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Substituted 1-(isoxazol-3-yl)methyl-1*H*-1,2,3-triazoles: Synthesis, palladium(II) complexes, and high-turnover catalysis in aqueous media

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ABSTRACT

New substituted 3-((1H-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles (aryl = Ph, *p*-Tol) and 2-(5-phenylisoxazol-3-yl)-5-(2-(1-((5-(*p*-tolyl)isoxazol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)ethyl)-1,3,4-oxadiazole were synthesized by means of click-chemistry procedures. The obtained compounds were used as ligands in preparation of palladium(II) complexes, and the latter proved to be high-turnover-number catalysts for C–C cross-coupling reactions under Green Chemistry conditions. One of the ligands was structurally characterized by single crystal X-ray diffraction, and the structure of complexes was determined by ^{1}H, ^{13}C, ^{15}N NMR spectroscopy and quantum-chemical modeling.

1. Introduction

The isoxazole and 1,2,3-triazole chemistry arouse considerable interest in recent years primarily due to the unique diversity of their biological and pharmacological properties. Isoxazole and 1,2,3-triazole heterocycles are structural fragments of a large number of the bioactive molecules used in medicine as anti-cancer, antiviral, antibacterial, anti-inflammatory, anti-tubercular agents, etc.[1] It has been found over the last decades that both isoxazoles and triazoles can be successfully used as ligands for the synthesis of palladium complexes, demonstrating high catalytic activity in cross-coupling reactions.[2] The structure and functional surrounding of the heterocycle in ligand molecule significantly affect its complexation, as well as the stability and catalytic activity of the complex.

During our previous investigations, we have synthesized the air and moisture stable square-planar *trans*-dichloropalladium(II) complex, containing a 5-(*p*-tolyl)isoxazol-3-amine ligand, which proved to be a high-turnover-number catalyst for Suzuki-Miyaura reaction with a low Pd loading (0.0001–0.1%) in neat water under air atmosphere.[3] It is reasonable to assume that the combination of the isoxazole and triazole heterocycles in the ligand structure can increase the catalytic activity of palladium complexes. Indeed, the triazole moiety contains effective coordination N-centers and readily forms complexes with transition metals.[2b] Moreover, the isoxazole and triazole rings differ in their electronic structure and donating capability, which will allow stabilizing both the Pd(0) and

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Pd(+2) species formed during the catalytic cycle in cross-coupling reaction. Recently, we have synthesized 5-(*p*-tolyl)isoxazol-3-(3-methyl-1*H*-1,2,4-triazol-5-yl)isoxazole ligand and its complex with $PdCl_2$, and have shown that catalytic activity of the latter is similar to that of the aminoisoxazole complex in Suzuki-Miyaura reaction in aqueous media under air but with Pd loading as low as 0.1%.[4]

In continuation of our studies of catalysts for cross-coupling reactions[5] and development of methods for the 1,2-azole synthesis,[6] in the present work we report the synthesis of isoxazole-1,2,3-triazole ligands with a methylene bridge between the heterocycles. The basicity values of the 1,2,3- and 1,2,4-triazoles (pK_B 1.17 and 2.19, respectively) differ by almost an order of magnitude, which certainly affects the stabilization of the complexes.[7] Furthermore, the flexibility of the nitrogen coordination of 1,2,3-triazoles provides additional opportunities in palladium catalysis.[2b] In addition, the methylene bridge between the heterocyclic fragments gives the ligand similarity to the well-studied 1-(2-picolyl)-1*H*-1,2,3-triazole ligand, which forms stable complexes with transition metals (Pd, Pt, Cu, etc.).[8] With this background in mind, we prepared new substituted 3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles **11**–**16** (Scheme 1) (aryl = Ph, *p*-Tol) and 2-(5-phenylisoxazol-3-yl)-5-(2-(1-((5-(*p*-tolyl)isoxazol-3-yl)methyl) -1*H*-1,2,3-triazol-4-yl)ethyl)-1,3,4-oxadiazole **20** (Scheme 2).

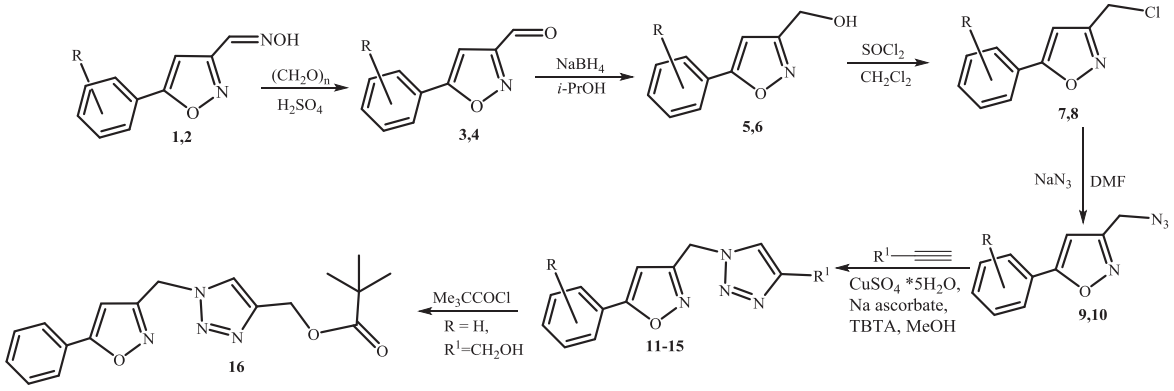
These ligands were reacted with Na_2PdCl_4 to give the palladium(II) complexes L^1PdCl_2–L^7PdCl_2. Herein, we present the detailed synthesis of the ligands and palladium(II) complexes together with their characterization and catalytic activity testing as new catalysts for C–C cross-coupling reactions in neat water under ambient atmosphere. It is also important to note that 3-((1H-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles are of special interest for biological testing in different domains, for example, as anti-cancer agents and isosteres of 3-(aryl-1*H*-1,2,3-triazol-1-yl)benzisoxazole that exhibit high anticancer activity in acute myeloid leukemia cell lines.[1b,9]

2. Results and discussion

2.1. Design and synthesis of ligands

Our synthetic strategy for the preparation of desired 3-((*1H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles **11**–**16** and bis-isoxazole-1,2,3-triazole-1,3,4-oxadiazole ligand **20** involved the formation of the (1*H*-1,2,3-triazol-1-yl)methyl molecular fragment in position 3 of the 5-arylisoxazoles by Cu(I) catalyzed 1,3-dipolar cycloaddition (click reaction)[10] of the isoxazole azides with respective acetylene derivatives (Scheme 1). As azide components we chose 3-(azidomethyl)-5-arylisoxazoles **9,10** which were synthesized by the action of NaN_3 on the 3-(chloromethyl)-5-arylisoxazoles **7,8**. The synthesis of azidomethylisoxazoles **9,10** was carried out in DMF solution at 40 °C giving the products in quantitative yield. Starting 5-arylisoxazoles **7,8** were obtained via successive transformation of available 5-arylisoxazole-3-carbaldehyde oximes **1,2** into corresponding 5-arylisoxazole-3-carbaldehydes **3,4** and then 5-arylisoxazol-3-yl methanols **5,6**[6b,11]. The obtained azidomethylisoxazoles **9,10** were introduced in the reaction of 1,3-dipolar cycloaddition with different alkynes (propargyl alcohol, 2-methylbut-3-yn-2-ol, phenylacetylene) under classic conditions of the click-chemistry ($CuSO_4 \cdot 5H_2O$, sodium ascorbate, TBTA – tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl] amine, MeOH) and it resulted in isolation of corresponding 3-((1H-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles **11**–**15** in high yields (91–99%). Acylation of (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methanol **11** with pivaloyl chloride, afforded (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl pivalate **16**, which turned out to be useful for further NMR studies of the Pd(II) complexes structure.

The 3-(azidomethyl)-5-(*p*-tolyl)isoxazole **10** was also applied in the synthesis of the polycyclic derivative - 3-((1H-1,2,3-triazol-1-yl)methyl)-5-arylisoxazole with several azole heterocycles in one molecule **7**. As alkyne co-reagent in the click reaction with azidomethylisoxazole **10**, 2-(but-3-yn-1-yl)-5-(5-phenylisoxazol-3-yl)-1,3,4-oxadiazole **19** was used which was synthesized from the previously described 3-(1*H*-tetrazol-5-yl)-5-phenylisoxazole **18**.[4] The tetrazole part of isoxazolyltetrazole molecule **18** was transformed into butynyl-1,3,4-oxadiazolic molecular fragment by selective recyclisation of tetrazole heterocycle (Scheme 2).[12] This was accomplished by treating isoxazolyltetrazole **18** with pent-4-ynoic acid in the presence of DCC (N,N′-dicyclohexylcarbodiimide). The process involved tetrazole acylation and elimination of nitrogen to form 2-butynyl-5-(5-phenylisoxazoyl)-1,3,4-oxadiazole **19** in 86% yield. The structures of synthesized isoxazolyl-1,2,3-triazoles **11**–**16**, bis-isoxazolyl-1,2,3-triazole-1,3,4-oxadiazole **20**, azidomethylisoxazoles **9,10** and isoxazolyl-1,3,4-oxadiazole **19** were confirmed by IR, ^1H and ^{13}C NMR spectra as well as by single crystal X-ray analysis of (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methanol **1**. The obtained isoxazole-1,2,3-triazoles **11**–**16** and bis-isoxazole-1,2,3-triazole-1,3,4-oxadiazole **20** were used then as ligands (L^1–L^7) in the synthesis of Pd(II) complexes L^1PdCl_2–L^7PdCl_2, aiming evaluation of the latter catalytic activity in cross-coupling reactions. They were synthesized by reaction of ligands with Na_2PdCl_4 in methanol solutions. Addition of 0.025 M solution of ligand (**11**–**16, 20**) in MeOH to a 0.1 M solution of



Scheme 1. Preparation of 3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazole derivatives **11**–**16**.