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New family of polydentate tetrazole-pyrazoline ligands prepared by the azido-Ugi reaction

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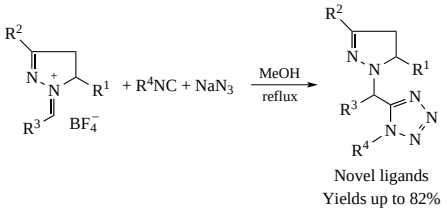
A new family of ligands containing fragments of tetrazole and pyrazoline was prepared in one step by the efficient azido-Ugi reaction of *N*-(arylidene)pyrazolinium salts with isocyanides and sodium azide in up to 86% yield. The utility of the ligands was demonstrated by the synthesis of coordination complexes with Cu and Pd.

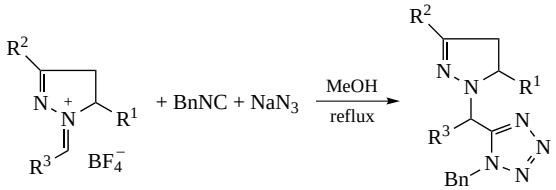


Keywords: tetrazoles, pyrazolines, azido-Ugi reaction, ligands, isocyanides, palladium complexes, copper complexes.

Tetrazole is one of the most important type of heterocycles whose derivatives are widely used in medicine, drug discovery and various branches of industry.[1] For example, FDA approved 23 drugs containing tetrazole fragment in the structure. These compounds exhibit antimicrobial, antiviral, antiallergic, cytostatic, hypertensive, nootropic and other biological activities[2] (for the structures, see Online Supplementary Materials, Figure S1). NH-Tetrazole is a bioisostere of carboxylic group whereas 1,5-disubstituted tetrazoles behave as bioisosteres of *cis*-amide fragment in peptidomimetics. A lot of methods to construct tetrazole ring are known, however multicomponent reactions are superb to create structures of complex organization.[3]

The azido-Ugi reaction is one of the most efficient approaches to construct 1,5-disubstituted tetrazoles.[4,5] This study is devoted to synthesis of a new family of ligands derived from pyrazoline-tetrazole conjugates prepared using pyrazolinium salts as reactants for the azido-Ugi reaction. The starting pyrazolinium salts **1a–i** are easily prepared by the reaction of NH-pyrazolines with aldehydes in the presence of HBF_4.[6] First, an optimization of the reaction conditions was performed using benzyl isocyanide as a model reactant. We have found that the reaction of pyrazolinium salt **1a**, benzyl isocyanide and sodium azide (1.2 equiv.) in methanol provided target product **2a** in a good yield (Scheme 1). In other solvents (CH_2Cl_2, Pr^iOH, BuOH, Bu^tOH) or their mixtures with water, product **2a** was obtained in lower yields or even was not formed at all. When more acidic trifluoroethanol was applied as a solvent, *N*-benzyltetrazole was mostly formed due to addition of hydrazoic acid at benzyl isocyanide. Therefore, methanol should be the solvent of choice.

Next, scope of the reaction was investigated with variation of substituents in the structure of starting salts **1**. The reaction turned to be very general to construct *N*-benzyl substituted tetrazole-pyrazoline derivatives **2a–i** bearing both aliphatic and aromatic substituents in the pyrazoline ring (see Scheme 1). No restrictions were found concerning the substituent R^3. However,



a $R^1 = R^3 = Ph$, $R^2 = Me$, 56%
b $R^1 = H$, $R^2 = Ph$, $R^3 = 4\text{-}MeC_6H_4$, 70%
c $R^1 = H$, $R^2 = Ph$, $R^3 = 4\text{-}MeOC_6H_4$, 72%
d $R^1 = H$, $R^2 = Ph$, $R^3 = 4\text{-}ClC_6H_4$, 58%
e $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = 2\text{-}MeC_6H_4$, 62%
f $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = 2\text{-}MeOC_6H_4$, 58%
g $R^1 = H$, $R^2 = Ph$, $R^3 = 2\text{-furyl}$, 77%
h $R^1 = H$, $R^2 = Ph$, $R^3 = 1,3\text{-dimethylpyrazol-4-yl}$, 86%
i $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = 1\text{-ethyl-4-methylpyrazol-3-yl}$, 82%

Scheme 1

slightly lower yields were observed for *ortho*-substituted products due to their steric hindrance. Moreover, some products **2g–i** having additional furan or pyrazole ring can be prepared in high yield by this procedure.

Structure of all products was unambiguously confirmed by NMR, IR and mass spectra. In ^1H NMR spectra, all the products have characteristic signal of methine carbon at 5.62–6.12 ppm. In addition, X-ray data were obtained for compounds **2a**,**c**,**f** (Figure 1).[†]

[†] *Crystal data for* **2a**. A colorless needle-like crystal, $C_{25}H_{24}N_6$ (M_r = 408.50), monoclinic, space group $P2_1/c$, T = 100 K, a = 14.2920(14), b = 16.2261(14) and c = 18.629(2) Å, β = 100.385(6)°, V = 4249.4(7) Å^3, Z = 8, d_{calc} = 1.277 g cm^{-3}, $F(000)$ = 1728, μ = 0.099 mm^{-1}. 53420 reflections (9631 independent reflections, R_{int} = 0.045) were measured and used in the refinement. The refinement converged to R_1 = 0.044 for 7849 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.125 for all independent reflections, S = 1.042.

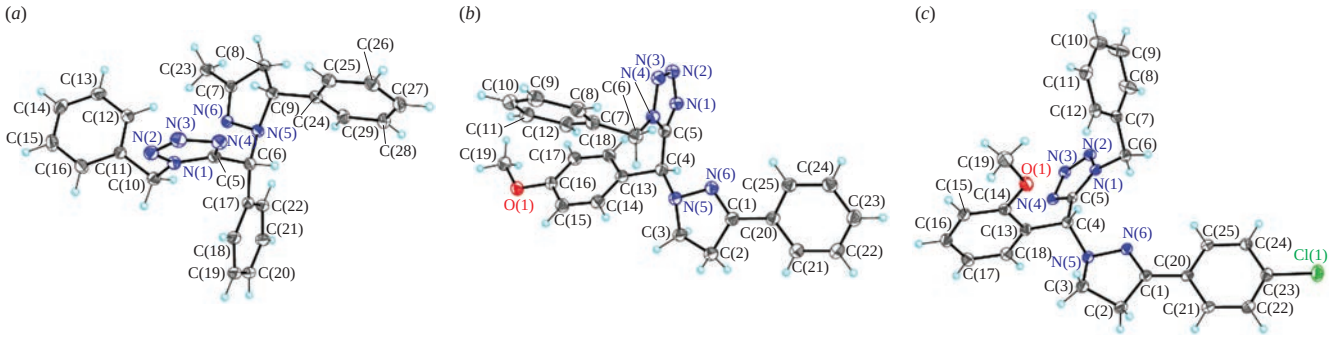
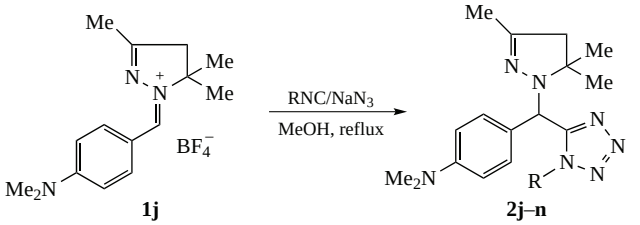


Figure 1 Molecular structures of compounds (*a*) **2a** (one of the two crystallographically independent molecules is given), (*b*) **2c** and (*c*) **2f**.

Compound **2a** crystallizes in the monoclinic space group $P2_1/c$ with two crystallographically independent molecules in the unit cell. These molecules have very similar geometries distinguishing only by rotation of the benzyl substituent relative to the tetrazole ring (see Online Supplementary Materials, Figure S1). The molecules of **2a**, **2c** and **2f** adopt a propeller-like mutual conformation of the three cycles of the central (1*H*-tetrazol-5-yl)(*N*-pyrazolinyl)(phenyl)methane fragment. The interplane angles between tetrazole (*A*), pyrazoline basal (*B*, N–N=C–C of the envelope) and phenyl (*C*) planes are equal to 89.55(5) and 88.87(5)° (*A*/*B*), 67.83(4) and 72.25(4)° (*A*/*C*) and 74.06(5) and 69.47(5)° (*B*/*C*) for the two crystallographically independent molecules of **2a**, 89.22(5)° (*A*/*B*), 84.32(5)° (*A*/*C*) and 50.17(6)° (*B*/*C*) for **2c** and 42.07(6)° (*A*/*B*), 73.08(6)° (*A*/*C*) and 81.51(7)° (*B*/*C*) for **2f**. The benzyl substituent in all compounds is practically perpendicular to both the tetrazole ring and the aryl substituent at the central tertiary carbon atom. The aryl substituent of the pyrazoline ring both in **2c** and **2f** is slightly twisted by 13.74(8) and 4.24(10)°, respectively, relative to the pyrazoline basal plane. The phenyl substituent of the pyrazoline ring in **2a** occupies a more sterically preferable equatorial position. The methoxy group in **2c** and **2f** is almost coplanar to the parent phenyl ring. It is important to point out the presence of the distant inductive effect in **2f**, which results in the elongation of the ordinary C_{tert}–$N_{pyrazoline}$ bond of 1.4755(17) Å as compared to those of 1.4579(14) and 1.4576(16) Å in **2a** and **2c**, respectively. The other bond distances within the (1*H*-tetrazol-5-yl)(*N*-pyrazolinyl)(phenyl)methane fragments of all compounds **2a**, **2c** and **2f** have very close values. Compounds **2a**, **2c** and **2f** are chiral and possess two (**2a**) or one (**2c** and **2f**) asymmetric centers. The crystals of **2a**, **2c** and **2f** are racemic; the relative configuration of the asymmetric centers in **2a** is *rac*-*RS*,*RS*.

Next, scope of isocyanides was investigated using trimethyl-substituted salt **1b**. Again, no restrictions were found and the corresponding products **2j**–**n** were prepared in good yield using benzyl, allyl and *tert*-butyl isocyanides as well as ester- and pyridine-containing substrates (Scheme 2).

Having in hand a new family of polydentate ligands, we performed some preliminary experiments to prepare metal complexes using **2c** as a model. It should be pointed out that pyrazoline ring has two nitrogen atoms while tetrazole ring bears four nitrogen atoms as potent coordination sites to form complexes with metal cations. To our delight, nice complexes with $PdCl_2$ and $CuCl_2$ were obtained, however, these complexes had different nature. The reaction with $PdCl_2$ resulted in a 1 : 1 complex whereas more sophisticated structure was obtained for complex with $CuCl_2$. Complex [**2c**·$PdCl_2$] is mononuclear with a four-coordinated palladium(II) center surrounded by one imino (tetrazole) and one amino (pyrazoline) nitrogen atoms of the neutral organic ligand **2c** and two chlorine atoms [(Figure 2(*a*)].‡ The geometry around the palladium atom is a distorted planar-



j R = Bn, 65%
k R = $CH_2CH{=}CH_2$, 59%
l R = Bu^t, 72%
m R = $(CH_2)_2CO_2Me$, 64%
n R = 2-(4-pyridyl)ethyl, 75%

Scheme 2

Crystal data for **2c**. A colorless prismatic crystal, $C_{25}H_{24}N_6O$ (M = 424.50), monoclinic, space group $P2_1/c$, T = 100 K, a = 9.9231(10), b = 8.2490(8) and c = 26.045(3) Å, β = 98.333(11)°, V = 2109.4(4) Å^3, Z = 4, d_{calc} = 1.337 g cm^{-3}, $F(000)$ = 896, μ = 0.108 mm^{-1}. 32925 reflections (4810 independent reflections, R_{int} = 0.042) were measured and used in the refinement. The refinement converged to R_1 = 0.042 for 4109 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.114 for all independent reflections, S = 1.047.

Crystal data for **2f**. A colorless prismatic crystal, $C_{25}H_{23}N_6OCl$ (M = 458.94), monoclinic, space group $P2_1/n$, T = 100 K, a = 13.196(3), b = 11.954(2) and c = 15.379(3) Å, β = 109.65(3)°, V = 2284.7(9) Å^3, Z = 4, d_{calc} = 1.334 g cm^{-3}, $F(000)$ = 960, μ = 0.261 mm^{-1}. 24013 reflections (5032 independent reflections, R_{int} = 0.055) were measured and used in the refinement. The refinement converged to R_1 = 0.044 for 4552 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.116 for all independent reflections, S = 1.020. X-ray diffraction data were collected on the 'Belok' beamline [λ = 0.79373 Å (**2a**,**f**) and 0.79272 Å (**2c**)] of the National Research Center 'Kurchatov Institute' (Moscow, Russian Federation) using a Rayonix SX165 CCD detector and corrected for absorption using the *Scala* program.[7] The data were indexed, integrated and scaled using the utility *iMOSFLM* in CCP4 program.[8] The structures were determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5U_{eq}(C) for the methyl groups and 1.2U_{eq}(C) for the other groups]. The calculations were carried out using the SHELXTL program.[9]

CCDC 2020213 (**2a**), 2020214 (**2c**) and 2020215 (**2f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

‡ *Crystal data for* [**2c**·$PdCl_2$]. An orange prismatic crystal, $C_{25}H_{24}N_6OCl_2Pd$ (M_r = 601.80), monoclinic, space group Cc, T = 100 K, a = 8.8750(18), b = 20.006(4) and c = 14.404(3) Å, β = 103.17(3)°, V = 2490.2(9) Å^3, Z = 4, d_{calc} = 1.605 g cm^{-3}, $F(000)$ = 1216, μ = 1.319 mm^{-1}. 13726 reflections (5550 independent reflections, R_{int} = 0.044) were measured and used in the refinement. The refinement converged to R_1 = 0.031 for 5463 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.083 for all independent reflections, S = 1.077.

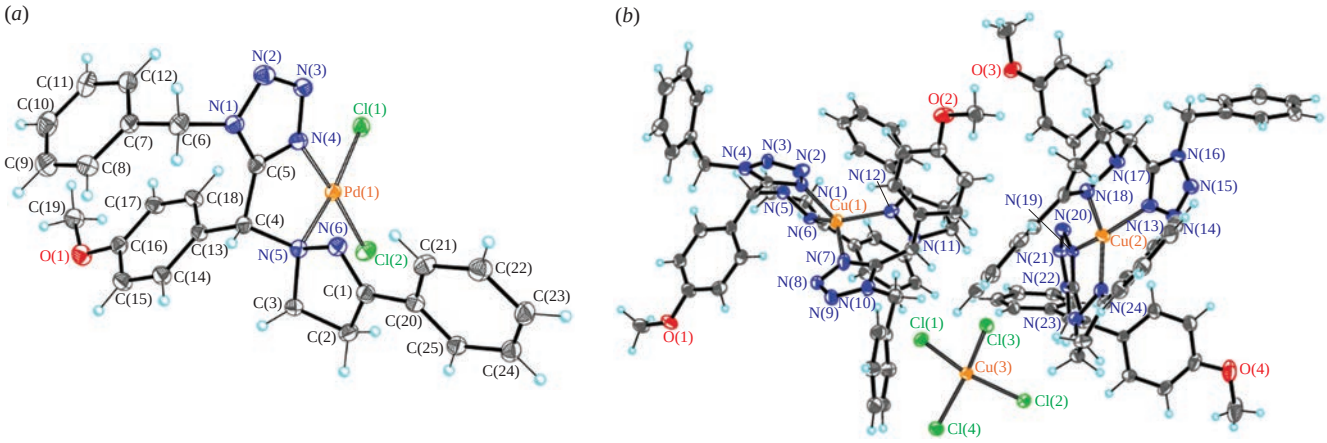


Figure 2 Molecular structures of complexes (*a*) [**2c**·$PdCl_2$] and (*b*) [**2c**·0.25Cu_3Cl_4].

square with *cis* N → Pd ← N and Cl–Pd–Cl angles. The ligand **2c** is bidentate and forms five-membered chelate cycle having an envelope conformation. In the structure of the ligand **2c** under complexation, mainly, (i) the C=N [1.333(7) Å] and C–N [1.326(6) Å] bond distances within the tetrazole ring are equalized, (ii) the N–N bond distance within the pyrazoline ring increases to 1.461(5) Å, (iii) the $C_{tetrazole}$–C_{tert}–$N_{pyrazoline}$ bond angle decreases to 103.2(3)°, and (iv) the benzyl and (*p*-methoxy)-phenyl planes adopt the parallel mutual conformation. Unexpectedly, complex [**2c**·0.25Cu_3Cl_4] represents a mixed-valence Cu^I/Cu^{II} salt containing the two tetracoordinate mononuclear Cu^IL_2 (L is ligand **2c**) monocations and the $Cu^{II}Cl_4$ dianion [Figure 2(*b*)]. In the cations, the copper(I) atom is a four-coordinated in the distorted tetrahedral fashion. Unlike the [**2c**·$PdCl_2$] complex, ligand **2c** in the [**2c**·0.25Cu_3Cl_4] complex forms a six-membered chelate ring in the distorted boat conformation by two imino-nitrogen atoms of the tetrazole and pyrazoline rings. It should be noted that, under complexation of [**2c**·0.25Cu_3Cl_4], the change in the bond lengths within the tetrazole rings is similar to those in complex [**2c**·$PdCl_2$], but the bond lengths within the pyrazoline rings remain practically unchanged in comparison with those in the free ligand **2c**. Moreover, the intrachelate $C_{tetrazole}$–C_{tert}–$N_{pyrazoline}$ bond angle also does not change. The benzyl and (*p*-methoxy)phenyl substituents in the cations of [**2c**·0.25Cu_3Cl_4] are turned away from each other. The $Cu^{II}Cl_4$ dianion has typical tetrahedral structure. In the crystal, the cations and anions are bound to each other *via* the C–H···Cl hydrogen bonding interactions (see Online Supplementary Materials, Table S1).

In conclusion, a new family of polydentate ligands was obtained employing the azido-Ugi reaction of pyrazolinium salts. Successful examples to form complexes with metals were demonstrated using palladium(II) and copper(II) chlorides.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.01.014.

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Crystal data for [**2c**·0.25Cu_3Cl_4]. A yellow prismatic crystal $C_{100}H_{96}N_{24}O_4Cl_4Cu_3$ (M = 2030.46), monoclinic, space group *Cc*, T = 100 K, a = 21.276(4), b = 21.381(4) and c = 20.738(4) Å, β = 102.603(17)°, V = 9207(3) Å^3, Z = 4, d_{calc} = 1.465 g cm^{-3}, $F(000)$ = 4204, μ = 1.168 mm^{-1}. 91604 reflections (18223 independent reflections, R_{int} = 0.116) were measured and used in the refinement. The refinement converged to R_1 = 0.082 for 15307 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.217 for all independent reflections, S = 1.055. X-ray diffraction data were collected on the 'Belok' beamline (λ = 0.79272 Å for **2c**·$PdCl_2$ and 0.79373 Å for **2c**·0.25Cu_3Cl_4), for the rest see Footnote†.

CCDC 2020216 (**2c**·$PdCl_2$) and 2020217 (**2c**·0.25Cu_3Cl_4) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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