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Mendeleev Commun., 2021, **31**, 176–178

Mendeleev Communications

3-Amino-1,2,4-triazolium salts as NHC-proligands: synthesis and postmodification of a new type of amino-functionalized Pd/NHC complexes

Dmitry V. Pasyukov,[a] Andrey Yu. Chernenko,[a] Konstantin E. Shepelenko,[a] Vadim V. Kutyrev,[a] Victor N. Khrustalev[b,c] and Victor M. Chernyshev*[a]

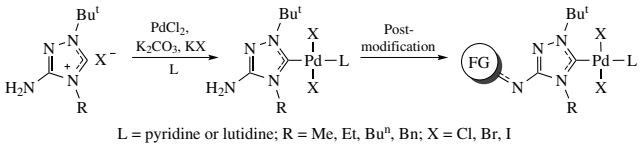
[a] *Platov South Russian State Polytechnic University (NPI), 346428 Novocherkassk, Russian Federation. E-mail: chern13@yandex.ru*

[b] *Peoples Friendship University of Russia (RUDN University), 117198 Moscow, Russian Federation*

[c] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2021.03.010

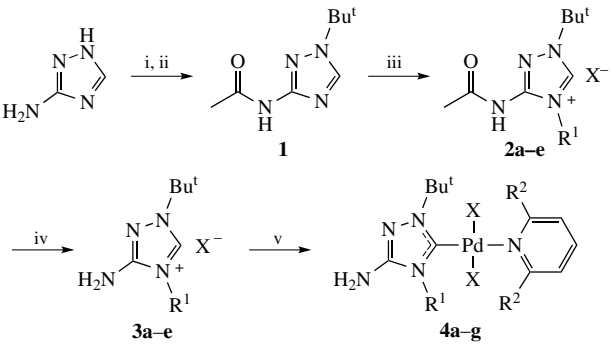
Palladium complexes with N-heterocyclic carbene ligands of a new type containing free NH_2 group were obtained by direct palladation of 3-amino-1,4-dialkyl-1,2,4-triazolium salts. These amino-functionalized complexes were found to be a versatile platform for postmodification *via* reactions of the NH_2 group with acyl and sulfonyl chlorides.



Keywords: 3-amino-1,2,4-triazole, N-heterocyclic carbenes, palladium complexes, postmodification, catalysis.

Complexes of palladium with N-heterocyclic carbenes (Pd/NHC) have received ubiquitous application in homogeneous catalysis.[1,2] NHC ligands have a number of important advantages over phosphines like lower toxicity, relative easiness of preparation, high variability of electronic and steric parameters, strong sigma electron-donation to the metal and enhanced stability of the metal–NHC frame.[3,4] In addition, Pd/NHC complexes are intensively studied as potential metallodrugs.[5,6] The structure of NHC-ligand usually has a great impact on the catalytic performance[1,4,7] and biological properties of Pd/NHC complexes.[5,6] Substituents in the NHC-ligands can significantly affect electronic and steric properties, polarity, solubility and stability of complexes. Modification of NHC-ligand structure is usually performed at the stage of ligand synthesis.[1–4,8] Alternative approach includes postmodification of pre-synthesized complexes involving functional groups in the NHC-ligands.[9,10] The postmodification approach opens up great opportunities for the preparation of libraries of new complexes for catalytic and biomedical studies. However, the last approach requires installation of special reactive groups to the NHC ligands. Common reactive groups installed in NHC ligands and used for the postmodification include halogenoalkyl, azide, alkyne, alkene, oxy, formyl, or active CH groups.[9,10] Amino group can be very attractive function for postmodification. Complexes with chelated NHC-ligands containing substituents bearing NH_2 groups involved in coordination with metals were described in the literature,[11–26] however examples of the use of NH_2 group for postmodification are rare.[21,26] Recently, 5-aminobenzimidazol-2-ylidene ligands with the amino group capable of conjugation with the π-electron system of the NHC-ligand were studied in the stabilization and postmodification of gold nanoparticles.[27] However, to the best of our knowledge, molecular M/NHC complexes with primary amino group directly connected to the NHC core are not documented. Continuing our works in the field of triazole derivatives, we focused on 3-amino-1,2,4-triazolium salts as potential NHC-proligands.[28]

Herein, we report the first synthesis of Pd/NHC complexes with NH_2-functionalized 1,2,4-triazol-5-ylidene ligands (Scheme 1) and postmodification of these compounds *via* reactions with electrophilic reagents. Amino-functionalized NHC proligands were prepared according to the reported procedure[28,29] from commercially available 3-amino-1,2,4-triazole which was alkylated with *tert*-butyl alcohol and then N-acylated with acetic anhydride to give compound **1**. Alkylation of compound **1** with alkyl halides in acetonitrile followed by hydrolytic N-deacetylation afforded the target NHC-proligands



2a, **3a** R^1 = Me, X = I, 92%, 90%
2b, **3b** R^1 = Et, X = I, 86%, 69%
2c, **3c** R^1 = Bu^n, X = Br, 84%, 78%
2d, **3d** R^1 = Bn, X = Br, 72%, 88%
2e, **3e** R^1 = Bn, X = Cl, 65%, 82%

a R^1 = Me, R^2 = H, X = I, 78%
b R^1 = Et, R^2 = H, X = I, 88%
c R^1 = Bu^n, R^2 = H, X = Br, 62%
d R^1 = Bn, R^2 = H, X = Br, 83%
e R^1 = Me, R^2 = Me, X = I, 74%
f R^1 = Et, R^2 = Me, X = I, 72%
g R^1 = Bn, R^2 = H, X = Cl, 78%

Scheme 1 *Reagents and conditions*: i, Bu^tOH, $HClO_4$; ii, Ac_2O; iii, R^1X, MeCN, 80 °C; iv, HCl (for **3a**,**b**,**e**) or HBr (for **3c**,**d**), EtOH, reflux; v, $PdCl_2$, pyridine or 2,6-dimethylpyridine, K_2CO_3, KX (for **4a–f**), 80 °C.

3a–e (see Scheme 1). The use of acetyl-protected compound **1** instead of 3-amino-1-*tert*-butyl-1,2,4-triazole at the alkylation stage was required to prevent undesired alkylation of NH_2 group inherent for 1-substituted 3-amino-1,2,4-triazoles.[28]

Palladation of compounds **3a–e** was performed according to a previously described procedure[30] using $PdCl_2$ as palladium source and pyridines as solvents and co-ligand. To prevent formation of mixtures of complexes with various halide ligands, KBr or KI were added in excess as sources of ligands X.[31] To our delight, under these conditions palladation of compounds **3a–e** proceeded selectively to give desired complexes **4a–g** in 62–88% yields (see Scheme 1).† Possible side-products like coordination polymers or complexes with Pd coordinated to NH_2 group were not detected by NMR both in crude products or reaction mixtures. However, attempted preparation of complexes using 3-chloropyridine as solvent and co-ligand gave inseparable multi-component mixtures. Apparently, this may be explained by lower nucleophilicity of 3-chloropyridine and side reactions involving NH_2 group of NHC-ligands into coordination with Pd instead of 3-chloropyridine, which can complicate the reaction course.

Complexes **4a–g** represent air-stable yellow to orange crystalline substances soluble in many organic solvents but almost insoluble in hexane and water. Their structure was confirmed by NMR spectroscopy and single crystal X-ray analysis of compound **4a**. The ^{1}H NMR spectra contain characteristic signals for NH_2 group at ~4 ppm ($CDCl_3$) or 6 ppm (DMSO-d_6), as well as characteristic signals for Pd-coordinated pyridine or 2,6-dimethylpyridine molecules. Methyl groups of 2,6-dimethylpyridine ligand demonstrate nonequivalence in ^{1}H and ^{13}C NMR spectra, apparently due to hindered rotation around the Pd–N bond caused by bulky *tert*-butyl group in the NHC-ligand. Spatial proximity between the nitrogen substituents of NHC-ligand and the methyl groups of 2,6-dimethylpyridine ligand is also observed in ^{1}H–^{1}H NOESY spectrum of compound **4e**, which contains the corresponding correlation signals (see Figure S4 in Online Supplementary Materials). According to X-ray diffraction data,‡ the molecular structure of compound **4a** (Figure 1) is similar to the previously described structures of palladium complexes with 1,2,4-triazole NHC-ligands and pyridine co-ligands.[30–34] The complex **4a** adopts typical slightly distorted square-planar geometry around the palladium center, with the pyridine ligand *trans* to the NHC ligand, the C(1)–Pd(1)–I(1) and C(1)–Pd(1)–I(2) angles are 86.97(13)° and 86.32(13)°, respectively. The length of the Pd(1)–C(1) bond [1.950(5) Å] is in the range of the bond lengths in Pd/NHC complexes of similar structure with (benz)imidazole NHC-ligands, pyridine and iodide co-ligands (1.94–1.97 Å).[35–38] The amino group adopts pyramidal configuration (the sum of the bond angles centered at the nitrogen atom is 346°); the N(4) atom deviates from the root-mean-square plane of the triazole ring by merely 0.089(9) Å.

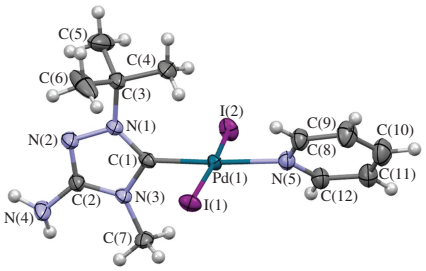
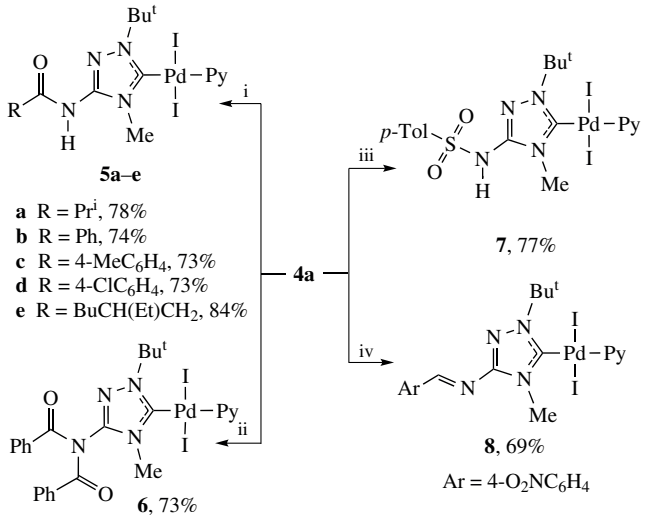


Figure 1 General view of complex **4a** in the representation of atoms *via* thermal ellipsoids at the 50% probability level. Selected bond lengths (Å): Pd(1)–C(1) 1.950(5), Pd(1)–N(5) 2.104(4), Pd(1)–I(2) 2.6039(8), Pd(1)–I(1) 2.6116(9), N(1)–C(1) 1.324(6), N(1)–N(2) 1.396(5), N(2)–C(2) 1.315(6), N(3)–C(1) 1.375(6), N(3)–C(2) 1.374(6), N(4)–C(2) 1.356(6), N(5)–C(8) 1.330(7), N(5)–C(12) 1.348(6); selected bond angles (°): C(1)–Pd(1)–N(5) 176.65(17), C(1)–Pd(1)–I(1) 86.97(13), C(1)–Pd(1)–I(2) 86.32(13), N(5)–Pd(1)–I(1) 93.58(11), N(5)–Pd(1)–I(2) 93.44(11), I(2)–Pd(1)–I(1) 171.356(19).

Ability of compounds **4** to undergo postmodification was studied on examples of reactions of complex **4a** with the appropriate reactants (Scheme 2). Compound **4a** reacted with equimolar amount or small excess of acyl chlorides in acetonitrile in the presence of pyridine to give amides **5a–e** in 73–84% yields. Reaction of **4a** with the excess of benzoyl chloride afforded dibenzoyl derivative **6** in 73% yield. Sulfonamide **7** was prepared by the reaction of compound **4a** with tosyl chloride at 110 °C in pyridine. Attempts to prepare azomethine derivatives by heating **4a** with benzaldehyde, 4-methyl- and 4-fluorobenzaldehydes in ethanol under reflux or in pyridine at 110 °C were unsuccessful: the corresponding products were formed in low yields and were hydrolyzed during purification by column



Scheme 2 *Reagents and conditions*: i, RCOCl, Py, MeCN, 0–20 °C; ii, PhCOCl (2.2 equiv.), Py, MeCN, 20 °C; iii, *p*-TolSO$_2$Cl, Py, 110 °C; iv, 4-O$_2$NC$_6$H$_4$CHO, EtOH, 80 °C.

† For characteristics of the compounds, see Online Supplementary Materials.

‡ *Crystal data for* **4a**. $C_{12}H_{19}I_2N_5Pd$ (M = 593.52), monoclinic, space group $P2_1/n$, at 100(2) K, a = 9.2838(19), b = 11.924(2) and c = 16.256(3) Å, β = 97.55(3)°, V = 1783.9(6) Å^3, Z = 4, d_{calc} = 2.210 g cm^{-3}, μ(MoKα) = 6.16 mm^{-1}, F(000) = 1112. Total of 30410 reflections were collected (3835 independent reflections, R_{int} = 0.112) and used in the refinement, which converged to $wR(F^2)$ = 0.112, GOOF 1.06 for all independent reflections [R_1 = 0.041 was calculated for 3775 reflections with $I > 2\sigma(I)$].

X-ray diffraction data were collected at the 'Belok' beamline of the National Research Center 'Kurchatov Institute' (Moscow, Russian Federation) using a Rayonix SX165 CCD detector. The data were collected using an oscillation range of 1.0° and corrected for absorption using the Scala program.[39] The data were indexed, integrated and scaled using the utility iMOSFLM in CCP4 program.[40] The structure was solved by direct method and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The amino-H atoms were objectively localized in the difference-Fourier map and refined isotropically with fixed displacement parameters [U_{iso}(H) = 1.2U_{eq}(N)]. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with fixed isotropic displacement parameters [U_{iso}(H) = 1.5U_{eq}(C) for the Me-groups and U_{iso}(H) = 1.2U_{eq}(C) for the other groups]. All calculations were carried out using the SHELXTL program.[41]

CCDC 2044892 contains 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.

chromatography to give starting compounds. Only 4-nitrobenzylidene derivative **8** was obtained in good yield (69%) after refluxing compound **4a** with 4-nitrobenzaldehyde, the most electrophilic aldehyde among studied.

In conclusion, Pd/NHC complexes of a new type containing NH_2 group in 1,2,4-triazol-2-ylidene ligands were obtained by direct palladation of 3-amino-1,4-dialkyl-1,2,4-triazolium salts. Amino group in these complexes is nucleophilic enough to react with acyl and sulfonyl chlorides and with highly electrophilic aldehydes and can be used as a functional group for postmodification. The developed synthesis of Pd/NHC complexes with amino-functionalized NHC-ligands seems promising in search for new effective catalysts and metallodrugs.

This work was supported by the Russian Science Foundation (grant no. 19-73-20085). X-ray study of compound **4a** was supported by the Ministry of Education and Science of the Russian Federation [award no. 075–03-2020–223 (FSSF-2020–0017)]. The authors are grateful to Academician of the Russian Academy of Sciences, Professor V. P. Ananikov for a fruitful discussion of the results of this work and valuable comments. The authors also thank the Shared Research Center 'Nanotechnologies' of the Platov South Russian State Polytechnic University and the Shared Research Center of Zelinsky Institute of Organic Chemistry for analytical services.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.010.

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Received: 18th November 2020; Com. 20/6372