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Cu-Catalyzed Pinner Reaction of Acetonitrile with Alcohols [†]

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Abstract: The Pinner reaction refers to the acid catalysed reaction of a nitrile with a variety of nucleophiles under anhydrous acidic conditions, affording a useful key intermediate salt for agrochemical and medicinal research. Acid catalyzed reaction of carbonitriles with alcohols gives an imino ester salts, another versatile heterocyclic building block found in various chemicals and pharmaceutics. However severe reaction conditions prevent the wide application of this reaction. We have found that the reaction of primary alcohols with acetonitrile under the action of a CuBr2 catalyst gives esters in 83–95% yield. The reaction we discovered paves the way for the use of copper catalysis in the Pinner reaction.

Keywords: Pinner reaction; nitriles; primary alcohol; esters; ethers; copper catalysts

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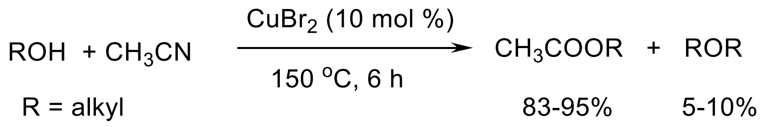
1. Introduction

In 1877 Pinner and Klein discovered the proton-induced imidate syntheses [1,2]. Thus, the Pinner reaction refers to the acid catalysed reaction of a nitrile with a variety of nucleophiles under anhydrous acidic conditions, affording a useful key intermediate salt for agrochemical and medicinal research. A plausible mechanism of the reaction starts with a protonation of the nitrile by the strong acid hydrogen chloride leading to a highly activated nitrilium cation, which can be attacked by the alcohol component. Acid catalyzed reaction of carbonitriles with alcohols gives an imino ester salts, another versatile heterocyclic building block found in various chemicals and pharmaceutics [3]. However severe reaction conditions prevent the wide application of this reaction.

2. Results and Discussion

Preliminary studies were carried out on the basis of the reaction of 1-heptanol with acetonitrile in the presence of various copper-containing catalysts ($CuBr_2$, $CuCl_2$, CuCl, CuI). The reaction was carried out in an autoclave at 150 °C for 6 h using from 10 to 40 mol. % of catalyst. We found that the best resulted were obtained in the reaction of 1-heptanol with 1 equivalent of acetonitrile in the presence of 10 mol. % of $CuBr_2$ catalyst at 150 °C for 6 h giving corresponding *n*-heptyl acetates in 95% yield (Scheme 1). Other copper-containing catalysts showed less activity. Decreasing the temperature to 130 °C sharply reduces the degree of conversion of the initial alcohol. Similar results were obtained with a number of other linear alkyl-substituted alcohols (1-propanol, 1-butanol, 1-pentanol, 1-hexanol) (Table 1). The yields of the corresponding alkyl acetates were 83-93%. The reaction was accompanied by the formation of small amounts of dialkyl ether, which is formed during the intermolecular dehydration of alcohol under the action of a catalyst [4,5].



Scheme 1. The preparation of alkyl acetates by the reaction of alkanols with acetonitrile.

Table 1. Copper-catalyzed Pinner reaction of acetonitrile with alcohols.

R	Conversion of ROH, %	Yield of CH_3COOR, %	Yield of ROR, %
n-Pr	95	83	10
n-Bu	95	85	10
n-Am	95	88	7
n-Hex	100	93	7
n-Hept	100	95	5

3. Conclusions

We have found that the reaction of primary linear alcohols with acetonitrile under the action of a $CuBr_2$ catalyst gives corresponding esters in 83-95% yield. The reaction we discovered paves the way for the use of copper catalysis in the Pinner reaction.

4. Experimental Part

Aliphatic alcohols and acetonitrile (Acros) were commercial reagents. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-II 400 Ascend instrument (400 MHz for ^1H and 100 MHz for ^{13}C in $CDCl_3$). Mass spectra were run on a Shimadzu GCMS-QP2010Plus mass spectrometer (SPB-5 capillary column, 30 m × 0.25 mm, helium as the carrier gas, temperature programming from 40 to 300 °C at 8 °C/min, evaporation temperature of 280 °C, ion source temperature of 200 °C, and ionization energy of 70 eV). The course of the reaction and the purity of the products were monitored by gas liquid chromatography on a Shimadzu GC-9A, GC-2014 instrument [2 m × 3 mm column, SE-30 silicone (5%) on Chromaton N-AW-HMDS as the stationary phase, temperature programming from 50 to 270 °C at 8 °C/min, helium as the carrier gas (47 mL/min)].

General methodology. 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 closed and heated at 150 °C for 6 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.

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