Tetrahedron 74 (2018) 2921–2924

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Insight into copper-catalyzed decarboxylative thiolation of carboxylic acids in the gas phase

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ARTICLE INFO

Article history:
Received 27 February 2018
Received in revised form
17 April 2018
Accepted 21 April 2018
Available online 22 April 2018

Keywords:
Organocopper complex
Collision-induced dissociation
Ion-molecule reaction
Decarboxylative thiolation
Bidentate nitrogen ligand

ABSTRACT

Organocopper complexes bearing bidentate nitrogen ligands were synthesized in the gas phase by electrospray ionization mass spectrometry. Gas-phase decarboylative thiolation reaction was carried out in the ion-trap analyzer by collision-induced dissociation and ion-molecule reaction. The carboxylic acids were finally converted to thioethers as a neutral loss via collision-induced dissociation. During this process, copper acetate acted as a catalyst, and the valence state change of copper was observed. Meanwhile, the mechanism of decarboxylative thiolation was examined. This reaction was also suitable for different carboxylic acids and bidentate nitrogen ligands in the gas phase.

1. Introduction

Transition-metal-catalyzed cross-coupling reaction has become a rapid and efficient method to the formation of carbon-heteroatom bond.[1,2] As sulfur-containing compounds usually have board applications in pharmaceuticals and agrochemicals,[3] the development of cross-coupling reactions to form C–S bonds have become more and more significant. However, methods and strategies for C–S bond formation are still limited compared to the ones for the construction of C–O and C–N bond.[4] Over the decades, the coupling of aryl halides with thiols or disulfides catalyzed by different transition metals have been reported.[5–9] Recently, copper-catalyzed oxdative C–H thiolation has been developed to be an attractive route to construct C–S bond.[10–12]

Decarboxylation reaction of metal carboxylates to produce organometallics[13] is a powerful strategy in synthetic applications due to widely available, inexpensive and environmental-friendly sources.[14,15] In the early years, copper-catalyzed proto-decarboxylation reaction was first reported by Shepard in 1930,[16] which was subsequently used to convert aromatic carboxylic acids to aromatic compounds.[17] However, there are still limited examples for the oxdative decarboxylative thiolation to form C–S bonds.[18–21] A Pd catalyst paired with a stoichiometric Cu or Ag salt oxidant could promote decarboxylation and C–S bond formation.[18] In 2016, Hoover and co-workers reported copper-catalyzed decarboxylative thiolation to produce diaryl sulfides using molecular oxygen as the terminal oxidant.[21] However, despite of applications and a number of key theoretical studies,[22,23] there is still a lack of detailed mechanistic insights into their reactivity and specific mode of action.[24–26]

One approach to understanding the reaction mechanisms and catalytic cycles is to study the gas-phase chemistry of organocopper complexes using multistage mass spectrometry experiments and ion-molecule reactions in ion-trapping instruments, where the additional effects of solvent and counterions are absent and the possibility for dimerization and clustering is avoided.[27] Although the solvent-free environment of gas-phase experiments does not have preparative-scale synthetic utility, it provides challenging information for mechanistic interpretation.[28–32] The formation, stability, and reactivity of organocopper complexes have been investigated by mass spectrometry in the gas phase in recent years.[33–39] We have also reported a novel strategy to synthesize

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https://doi.org/10.1016/j.tet.2018.04.073
0040-4020/

ligand-ligated Cu^+-benzyne complexes in electrospray ionization mass spectrometry (ESI-MS), and their gas-phase reactivities were carefully examined by tandem mass spectrometry.[40] The charge states changing of Cu in the reactive complexes is the most hot area of organocopper chemistry. It helps to get knowledge about how the nature of the metal center influences reactivity and mechanism, and provides support for the current exploration of roles for different charge state of Cu as catalysts in organic synthesis. Moreover, the studies of charge states of Cu intermediates are highly promising for investigating the mechanism of catalysis and rapidly screening catalytic activities.[41]

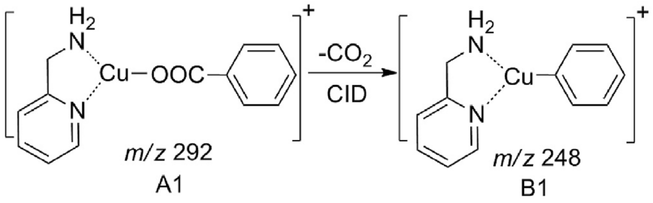
Therefore, we designed a research program to synthesize ligand-ligated organocopper complexes by ESI-MS with copper acetate, bidentate nitrogen ligands, and carboxylic acids. By collision-induced dissociation (CID) and ion-molecule reaction (I-MR) with 1,2-dimethyldisulfane, we created a novel decarboxylative thiolation reaction in the gas phase, as the valence state change of copper was also observed. Here we report the gas-phase chemistry of these organocopper complexes, and the insight of mechanistic investigation of copper-catalyzed decarboxylative thiolation of carboxylic acids.

2. Results and discussion

In this study, copper acetate, 2-(aminomethyl)pyridine (2-AMP) were used as the central transition metal and the ligand, respectively. The final ternary complex A1 is consist of benzoic acid, Cu^{2+}, and bidentate nitrogen ligand, shown in Scheme 1. The complex is easily transferred from solution to gas phase *via* ESI-MS. To achieve the decarboxylation reaction, we made CID experiment of complex A1 (the single isotope ion with ^{63}Cu was isolated and used in MS/MS and next ion-molecule reaction). The CID spectra of A1 is shown in Fig. 1a. The decarboylative product complex B1 was generated. The element compositions of A1 and B1 was confirmed by high resolution mass spectrometry (Table S1).

To further investigate the gas-phase reactivity of the organocopper complex, the ion B1 was isolated and reacted with 1,2-dimethyldisulfane. The mass spectra shown in Fig. 1b represents the mass-selected B1 with 1,2-dimethyldisulfane. When ion B1 reacts with 1,2-dimethyldisulfane, the reaction according to Fig. 1b occurs with a rate constant of $k = 1.25 \times 10^{-12}\ cm^3\ molecule^{-1}\ s^{-1}$.[42] The relative abundance and proposed compositions of each peak in Fig. 1b are given in Table 1.

As shown in Table 1, products obtained from ion-molecule reaction of ion B1 and 1,2-dimethyldisulfane were *m/z* 218, 265, and 295. The ion *m/z* 218 was formed under the elimination of phenyl group and the addition of methylthiol group. The ion *m/z* 265 was formed under the elimination of phenyl group and the addition of 1,2-dimethyldisulfane. It is remarkable that methylthiol group could addict to ion B1 to generate ion C1 (*m/z* 295), shown in Scheme 2. It means that methylthiol group transferred from 1,2-dimethyldisulfane to the Cu(II) complex B1 and oxidated B1 to generate the Cu(III) complex C1. It is a radical transfer induced oxidative addition reaction.



Scheme 1. Gas-phase synthesis of ligand-ligated organocopper complexes A1 and B1.

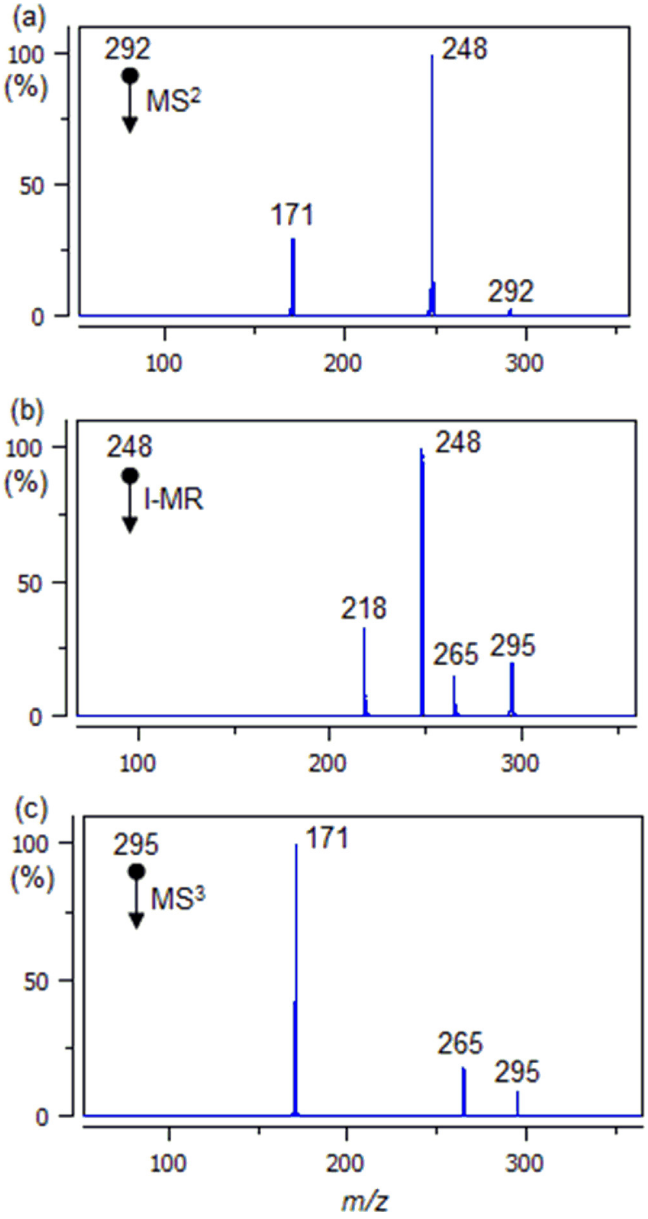


Fig. 1. (a) CID mass spectrum of ion A1 (*m/z* 292), (b) ion-molecule reaction mass spectrum of B1 (*m/z* 248) and 1,2-dimethyldisulfane, and (c) CID mass spectrum of ion B1 (*m/z* 295).

Table 1
Relative abundance and proposed compositions of each peak in Fig. 1b.

m/z	Composition	Relative abundance (%)
218	$(C_6H_8N_2)Cu(SCH_3)^+$	35.1
248	$(C_6H_8N_2)Cu(C_6H_5)^+$	100.0
265	$(C_6H_8N_2)Cu(SCH_3)_2^+$	22.7
295	$(C_6H_8N_2)Cu(C_6H_5)\ (SCH_3)^+$	23.3

After the Cu(III) complex C1 was synthesized and generated in the gas phase, the CID experiment was carried out to further study the gas-phase reactivity of C1. As shown in Fig. 1c, the CID of C1 mainly produced two peaks. One is ion D1 (*m/z* 171). As shown in Scheme 3, ion D1 was generated by the fragmentation of C1 to lose one molecule of methyl phenyl sulfane upon CID. The other peak *m/z* 265, which was also observed in Fig. 1b, was generated from the