-Cu (2.5 mol%), 8 mg, RT, 1 h, N$_2$, isolated yield. *3h, RT. **24h, RT.](image)

We then proceeded to investigate alkenes and the potential of reacting more challenging alkynes. Unfortunately reaction of styrene with benzyl azide in the presence of 2.5 mol% 1-Cu, even at 60 °C for 24 h, shows only unreacted starting materials by $^1$H NMR. Likewise, activated alkenes such as methyl- and butylacrylate do not react even with prolonged heating at 60 °C. No reaction is observed with the internal alkyne methyl-2-butynoate, however, dimethylacetylene dicarboxylate does give good yield of the corresponding triazole after 1 h at RT. It should be noted that this transformation is in fact not a catalytic one and the cycloaddition occurs readily at RT catalyst-free (Scheme 3). In the presence of 2.5 mol% 1-Cu, 73% 9a and 61% 9b is obtained.

Finally the competency of 1-Cu at catalysing the polymerisation of diazides and diynes was explored (Table 2). The oligomeric pre-polymers are insoluble in organic solvents but DSC analysis shows that both products have good thermal stability, where 10b has a Tg of 80.1 °C and a Tm of 248.4 °C. In comparison 10a has a much reduced Tg (18.1 °C), but this is contrasted by a high Tm of 283.2 °C. Analysis by MALDI-ToF indicates both products form pre-polymer with very similar molecular weights (1,800 gmol$^{-1}$). This is the first time these oligo(triazole) structures have been reported and we are currently investigating the potential of high molecular weight polymer synthesis through vacuum condensation and subsequent post-polymerisation functionalisation.

**Table 2. Oligo(azide-alkyne) cycloaddition to give products 10a and 10b.**

<table>
<thead>
<tr>
<th>Property</th>
<th>10a</th>
<th>10b</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_w$ (gmol$^{-1}$)</td>
<td>1800</td>
<td>1800</td>
</tr>
<tr>
<td>PDI</td>
<td>1.06</td>
<td>1.07</td>
</tr>
<tr>
<td>DP</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Tg (°C)</td>
<td>18.1</td>
<td>80.1</td>
</tr>
<tr>
<td>Tm (°C)</td>
<td>283.2</td>
<td>248.4</td>
</tr>
<tr>
<td>$T_c$ (°C)</td>
<td>188.5</td>
<td>207.4</td>
</tr>
</tbody>
</table>

Measurements: *MALDI-ToF. **DSC.
an anionic ligand similar to the ubiquitous acac motif; these studies are on-going.

**Experimental**

**General considerations**

Reagents were purchased from Sigma Aldrich and used without further purification. Laboratory grade solvents were purchased from Fisher Scientific and used without further purification. NMR data was collected at 250, 300, 400 or 500 MHz on Bruker instruments in CDCl₃ at 298 K and referenced to residual protic acetone. Heated and anhydrous reactions were undertaken in Schlenk tubes or J-Young reaction tubes.

**Method for the preparation of 1.**

NEt₃ (1 mL, 7.17 mmol) followed by disopropylamine (1 mL, 7.14 mmol) each in CH₂Cl₂ (5 mL) were added dropwise to a stirred solution of malonic acid (312 mg, 3 mmol, 1 eq) and Mukaiyama’s reagent (2-chloro-N-methylpyridinium iodide, 1.61 g, 6.3 mmol, 2.1 eq) in CH₂Cl₂ (50 mL) at 0 °C. The solution was left to stir at 0 °C for 30 minutes and then allowed to warm to RT and stirred for a further 4 hours. The resulting mixture was concentrated to 160 °C and stirred for 18 hours. The same protocol can be used to prepare ligands 10a with distillation of methanol using a metal cannula with a glass paper frit, the reaction solution was filtered away from the precipitate leaving a lilac solid which was then washed with toluene (3 x 1 mL). The solid was then dried under vacuum before storing in a glovebox. See ESI for analytical data.

**General procedure for the synthesis of triazoles 8a to 8l and 9a and 9b.**

Alkyne (0.5 mmol) was added to azide (0.5 mmol) and the appropriate copper malonamide complex (2.5 mol%) in a small Schlenk tube and stirred for one hour at room temperature. The reaction was quenched with water and the product extracted into EtOAc. The extractions were filtered through a pipette fitted with glass paper and MgSO₄ before being dried under nitrogen. 1,2-DCE (0.5 mmol) was then added to optimisation reactions for the synthesis of 8a and the sample analysed by ¹H NMR prior to purification. Spectroscopic yield was obtained by integrating the CH₂ product peak relative to 1,2-DCE. Products could be isolated recrystallisation from EtOAc/pentane as necessary. See ESI for analytical data. The procedure to synthesise 9a and 9b was identical, but can be carried out in the absence of catalyst.

**General procedure for the step growth synthesis of 10a and 10b.**

Diyne (0.5 mmol) was added to diazide (0.5 mmol) and the appropriate copper malonamide complex (2.5 mol%) in a small Schlenk tube and stirred for one hour at room temperature to give low M₁ pre-polymer. The pre-polymer was washed with CH₂Cl₂ (2 x 2 mL) followed by MeOH (2 x 2 mL), before drying under a stream of N₂. Analysis by of the sample by carried out using MALDI-ToF, with the sample loaded as a solid.

**Acknowledgements**

We thank the Royal Society of Chemistry for an Undergraduate Summer Research Bursary (SJB) and the University of Bath for additional financial support.

**Notes and references**


10) Crystal data for Cu₂H₂B₂CuF₄N₂O₂: S: M = 796.00, λ = 1.54184 Å, orthorhombic, space group Cmc2₁, a = 21.1798(2), b = 12.69988(12), c = 14.89542(16) Å, U = 4006.58(7) Å³, Z = 4, Dd = 1.320 g cm⁻³, μ = 1.446 mm⁻¹, f(000) = 1684. Crystal size = 0.19 × 0.11 × 0.04 mm, unique reflections = 3909 [R(int) = 0.0583], observed reflections [λ(2θ(μ))] = 3822, data/restraints/parameters = 3909/28/274. Observed data; R₁ = 0.0410, wR₂ = 0.1043. All data; R₁ = 0.0419, wR₂ = 0.1058. Max peak/hole = 0.492 ± 0.438 e Å⁻³, respectively. CCDC 1050824.