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A facile direct conversion of aldehydes to esters and amides using acetone cyanohydrin

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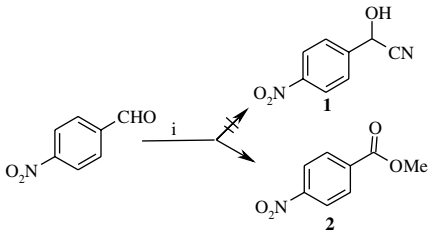
Abstract—Aromatic aldehydes with electron-withdrawing groups undergo rapid reactions with a variety of alcohols and secondary amines to afford the corresponding esters and amides, respectively, in high yields, when treated with NaCN or acetone cyanohydrin and base under ambient reaction conditions. In case of α,β-unsaturated aldehydes, simultaneous reduction of the C=C bond along with esterification occurred to produce the saturated esters in high yields.

1. Introduction

The direct transformation of aldehydes into the corresponding esters[1] and amides[2] under mild conditions is often required in organic synthesis especially in the synthesis of natural products.[3] Although such functional group transformation of aldehydes into esters in the presence of alcohols has been reported,[4] these methods usually require harsh conditions and are effective for a limited range of substrates (electron-rich aldehydes[5] and primary alcohols). Recently, several new procedures involving oxone,[6] SnO_2/SBA-1-H_2O_2[7] and pyridinium hydrobromide perbromide[8] have been employed for the direct oxidative conversion of aldehydes to esters. This transformation generally involves an oxidative pathway and requires more than stoichiometric amount of oxidants and long reaction times. Also these reagents are unsatisfactory for aldehydes containing electron-withdrawing groups. Moreover, formation of minor amounts of acids often complicates the oxidative process. Direct transformation of aldehydes into amides is also an important method in organic synthesis and usually requires transition metal catalysts such as palladium,[9] ruthenium[10] and rhodium.[11] However, these systems suffer from use of stoichiometric amount of oxidants coupled with low yields of the products. We wish to report a facile method for the direct conversion of electron deficient aldehydes to esters and amides mediated by acetone cyanohydrin in the presence of base.

During our investigation of the hydrocyanation of 4-nitrobenzaldehyde with acetone cyanohydrin in the presence of Et_3N in methanol as solvent, we found surprisingly that the corresponding methyl ester **2** was obtained in 92% yield instead of the expected cyanohydrin **1** (Scheme 1). Control experiments indicated that no reaction took place in the absence of either the acetone cyanohydrin or Et_3N. Both KOH and Et_3N could be used as the base for this transformation although *t*-BuOK and DABCO were found to be less effective. The results in Table 1 show that a variety of solvents could be employed successfully for the reaction of 4-nitrobenzaldehyde with methanol. Although most of the polar solvents displayed comparable activity, methanol was found to give the best yield. However, when



Scheme 1. Reaction conditions: (i) 4-nitrobenzaldehyde (5 mmol), acetone cyanohydrin (5 mmol), Et_3N (7.5 mmol), MeOH (5 mL), 25 °C, 2 h.

Keywords: Esterification; Amidation; Reduction; Sodium cyanide.
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Table 1. Esterification of 4-nitrobenzaldehyde with methanol using acetone cyanohydrin: effect of solvents

Entry	Solvent	Yield[a] (%)
1	CH_3OH	92
2	CH_3CN	70
3	THF	54
4	Benzene	20
5	CH_2Cl_2	23
6	DMF	57
7	Acetone	83
8	H_2O	81[b]

[a] Isolated yield after column chromatographic purification.
[b] 4-Nitrobenzoic acid was obtained.

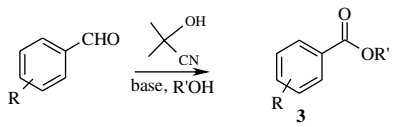
water was employed as solvent, the only product obtained was the corresponding carboxylic acid. In order to understand the scope and generality of the reaction, a wide range of aldehydes was subjected to the reaction with a variety of alcohols under these reaction conditions. As can be seen, the method worked exceedingly well in the case of aromatic aldehydes with electron-withdrawing groups such as halo, nitro, CF_3, cyano, etc. (Table 2). Unfortunately, the reaction failed for electron-rich benzaldehydes as well as aliphatic aldehydes perhaps because the nucleophilic addition of cyanide ion onto electron-rich aromatic substrates is more difficult.

Alcohols such as ethanol, allyl alcohol, propargyl alcohol and 2-propanol, etc., when subjected to the reaction, afforded esters in excellent yields. When 4-nitrobenzaldehyde was treated with ethane-1,2-diol the corresponding diester was obtained in 35% yield.

A noteworthy feature of this protocol is that α,β-unsaturated aldehydes when subjected to these reaction conditions gave the corresponding saturated esters (Table 3). de Vries et al.[12] and Kawabata and Hayashi et al.[13] have reported similar observations using $RuCl_3{\cdot}H_2O$/PCy_3 and a Lewis base, respectively. However, these reactions suffer from disadvantages such as high temperatures, low yields, expensive ligands etc. The present method is superior to the ruthenium-catalyzed method from the viewpoint of the high yield of the product, the use of inexpensive reagents and the mildness of the reaction conditions. Thus both ester formation and reduction of the C=C bond were achieved in a single step for α,β-unsaturated aldehydes when treated with NaCN or acetone cyanohydrin in the presence of an alcohol. A wide range of substituted cinnamaldehydes can be converted into saturated esters when subjected to these conditions.

We have applied the ester formation–reduction strategy to the synthesis of nabumetone **8**, a non-steroidal anti-inflammatory drug[14] (Scheme 2). Thus, alcohol **5**[15] on reaction with Vilsmeyer–Haack reaction, gave the unsaturated aldehyde **6**, which was subjected to the cyanide-mediated ester formation–reduction to afford

Table 2. Acetone cyanohydrin-mediated esterification of activated aromatic aldehydes with alcohols

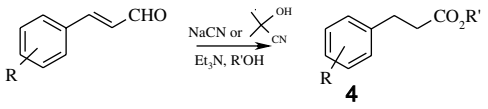


3

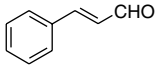
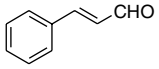
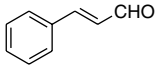
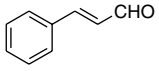
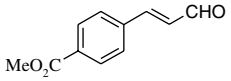
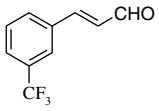
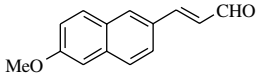
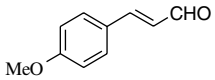
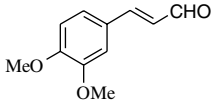
Entry	R	Base	Yield of **3**[a] (%)		
			R′ = methyl	Allyl[b]	Propargyl[b]
a	3-NO_2	Et_3N	78 (49)[c]	64	75
b	4-NO_2	Et_3N	92 (75)[c]	70	63
c	4-Cl	KOH	82	78	75
d	4-Br	KOH	73	62	85
e	4-CN	Et_3N	80	76	83
f	3-CF_3	KOH	70	62	85
g	4-F	KOH	60	62	65
h	2-CN	Et_3N	61	67	58

[a] Isolated yield after column chromatographic purification.
[b] Acetonitrile was used as solvent.
[c] The number in the parentheses refers to yields when 2-propanol was used as the alcohol component.

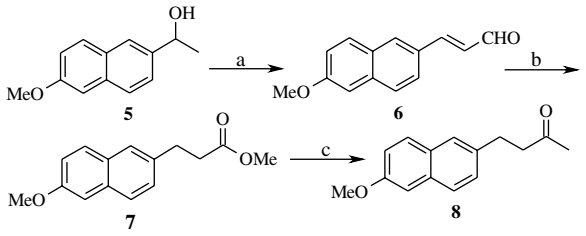
Table 3. Cyanide mediated esterification and reduction of α,β-unsaturated aldehydes with alcohols



4

Entry	Aldehyde	Alcohol	Yield of **4**[a] (%)
1		CH_3OH	93
2			86
3			69
4			88
5			76
6			66
7			61
8			64
9			57

[a] Isolated yield after column chromatographic purification.



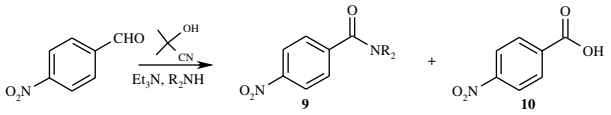
Scheme 2. Reagents and conditions: (a) $POCl_3$, DMF, 100 °C, 47%; (b) acetone cyanohydrin or NaCN, Et_3N, CH_2Cl_2, 25 °C, 2 h, 61%; (c) MeMgI, THF, −55 °C, 51%.

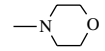
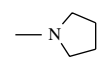
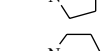
the saturated ester **7** in 61% yield. Treatment of ester **7** with a Grignard reagent gave nabumetone in 51% yield.

The methodology also worked very well for the direct conversion of aldehydes into amides. When 4-nitrobenzaldehyde was treated with cyclic secondary amine such as morpholine, pyrrolidine, piperidine, etc., under the same reaction conditions, the corresponding carboxylic amides were obtained in good yields (54–63%) (Scheme 3).

Mechanistically, we believe that the transformation of the aldehydes into esters or amides proceeds through an acyl cyanide intermediate **A**, as confirmed by its isolation and characterization. The first step may involve the formation of cyanohydrins. Subsequently, the cyanohydrins are converted to the acyl cyanides **A** by the way of hydride transfer to acetone (Fig. 1). In the case of α,β-unsaturated aldehydes, the formation of enol **B** by double bond migration of cyanohydrin followed by tautomerization, provides the corresponding saturated acyl cyanide **C** (Fig. 2). The intermediates **A** and **C** may then be converted to esters or amides by reaction with alcohols and amines, respectively.

In conclusion, this methodology provides a simple procedure for the single-step conversion of electron-deficient aldehydes into the corresponding esters and amides on reaction with either an alcohol or a secondary amine in excellent yields mediated by acetone cyanohydrin or NaCN and base. This protocol is complementary to existing methods of ester formation, which fail in the case of electron-deficient aldehydes.



R_2N =	Yield of **9** (%)	Yield of **10** (%)
	63	31
	57	33
	54	34

Scheme 3. Direct amidation of aldehydes.

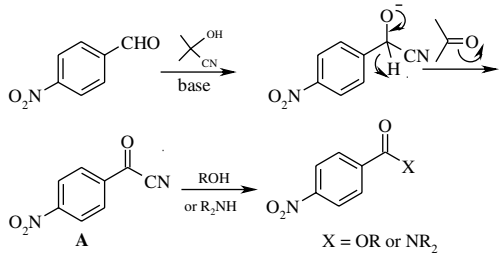


Figure 1. Proposed mechanism for the conversion of aldehydes into esters and amides.

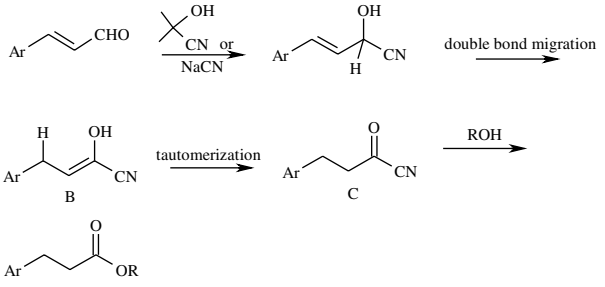


Figure 2. Proposed mechanism for the conversion of enals into saturated esters.

2. Experimental

2.1. General procedure for the esterification and amidation reactions

A mixture of the aldehyde (5.0 mmol), Et_3N or KOH (7.5 mmol), alcohol or secondary amine (7.5 mmol) and acetone cyanohydrin (5.0 mmol) in 5 mL of solvent was stirred for 3 h under an argon atmosphere at 25 °C. The progress of the reaction was monitored by TLC. After completion, the solvent was removed under reduced pressure. The crude product so obtained was further purified by column chromatography (silica gel) using a mixture of petroleum ether and ethyl acetate (9:1) as eluent.

2.2. Selected spectral data

2.2.1. Propargyl 4-bromobenzoate. Yield: 85%; gum. IR (Neat, cm^{-1}): 1216, 1531, 1608, 1733, 3021, 3306; ^1H NMR (200 MHz, $CDCl_3$): δ 2.53–2.50 (t, $J = 4.0$ Hz, 1H), 4.91–4.89 (d, $J = 4.0$ Hz, 2H), 7.60–7.56 (d, $J = 8.0$ Hz, 2H), 7.94–7.90 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.57, 75.33, 128.33, 129.62, 130.87, 131.74, 135.14, 139.29, 164.69; MS (*m/z*, % relative intensity): 238 (M^+, 2) 183 (54), 155 (25), 115 (34), 104 (27), 75 (64), 50 (100). Analysis $C_{10}H_7BrO_2$ requires C, 50.24; H, 2.95; Br, 33.42. Found C, 50.20; H, 2.91; Br, 33.40.

2.2.2. 4-Nitrobenzoyl nitrile. Yield: 32%; colourless solid; mp: 115 °C (lit.[16] 116 °C). IR ($CHCl_3$, cm^{-1}) 1102, 1526, 1606, 1731, 2245, 2450, 2924, 3453; ^1H NMR (200 MHz, $CDCl_3$): δ 8.33–8.16 (m, 4H); ^{13}C NMR (75 MHz $CDCl_3$): δ 72.75, 121.31, 126.52, 133.80,

137.22, 153.90. Analysis $C_8H_4N_2O_3$ requires C, 54.55; H, 2.29; N, 15.91. Found C, 54.51; H, 2.25; N, 15.89.

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