ABSTRACT

Synthesis and characterization of organometallic complexes gained significant importance in recent decades as their use as catalysts in chemical reactions is increasing. In addition, bioactive organometallic coordination compounds offer new approach in drug discovery with the potential to increase the therapeutic effect with the concomitant decrease of side effects.

Through the *ortho*-C–H activation of C2-(hetero)aryl substituted quinazoline derivatives with $[RuX_2(p\text{-cymene})]_2$ in MeOH in presence of KOAc a series of novel *C,N*-organoruthenium(II) complexes were synthesized. Fast formation of three ruthenium(II) complexes occurred during the cycloruthenation reaction, followed by the reaction with bidentate *C,N*-quinazoline ligand. Initially, kinetically favorable Ru^{II}–OAc complex was formed followed by the transition to its thermodynamically more stable Ru^{II}–Cl analogue. We have shown that cycloruthenation is an equilibrium process, as the addition of excess amount of KOAc decreased the reaction rate. Furthermore, we have confirmed that cycloruthenation reaction of *C,N*-quinazoline ligands occurs successfully also in 1,4-dioxane and that addition of AcOH accelerates the reaction rate.

A detailed study of the 2-arylquinazoline halidoruthenacycles reactivity in the arylation reaction confirmed positive effect of carboxylate ligand also on oxidative addition of aryl halide on ruthenium(II) center, as the reaction occurs through ruthenium(II) acetato complex as the key intermediate. Arylation reaction was additionally accelerated in the presence of AcOH. Further studies revealed that the oxidative addition undergoes single-electron transfer C–X (X = Br, Cl, I) bond cleavage and that for electron-rich aryl halides oxidative addition is a rate limiting step of the arylation reaction of *C,N*-organoruthenium(II) quinazoline complexes. We have also shown the formation of bromide anion during the arylation process, which causes ligand exchange of complexes Ru^{II}–Cl and/or Ru^{II}–OAc, where for further functionalization less reactive Ru^{II}–Br analogue is formed *in situ*.

Direct *ortho*-C–H arylation of C2-(hetero)aryl substituted quinazoline derivatives with aryl bromides was performed in 1,4-dioxane at 120° C in the presence of catalyst system $[RuCl_2(p\text{-cymene})]_2$/PCCA/$PPh_3$/$K_2CO_3$. With the follow-up experiments we confirmed no significant impact of electron-withdrawing or electron-donating functional groups present on *para*-substituted phenyl ring of C2 substituted quinazoline derivatives on the process of direct C–H bond functionalization.

C,N-organoruthenium(II) quinazoline complexes were biologically evaluated. We have shown that the *C,N*-organoruthenium(II) 2-(tiophene-3-yl)quinazoline complex **4s** exhibited

selective cytotoxicity towards leukemic cells with the half maximal inhibitory concentration of 2 μM.

Key words: quinazolines, *C,N*-organoruthenium(II) quinazoline complexes, *ortho*-C–H arylation, selective cytotoxicit