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Direct synthesis of N-alkylated amides via tandem hydration/N-alkylation reaction from nitriles, aldoximes and alcohols†

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The novel strategy for direct synthesis of N-alkylated amides from nitriles, aldoximes and alcohols was proposed and accomplished in the presence of Cp*Ir complex.

The N-alkylated amides represent an important class of chemical compounds that have ubiquitous application in natural products, pharmaceuticals, fine chemicals and polymers, etc.1 Traditional procedures for the synthesis of N-alkylated amides are couplings of carboxylic acids or their derivatives, such as acid chlorides, anhydrides and esters, with N-alkylated amines.2 However, these procedures suffer from the use of the stoichiometric amount of hazardous and/or expensive reagents and the generation of a large amount of harmful by-products.

In recent several years, much attention has been paid to the development of catalytic strategies for the synthesis of N-alkylated amides using alcohols as starting materials because alcohols are less toxic, abundant and renewable feedstock reagents. Several groups have developed direct couplings of amines and primary alcohols for the preparation of N-alkylated amides using transition metal catalysts, such as PNN-type ruthenium complex,3 the combination of N-heterocyclic carbene (NHC) precursor, and [Ru(cod)Cl]2,4 [Ru(p-cymene)Cl]2, [Ru(benzene)Cl]2,5 or [RuH2(PPh3)3]6 systems,6 N-heterocyclic carbene based ruthenium complexes,7 ruthenium diphosphine diamine complexes.8 However, it is still extreme challenge to control the selectivity of reaction and reduce the generation of by-products N-alkylated amines (Scheme 1, A). In 2013, we demonstrated the direct synthesis of N-alkylated amides from aldoximes and alcohols via tandem rearrangement/N-alkylation reaction catalyzed by Ru/Ir dual catalyst system, which exhibited excellent selectivity for target products (Scheme 1, B).9 However, most of aldoximes are not commercially available and must be synthesized via the condensation of corresponding aldehydes with hydroxylamine hydrochloride in the presence of base, and the single catalyst (ruthenium or iridium complex) is not efficient for such tandem transformation. More recently, Hong and co-workers reported a catalytic strategy for the synthesis of N-alkylated amides from nitriles and alcohols with complete atom economy based on “hydrogen transfer” (Scheme 1, C),10 exhibiting significant advantages over traditional Ritter reaction (Amidation of nitriles with alcohols or alkenes in the presence of at least stoichiometric amount of concentrated sulfuric acid).11 This procedure still has some limitations and it required 10 mol% catalyst loading, 10 mol% ligand, 20 mol% strong base (NaH) and long reaction time (48 h).

The selective hydration of nitriles with aldoximes as water surrogates to form amides, nitriles with alcohols or alkenes in the presence of at least stoichiometric amount of concentrated sulfuric acid,11 This procedure still has some limitations and it required 10 mol% catalyst loading, 10 mol% ligand, 20 mol% strong base (NaH) and long reaction time (48 h).

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which are further N-alkylated with alcohols as alkylating agents to N-alkylated amides (Scheme 1, D). Compared with Hong’s method, this procedure would provide different N-alkylated amides from same starting materials (nitriles and alcohols).

In our previous work, a range of commercially available transition metal complexes, including [Ru(p-cymene)Cl]2, [Cp*RhCl]2 (Cp* = pentamethylcyclopentadienyl), [Rh(cod)Cl]2 (cod = 1,5-cyclooctadienyl), [Cp*IrCl]2, and [Ir(cod)Cl]2, were assayed for their ability to catalyze the N-alkylation of benzamide with benzyl alcohol to the N-benzylbenzamide and [Cp*IrCl]2 was found to be the most efficient catalyst. As a result of it, our initial efforts in this work focused on the hydration of benzonitrile 1a with commercially available aldoxime, such as acetylaldoxime 2a and n-butyraldoxime 2b, as the water surrogate catalyzed by [Cp*IrCl]2. The reaction of 1a with 2a (1.1 equiv.) was carried out in the presence of [Cp*IrCl]2 (1 mol%) at 100 °C for 6h to give benzamide 3a with 81% yield. To our delight, the product 3a could be obtained with 90% yield when 2b was used for this reaction [Equation (1)]. The n-butyraldoxime 2b was chosen as the water surrogate for further research. After the reaction of 1a with 2b was carried out at 100 °C for 6h, benzyl alcohol 3a (1.3 equiv.) and Cs2CO3 (0.2 equiv.) were added into above reactor. This reaction continued to proceed at 130 °C for another 12h to afford the desired N-alkylated amide 5aa with 85% yield [Equation (2)].

Having established the catalyst system and reaction conditions, a variety of alcohols 3 were used as substrates instead of benzyl alcohol 3a for the investigation and the results are summarized in Table 1. Similar to the case of 3a, reactions with benzylic alcohols bearing an electron-donating group, such as methyl 3b and methoxy 3c, afforded the corresponding products 5ab and 5ac with 80% and 86% yields, respectively. Benzylic alcohols bearing one or two halide atoms, such as fluoro 3d, chloro 3e-f, dichloro 3g and bromo 3h, were successfully converted into the desired products 5ad-5ah with 75-85% yields. Furthermore, transformations of benzylic alcohols bearing a strong electron-withdrawing group, such as trifluoromethyl 3i and trifluoromethoxy 3j, gave the corresponding products 5ai and 5aj with 82% and 84% yields, respectively. When 2-naphthenecarboxaldehyde 3k, furan-2-ylmethanol 3l and thiophen-2-ylmethanol 3m were tested, the desired products 5ak-5am were obtained with 80%-85% yields, respectively. Apart from benzyl-type alcohols, aliphatic alcohols, including linear n-butanol 3n and n-hexanol 3o, and cyclohexylmethyl 3p, were proven to be suitable substrates and reactions gave the corresponding products 5an-5ap with 78-85% yields.

To expand further the scope of reaction, a series of nitriles 1 were used as substrates for the examination. As shown in Table 2, reactions of benzonitriles bearing one or two electron-donating substituents, such as methyl 1b and methoxy 1c, gave the corresponding products 5ba-5ca with 81% and 76% yields, respectively. Transformation of benzonitriles bearing one or two halogen atoms, such as fluoro 1d, chloro 1e, dichloro 1f and bromo 1g, gave the desired products 5da-5ga with 81-90% yields. In the case of benzonitriles bearing a strong electron-withdrawing substituent, such as trifluoromethyl 1h and trifluoromethoxy 1i, the corresponding products 5ha and 5ia were obtained with 80% and 82% yields, respectively. Reactions of heterocyclic nitriles, such as furan-2-carbonitrile 1j and thiophene-2-carbonitrile 1k, gave the desired products 5ja and 5ka with 84% and 86% yields, respectively. This tandem reaction was also applied to aliphatic nitriles, such as 2-phenylacetanilide 1l and n-butryronitrile 1m (2a was used as the water surrogate), affording the corresponding products 5la and 5ma with 76% and 78% yields, respectively.

A plausible mechanism is proposed to account for this present reaction (Scheme 2). The initial step involves the formation of iridium-nitrile species A, followed by the resulting species A were subsequently attacked by one molecular of aldoximes to afford five-membered cyclic species B, which decomposed to release amides and nitriles, and to regenerate the catalytic active iridium species. Finally, the resulting amides were further N-alkylated with alcohols to

Table 1 Reaction of benzonitrile 1a, n-butyraldoxime 2b and a variety of alcohols 3

* Reaction conditions: 1) 1a (1 mmol), 2b (1.1 mmol), [Cp*IrCl]2 (1 mol%), toluene (1 ml), 100 °C, 6h; 2) 1a (1 mmol), Cs2CO3 (0.2 equiv.).
more strong reaction conditions are necessary for the N-alkylation of aliphatic amides with alcohols. To transform aliphatic nitriles (11-1m) into the corresponding N-alkylated amides (5a-5m), \([\text{IrCl}_2]\) \((2 \text{ mol\%})\) and 1.3 equiv. ofaldoxime in the step of hydration, and 2 equiv. of alcohol and 0.4 equiv. of KOtBu in the step of N-alkylation were required. In this process, \(N\)-benzyl butyramide or \(N\)-benzyl acetamide were also generated as by-products.

In summary, we have demonstrated a novel strategy for the direct synthesis of N-alkylated amides via tandem hydration/N-alkylation from nitriles, aldoximes and alcohols. The protocol is highly attractive due to the use of single catalyst with low loading, high yields and operational convenience.

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Notes and references