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RUTHENIUM CATALYZED OXIDATION OF CYANOHYDRINS TO ACYL CYANIDES USEFUL REAGENTS FOR SELECTIVE N-BENZOYLATION OF AMINOALCOHOLS

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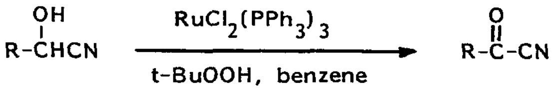
Ruthenium catalyzed oxidation of cyanohydrins with tert-butyl hydroperoxide gives the corresponding acyl cyanides in good to excellent yields. Acyl cyanides thus obtained are useful reagents for selective N-benzoylation of aminoalcohols.

We have found that the ruthenium catalyzed dehydrogenation of alcohols and diols gives the corresponding esters and lactones highly efficiently.[1] The reaction proceeds fast when the hydrogen is trapped with an appropriate hydrogen acceptor. During the course of searching for a suitable oxidant to trap the hydrogen, we have found that tert-butyl hydroperoxide is an excellent oxidant for the ruthenium catalyzed oxidation of alcohols. The oxidation of alcohols with t-BuOOH in the presence of 5 mol% of $RuCl_2(PPh_3)_3$ in benzene at room temperature under argon gives aldehydes and ketones in good to excellent yields. Watanabe et al. have also found the similar ruthenium catalyzed oxidation of alcohols with t-BuOOH.[2]

In this paper, we wish to report that ruthenium catalyzed oxidation of cyanohydrins with t-BuOOH gives acyl cyanides efficiently under mild conditions. Recent paper[3] which reports the ruthenium catalyzed synthesis of α-keto acid derivatives prompted us to report our efficient method.[4]



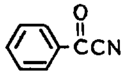
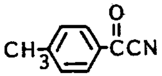
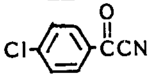
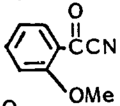
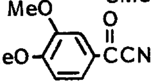
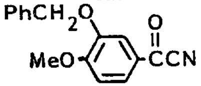
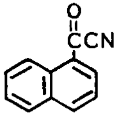
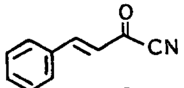
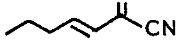
$$\text{R-}\overset{\text{OH}}{\overset{|}{\text{C}}}\text{HCN} \xrightarrow[\text{t-BuOOH, benzene}]{RuCl_2(PPh_3)_3} \text{R-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-CN}$$

Acyl cyanides are versatile synthetic intermediates and have been utilized in a variety of transformation of CO and CN functions,[5] nucleophilic reaction with enolates,[6] and Michael addition.[7] Generally, acyl cyanides have been prepared by the reactions of acid halides with a variety of metal cyanides[5,8] and trimethylsilyl cyanide.[6,9] Alternative method is the oxidation of cyanohydrins with active manganese dioxide[10] or pyridinium dichromate.[11] The former method is advantageous for the conversion of sensitive aldehydes into esters, although acyl cyanides are not isolated.[10]

Acyl cyanides can be conveniently prepared by the $RuCl_2(PPh_3)_3$ catalyzed oxidation of cyanohydrins, which are readily prepared upon treatment of aldehydes with $NaHSO_3$-KCN[12] or $(CH_3)_3SiCN/ZnI_2$-HCl.[13] Table 1 summarizes the representative results of the synthesis of acyl cyanides. Aromatic and α,β-unsaturated cyanohydrins are converted efficiently into acyl cyanides, while aliphatic cyanohydrins are converted into the corresponding carboxylic acids because of the hydrolysis of unstable acyl cyanides. For the conversion of conjugated aldehydes, the present method is advantageous over the previous methods,[10] because versatile acyl cyanides can be easily isolated.

The catalytic activity of various metal complexes has been examined for the oxidation of benzaldehyde cyanohydrin. $RuCl_2(PPh_3)_3$ is the best catalyst for the formation of benzoyl cyanide (92%). $RuCl_3 \cdot nH_2O$ and $RuH_2(PPh_3)_4$ gave lower yields (86% and 31%), and $RhCl(PPh_3)_3$ and $Pd(OAc)_2$ gave unsatisfactory results. The solvent effect is important. Benzene, CH_2Cl_2, and CCl_4 are good solvents; benzene (92%) > CH_2Cl_2 (81%) > CCl_4 (80%) > THF (35%) > pyridine (23%) > DMF (0%). t-BuOOH in dry benzene[14] is the best oxidant among the oxidants examined.

Table 1. Conversions of Cyanohydrins to Acyl Cyanides a)

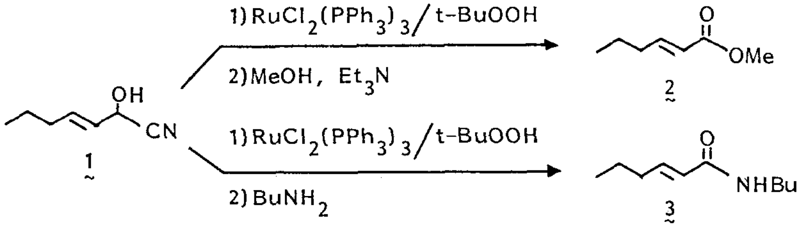
	Acyl Cyanide b)	Synthetic Method of Cyanohydrin c)	Time(h)	Isolated Yield(%)
1		A	3	87
2		A	3	99
3		A	3	77
4		A	11	82
5		A	2	89
6		B	15	87
7		B	24	65
8		B	9	92
9		B	8	81

a) All reactions were carried out following the standard procedure described in the text. b) All products showed satisfactory IR, NMR, and Mass spectral data. c) Cyanohydrins were prepared in 90-95% yields according to the following methods. A; $NaHSO_3$-KCN, B; Me_3SiCN/ZnI_2-2N·HCl.

Hydrogen peroxide, m-chloroperbenzoic acid, benzoyl peroxide, sodium periodate, and oxygen gave unsatisfactory results. The oxidation of α,β-unsaturated cyanohydrins proceeds slowly, and hence t-BuOOH should be added slowly (5-6 hr) to complete the oxidation.

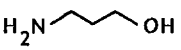
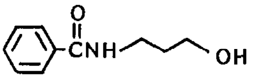
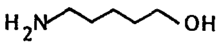
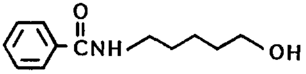
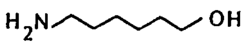
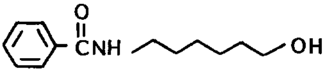
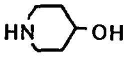
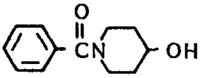
Typical procedure for the oxidation of cyanohydrins is as follows. To a mixture of benzaldehyde cyanohydrin (0.266 g, 2.0 mmol) and $RuCl_2(PPh_3)_3$ (0.096 g, 0.1 mmol) in dry benzene (4.0 mL) was added a solution of t-BuOOH in dry benzene (4.0 mmol, 1.2 mL) dropwise at room temperature over 20 min. After stirring for 3 hr palladium black was added to decompose excess t-BuOOH. Filtration, removal of the solvent, and short column chromatography (florisil, dry ether) gave benzoyl cyanide (0.228 g, 87%).

Smooth formation of carboxylic acid derivatives from acyl cyanides is particularly advantageous for the transformation of sensitive aldehydes into acid derivatives. Typically, the ruthenium catalyzed oxidation of 2-hydroxy-3-heptenenitrile (1) followed by treatment with methanol in the presence of triethylamine afforded the corresponding ester 2 in 85% yield. Similar treatment with butylamine gave the amide 3 in 77% yield.



Selective N-protection of an amino group in the presence of a hydroxy group is of importance in the synthesis of alkaloids,[15] amino sugars,[16] and related compounds. We have found that benzoyl cyanides are highly useful reagents for the selective benzoylation of an amino group.[17] The representative examples are listed in Table 2. Typically, to a solution of 3-amino-1-propanol (0.377 g, 5.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of benzoyl cyanide (0.659 g, 5.0 mmol) in CH_2Cl_2 (4 mL) at -10°C. After removal of the solvent

Table 2. Selective N-Benzoylation of Aminoalcohols[a]

Entry	Aminoalcohol	Product[b]	Isolated Yield (%)
1			92
2			93
3			91
4			99

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[a] All reactions were carried out following the standard procedure described in the text.
[b] All products showed satisfactory IR, NMR, and Mass spectral data.

the residue was subjected to column chromatography (SiO_2). The hydrogen cyanide generated was trapped with a sodium hydroxide solution and then treated with antiformin (NaClO). Elution with a mixture of ether and methanol (4:1) gave N-(3-hydroxypropyl)benzamide (0.830 g, 92%).

Benzoyl cyanides are clean and mild acylating reagents. Further work is now in progress on the extention of this reaction to the other system and application to the synthesis of natural products.

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