Reductive Alkylation of Amines with Carboxylic Ortho Esters

Renat Kadyrov,*
Evonik Resource Efficiency GmbH, Rodenbacher Chaussee 4, 63457 Hanau, Germany
**Corresponding author: +49 6181 59-78710, renat.kadyrov@evonik.com*

Abstract: We have demonstrated for the first time that carboxylic ortho esters could be used as an alkylating agent in the reductive alkylation of amines. A variety of amines, including amino acids, were alkylated affording mono-alkylated products with high selectivity in practical to high yields.
Keywords: Amines, Hydrogenation, Alkylation.

1. Introduction

Amines are an interesting target in organic chemistry with great potential in the pharmaceutical and fine chemical industries. Reductive alkylation of ammonia, primary or secondary amines with carbonyl compounds constitutes one of the most convenient and practical approaches for synthesis of higher alkylated amines. Using hydrogen as a reducing agent is one of the powerful methods for carrying out this transformation. Although diverse modifications have been developed, there are some drawbacks to the requirement of excess amounts of primary amines because undesirable overalkylation of produced secondary amines must be depressed. Hence, the development of selective methods using commercially available heterogeneous catalysts is of significant interest for the fine chemical and pharmaceutical industries.

2. Experimental

A 100 mL autoclave was charged with (0.5 mmol) of dried powder catalyst, purged with nitrogen twice, a solution of amine (50 mmol), ortho ester (55 mmol) and p-toluenesulfonic acid (5 mmol) in alcohol (50 ml) was added and autoclave was purged twice with hydrogen. The autoclave was heated to 120°C, pressurized with hydrogen to 40 bar and stirred at constant pressure until no hydrogen consumption was observed. Autoclave was cooled and depressurized, reaction mixture filtered through celite and solids washed with alcohol, to the combined filtrates 2M hydrochloric acid (25 mL) was added and concentrated on rotary evaporator. Residue was washed twice with diethyl ether. Diethyl ether extracts were discarded. Aqueous layer was made basic with NaOH solution and extracted with diethyl ether. Combined organic layers were dried over K2CO3 and concentrated on rotary evaporator. The crude product wan purified by vacuum distillation or chromatography on silica gel.

3. Results and discussion

From this study, it was confirmed that carboxylic ortho esters could be used as alkylating agents in the reductive alkylation of amines. Piperidine and methyl orthoformiate were used as substrates to check reaction feasibility and establish best reaction conditions. It was found that performing the reaction in the temperature range of 110-130°C and using catalytic amounts of water-free p-toluenesulfonic acid afforded the desired product in the best yield. Furthermore, the hydrogenation proceeded smoothly at these conditions over almost every hydrogenation catalyst such as Pd/C, Pt/C, Ru/Al2O3, Ru/C, Rh/C and [(dppb)Rh(cod)]BF_4. As shown in Table 1, a number of secondary and tertiary amines, including aminoacids, have been prepared using this method in synthetically useful to excellent yields with very good selectivity toward monoalkylation.

The standard route for the formation of carboxylic ortho ester is the Pinner reaction (A). However, this approach is limited to nitriles. The method (B) provides ortho esters direct from carboxylic acids. The latter method provides the facile formation of a variety of ortho esters with different substitution patterns.

Following the above mentioned developed procedure of the reductive alkylation, the reaction of bicyclic ortho esters and aminoacids proceeded smoothly to produce the mono N-alkylated aminoacids (Table 1).

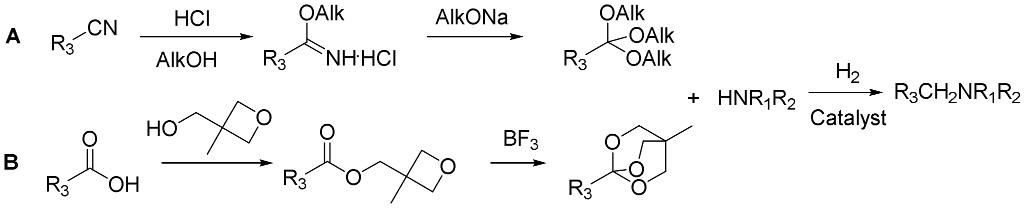
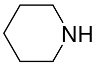
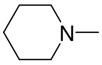
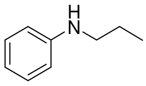
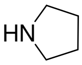
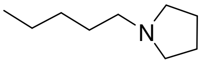
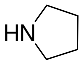
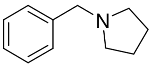
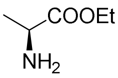
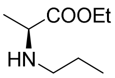
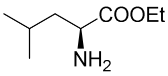
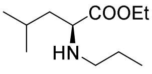
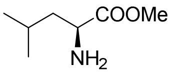
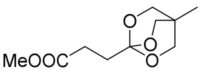
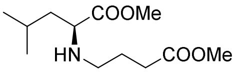
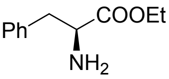
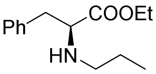
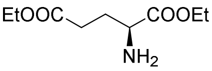
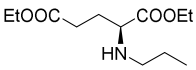
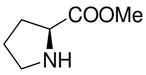
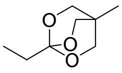
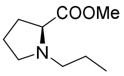
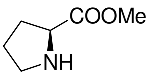
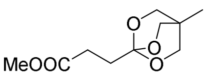
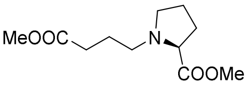
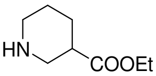
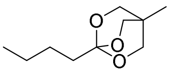
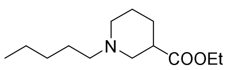
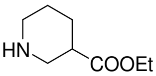
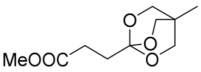
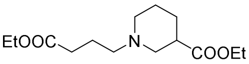


Figure 1. Two general methods for synthesis of ortho esters.

Table 1. Selected examples of alkylation of amines with carboxylic ortho esters.

Catalyst	Amine	Orthoester	Product	Yield, %
5% Ru/Al$_2$O$_3$		HC(OMe)$_3$		98
5% Pt/C	PhNH$_2$	EtC(OMe)$_3$		66
5% Pt/C		n-BuC(OMe)$_3$		95
5% Pt/C		PhC(OMe)$_3$		93
5% Pt/C		EtC(OMe)$_3$		69
5% Rh/C		EtC(OMe)$_3$		85
5% Ru/C				90
5% Rh/C		EtC(OMe)$_3$		90
5% Ru/C		EtC(OMe)$_3$		93
5% Pd/C				82
5% Pd/C				49
5% Pt/C				91
5% Rh/C				48

4. Conclusions

It was for the first time demonstrated that carboxylic ortho esters could be used as an alkylating agent in the reductive alkylation of amines. The present method is especially useful for selective monoalkylation of primary amines and methylation under water-free conditions. Furthermore, the developed method has several advantages, especially as off-the-shelf catalysts could be utilized and that the reaction displays good functional group tolerance.