

Proceeding Paper

CuBr₂-An Effective Catalyst in the Synthesis of Amides from Secondary Alcohols by the Ritter Reaction †

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Abstract: The Ritter reaction is widely used in the synthesis of antiallergic, antibiotic, antitumor, antibacterial, influenza antiviral, antiproliferative and antimicrobial drugs. In this regard, the search for new effective catalysts for the synthesis of amides in mild conditions is an urgent task. Of particular interest is the use of an alcohol as a second substrate. We were the first to carry out the CuBr₂-catalyzed reaction of acetonitrile with secondary alcohols such as 2-propanol, 2-butanol, cyclohexanol, cyclopentanol 2-phenylethanol and 2-adamantanol, which gives the corresponding amides in 80–100% yield. CuBr₂-catalyzed reaction of cyclohexanol with a number of nitriles (MeCN, EtCN, PhCN, *o*-MeC₆H₄CN) was studied. It was found that the reaction of cyclohexanol with nitriles in the presence of CuBr₂ proceeds in three directions giving dicyclohexyl ether, amides and esters (in particular, cyclohexyl acetate and cyclohexyl propionate) depending on the reaction conditions, catalyst concentration and the nature of the nitrile. The methodology we have discovered opens up prospects for the use of copper catalysis in the synthesis of practically useful amides.

Keywords: amides; copper bromide; Ritter reaction; secondary alcohols

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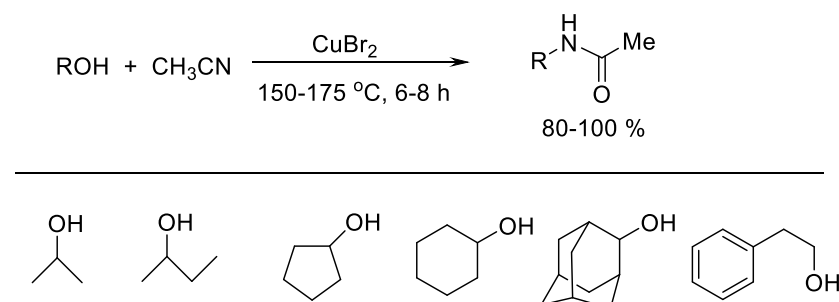
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1. Introduction

The Ritter reaction is used in the synthesis of biologically active molecules, such as antiallergic, antibiotic, antineoplastic, antibacterial, anti-influenza, antiproliferative and antimicrobial drugs [1]. In the classical Ritter reactions, alkenes or alcohols are used as a source of carbocations, but in non-classical reactions, any groups that form carbocations, such as ethers, esters, halocarbons, alkanes, carboxylate salts, epoxides and carboxylic acid, etc. can be used [1–3]. The classical method for the synthesis of amides by the Ritter reaction takes place under the action of equimolar amounts of strong acids: sulfuric, phosphoric, which is the cause of the formation of large amounts of waste. Waste reduction problems can be solved by using metal complex and heterogeneous catalysts. Since the Ritter reaction requires the formation of carbocation species, it is well suited for the synthesis of hindered amides. Unfortunately, the traditional harsh reaction conditions (eg, sulfuric acid stoichiometry) required for the formation of carbocations limits the choice of reaction substrate. Considering the importance of using the Ritter reaction, the search for catalysts for carrying out the Ritter reaction under mild conditions is an urgent task. Of particular interest is the use of alcohol as a second substrate. This work reports on the synthesis of amides by the reaction of secondary alcohols with nitriles under the action of a copper-containing catalyst.

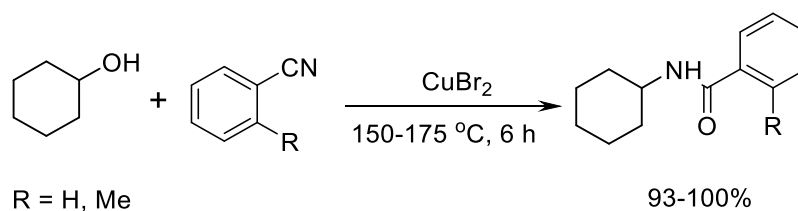
2. Results and Discussion

Secondary alcohols such as 2-propanol, 2-butanol, cyclohexanol, cyclopentanol, 2-phenylethanol and 2-adamantanol were involved in the Ritter reaction with acetonitrile. The reaction is catalyzed by copper compounds, the most effective of which was copper (II) bromide. The yields of 2-propylacetamide, 2-butylacetamide, 2-phenylethylacetamide and 2-adamantylacetamide reach 80–100% (Scheme 1). The resulting compounds were reliably characterized using mass- and NMR-spectroscopy data.



Scheme 1. The reaction of secondary alcohols with acetonitrile under the action of CuBr_2 catalyst.

It should be noted that the reaction of cyclohexanol and cyclopentanol with acetonitrile in the presence of CuBr_2 proceeds in three directions with the formation of dicycloalkyl ether, amides, and cycloalkyl acetate. It is obvious that dicyclohexyl ether is formed by intermolecular dehydration of cyclohexanol under the action of a catalyst, while *N*-amides are formed by the Ritter reaction. Cyclohexyl esters of acetic acid are formed by the reaction of acetonitrile with alcohols through in situ formation of cyclohexyl acetimidate ($\text{CH}_3\text{C}(\text{=NH})\text{OCy}$), the subsequent hydrolysis of which leads to the corresponding ester and ammonia. Therefore, using cyclohexanol as an example, the reaction of the latter with nitriles (MeCN , EtCN , PhCN , *o*- $\text{MeC}_6\text{H}_4\text{CN}$) in the presence of a copper-containing catalyst CuBr_2 was studied. The reaction was carried out in an autoclave at 150–175 °C for 6 h. *N*-Cyclohexylamides were obtained in quantitative yield at the following molar ratio of catalyst and reagents: [catalyst]:[cyclohexanol]:[RCN] = 45–50:100:100. The reactions of benzonitrile and *o*-tolynitrile with cyclohexanol proceed in only one direction, leading to the formation of amides. Thus, at a molar ratio of catalyst and reagents: [catalyst]:[cyclohexanol]:[ArCN] = 10:100:100, *N*-cyclohexylbenzamide and *N*-cyclohexyl-*o*-tolylamide were obtained in 93 and 100% yields, respectively (Scheme 2).



Scheme 2. The synthesis of *N*-cyclohexylbenzamide and *N*-cyclohexyl-*o*-tolylamide by Ritter reaction.

3. Conclusions

Selective synthesis of amides from secondary alcohols (cyclohexanol, cyclopentanol, 2-butanol, 2-propanol, 2-phenylethanol, 2-adamantanol) with acetonitrile under the action of a CuBr_2 catalyst has been carried out.

4. Experimental Part

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer in CDCl_3 , chemical shifts were reported relative to TMS. Mass spectra were obtained on a Shimadzu GCMS QP2010 Plus GC-MS instrument (capillary column SPB-5 of $30\text{ m} \times 0.25\text{ mm}$, carrier gas–helium, from 40 to 300 °C at a rate 8 deg/min, temperature of vaporizer 280 °C, ion source temperature 200 °C, ionization energy 70 eV). Chromatographic analysis was carried out on a chromatograph Shimadzu GC-9A, GC-2014 [column of $2\text{ m} \times 3\text{ mm}$, stationary phase silicone SE-30 (5%) on Chromaton N-AW-HMDS, from 50 to 270 °C, heating rate 8 deg/min, carrier gas–helium (47 mL/min)].

General procedure. The reaction was carried out in a 10 mL glass ampule placed in a 17 mL stainless steel pressure microreactor. In the ampule under argon 0.2 mmol of CuBr_2 , 2 mmol of ROH, 2 mmole of nitrile were charged. The sealed ampule was placed in the reactor, which was hermetically closed and heated at 150–180 °C for 6–8 h. After the completion of the reaction the reactor was cooled to room temperature, the ampule was opened, the reaction mixture was neutralized with Na_2CO_3 and filtered. The solvent was distilled off and the residue distilled at atmospheric pressure or in a vacuum, or crystallized.

Author Contributions: Conceptualization, A.R.B. and I.R.R.; methodology, A.R.L.; software, A.R.B.; validation, A.R.L., I.R.R. and A.R.; formal analysis, A.R.L.; investigation, A.R.L.; resources, I.R.R.; data curation, A.R.; writing—original draft preparation, A.R.L.; writing—review and editing, A.R.L.; visualization, I.R.R.; supervision, A.R.B.; project administration, I.R.R.; funding acquisition, I.R.R. All authors have read and agreed to the published version of the manuscript.

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