

Investigating the use of Copper and Silver in Click Chemistry

Samuel Kilsby, E. Stubbs, Dr B Buckley, Dr S. Dann, Department of Chemistry, Loughborough University, Leicestershire, LE11 3TU

Introduction

With the concept of 'click' chemistry becoming readily used synthetically, more and more research is being undertaken in the catalysis of this expanding field. Sharpless *et al*¹ branded the ring forming reaction to form 1,2,3-triazoles, from alkynes and azides, the 'cream of the crop' of click chemistry. Meldel *et al*² found using a copper(I) catalyst significantly increased the rate of reaction, and also produced only 1 product opposed to a mixture of 2. An example of a copper catalyst used in this 'click' reaction, is copper(I) acetylide, which is synthesised in-situ between copper hydroxyacetate and an alkyne.

Aim

The aim of this research is to synthesise and test the possible catalytic properties of dual metal acetylides. This involves use of these catalysts in the 1,2,3-triazole forming reaction and monitoring any differences in yields etc. Also explored is a different way of synthesising the original copper(I) acetylide, from copper(II) acetate rather copper hydroxyacetate. Finally a safer synthesis for azides is investigated to reduce the hazardous use of sodium azide.

The Acetylide Structure

The discovery of the acetylide, and its structure, was found when using $\text{Cu}(\text{OH})_2\text{NO}_3$, gerhardtite, as a catalyst in the triazole click reaction. Upon changing the NO_3 group to an acetate, OAc, a noticeable change was visible after the new $\text{Cu}(\text{OH})_2\text{OAc}$ was used in the reaction. The newly formed yellow solid was later identified, using x-ray³, as a polymeric 'ladder' like structure. So called because the central column of copper atoms resembles a ladder. The branches coming off the copper backbone, are the alkyne 'R' group, in this case a phenyl ring. The fact that they protrude gives rise to the selectivity in the product.

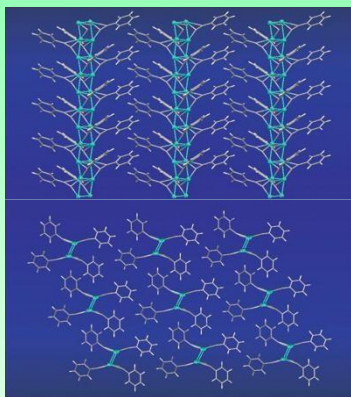


Fig 1: Phenylethynylcopper(I) structure

Triazole click reaction

The reaction to form a 1,2,3-triazole is a ring forming, or cyclisation, reaction between an alkyne and an azide. With the use of a catalyst, copper(I), the orientation of the reaction can be controlled, regiochemistry, ultimately forming only a single product opposed to a mixture of 2. Only small catalytic amounts are required to achieve vast improvements in reaction rate, and the all important regioselectivity.

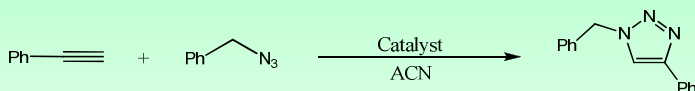


Fig 2: Click reaction between phenyl acetylene and benzyl azide

Acetylide Formation

The copper(I) acetylide, the compound in which a lot of current research surrounds, is synthesised using copper hydroxyacetate and an alkyne. The silver equivalent is created in a similar fashion, but the source of silver is silver trifluoroacetate. An interesting development is the preparation of a Cu-Ag dual-metal acetylide. This is achieved by the combination of the 2 individual syntheses. It should be noted that research into a different source of copper, copper(II) acetate, has also undertaken.

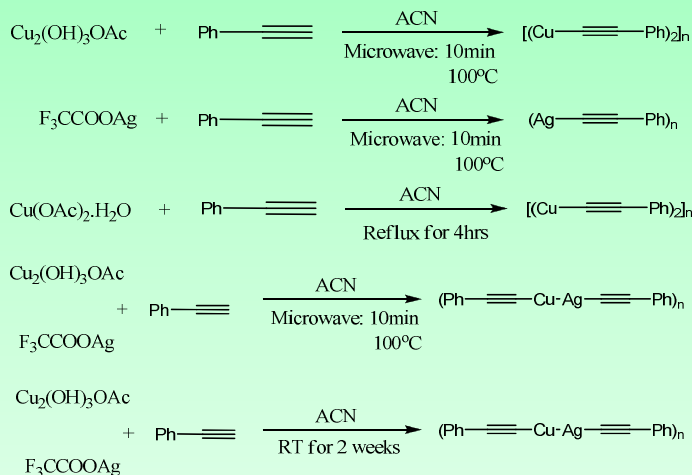


Fig 3: Syntheses for copper, silver and copper silver acetylides

Cu-Ag Acetylide reaction

As shown previously, by combining the synthesis of the individual copper and silver acetylides, a dual-metal acetylide can be formed. The exact ordering of the Cu and Ag atoms within the acetylide structure is unknown, but it is theorised that in order to catalyse the triazole click reaction, a Cu-Cu bond must be present. Therefore the degree of success in the click reaction could give an indication as to whether or not this bonding arrangement is present. This is far from being a clear indication as, due to the preparative route, some copper acetylide may be present in the Cu-Ag acetylide sample, giving rise to its apparent catalytic nature.

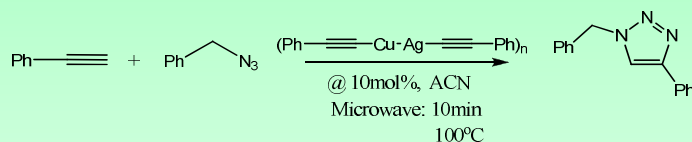


Fig 4: Use of dual metal acetylide in click reaction

As there are 2 different preparative routes to make the dual metal acetylide, microwave and room temperature, each was used in the click reaction and their yields compared. It was found that the room temperature synthesised compound had a crude yield of 68%, which purified to 58%, whereas the microwave equivalent produced 92% crude leading to 69% pure.

Azide preparation

The usual synthesis of an azide is through the substitution of a Br atom using a source of N_3^- , which is usually NaN_3 . Although these reactions achieve high yields, they involve the use of sodium azide, which is extremely hazardous. Therefore an alternate azidation reagent was considered, tetramethylguanidinium azide.

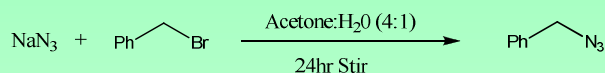


Fig 5: Original sodium azide synthesis for azides

Tetramethylguanidinium azide is initially synthesised by using sodium azide but the further use of the TMGA is safer, justifying NaN_3 's use.

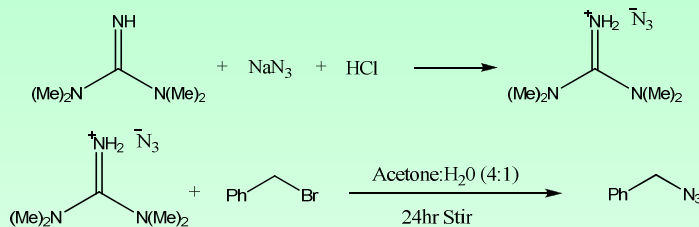


Fig 6: Synthesis and use of tetramethylguanidinium azide

Although successful in synthesising benzyl azide, the yield was lower when using TMGA in comparison with NaN_3 (Sodium azide yield >95%, TMGA yield 45%).

Conclusion

Although the project is still ongoing, the conclusions that can be drawn is that a range of acetylides can be created, with alternatives being successfully found for their synthesis. Also an alternative to the hazardous sodium azide has been found. Although lower yields are obtained, the preparation of azides has been made far safer for future use.