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Synthesis of Alkylated Nitriles by [RuHCl(CO)(PPh$_3$)$_3$]-catalyzed Alkylation of Acetonitrile Using Primary Alcohols

Takashi Kuwahara, Takahide Fukuyama,* and Ilhyong Ryu*
Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531

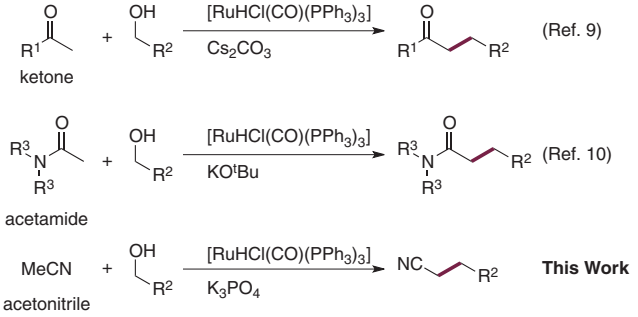
(Received May 17, 2013; CL-130465; E-mail: ryu@c.s.osakafu-u.ac.jp, fukuyama@c.s.osakafu-u.ac.jp)

Alkylation reaction of acetonitrile using primary alcohols is effectively catalyzed by [RuHCl(CO)(PPh$_3$)$_3$] in the presence of K_3PO_4 as a base. Both benzylic and non-benzylic alcohols coupled with acetonitrile to give alkylated nitriles in good yields.

The nitrile moiety is intrinsically important in organic synthesis, since it can be transformed to a variety of functional groups including amides, amines, and carboxylic acids.[1] The most common protocol for alkylated nitrile synthesis is substitution of alkyl halides by cyanide ion.[2] However, cyanide reagents, such as KCN and NaCN, are highly toxic and therefore careful handling is required for their use. Alkylation of acetonitrile using organic halides can provide an alternative method for the synthesis of nitriles.[3] While in this protocol acetonitrile can serve as a C2 nitrile source, it inevitably forms a stoichiometric amount of inorganic salts as by-product.

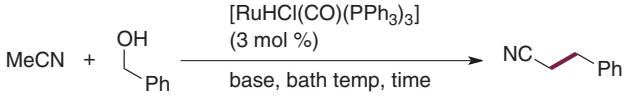
In the past decade, in pursuit of a greener reaction process, transition-metal-catalyzed alkylation reaction of carbonyl and related compounds using primary alcohols has been pursued vigorously by several groups including us.[4] In these methodologies, alcohols have been transformed to aldehydes in situ via metal-catalyzed dehydrogenation, then the latent aldehydes act as electrophiles for C–C bond formation, in which only water is the by-product. While a variety of metal complexes have been used for α-alkylation of α-functionalized acetonitriles,[5] as for alkylation of the parent acetonitrile only Ir complexes have been examined.[6,7] Cossy and co-workers reported alkylation of acetonitrile using primary alcohols catalyzed by [IrCl(cod)]$_2$ under microwave irradiation.[6] Obora's group used [Ir(OH)(cod)]$_2$ for the alkylation of acetonitrile.[7] Since we found that [RuHCl(CO)(PPh$_3$)$_3$],[8] combined with the use of nitrogen ligands, effectively catalyzed the α-alkylation reaction of ketones[9] and acetamides[10] using primary alcohols (Scheme 1), we were motivated to examine the same catalyst for α-alkylation of acetonitrile. In this paper, we report that [RuHCl(CO)(PPh$_3$)$_3$] is indeed an effective catalyst even for the α-alkylation reaction of acetonitrile using primary alcohols.

The alkylation of acetonitrile (**1**) was investigated with benzyl alcohol (**2a**) as a test alcohol (Table 1). When the reaction of **1** (1.5 mL) with **2a** (1 mmol) was carried out in the presence of [RuHCl(CO)(PPh$_3$)$_3$] (3 mol %) and KO*t*-Bu (1.1 equiv) as a base at 110 °C for 20 h, no alkylated product was obtained (Entry 1). When we used Cs_2CO_3 as a base, the desired alkylated product **3a** was obtained in 61% yield (Entry 2). It was found that K_3PO_4 was further more effective to give 76% yield of **3a** (Entry 3). Either lowering the temperature to 90 °C (Entry 4) or shorter reaction time of 5 h (Entry 5) resulted in lower conversions, in which a significant amount of benzyl alcohol (**2a**) was recovered (Entries 4 and 5).



Scheme 1. [RuHCl(CO)(PPh$_3$)$_3$]-catalyzed α-alkylation using primary alcohols.

Table 1. Optimization of the reaction conditions[a]



1 **2a** **3a**

Entry	Base (equiv)	Temp/°C	Time/h	Yield[b]/%
1	KO*t*-Bu (1.1)	110	20	0
2	Cs_2CO_3 (1.1)	110	20	61
3	K_3PO_4 (1.1)	110	20	76 (67)
4	K_3PO_4 (1.1)	90	20	49
5	K_3PO_4 (1.1)	110	5	27
6	K_3PO_4 (0.5)	110	20	21

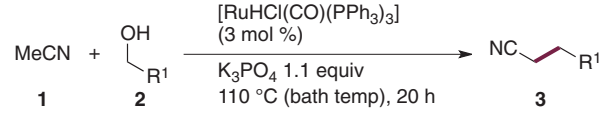
[a]Conditions: **2a** (1 mmol), [RuHCl(CO)(PPh$_3$)$_3$] (3 mol %), base, MeCN (**1**) (1.5 mL). [b]NMR yield. Isolated yield is shown in parenthesis.

The use of a reduced amount of K_3PO_4 also caused the decrease in the yield of **3a** (Entry 6).

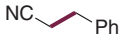
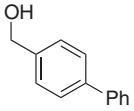
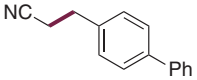
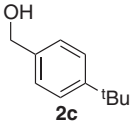
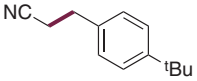
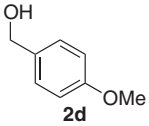
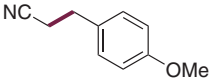
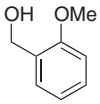
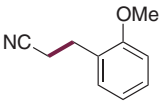
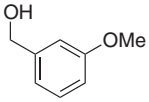
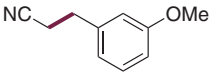
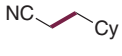
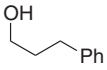
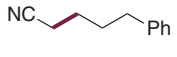
Having the optimized conditions of Entry 3 in hand, we then examined the generality of the alkylation reaction of acetonitrile (**1**). The results are summarized in Table 2. The reaction of **1** with substituted benzyl alcohols **2b**–**2f**, gave the corresponding 3-arylpropanenitriles **3b**–**3f** in good yields (Entries 2–6). The reaction of non-benzylic alcohols, cyclohexanemethanol (**2g**) also gave the corresponding nitrile **3g** but in lower yield. The use of higher temperature of 140 °C gave **3g** in 75% yield (Entry 7). Using similar conditions alkylation of **1** with 3-phenylpropanol (**2h**) gave 5-phenylpentanenitrile (**3h**) in 70% yield (Entry 8).

To gain insight into the reaction mechanism, we conducted control experiments (Scheme 2). The reaction of acetonitrile (**1**) and benzaldehyde (**4**) leading to cinnamonitrile (**5**) was investigated under basic conditions. Regardless of the Ru–H complex, **5** was formed in similar yields (eq 1). This suggests that the Ru–H complex would not play a special role in the C–C bond-

Table 2. [RuHCl(CO)(PPh_3)$_3$]-catalyzed alkylation of acetonitrile (**1**) using primary alcohols **2**[a]



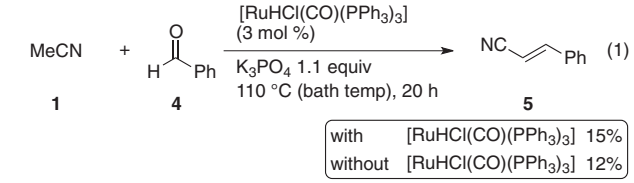
1 2 3

Entry	Alcohol **2**	Product **3**	Yield[b]/%
1	 **2a**	 **3a**	67
2	 **2b**	 **3b**	83
3[c,d]	 **2c**	 **3c**	76
4	 **2d**	 **3d**	73
5[c,d]	 **2e**	 **3e**	75
6[c,d]	 **2f**	 **3f**	71
7[c]	 **2g**	 **3g**	75
8[c]	 **2h**	 **3h**	70

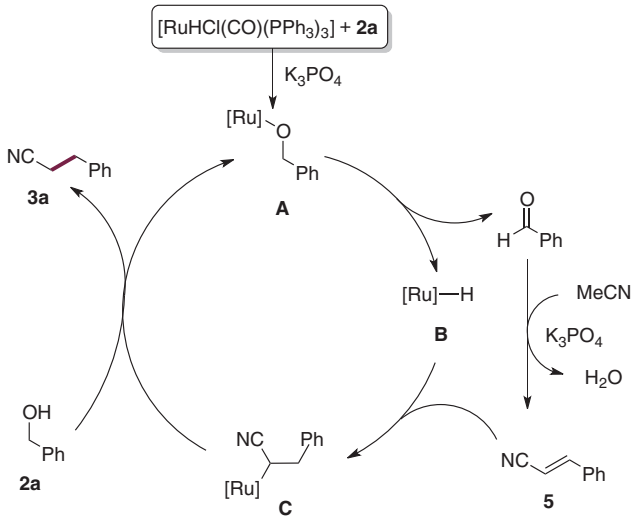
[a]Conditions: Alcohol **2** (0.5 mmol), [RuHCl(CO)(PPh_3)$_3$] (3 mol %), K_3PO_4 (1.1 equiv), MeCN (1.5 mL), 110 °C for 20 h. [b]Isolated yields. [c]140 °C. [d][RuHCl(CO)(PPh_3)$_3$] (5 mol %).

forming step. The reaction of 3-phenyl-substituted acrylonitrile **5** with 1 equiv of benzyl alcohol (**2a**) was also carried out with or without the Ru–H catalyst (eq 2). Only with the Ru–H complex, **3a** was formed. These results confirmed that the Ru–H should affect the transfer hydrogenation of unsaturated nitriles by alcohols.

Taking these observations into consideration, the plausible reaction mechanism is shown in Scheme 3. An alkoxoruthenium complex **A** would be formed in situ from [RuHCl(CO)(PPh_3)$_3$] and an alcohol **2a**, which would then afford Ru–H **B** via β-hydride elimination to give an aldehyde. The resultant benzaldehyde would undergo base-promoted aldol condensation with acetonitrile to give cinnamonitrile (**5**). Addition of the ruthenium hydride **B** to **5** would give Ru-complex **C**, which would then



Scheme 2. Control experiments.



Scheme 3. Possible reaction mechanism.

undergo protonolysis by alcohol **2a** to give α-alkylated nitrile **3a** and alkoxoruthenium **A**, thus creating the catalytic cycle.

In summary we have found that the alkylation reaction of acetonitrile with primary alcohols can be effectively catalyzed by [RuHCl(CO)(PPh_3)$_3$] as a catalyst and K_3PO_4 as a base. The reaction is useful to obtain higher nitriles from readily available reagents and catalyst.[11]

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