Copper(I)-promoted Cycloaddition Reactions of Pyridine-2-carbonitrile, 2-Pyridylacetonitrile and Isoquinoline-3-carbonitrile with Ketones[†]

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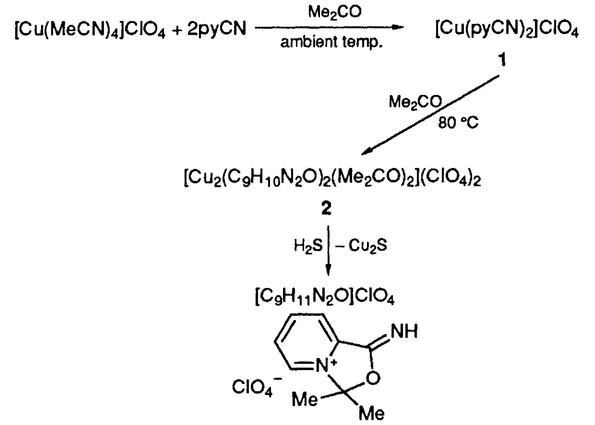
The copper-promoted cycloaddition between nitrogen heterocyclic compounds (pyridine-2-carbonitrile, 2-pyridylacetonitrile and isoquinoline-3-carbonitrile) and ketones (acetone, pentan-2-one and pentan-3-one) has been studied, and a mechanism proposed on the basis of single crystal X-ray analysis, and ^1H NMR and IR spectra of intermediate products.

Of all the transition metal organometallic reagents developed for applications in organic synthesis, organocopper complexes are by far the most extensively used and readily accepted.[1] Copper(I) ions coordinate to pyridine derivatives containing a donor group at the 2-position such as 2-vinylpyridine, pyridine-2-thiol and 1,8-naphthyridine to give the corresponding polynuclear copper(I) complexes.[2] We have found that pyridine-2-carbonitrile (pyCN) reacts with acetone in the presence of copper(I) to give the novel cyclic compound **3** (Scheme 1).

In order to elucidate the mechanism of this reaction the two intermediates, **1**[†] and **2**[†] were isolated and characterized. The IR spectrum of **1** exhibits a weak band assigned to the C≡N stretching frequency at 2341 cm^{-1} which is slightly to high frequency compared with free pyCN (2237 cm^{-1}). The ^1H NMR signals of 3-H, 4-H and 6-H of pyCN shifted downfield on coordination to copper(I) by 0.19, 0.16, 0.16 and 0.10 ppm, respectively. This indicates that the C≡N group is more strongly coordinated to copper than the pyridine group because the coordination shift of 6-H adjacent to the nitrogen atom is the smallest.

The structure of **2** (Fig. 1), determined by X-ray crystallography consists of a centrosymmetric dimer cation and perchlorate anions which are not coordinated to copper.[‡] Fig. 1 demonstrates the formation of the 1-iminido-3,3-dimethyloxazolo[3,4-*a*]pyridinium zwitterion ($C_9H_{11}N_2O$) from pyCN and acetone. This is the first example of the cycloaddition of pyCN with ketones. Each coppper atom is coordinated by the oxygen atom of the acetone molecule, and the oxygen and nitrogen atoms of the cycloadducts. Cu, O(5), O(6) and N(2′) atoms essentially lie in a plane. The angle N(2′)–Cu–O(6) [165.2(2)°] is much larger than 120°, whereas two other angles, O(5)–Cu–O(6) [105.2(2)°] and O(5)–Cu–N(2′) [89.5(2)°], are smaller than 120°. The complex is also the first case of a



Scheme 1

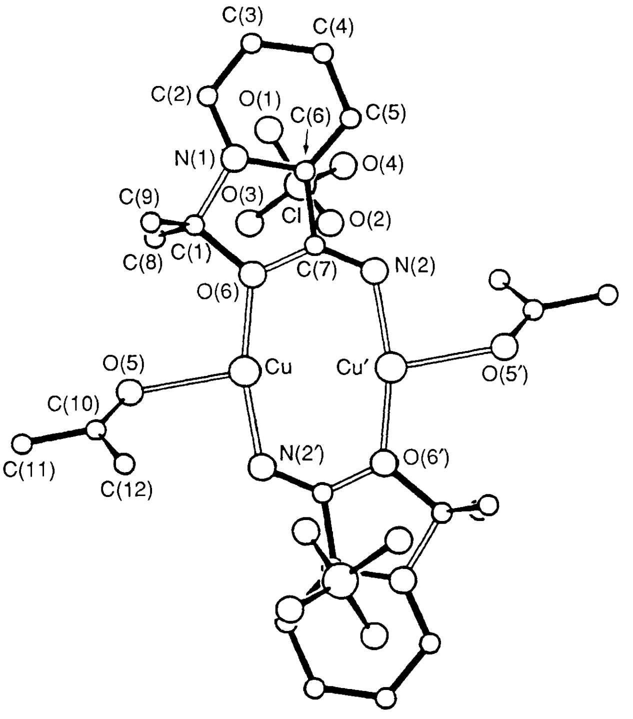


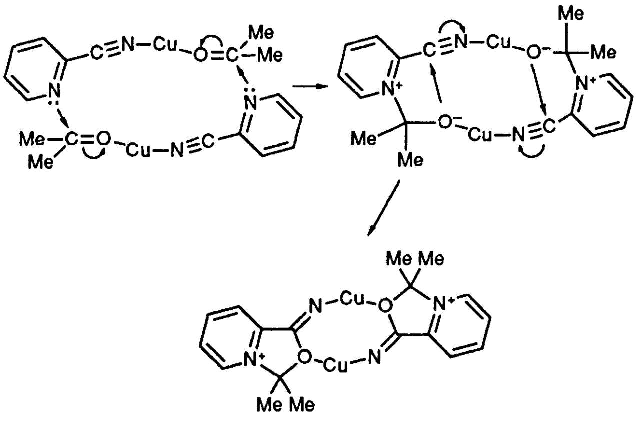
Fig. 1 Molecular structure of **2**. Selected bond distances (Å) and angles (°): Cu–N(2) 1.909(5); Cu–O(5) 2.235(2); Cu–O(6) 1.900(5); C(7)–N(2) 1.237(7); C(1)–O(6) 1.468(8); C(1)–N(2) 1.237(7); N(1)–C(1) 1.521(8); C(10)–O(5) 1.196(10); C(11)–O(5) 1.196(10); Cu · · · Cu 2.79(2); O(5)–Cu–N(2′) 89.5; O(6)–Cu–N(2′) 165.2(2); O(5)–Cu–O(6) 105.2(2).

[†] Synthesis of **1**. Tetrakis(acetonitrile)copper(I) perchlorate (13.7 mg, (42 μmol) reacts with pyridine-2-carbonitrile (84 μmol) in acetone (6 ml) for 5 min at ambient temperature under Ar to give a yellow solution which was sealed in a glass tube. After 1 day, yellowish prisms of **1** were obtained (yield 85%), which gave satisfactory elemental analyses.

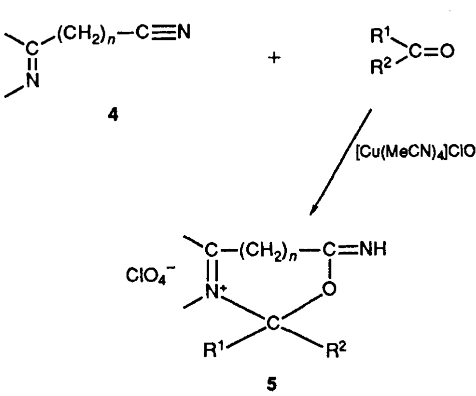
Crystal data for **1**: $C_{12}H_8O_4N_4ClCu$, M = 371.20, orthorhombic, a = 17.50(1), b = 18.96(2), c = 17.34(1) Å, V = 5755(8) $Å^3$.

Synthesis of **2**. Compound **1** (40 μmol) was added to acetone (4 ml) and the suspended solution was sealed in a glass tube under Ar. The glass tube was heated for 8 h in a water bath (80 °C) and then left at ambient temperature for 2 days. Reddish brown single crystals of **2** were obtained (yield 54%). Compound **2** can be directly synthesized from an acetone solution (4 ml) of $[Cu(MeCN)_4]ClO_4$ (40 μmol) and pyridine-2-carbonitrile (80 μmol).

[‡] *Crystal data* for **2**: $C_{24}H_{32}Cl_2Cu_2O_{12}$, M = 766.55, triclinic, space group $P\bar{1}$, $a = 10.560(3)$, $b = 10.935(6)$, $c = 7.130(3)$ Å, $\alpha = 91.63(4)$, $\beta = 92.91(3)$, $\gamma = 70.17(3)°$, $V = 773.5$ $Å^3$, $D_c = 1.594$ g cm^{-3}, $Z = 1$. Diffraction intensity data were collected for 2θ from 2 to 120° (Mo-Kα radiation; λ = 0.71073 Å) with a Rigaku AFC-6B automatic diffractometer. Of the 5061 unique reflections measured, 2380 with $F_o > 3\sigma(F_o)$ were used in the subsequent structure analysis. The structure was solved by KPPXRAY (T. Taga, T. Higashi and H. Iizuka, KPPXRAY, *Kyoto Program for X-ray Crystal Structure Analysis*, University of Kyoto, Japan, 1985) and refined by full-matrix least-squares analysis to R = 0.070, R_w = 0.070. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 2



(*n* =0,1; uncertain for *n* >1)

Scheme 3

three-coordinate T-shaped copper(I) complex with one nitrogen and two oxygen donor atoms,[3–5] and has the characteristic of a T-shaped complex[3] in that the middle bond [Cu–O(5)] distance [2.235(5) Å] is much longer than the terminal bond distances, 1.900(5) Å [Cu–O(6)] and 1.909(5) Å [Cu–N(2′)]. The Cu · · · Cu distance of 2.79(2) Å indicates the absence of a Cu · · · Cu interaction.

The IR spectrum of **2** does not exhibit a $\nu(C\equiv N)$ band, but rather a $\nu(C=N)$ band at 1660 cm^{-1}, indicating the formation of an imino group in the reaction between the C≡N group and acetone. The ^{1}H NMR spectrum of **2** could not be recorded in acetone, methanol and tetrahydrofuran because of poor solubility. Taking into account the structures of **1** and **2**, the mechanism in Scheme 2 can be proposed for the cycloaddition of pyCN with acetone.

Compound **3** was synthesized as follows. A solution of compound **1** (1.0 mmol) in acetone (80 ml) was heated under reflux for 10 h under Ar. After 1 h at ambient temperature H_2S gas was passed into the resulting brown solution. The mixture was filtered through sintered glass. The filtrate was evaporated to dryness under reduced pressure, leaving grey crystals together with a pale green oil which was removed by washing with chloroform. The residue was washed with a minimum amount of acetone to give white crystals of **3** (yield 45%).

The ^{1}H NMR spectrum of **3** exhibits five signals at δ 2.21 (s), 8.65 (t), 9.05 (t), 9.76 (t) and 9.85br which are assigned to Me, 3,5-H, 4-H, 6-H and =NH, respectively. The IR spectrum of **3** shows a pattern similar to that of **2**, and exhibits strong bands due to $\nu(C=N)$ of the imino group (1741 cm^{-1}) and $\nu(Cl–O)$ of ClO_4^- (1090 and 1146 cm^{-1}). The stretching frequency of the imino group of **3** is higher than that of **2** because of the absence of coordination to copper. These spectral data show that the structure of **3** and **2** remains unchanged after removal of the copper from **2**.

It was found that the cycloadditions of 2-pyridylacetonitrile and isoquinoline-3-carbonitrile also take place with acetone. In particular, 2-pyridylacetonitrile reacts readily with acetone even at ambient temperature.§ Furthermore, the cycloaddition reaction of pyridine-2-carbonitrile also took place with other ketones such as pentan-2-one and pentan-3-one. These cycloadditions were confirmed by disappearance of $\nu(C\equiv N)$ and the ^{1}H NMR spectrum of each product.

In conclusion the cycloaddition reactions of ketones with the nitrogen heterocyclic compounds **4** having a carbonitrile or acetonitrile group at the α-position to the nitrogen atom can be widely applied to the synthesis of compounds having the ring skeleton **5** (Scheme 3).

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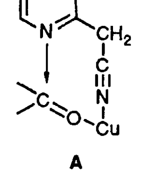
§ The intramolecular reaction between 2-pyridylacetonitrile and acetone is sterically possible because the pyridyl nitrogen of the 2-pyridylacetonitrile coordinated to copper can approach the carbonyl cation of the acetone coordinated to the same copper (structure A). It should be more advantageous for the cycloaddition reaction than the intermolecular reaction for pyCN (Scheme 2).



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