

Consecutive nucleophilic substitution and aza Diels–Alder reaction—an efficient strategy to functionalized 2,2'-bipyridines

Dmitry N. Kozhevnikov,^{a,b,*} Valery N. Kozhevnikov,^{a,b} Anton M. Prokhorov,^a Maria M. Ustinova,^a Vladimir L. Rusinov,^a Oleg N. Chupakhin,^b Grigory G. Aleksandrov^b and Burkhard König^c

^aUral State Technical University, Mira 19, 620002 Ekaterinburg, Russia

^bInstitute of Organic Synthesis, Ural Branch of Russian Academy of Sciences, Kovalevskoy 22, 620219 Ekaterinburg, Russia

^cInstitut für Organische Chemie, Universität Regensburg, D-93040 Regensburg, Germany

Received 18 October 2005; revised 29 November 2005; accepted 1 December 2005

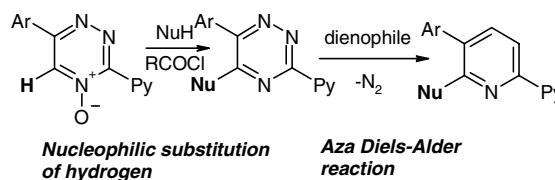
Abstract—An efficient strategy for the synthesis of functionalized 2,2'-bipyridines is reported. The strategy is based on readily available 3-pyridyl-1,2,4-triazine 4-oxides and uses a reaction sequence of nucleophilic substitution of hydrogen and aza Diels–Alder reaction.

© 2005 Elsevier Ltd. All rights reserved.

Polypyridines (i.e., 2,2'-bipyridines, 2,2':6',2''-terpyridines, phenanthrolines and their azaanalogues, etc.) continue to attract appreciable attention with practical applications ranging from catalysis¹ and photocatalysis² to analytical reagents³ and selective extracting agents in the management of nuclear wastes.⁴ Thus it still needs to develop directed synthetic routes to suitable polypyridine units and effective methods for their functionalization. In particular, introduction of an aryl substituent increases luminescence. The highest emission quantum yields (up to $\Phi_f = 0.80$) were achieved for 5-aryl-2,2'-bipyridines.⁵ Acetylene moiety is a very desirable function in polypyridines. It serves as a conjugating linkage between functional parts of molecular devices.⁶ It opens a way to polymers with special properties.⁷ Introduction of an ethynyl group improves significantly photo physical,⁸ magnetic⁹ properties, etc. The carborane cage changes electronic properties of polypyridines and their complexes.¹⁰ The *nido*-carborane moiety forms the 13-vertex metallocarboranes.¹¹ Pyridines containing thiophene residue in the α -position forms cyclometallated Pt-, Pd-, Ir-complexes with significant phosphorescent properties¹² and catalytic activity.¹³ The presence of *o*-

hydroxy- or *o*-alkoxyphenyl in α -position of a pyridine ligand gives additional *O*-chelating centres.¹⁴

Recently we reported a strategy for the synthesis of substituted 2,2'-bipyridines based on readily available pyridyl-1,2,4-triazine 4-oxides **1**.¹⁵ The strategy includes two steps (Scheme 1). The first one is an aromatic nucleophilic substitution of hydrogen—the typical reaction for 1,2,4-triazines that provides one-step introduction of various functional substituents into the heterocycles.¹⁶ The second step is a transformation of 1,2,4-triazines to pyridines with retention of all substituents via an aza Diels–Alder reaction.¹⁷ It is also noteworthy that the intermediate substituted pyridyltriazines are interesting compounds in their own right due to their application in transition metal analysis³ or in the separation



Scheme 1. Synthetic strategy towards functionalized bipyridines.

* Corresponding author. Tel.: +7 343 375 4501; fax: +7 343 374 0458; e-mail: dnk@htf.ustu.ru

of lanthanides and actinides in the management of nuclear waste.⁴

We describe here an application of the methodology for the synthesis of different α -substituted 2,2'-bipyridines. The starting materials for all transformations were 3-(2-pyridyl)-1,2,4-triazine 4-oxides (**1a–c**), obtained in three steps from available acetophenones and pyridine-2-carboxaldehyde.¹⁵

Thus, triazine **1b** underwent nucleophilic substitution of hydrogen with the lithium salt of (trimethylsilyl)acetylene yielding 5-(trimethylsilyl)ethynyl-6-tolyl-3-(2-pyridyl)-1,2,4-triazine (**2b**) in 39% yield (Scheme 2). Treatment on the reaction mixture with acetyl chloride was necessary to provide aromatization of the intermediate σ -adducts (Scheme 1). The following aza Diels–Alder reaction of **2b** with 2,5-norbornadiene as dienophile afforded the desired 6-(trimethylsilyl)ethynyl-5-tolyl-2,2'-bipyridine (**3b**) in good yield (67%). Hydrolysis of **3b** in $K_2CO_3/MeOH$ led to the formation of 6-ethynyl-5-tolyl-2,2'-bipyridine (**4**) in 80% yield (Scheme 2).¹⁸ The reaction of phenylacetylene with 1,2,4-triazine 4-oxide **1a** proceeded by the same manner. Following refluxing of 6-phenyl-5-phenylethynyl-3-(2-pyridyl)-1,2,4-triazine (**5a**) with 2,5-norbornadiene gave 5-phenyl-6-phenylethynyl-2,2'-bipyridine (**6a**) in 52% overall yield (Scheme 2).

It is noteworthy that 6-substituents on bpy often interfere with complexation. In spite of this, reaction of

ethynylbipyridine **6a** with $CuCl_2 \cdot 2H_2O$ in acetonitrile resulted in complex $[Cu(6a)Cl_2]$. The X-ray diffraction study¹⁹ confirms that the ligand **6a** behaves as bidentate ligand and that co-ordination around the Cu(II) ion is distorted tetragonal. A view of $[Cu(6a)Cl_2]$ is given in Figure 1.

The same approach was used for the synthesis of carborene-substituted bpy. Lithiation of 2-phenyl-1,2-dicarba-*closo*-dodecaborane gave the corresponding 1-lithium-1,2-dicarba-*closo*-dodecaborane and this was reacted with 1,2,4-triazine 4-oxide **1a** in THF. Treat-

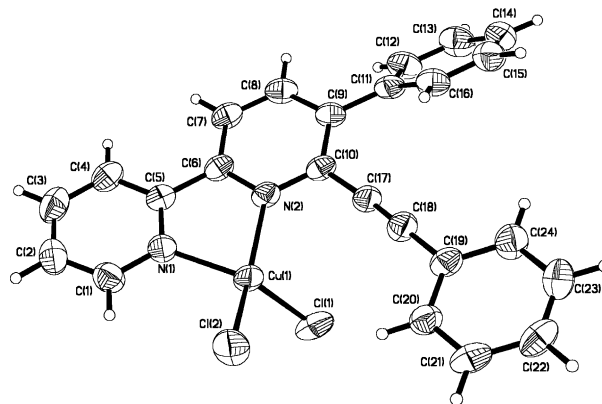
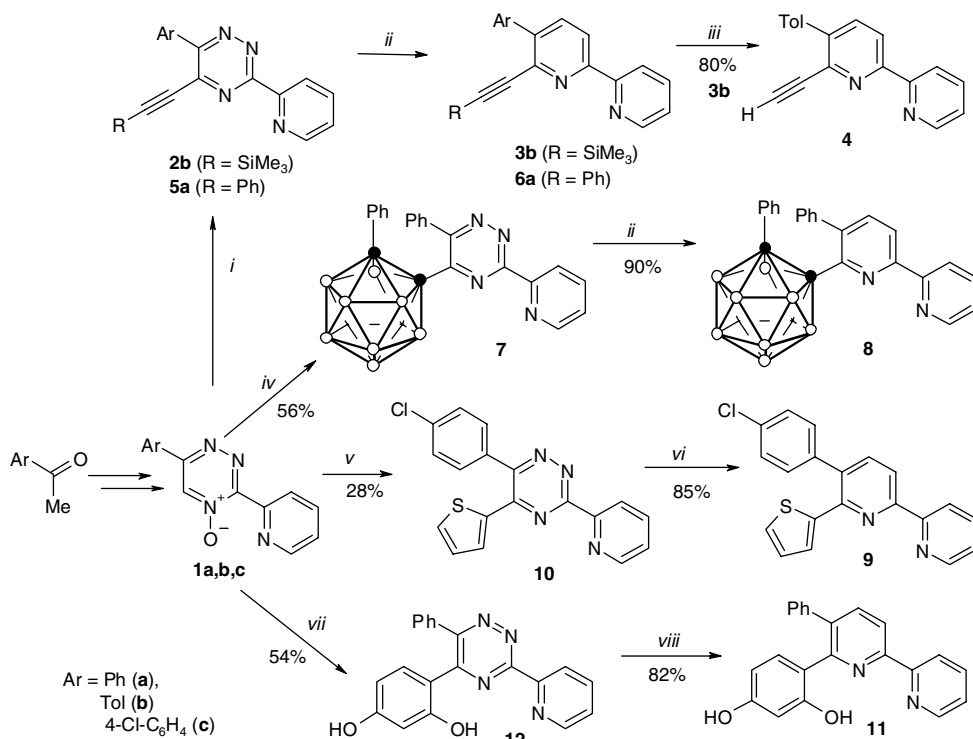


Figure 1. ORTEP view of $[Cu(6a)Cl_2]$. Selected bonds length (Å): Cu(1)–Cl(1) 2.229, Cu(1)–N(1) 2.011, Cu(1)–N(2) 1.992, C(17)–C(18) 1.196.



Scheme 2. Reagents and conditions: (i) Me_3SiCCH or $PhCCH$, BuLi, then **1a** or **1b**, $-78^\circ C$, 20 min, then $MeCOCl$; (ii) 2,5-norbornadiene, toluene, reflux, 5 h; (iii) $K_2CO_3/MeOH$, rt, 1 h; (iv) $Ph-C_2B_{10}H_{11}$, BuLi, 15 min, then **1a**, $-50^\circ C$, 20 min and then $(MeCO)_2O$; (v) 2-bromothiophene, Mg rt, 3 h, then Me_2NCOCl , 15 min; (vi) 2,5-norbornadiene, *o*-xylene, reflux, 8 h; (vii) resorcinol, TFA, rt, 14 h; (viii) 2,5-norbornadiene, *o*-xylene, reflux, 32 h.

ment of the resulting mixture with *N,N*-dimethylcarbamoyl chloride resulted in the formation of 1,2,4-triazinyl-1,2-dicarba-*closo*-dodecaborane (**7**) in 48–55% yield (Scheme 2). The electron withdrawing *closo*-carborane moiety facilitates the inverse electron demand aza Diels–Alder reaction of 1,2,4-triazines. Thus, refluxing of the triazine **7** with 2,5-norbornadiene in toluene yielded corresponding 1-(2,2'-bipyridine-3-yl)carborane **8** (Scheme 2). The structure of the latter was defined by ^1H , ^{13}C and ^{11}B NMR spectroscopy.

6-Thienyl-2,2'-bipyridine **9** was obtained through the suggested approach. Thus, the reaction of triazine **1c** with 2-bromothiophene in THF solution in the presence of magnesium (in situ formation of a Grignard reagent) and treatment of the resulting mixture with *N,N*-carbamoyl chloride gave 6-(4-chlorophenyl)-3-(2-pyridyl)-5-(2-thienyl)-1,2,4-triazine (**10**) in 35% yield. The following aza Diels–Alder reaction of **10** with 2,5-norbornadiene proceeded in refluxing *o*-xylene resulting in the desired thienyl-substituted 2,2'-bipyridine **9** in good yield (78%) (Scheme 2).

Theoretically, the thiophene residue in **9** and **10** can play a vital role in the formation of cyclometallated complexes,¹² or can act as a bulk substituent interfering with complexation. Our preliminary studies show that triazine **10** co-ordinates a metal cation by N-1 and N-2, but not N-4 due to steric hindrances by the thienyl. Thus, reaction of **10** with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in acetonitrile gave complex $[\text{Cu}_2(\mathbf{10})_2\text{Cl}_3]_2[\text{Cu}_2\text{Cl}_6]$. In accordance with X-ray crystallographic study,²⁰ two Cu(II) atoms in the complex cation $[\text{Cu}_2(\mathbf{10})_2\text{Cl}_3]$ (Fig. 2) have distorted square pyramidal co-ordination: chelating nitrogen atoms of the pyridyl and the 1,2,4-triazine (N-2 atom) moieties of the first ligand **10**, and two chlorine atoms (one is bridging between Cu(II) atoms) are in the base, and N-1 nitrogen of the 1,2,4-triazine moiety of the second ligand **10** is in the vertex. The heterocyclic part of every ligand is planar, the chlorophenyl is distorted due to the bulk thienyl (torsion angles are 67.2° and 88.1°). At the same time, the heterocyclic fragment

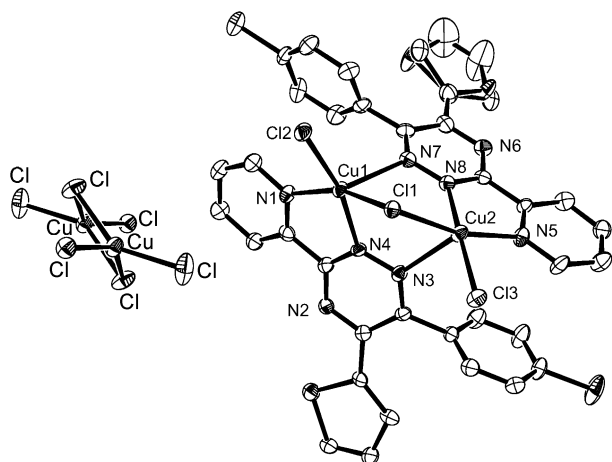


Figure 2. ORTEP view of $[\text{Cu}_2(\mathbf{10})_2\text{Cl}_3][\text{Cu}_2\text{Cl}_6]$. Selected bonds length (Å): Cu(1)–Cl(1) 2.279, Cu(1)–N(1) 2.014, Cu(1)–N(4) 2.028, Cu(2)–N(3) 2.438.

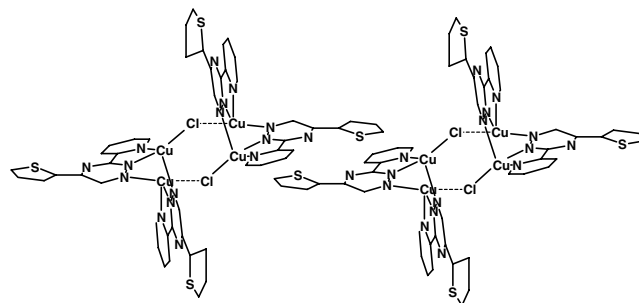


Figure 3. Formation of chains of $[\text{Cu}_2(\mathbf{10})_2\text{Cl}_3]^+$ along the axis *c* (hydrogens, chlorophenyls and non-bridging chlorines are omitted).

of the first ligand and the aryl substituent of the second ligand are almost co-planar (distances between the planes are 3.5 and 3.6 Å) that causes π – π -interaction between both ligands and their orthogonal orientation. Thus, the thienyl in **10** defines regioselectivity of the co-ordination (N-1 and N-2 instead of N-4), and geometry of the final complex as well.

In the crystal cell, the cations $[\text{Cu}_2(\mathbf{10})_2\text{Cl}_3]^+$ form dimmers due to an interaction of one of the non-bridging Cl atoms with one of the Cu(II) atom of the second cation (distance Cu(1)–Cl(3A) is 2.961 Å). These dimmers form chains along the *c* axis due to π -stacking between thienyl-1,2,4-triazine moieties (distance between the heterocyclic planes is 3.6 Å) (Fig. 3).

The complex anions $[\text{Cu}_2\text{Cl}_6]^{2-}$ lie in corners of the crystal cell. In these binuclear anions $[\text{Cu}_2\text{Cl}_6]^{2-}$, two Cu(II) atoms are bridged through two chlorine atoms; twisted tetragonal co-ordination of each Cu(II) is completed with two additional chlorine atoms. Distance between Cu(II) atoms in $[\text{Cu}_2\text{Cl}_6]^{2-}$ is 3.389 Å (Fig. 2).

6-(2,4-Dihydroxyphenyl)-2,2'-bipyridine (**11**) was obtained through modified route. Triazine **1a** reacted with the neutral nucleophile—resorcinol in trifluoroacetic acid to give the product of nucleophilic substitution of hydrogen—hydroxyphenyltriazine **12** in 65% yield. The next step—the aza Diels–Alder reaction proceeded after 32 h refluxing of **12** in *o*-xylene to afford hydroxyphenylbipyridine **11** (Scheme 2). Significantly low rate of the reaction is due to electron donating properties of the resorcinol moiety that deactivates the 1,2,4-triazine as diene in the inverse electron demand Diels–Alder reaction.

In conclusion, functionalized bi- and terpyridines are available from 1,2,4-triazine 4-oxides. The sequence of introduction of additional substituents by nucleophilic substitution of hydrogen and transformation of the 1,2,4-triazines to pyridines by aza Diels–Alder reaction gives access to various substituted 2,2'-bipyridines. Each step of the synthesis allows diversification, if desired. The method is limited by 5-(hetero)aryl bipys, however it could be considered as a strong feature because of lack of other convenient methods for the synthesis of such compounds and good luminescent properties expected for them. The second limitation is nucleophiles with

strong electron donating properties are expected to prevent the transformation of 1,2,4-triazines to pyridines.

Acknowledgement

The authors thank the Russian Foundation for Basic Researches (grant no. 05-03-32134) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2005.12.006](https://doi.org/10.1016/j.tetlet.2005.12.006).

References and notes

- Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129–3170.
- Ziessel, R. In *Photosensitization and Photocatalysis Using Inorganic and Organic Compounds*; Kalyanasundaram, K., Grätzel, M., Eds.; Kluwer Academic Publishers: Dordrecht, 1993; pp 217–246.
- Croot, P. L.; Hunter, K. A. *Anal. Chim. Acta* **2000**, *406*, 289–295.
- Kolarik, Z.; Mullich, U.; Gassner, F. *Solv. Extr. Ion Exch.* **1999**, *17*, 23–32.
- Loren, J. C.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 754–757.
- (a) Ziessel, R.; Grossshenny, V.; Hissler, M.; Stroh, C. *Inorg. Chem.* **2004**, *43*, 4262–4271; (b) Altuna-Urquijo, M.; Stanforth, S. P.; Tarbit, B. *Tetrahedron Lett.* **2005**, *46*, 6111–6113.
- Goeb, S.; De Nicola, A.; Ziessel, R. *J. Org. Chem.* **2005**, *70*, 1518–1529.
- Birckner, E.; Grummt, U.-W.; Goller, A. H.; Pautzsch, T.; Egbe, D. A. M.; Al-Higari, M.; Klemm, E. *J. Phys. Chem. A* **2001**, *105*, 10307–10315.
- Ziessel, R.; El-Ghayoury, A. *Synthesis* **2000**, *14*, 2137–2140.
- Armstrong, D.; Constable, E. C.; Housecroft, C. E.; Neuburger, M.; Zehnder, M. *J. Organomet. Chem.* **1998**, *550*, 193–206.
- Hodson, B. E.; McGrath, T. D.; Gordon, F.; Stone, A. *Organometallics* **2005**, *24*, 3386–3394.
- (a) Balashev, K. P.; Puzyk, M. V.; Kotlyar, V. S.; Kulikova, M. V. *Coord. Chem. Rev.* **1997**, *159*, 109–120; (b) Yersin, H.; Donges, D.; Humbs, W.; Strasser, J.; Sitters, R.; Glasbeek, M. *Inorg. Chem.* **2002**, *41*, 4915–4922; (c) Brooks, J.; Babayan, Y.; Lamansky, S.; Djurovich, P. I.; Tsyba, I.; Bau, R.; Thompson, M. E. *Inorg. Chem.* **2002**, *41*, 3055–3066.
- Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051.
- (a) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219–3222; (b) Bardwell, D. A.; Jeffery, J. C.; Ward, M. D. *Polyhedron* **1996**, *15*, 2019–2022.
- Kozhevnikov, V. N.; Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. N.; Zabel, M.; König, B. *J. Org. Chem.* **2003**, *68*, 2882–2888.
- Kozhevnikov, D. N.; Rusinov, V. L.; Chupakhin, O. N. *Adv. Heterocycl. Chem.* Katritzky, A. R., Ed. **2002**, *82*, 261–305, and references cited therein.
- (a) Pabst, G. R.; Pfüller, O. C.; Sauer, J. *Tetrahedron* **1999**, *55*, 8045–8064; (b) Branowska, D.; Rykowski, A.; Wysocki, W. *Tetrahedron Lett.* **2005**, *46*, 6223–6226; (c) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Shabunina, O. V.; Rusinov, V. L.; Chupakhin, O. N. *Tetrahedron Lett.* **2005**, *46*, 1791–1793.
- Ethynyl-2,2'-bipyridine (4)*. BuLi (2 mL of 2.5 M solution in hexane, 5 mmol) was added under argon to a solution of (trimethylsilyl)acetylene (0.705 mL, 5 mmol) in dry THF (30 mL). The resulting solution was added dropwise to a suspension of 1,2,4-triazine 4-oxide **1b** (1.32 g, 5 mmol) in THF (30 mL) at -78°C . The mixture was stirred for 20 min, and acetyl chloride (0.356 mL, 5 mmol) was added. The solvent was removed under reduced pressure and the residue was treated with toluene (20 mL). The toluene solution was separated from solids, and the solvent was removed. The residue was treated with acetonitrile (1 mL), yellow crystals were filtered off and recrystallized from acetonitrile to give **2b** (670 mg, 39%). The ethynyltriazine **2b** (344 mg, 1 mmol) and 2,5-norbornadiene (0.54 mL, 5 mmol) were dissolved in toluene (20 mL) and heated at reflux for 5 h. The solvent was removed under reduced pressure, and the residue was treated with acetonitrile. Resulting solids were filtered off to yield **3** (230 mg, 67%). To remove the trimethylsilyl group bipyridine **3b** (171 mg, 0.5 mmol) was dissolved in MeOH (20 mL), K_2CO_3 (350 mg, 2.5 mmol) was added, and the mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure and the residue extracted with hot hexane. Evaporation of hexane gave the desired ethynylbipyridine **4** (108 mg, 80%).
- Complex [Cu(6a)Cl₂]*. Solution of the ligand **6a** (50 mg, 0.15 mmol) in acetonitrile (30 mL) was added to a solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (26 mg, 0.15 mmol) in acetonitrile (30 mL). The resulting dark brown solution was kept for 3 days at rt. Dark-green crystals that appeared were filtered off. *Crystal data for [Cu(6a)Cl₂]*: $\text{C}_{24}\text{H}_{16}\text{N}_2\text{Cl}_2\text{Cu}$, $FW = 466.83$, triclinic, $a = 9.114(2)$, $b = 10.008(2)$, $c = 12.397(3)$ Å, $\alpha = 112.34(3)^{\circ}$, $\beta = 102.08(3)^{\circ}$, $\gamma = 92.20(3)$, $V = 1014.0(4)$ Å³, $T = 293(2)$ K, space group $P\bar{1}$, $Z = 2$, 4688 reflections measured, 4631 unique ($R_{\text{int}} = 0.0156$), which were used in all calculations. $R1 = 0.0336$, $wR2 = 0.0768$.
- Complex [Cu₂(10)₂Cl₃]₂[Cu₂Cl₆]*. Solution of the ligand **10** (53 mg, 0.15 mmol) in acetonitrile (30 mL) was added to a solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (26 mg, 0.15 mmol) in acetonitrile (30 mL). The resulting dark brown solution was kept for 3 days at rt. Dark-green crystals that appeared were filtered off. *Crystal data for [Cu₂(10)₂Cl₃]₂[Cu₂Cl₆]*: $\text{C}_{36}\text{H}_{22}\text{Cl}_8\text{Cu}_3\text{N}_8\text{S}_2$, $FW = 1104.96$, triclinic, $a = 10.7873(16)$, $b = 12.9549(19)$, $c = 15.241(2)$ Å, $\alpha = 69.217(4)^{\circ}$, $\beta = 85.042(4)^{\circ}$, $\gamma = 86.426(4)$, $V = 1982.7(5)$ Å³, $T = 120(2)$ K, space group $P\bar{1}$, $Z = 2$, 6693 reflections measured, 5233 unique ($R_{\text{int}} = 0.0557$), which were used in all calculations. $R1 = 0.0810$, $wR2 = 0.1698$.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 290967 and 290968. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].