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Alkylation of cyclic amines with alcohols catalyzed by Ru(II) complexes bearing *N*-Heterocyclic carbenes

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ABSTRACT

This paper includes the synthesis of 2-(1,3-dioxane-2-yl)ethyl substituted benzimidazole substituted *N*-heterocyclic carbenes precursors and their ruthenium complexes. Synthesized compounds were characterized by elemental analysis and NMR spectroscopy. All complexes have been tested in the alkylation of pyrrolidine and morpholine with alcohols, showing an excellent activity in this reaction.

1. Introduction

N-heterocyclic carbenes (NHCs) are ubiquitous ligands in chemistry.[1] Due to their bonding properties and being stable to air and moisture relative to similar ligands, NHCs are named as unique ligands and their transition metal complexes are successfully applied in organometallic chemistry,[2] catalysis[3] and medicinal chemistry.[4]

Amines are one of the most important compounds for the chemical industry and find successful application in pharmaceuticals, natural products, agrochemicals or food additives.[5] Therefore, a number of efficient methods like Buchwald-Hartwig,[6] Ullmann reactions,[7] reductive elimination[8] or hydroamination[9] are used for synthesis of amines. Although these methods are efficient, the formation of side products and waste represents a drawback. In recent years, to solve these problems an exclusive method for the direct coupling of alcohols with amines has been used known as the borrowing hydrogen method.[10] Using alcohols as the alkylating agent and the formation of water as a stoichiometric by-product are the basic features of this reaction. Grigg[11] and Watanabe[12] reported the N-alkylation of amines with alcohols in 1980s. Grigg and coworkers described the reaction of different alkyl amines with alcohols catalyzed by rhodium catalyst. Similarly, Watanabe reported the N-alkylation of aniline with primary alcohols catalyzed by Ru catalyst. After these, a number of reports deal with N-alkylation of amines using metal complexes especially based on ruthenium[13–19] and iridium.[20–24] Ru–NHC complexes have long been used in many research areas such as catalysis and photochemistry.[25,26] They are also efficient catalysts in numerous reactions including C–H activation,[27] olefin metathesis,[28] transfer hydrogenation,[29] hydrosilylation[30] and cyclopropanation.[31] The first application of alkylation of catalyzed by Ir–NHC complexes using the borrowing hydrogen method, highlighted the activity of these ligands.[32] This reaction has been successfully catalyzed by diverse Ir–NHC complexes,[33] but has lately been validated for Ru–NHC catalysis.[34]

To the best of our knowledge, the studies of using Ru–NHC complexes in the alkylation of amines with alcohols are rare in the literature. Recently our group has investigated ruthenium-carbene complexes, *in situ* prepared catalyst system in the alkylation of amines with alcohols.[35] In current work, the new benzimidazolium salts containing 2-(1,3-dioxane-2-yl)ethyl that are precursors to these NHC ligands are readily synthesized and the subsequent formation of complexes of Ag–NHC has proved facile. The reaction of the Ag–NHC complexes with $[RuCl_2(p\text{-cymene})]_2$ in dichloromethane afforded the Ru–NHC complexes (**2a-g**). The obtained Ru–NHC complexes were characterized by ^1H and ^{13}C NMR, IR and elemental analysis. These complexes are efficient catalyst for

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alkylation of cyclic amines with diverse alcohols.

2. Results and discussion

2.1. Preparation of benzimidazolium salts

Dialkylbenzimidazolium salts, (**1a**-**g**) were prepared according to known methods by the reaction of 1-alkylbenzimidazole with 2-(2-bromoethyl)1,3-dioxane in dimethylformamide at 80 °C, and isolated in 84–90% yields.[32,36] The structure of benzimidazolium salts (**1a**-**1g**) was showed in Scheme 1. The salts are air- and moisture stable both in the solid state and in solution and soluble in chlorinated solvents, alcohols and water. The benzimidazolium salts (**1a-g**) were isolated as solids in very good yields and fully characterized by ^{1}H and ^{13}C NMR, and IR spectroscopy, elemental analyses, and their melting points were determined. ^{13}C NMR chemical shifts were consistent with theproposed structure; the imino carbon appeared as a typical singlet in the ^{1}H-decoupled mode at 143.3, 143.4, 153.7 and 152.3 ppm, respectively for benzimidazolium salts **1a-c** and **1g**. The ^{1}H NMR spectra of the benzimidazolium salts further supported the assigned structures; the resonances for C(2)–H were observed as sharp singlets at 11.32, 9.97, 10.38 and 11.36 ppm characteristic of NC*H*N proton, respectively for **1a-c** and **1g**. The IR data for benzimidazolium salts 1a-g clearly indicate the presence of the –C=N– group with a ν(C=N) vibration at 1568, 1567, 1562 and 1566 cm^{-1}, respectively for **1a-c** and **1g**. These values are in good agreement with the previously reported results.[33,35,36]

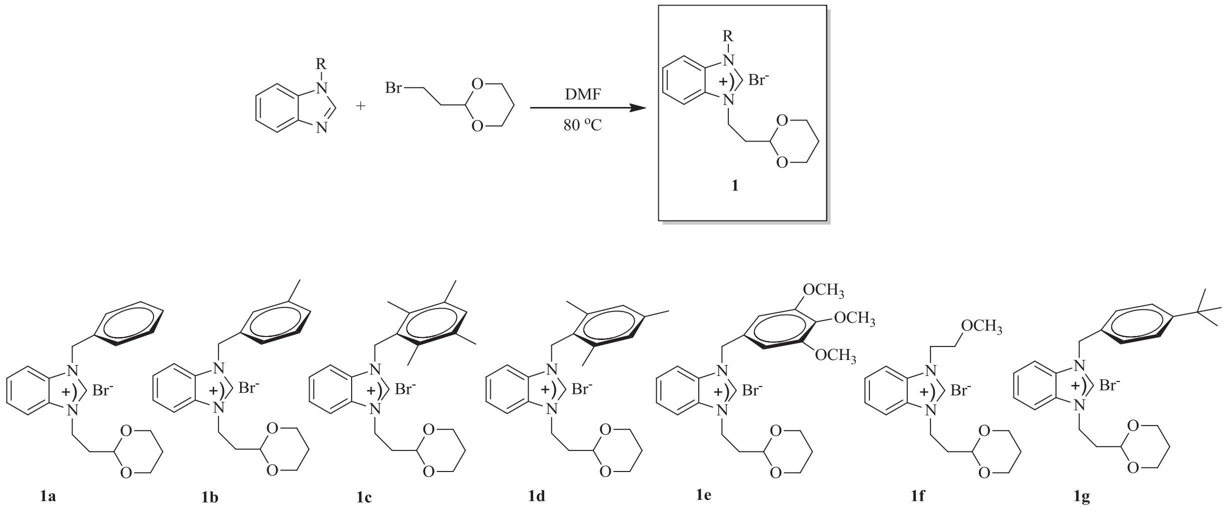
2.2. Preparation of ruthenium-carbene complexes 2a-g

The procedure involving Ag–NHC carbene is probably one of the most general methods, because it generates an air stable intermediate under mild reaction-conditions, thus allowing an easy access to a wide range of transition metal complexes. The ruthenium complexes were prepared according to the Ag(I)–NHC transfer method. The silver complexes were synthesized according to the general method described by Wang and Lin.[37] The silver carbene complexes, which should subsequently serve as a carbene-transfer agent, were synthesized by the reaction of Ag_2O with 2 equiv. of salts (**1a-1g**) in CH_2Cl_2 at ambient temperature. The non-isolated Ag–NHC complexes were converted into the red brown monocarbene Ru–NHC complexes (**2a-2g**) in dark condition at room temperature (Scheme 2). The air and moisture-stable ruthenium carbene complexes (**2a**-**2g**) were soluble in solvents such as dichloromethane, chloroform, toluene, and tetrahydrofuran and insoluble in non-polar solvents. Ru–NHC complexes were characterized by NMR, FT-IR and elemental analysis. Ruthenium complexes exhibit a characteristic $\upsilon_{(NCN)}$ band typically at 1468, 1485, 1465, 1471, 1470, 1466 and 1469 cm^{-1} respectively for **2a-2g**. ^{13}C chemical shifts provide a useful diagnostic tool for this type of metal carbene complexes. The chemical shifts for the carbene carbon atom are located in the 189–190 ppm range, and are similar to those found in other ruthenium-carbene complexes. These complexes show typical spectroscopic signatures, which are in line with those recently reported for other [RuCl$_2$(NHC)(arene)] complexes.[29]

2.3. Catalytic alkylation and dialkylation of cyclic amines with alcohols

A one-step process for the simultaneous alkylation of both the N atom and the unactivated C(3) carbon of secondary amines corresponding to a formal sp^{3}C–H activation was unknown until Bruneau et al. reported the *N*– and *C*(3)-dialkylation of saturated cyclic amines in the presence of ruthenium precatalysts equipped with a phosphinesulfonate ligand acting as a P,O chelate.[38] Recently our research group has investigated catalytic activity of Ru–NHC complexes in similar reaction.[35b] In this work, Ru complexes (2a-g) featuring dioxane moieties, which upon hydrolysis generates an aldehyde as a potential internal hydrogen acceptor, were evaluated to explore their activities in the alkylation of cyclic amines. The presence of an NHC ligand and a second different donating group on the metal can radically alter the catalytic properties. Also, the chelating nature of these ligands results in the production of highly stable complexes. NHCs are known to be compatible with a wide set of electron donor nitrogen-, oxygen-, arene-containing functionalities.[39] The hemilable arm in such ligands is capable of reversible dissociation to produce vacant coordination sites allowing complexation of substrates during the catalytic cycle. At the same time the strong donor carbene moiety remains connected to the metal center.

The alkylation of pyrrolidine with benzyl alcohol was investigated as a model reaction (Table 1). All reactions were carried out with 1.0 mol% catalyst loading in toluene under an argon atmosphere, by using a 1:2.5 amine/alcohol ratio in the presence of D-(+)-camphorsulfonic acid (CSA) (40 mol %) corresponding to the



Scheme 1. The synthesis of benzimidazolium salts.