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An Efficient Method for Acylation Reactions

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Abstract: $Cu(OTf)_2$ was found to be an efficient catalyst in the acylation reaction of alcohols, phenols, amines and thiols with acetic anhydride in CH_2Cl_2 or acetic acid. A catalytic cycle has been proposed for the acylation reaction. © 1999 Elsevier Science Ltd. All rights reserved.

The base catalyzed acylation of alcohols, phenols, amines, and thiols by acid anhydride or acyl chloride is an established procedure in organic synthesis.[1] 4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) are known to catalyze the acylation of alcohols.[2] A variety of other catalysts such as $TaCl_5$,[3] TMSOTf,[4] $Sc(OTf)_3$,[5] Bu_3P,[6] $COCl_2$,[7] Montmorillonite K-10 and KSF,[8] etc.[9] have been used for acyl transfer reactions in alcohols. Some of these catalysts have also been used in a chiral environment to impart asymmetric induction in non-enzymatic kinetic resolution of secondary alcohols.[10] While working on enantioselective reactions using chiral copper complexes,[11] we discovered that copper (II) trifluoromethanesulfonate [$Cu(OTf)_2$] is an efficient catalyst for TMSCN addition to carbonyl compounds,[12a] opening of epoxides[12b] and aziridines[12c] with less reactive aromatic amines under very mild conditions. This prompted us to use this catalyst for acylation reactions. In this communication we report that $Cu(OTf)_2$ is an efficient catalyst for acylation of alcohols using acetic anhydride/acetic acid. We also report that other functional groups such as phenols, amines, and thiols can also be acylated under the same conditions.

1-Dodecanol was chosen as a model substrate for the acylation reactions. It was treated with 2 equivalents of acetic anhydride (Ac_2O) in the presence of 2 mole % of $Cu(OTf)_2$ in CH_2Cl_2 (Method A) at rt and the reaction was complete in 1 h (99% isolated yield). Other solvents such as toluene, ether, and MeCN were also found to be satisfactory for the above reaction. It was also observed that the above acylation reaction could also be carried out with acetic acid (Method B), but the reaction was very slow at rt. Although primary alcohols (entries 1 - 8) could be acylated in AcOH in the presence of 2 mole % of $Cu(OTf)_2$ at rt, secondary alcohols required higher temperature (60-65 °C) for completion of the reaction.

The acylation reaction was extended to a variety of alcohols and quantitative yields of acetates were obtained in all the cases (Table). Tertiary alcohols could also be acylated in a satisfactory manner. For example, tetraol (entry 24) was treated with 12 equivalents of Ac_2O at rt for complete acylation, and there was no elimination product in the mixture. However, in the case of linalool (entry 26), the reaction was not clean at rt, but at 0 °C the reaction proceeded cleanly and an 80% yield of acylated product was obtained. In order to extend the scope of the catalyst further, the acylation of phenols, amines, and thiols was investigated. In the case of phenols, Method B did not work at all and none of the required product was seen (by tlc). However, these were easily acylated under the conditions of Method A. Even hindered phenols were acylated in a quantitative yield (entry 32).

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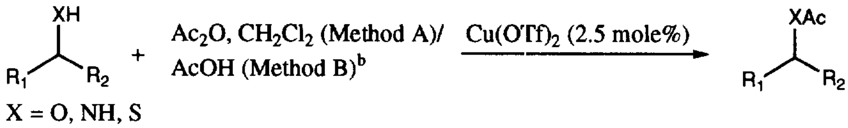
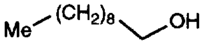
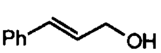
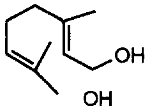
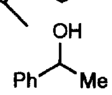
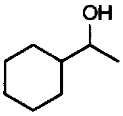
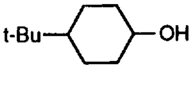
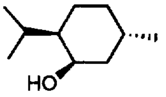
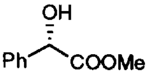
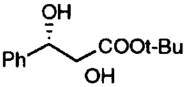
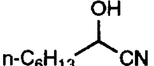
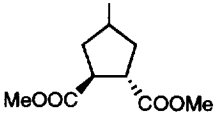
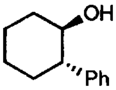
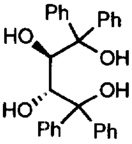
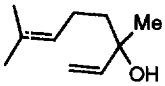
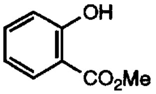
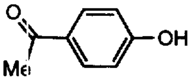
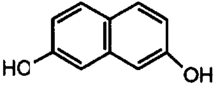
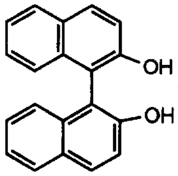
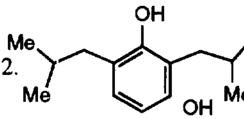
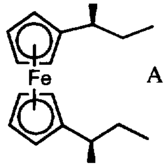
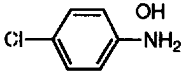
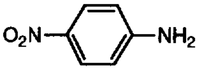
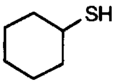
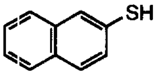
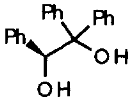
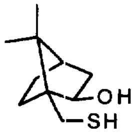


Table: Cu(OTf)$_2$ catalyzed acetylation reactions.[a]

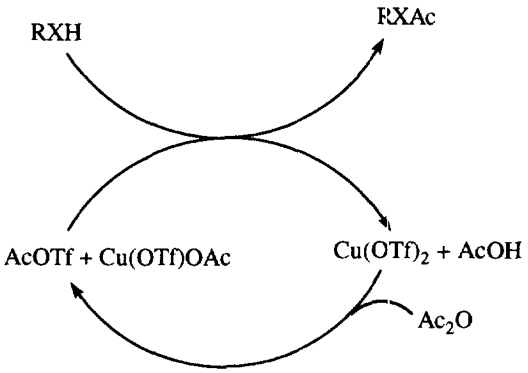
Entry	Substrates	Method	Time	Yield
1.		A	1 h	99 %
2.		B	6 h	96 %
3.	PhCH$_2$OH	A	0.5 h	97 %
4.		B	8 h	94 %
5.		A	0.5 h	91 %
6.		B	8 h	79 %
7.		A	0.5 h	92 %
8.		B	6 h	91 %
9.		A	1 h	92 %
10.		B	14 h	94 %
11.		A	0.5 h	96 %
12.		B	10 h	89 %
13.		A	1 h	98 %
14.		B	10 h	96 %
15.		A	0.5 h	98 %
16.		B	12 h	96 %
17.		A	1 h	97 %
18.		B	12 h	96 %
19.		A	3 h	92 %
20.		A	1 h	99 %
21.		A	2 h	90 %
22.		A	1 h	99 %
23.		B	10 h	97 %
24.		A	8 h	86 %
26.		A[d]	12 h	79 %
27.		A	1 h	98 %
28.		A	2 h	96 %
29.		A	2 h	93 %
30.		A	2 h	82 %
31.		A	2 h	87 %
32.		A	1 h	98 %
33.		A	1 h	95 %
34.		A	2 h	91 %
35.		A	2 h	96 %
36.	PhCH$_2$NHMe	A	2 h	98 %
37.	t-BuNH$_2$	A	3 h	92 %
38.		A	5 h	84 %
39.		A	3 h	89 %

25.		A^c	2 h	88 %	40.		A^e	4 h	90 %

[a]The reaction was done at rt unless it is stated otherwise. [b] For secondary alcohols, this method required 65 °C. [c]1.2 equivalents of Ac_2O were used for monoacetylation of the secondary alcohol. [d]Entry 26 was done at 0 °C. [e]4 equivalents of Ac_2O were used in order to get acetylation at both of the functional groups.

Aromatic and aliphatic amines were successfully acylated using Method A (entries 34 to 37). The notable feature of the reaction is that even a hindered amine was acylated in very high yield (entry 37). Aliphatic and aromatic thiols were also acylated in high yields using the method A procedure (entry 38 to 40).

Although we do not have any proof of the mechanism of the $Cu(OTf)_2$ catalyzed acylation reaction, we propose that Ac_2O reacts with $Cu(OTf)_2$ to generate the acyl triflate which is attacked by RXH to give the acylated product and triflic acid. The triflate ion/triflic acid then reacts with Cu(OTf)OAc to generate $Cu(OTf)_2$ and acetic acid. The same catalytic cycle can also be used for Method B where acetic acid reacts with $Cu(OTf)_2$ to give Cu(OTf)OAc and AcOTf. The slow formation of these species, in this case, is perhaps responsible for the slower reaction when using the Method B procedure.



Proposed Catalytic Cycle for Acylation Reactions

In conclusion, we have shown that $Cu(OTf)_2$ is an efficient and a versatile catalyst for acylation reactions of alcohols, phenols, amines, and thiols. The advantage of the method is that even hindered substrates can be acylated in high yield under mild conditions. Further work is in progress for an asymmetric version of this reaction where $Cu(OTf)_2$ can be complexed with a suitable chiral nonracemic ligand and used in kinetic resolution of secondary substrates.

General Procedure for acylation Reactions

Method A: Acetic anhydride (2 mmol) was added dropwise to a solution of the alcohol, phenol, amine, or thiol (1 mmol) and $Cu(OTf)_2$ (2.5 mole %) in CH_2Cl_2 (2-3 mL) at rt and the reaction mixture was stirred until the tlc showed complete disappearance of the starting material. The reaction mixture was diluted with more CH_2Cl_2

and washed with water and brine. After drying and solvent removal, the acetate was obtained in pure form and did not require any chromatography.

Method B: A solution of alcohol (1 mmol) and $Cu(OTf)_2$ (2 mole %) in acetic acid (2-3 mL) was stirred at rt (or at 65 °C). After completion of the reaction, it was worked up as mentioned in Method A.

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