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Screening of Lewis acids catalyzed amidation of benzylic alcohols

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Abstract: In this work, a screening of different transition metal complexes for their ability to catalyze different substitution reaction of benzylic alcohols and benzamide was performed.

Keywords: Lewis acid, Benzylic alcohols, Amidation.

Introduction

Modification of already existing synthetic methodologies has received greater attention in recent years from both industrial and academic research communities. The construction of carbon– nitrogen bond is one of the most important fundamental processes in organic and bioorganic chemistry as peptides and proteins are formed by amide bonds. Amides are pharmaceutically important compounds in pharmaceutical industries and serve as precursors to the corresponding amines. Therefore there is a great deal of interest in the synthesis of amides [1-8].

Amides are common moieties in naturally occurring substances like peptides and proteins and are also found in various synthetic materials [1,2]. This makes the amide functionality an important building block in synthetic chemistry and many methods for its synthesis were reported in the literature [9,10].

C–N bond formation is an important reaction in organic synthesis. Hence, the development of simple, efficient and environmentally friendly C–N bond forming reactions is of paramount importance in organic synthesis. Among the various methods for the construction of C–N bonds [11], transition metal catalyzed substitution reactions of derivatives of alcohols with nitrogen nucleophiles such as amines/amides is one of the most efficient and reliable methods [12]. However, these methods produce stoichiometric amounts of salt waste both in derivatization of the alcohols and the C–N bond formation steps. Thus, in view of the demand for efficient, economic and environmentally viable processes for the direct catalytic substitution of alcohols [13] with nitrogen nucleophiles, a method for the formation of C–N bonds, which is salt-free, highly atom-economic [14], environmentally friendly with water as the only byproduct is highly desirable. Although a number of C–N bond forming reactions by direct substitution of alcohols with amines catalyzed by transition metals have been reported [15], the use of weak nitrogen nucleophiles such as amides which are easily available are extremely rare and require high temperatures [16].

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Results and discussion

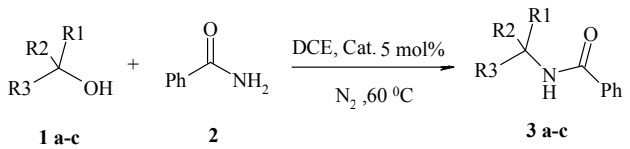
The reaction of benzyl alcohol and benzamide proved to be unreactive in the presence of all catalyst and different reaction conditions such as temperature, solvent (CCl_4, CH_2Cl_2, DCE) and varying amount of the catalyst. The yield of the reaction was increased to 94% by using the 4-methoxybenzyl alcohol (**1a**). Reactions involving diphenylmethanol (**1b**) and benzamide (**2**) worked well and yielded 98% of the desired product (**3b**) in the presence of $NaAuCl_4$. Amidation of triphenylmethanol (**1c**) afforded the desired product but only in poor yield 19%.

Screening of transition metals:

During the reactions, samples were taken out regularly for ^{1}H-NMR spectroscopic analysis. The

samples were filtered through silica to remove the catalyst and the solvent was evaporated *in vacuo*. To the samples 1,4-dioxane was added as internal standard and quantification of the products was performed by comparing signals. The results of these experiments are shown in Table **1.**

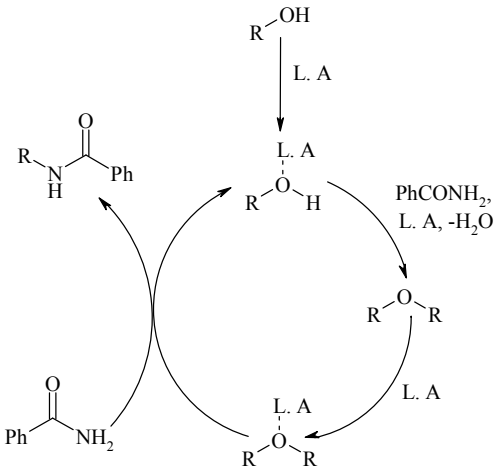
Table 1: Screening of different Lewis acids



1 a-c **2** **3 a-c**

1	R1	R2	R3	Cat	time (hr)	Yielde%, **3a-c**
				$FeCl_3$	26	98
				$PdCl_2$	26	94
a	4-Meo-Ph	H	H	$ReBr(CO)_5$	26	40
				$NaAuCl_4$	26	78
				$ReMeO_3$	26	35
				$FeCl_3$	24	45
				$PdCl_2$	24	65
b	Ph	Ph	H	$ReBr(CO)_5$	24	25
				$NaAuCl_4$	24	98
				$ReMeO_3$	24	10
				$FeCl_3$	16	19
				$PdCl_2$	16	12
c	Ph	Ph	Ph	$ReBr(CO)_5$	16	13
				$NaAuCl_4$	16	18
				$ReMeO_3$	16	9

From the information available in the literature [7-8], it was found that all these reactions proceed via the symmetrical ether and the following mechanism can be proposed (Scheme **1**).



Scheme 1: Proposed mechanism for the Lewis acid catalyzed substitution reaction of benzylic alcohols

Conclusion

In this work, a screening of different transition metal complexes for their ability to catalyze different substitution reaction of benzylic alcohols was performed. The screening was designed for the comparison of the reactivities of $FeCl_3$, $PdCl_2$, $ReBr(Co)_5$, $NaAuCl_4$ and $ReMeO_3$ For S_N1 reactions using nitrogen central nucleophiles.

Experimental

Compounds **1-3** were obtained from Merck and used without further purification. IR spectra: Shimadzu IR-460 spectrometer; in cm^{-1}. ^{1}H-, ^{13}C-NMR Spectra: Bruker DRX-500-Avance instrument or Varian 500-INOVA in $CDCl_3$ at 500, 125.0.; δ in ppm, *J* in Hz. Elemental analyses (C, H, N): Heraeus CHN-O-Rapid analyzer.

*General procedure for synthesis of compounds **3**.*

A well dried round flask was charged with the catalyst (5 mol%), the substrate (1mmol) was added and the flask was purged with nitrogen for 1 minute then the nucleophile (8 mmol), and solvent (5 ml) was added. Then heated to 60 ℃ for appropriate time. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–400 mesh) column chromatography using n-Hexane–EtOAc (8:1) mixture as eluent to get pure product 3.
Spectrocopic Data:

*N'-(4-methoxybenzyl)benzamide (**3a**):*

White solid, ^{1}H-NMR: 3.81 (3 H, s, O-CH_3), 4.59 (2 H, d, ^3J = 5.5, N-CH_2), 6.33 (1 H, br d, ^3J = 5.5, HN), 6.87 (2 H, d, ^3J = 7.1, 2 CH), 7.23 (2H, *d*, ^3J = 7.1, 2 CH), 7.40-7.82 (5 H, m, 5 CH). ^{13}C-NMR: 14.0 (CH_3), 19.6 (CH_2), 32.1 (CH_2), 55.4 (OCH_3), 70.1 (OCH_2), 72.7 (OCH2-Ph), 114 (2 CH), 129.2 (2 CH), 131.1 (C), 159.3 (C). Anal. Calc. For $C_{12}H_{18}O_2$ (194.28): C 74.19, H 9.34; found: C 74.25, H 9.20.

*N'-benzhydrylbenzamide (**3b**):*

White solid, ^{1}H-NMR: 6.48 (1 H, d, ^3J = 7.9, N-CH), 6.69 (1 H, br d, ^3J = 7.9, NH), 7.28-7.85 (15 H, m, 15 CH). ^{13}C-NMR: 57.7 (N-CH), 127.2 (4 CH), 127.6 (4 CH), 128.8 (2 CH), 128.9 (2 CH), 131.8 (2 CH), 135.6 (2 C), 141.7 (C), 164.3 (C=O). Anal. Calc. For $C_{20}H_{17}NO$ (287.36): C 83.60, H 5.96, N 4.87; found: C 83.80, H 5.72, N 5.0.

*N'-tritylbenzamide (**3c**):*

White solid, ^{1}H-NMR: 7.27-7.35 (15 H, m, 15 CH), 7.43-7.47 (2 H, m, 2 CH), 7.50.7.53 (1 H, m, 1 CH), 7.81-7.83 (2 H, m, 2 CH). ^{13}C-NMR: 71.1 (N-CPh_3), 127.1 (6 CH), 127.3 (6 CH), 128.2 (2 CH), 128.8 (2 CH), 131.6 (3 CH), 135.7 (3 C), 145.0 (C), 164.4 (C=O). Anal. Calc. For $C_{26}H_{21}NO$ (363.458): C 85.92, H 5.82, N 3.85; found: C 85.81, H 5.75, N 4.0.

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