SYNTHETIC COMMUNICATIONS, 28(11), 1923-1934 (1998)

SELECTIVE ACETYLATION OF PRIMARY ALCOHOLS: ACETYL AND FORMYL TRANSFER REACTIONS WITH COPPER(II) SALTS

N.Iranpoor*, H.Firouzabadi* and M.A. Zolfigol

Chemistry Department, Shiraz University, Shiraz 71454, Iran

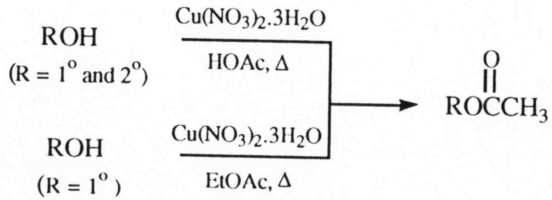
Abstract: The efficient esterification of primary and secondary alcohols in acetic acid was achieved in the presence of $Cu(NO_3)_2 . 3H_2O$ in high yields. Selective acetylation of primary in the presence of secondary hydroxyl groups in excellent yields were performed in EtOAc. Formylation of primary and secondary alcohols was also achieved easily in ethyl formate. High retention of configuration was observed in the acetylation and formylation of (-) menthol in the presence of $Cu(NO_3)_2 . 3H_2O$ and $Cu(OAc)_2 . H_2O$.

Esterification of hydroxyl groups is an important and well-established reactio in organic synthesis.[1] This reaction is mainly achieved in the presence of eithe different bases, acids and varieties of acetylating agents.[2] In addition to the acid and bases, the use of many heterogenous and homogenous catalysts or reagen [3-14] are also reported. Some of these reagents or catalysts are highly acidic i

*To whom correspondence should be addressed.

nature and there is a fear of unfavorable side reactions such as dehydration. Other problems with some of the reported methods are high reaction temperatures[9,12], long reaction times,[7b]bulk requirement of the solid bed[7b] and availability of the catalyst.[7,11]

In continuing our studies about C-O bond cleavage in alcohols and esters,[15] we observed that Cu(II) as $Cu(NO_3)_2.3H_2O$, $Cu(NO_3)_2$ $3H_2O/SiO_2$, $CuCl_2$ and $Cu(OAc)_2.H_2O$ are effective reagents for acetylation of primary and secondary alcohols in acetic acid and for selective transesterification of primary alcohols in ethyl acetate. Among the copper salts we have studied, $Cu(NO_3)_2.3H_2O$ was found to be the most effective reagent in acetylation reactions (scheme 1).



Scheme 1

Acetylation of primary and secondary alcohols in the presence of $Cu(NO_3)_2.3H_2O$ was performed in refluxing acetic acid and produced the desired esters in excellent yields (Table 1). Acetylation of benzylic alcohols carrying electon-withdrawing groups is rare in the literature. We have performed this reaction with $Cu(NO_3)_2.3H_2O$ in acetic acid with high yields.(Table 1, Entries 13,14).

Table 1. Acetylation of Alcohols by Equimolar Amounts of $Cu(NO_3)_2.3H_2O$ in Refluxing Acetic Acid.

Entry	Alcohol	Time (h) (Yield %)	Bp (°C)/Torr or Mp (°C) Found	Reported
1	Octan-1-ol	0.5 (95)	198-199/760	199/760[25]
2	Octan-2-o1	2 (88)	200/760	194.4/744[24]
3	Octadecan-1-o1	3.5 (90)	32-33	32.5[7b]
4	Cyclohexanol	2.5 (97)[b]	174-175/760	175/760[24]
5	Cyclopentanol	1 (98)[b]	153/760	152-53/760[24]
6	Cholesterol	2 (80)[c]	113-114	114-115[24]
7	2-Phenylethan-1-o1	0.75 (91)	230-231/760	232/760[24]
8	1-phenylethan-1-o1	2 (90)	222/760	222/760[24]
9	3-phenylpropan-1-o1	1 (92)	90-91-/10	109-110/16[28a]
10	1-phenylpropan-1-o1	2 (90)	96-97/10	105/16[28b]
11	(-) Menthol	3.5 (98)[d]	227-228/760	227/760[25]
12	4-Methoxybenzyl alcohol	0.5 (72)	137-139/12	110-117/3.5[29]
13	4-Bromobenzyl alcohol	2.5 (81)	31-32	32[30]
14	4-Nitrobenzyl alcohol	8 (85)	80	79-80[8b]

[a] **Yield refers to isolated product.**
[b] **GC yield.**
[c] **2 Molar equivalents of the reagent were used.**
[d] **Acetylation occurs with high retention of configuration (see table 2).**

An interesting observation was made on the reaction of (-) menthol with the above mentioned copper salts in acetic acid. Transesterification of the optica active menthol in the presence of hydrous zirconium oxide and zinc acetate ha been reported.[12,16] In the former case, the formation of 43%, 10-42% and 99% o the acetate has been reported in vapour phase, in solution at high temperature an in outoclave respectively without configuration assignment and in the latte reaction , complete inversion of configuration has been observed with the formatio

Table 2. Acetylation of (-) Menthol[a] with Equimolar of the Cu(II) Salts in Refluxing Acetic Acid.

Copper salt	Time(h)	Yield %[b]	$[\alpha_D]/CHCl_3$	
			Observed	Reported
$Cu(NO_3)_2.3H_2O$	3.5	98	-80.1°	-79.42[17]
$Cu(CH_3CO_2)_2.H_2O$	28	90	-78°	"
$CuCl_2$	22	92	-75°	"
$Cu(NO_3)_2.3H_2O/SiO_2$	5	93	-47°	"

[a](-) Menthol, the product of Fluka with $[\alpha]_D$ = - 50° was used without further purification.

[b]Yield refers to isolated product.

of (+) neomenthyl acetate in 80% yield. We have observed that various copper salts under our investigation can bring about this reaction with excellent retention of configuration and with high yield (Table 2).

Among the reported acetylation reactions, as far as we know, there is only one reagent which has been used for selective acetylation of primary alcohols.[7b] In order to explore the ability of copper salts for selective acetylation of primary in the presence of secondary alcohols, the transesterification was studied in EtOAc. It was observed that $Cu(NO_3)_2.3H_2O$ acetylates primary aliphatic alcohols in refluxing EtOAc in high yields, but secondary alcohols remained unreacted. Competitive reactions were also performed on a mixture of primary and secondary alcohols with high selectivity (Table 3, entries 8,9). The reaction of phenylethanediol carrying both primary and seconary hydroxy groups was also examined (Table 3,

Table 3. Selective Acetylation of Primary Alcohols with $Cu(NO_3)_2.3H_2O$ in Refluxing EtOAc.

Entry	Alcohol	Time(h)	Yield (%)[a]
1	Octan-1-ol	2.5	91
2	2-Phenylethan-1-ol	3	92
3	3-Phenylpropan-1-ol	3.5	95
4	Octadecan-1-ol	30	85
5	Octan-2-ol	3	5
6	1-Phenylpropan-1-ol	3	6
7	Phenylethanediol	6	82+14+4[b]
8	Octan-1-ol Octan-2-ol	6	100[c] 9[c]
9	3-Phenylpropan-1-ol 1-Phenylpropan-1-ol	6	100[c] 10[c]

[a] Isolated yields. [b] The products from this reaction were isolated using thicl layer chromatography and identified by spectral analysis. The majore reactior was found to be acetylation of primary hydroxy group(82%). Other reaction: were found to be acetylation of secondary hydroxy group(14%) and acetylatior of both hydroxy groups (4%). [c] GC yields.

entry 7). Analysis of the products showed the formation of 2-acetoxy-1-phenyl-1 ethanol as the major (82%) and 1-acethoxy-1-phenyl-2-ethanol as the minc product (14%) products. In the case of more structurally complex molecules lik sugers, complexation with Cu(II) prevents the ocurrance of acetylation reaction .

Table 4. Formylation of Primary and Secondary Alcohols with 1.5 Molar Equivalents of $Cu(NO_3)_2.3H_2O$ in Refluxing Ethyl Formates.

Entry	Alcohol	Time (Yield%)[a] (h)	Bp (°C)/Torr, Mp (°C) or n_D^{20} Found	Reported
1	Octan-1-ol	1 (90)	197-198/760	198/760[21b]
2	Octan-2-ol	3 (91)	81-82/20	181-183/760[26]
3	2-phenylethan-1-ol	2 (92)	99-100/15	73-5/3[27]
4	Octadecan-1-ol	4 (99)[b]	53-54	52-53[21a]
5	Cyclohexanol	8 (78)[c]	161/760	160/760[21b]
6	Cyclopentanol	1.5 (100)[c]	138/760	138-139/760[22b]
7	Cholesterol	1.5 (98)[b]	111-112	112[21b]
6	3-phenylpropan-1-ol	3 (88)	1.4921	e[32]
7	(-) Menthol	3.5 (98)	96-98/15	45-60/0.01[21b]
8	4-Chlorobenzyl alcohol	6 (60)[d]	1.5299	e[21c]
9	4-Bromobenzyl alcohol	10 (62)[d]	1.5352	e[33]
10	4-Nitrobenzyl alcohol	36 (40)[d]	31	30[31]

[a] Isolated yields. [b] 4 Molar equivalents of the reagent were used. [c] GC yields. [d] Accompanied with oxidation. [e] Identified by comparison with authentic samples.

Although there are various formylating agents have been reported,[18] but there are serious limitations for the preparation of formates due to the drastic reaction conditions (e.g., heating the alcohol in 85% formic acid at 70°C),[19a] or use of rather uncommon reagents (e.g., acetic-formic anhydride,[19b] N,N-diformyl-acetamide,[20] polymer-supported phosphine-halogen complexes/DMF,[21a] benzoylchloride-DMF adduct,[21b] Cl_2SO-DMF/KI,[21c] enol formates,[22a] cyanomethyl formate,[22b,c] N-formyl formamide,[23a] and N-formyl benzotriazole[23b]. However, due to unstability of the anhydride and the acid chloride of formic acid,[13a,23b] formylation of alcohols by ethyl formate is an important synthetic reaction.

Table 5. Formylation of (-) Menthol with 1.5 Molar Equivalents of the Cu(II) Salts in Refluxing Ethyl Formate.

Copper salt	Time h	Yield(%)[a]	$[\alpha_D]/CHCl_3$ Observed	Reported
$Cu(NO_3)_2.3H_2O$	3.5	100	-69.0°	-79.1°[17]
$Cu(CH_3CO_2)_2.H_2O$	2	98	-63°	"
$CuCl_2$	0.5	99	-60°	"
$Cu(NO_3)_2.3H_2O/SiO_2$	4.5	96	-37.8°	"

[a] Yield refers to isolated product.

We therefore, extended our studies with this reagent for formylation of alcohols in ethyl formate. The transesterification was performed efficiently witht both primary and secondary alcohols in refluxing ethyl formate (Table 4). Yields of the reactions are high (62-100%) except for formylation of 4-nitrobenzyl alcohol which the ester is produced in only 40% yield.

Formylation of (-) menthol with the copper salts under our studies was alsc investigated in ethyl formate. Highest retention of configuration was observec with $Cu(NO_3)_2.3H_2O$ (Table 5).

In conclusion, efficient acetylation and formylation of primary and secondar alcohols and selective acetylation of primary in the presence of secondary alcohol were achieved by the present methodology. Excellent stereospecificity of th reaction of (-) menthol in both acetylation and formylation reactions, cheapnes and availability of the reagent, easy procedure and workup make this method useful addition to the present methodologies.

Experimental:

Chemicals were purchased from Fluka, Aldrich, Merck. (-) Menthol, the product of Fluka with $[\alpha]_D$ = - 50° was used without further purification. Products were characterized by comparison of their physical data IR, NMR and mass spectra with those prepared as reported in the literature procedures. Infrared spectra were recorded on a Perkin Elmer IR-157 G and a Perkin Elmer 781 spectrometer. NMR spectra were recorded on a Bruker Avance DPX-250 . Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX . The purity determination of the substrates and reactions monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a shimadzu GC-10A instrument with a flame ionization detector using a column of 15% carbowax 20M chromosorb-w acid washed 60-80 mesh. Column chromatography was carried out using Silica gel 60. Yields refer to isolated pure products after column chromatography.

Acetylation of (-) menthol with $Cu(NO_3)_2.3H_2O$ in acetic acid as typical procedure

Menthol (0.312g, 2mmol) and $Cu(NO_3)_2 . 3H_2O$ (0.482 g, 2 mmol) were mixed together in AcOH (4 mL). The mixture was stirred vigorously under reflux condition for 3.5 h. Silica gel (5 g) was added to the reaction mixture and then was chromatographed on a Silica gel column using petroleum ether as eluent. (-) Menthyl acetate was obtained as a colorless liquid(0.39 g, 98%).

Formylation of (-) menthol with $Cu(NO_3)_2.3H_2O$ in ethyl formate

A mixture of (-)menthol (0.312 g, 2 mmol) and $Cu(NO_3)_2.3H_2O$ (0.723g, 3mmol) in ethyl formate (4 mL) was prepared, The resulting mixture was stirred

vigorously under reflux condition for 3.5 h. Solvent was evaporated and the residue was chromatographed on a Silica gel column with petroleum ether . (-) Menthyl formate was obtaind as colorless liquid (0.368 g, 100%).

Acknowledgement The authors wish to thank Shiraz University Research Council for the partial support of this work. The assistance of Dr.A.A. Jarahpour for running mass spectra and Mr. N. Maleki for running NMR spectra are also appreciated.

References

(1) For a review see: Haslam, E. *Tetrahedron* **1980**, *36*, 2409 and the references cited therein.

(2) Patai, S.; Ed., The Chemistry of Carboxylic Acids and Esters, Interscience Publishers, New York, 1969.

(3) Santacesavia, E.; Gelosa, D.; Danise, P.; and Carra, S. *J. Catal.*. **1983**,*80*, 427.

(4) Olah, G. A.; Keumi, T.; Meidar, D. *Synthesis* **1978**, 929.

(5) Hino, H.;Arata, K. *Chem. Lett.*. **1981**,1671.

(6) Tanabe, K.; Hattori, H.; Ban'i, Y.; Mitsutani, A. Jpn. Pattent Appl., 1980, No. 55-115570.

(7) (a) Posner, G. H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 478. (b) Posner, G. H.; Oda, M. *Tetrahedron Lett.*, **1981**,*22*, 5003. (c) Posner, G. H.; Okada, S. S.; Babiak, K. A.; Miura, K.; Rose, R. K. *synthesis*

1981,789. (d) Costa, A.; Riego, J.M. *Can. J. Chem.* **1987**, *65*, 2327.

(8) (a) Kim, S.; Lee, J. I. *J. Org. Chem.* **1984**, *49*, 1712.(b) Ueda, M., Seki, K., Imai, Y. *Synthesis* **1981**,991.

(9) Angeletti, E.; Tundo, P.; Venturello, P. *J. Org. Chem.* **1983** ,*48*, 4106.

(10) Nascimento, M. G.; Zanotto, S. P.; Scremin, M.; Rezende, M. C. *Syntheic Commun.* **1996**, *26*, 2715 .

(11) (a) Kobayashi, S.; *Synlett.* **1994**, 689. (b) Shina, I.; Mukaiyama, T. *Chem. Lett.*, **1992**, 2319. (c) Izumi, J.; Shina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141.

(12) Takahashi, K.; Shibagaki, M.; Matsushita, H.; *Bull. Chem. Soc. Jpn.* **1989**,*62*, 2353.

(13) (a) Nishiguchi, T.; Taya, H.; *J. Chem. Soc. Perkin Trans. 1* **1990**,172.(b) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.***1992**,*57*, 2166. (c) Ho, T. L. *Synthtic Commun.*. **1989**, *19*, 2897.

(14) Kumar, B;. Kumar, H; Parmar, A. *Indian J. Chem.* **1993**, *32B*, 292 .

(15) (a) Iranpoor, N.; Mottaghincjad, E.; *Tetrahedron* **1994**,*50*, 1859, (b) Iranpoor, N.; Mottaghinejad, E. *Tetrahedron* , **1994**,*50*, 7299.

(16) Rollin, P. *Synthtic Commun.* **1986**,*16*, 611.

(17) (a) Tschugaeff, L. *Ber.* **1898**,*31*, 360, (b) Pvelich, W. A., Taft, R. W. *J. Am. Chem. Soc.* **1957**,*79*, 4935.

(18) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671.

(19) (a)Ringold, H.J.; Locken, B.; Rosenkranz, G.; Sondheimer,F. *J. Am. Chem. Soc.* **1956**,*78*, 816. (b) McOmie, J.F.W.; "Protective Groups in Organic Chemistry" Plenum Press, London, 1973, pp 111-112.

(20) Gramain, J.C.; Remuson, R. *Synthesis* **1982**, 264.

(21) (a) Caputo, R.; Ferreri, C. Palumbo,G. *Synthtic Commun.* **1987**,*17*, 1629. (b) Barluenga, J.; Campos, P. J.; Gonzalez-Nunez, E.; Asensio, G. *Synthesis* **1985**, 426. (c) Fernandez, I.; Garcia, B.; Munoz, S.; Pedro, J. R.; Salud, R. *Synlett* **1993**,489.

(22) (a) Neveux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc. Perkin. Trans. 1* **1991**,1197. (b) Deutsch, J.; Niclas, H-J. *Synthetic Commun.*, **1993**, *23*, 1561. (c) Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, J-H . *Synthesis* **1996**,37. (d) van Melick, J. E. W.; Wolters, E. T. M. *Synthetic Commun.* **1972**, 2, 83.

(23) (a) kashima, C.; Arao, H.; Hibi, S.; Omote,Y. *Tetrahedron Lett.*. **1989**,*30*, 1561. (b) Katritzky, A. R.; Chang, H. X.; Young, B. *Synthesi.* **1995**, 503.

(24) Buckingham, J. Dictionary of Organic Compounds, 5th Ed. Chapman and Hall, 1982.

(25) Budavri, S. The Merck Index an Encyclopedia of Chemicals, Drugs and Biologicals, 11th Ed. 1989.

(26) Fort, A.W.; Girard, C.A. *J. Am. Chem, Soc.* **1961**, 83, 3449.

(27) Buckels, R.E.; Maurer, E.J. *J. Org. Chem.* **1953**, 18, 1585.

(28) (a) Francaise, C.; Colrantes, M.C.A., **1963**, 58, 8972a (b) Giordano, G.; Belli, A.; Casagrande, F.; Guglielmetti, G. *J. Org. Chem.* **1981**, 46, 3149.

(29) Summers, L. *J. Am. Chem. Soc.* **1954**, 76, 3481.

(30) Costa, G. *Pubbl. Facolta. Sci. Ing. Univ. Triste. Ser. B.***1947**, 12, 3. C.. 1952, 46, 3609 c.

(31) Fabre, J.L; Julia, M.; Mansour B.; Saussine, J. *J. Organomet.Chem.* **1987**, 19, 161.

(33) Watson, J.R.; Cresuolo, P. *J. Chromatography* **1979**, 52, 63.

(Received in Japan 13 May 1997)

SYNTHETIC COMMUNICATIONS, 28(11), 1935-1945 (1998)

A SIMPLE AND EFFICIENT PROCEDURE FOR THE SYNTHESIS OF OPTICALLY ACTIVE 4-METHOXY-α-METHYLPHENYLETHYLAMINE FROM TYROSINE

Harumichi Kohno, Takeo Iwakuma,[a)] and Koichiro Yamada*

Lead Optimization Research Laboratory, Tanabe Seiyaku Co., Ltd,
2-2-50, Kawagishi Toda-shi, Saitama 335, Japan.

Abstract: Optically active 4-methoxy-α-methylphenylethylamine (**1**), a useful chiral building block in medicinal chemistry, was synthesized from *L*- or *D*-tyrosine by using a simple and efficient procedure *via* one-pot zinc reduction of the corresponding *O*-tosylate (**4**) in the presence of H_2O and NaI in pure form.

Optically active α–methylphenylethylamines, such as 4-methoxy-α-methylphenylethylamine (**1**), are important chiral building blocks in medicinal chemistry. For example, one of our research targets is **TA-2005**,[1] (*R,R*)-8-hydroxy-5-[1-hydroxy-2-[*N*-2-(4-methoxyphenyl)-1-methylethyl]amino-ethyl]quinolin-2(1*H*)-one hydrochloride, which proved to be a potent, long-acting, and β_2-selective agonist. The pure *R* form of amine **1** in large enough quantities is required for the bulk preparation of **TA-2005** (*R, R*-isomer). Synthesis of the enantiomers of **1** *via* fractional crystallization of the tartrate[2] of (±)-**1** or *via* asymmetric reduction[3] of the corresponding imine derivatives of 4-methoxyphenylacetone and (+)- and (-)- α-methylbenzylamines has been described previously. These methods have a number of disadvantages that include low resolution yield (9 %) for the former reported method and loss of the chiral amine source in the hydrogenolysis step for the latter method. We therefore attempted to develop a new synthetic approach to both enantiomeric forms of **1**.