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Iridium-catalyzed α-Alkylation of Acetonitrile with Primary and Secondary Alcohols

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Acetonitrile is successfully alkylated with primary and secondary alcohols in the presence of *t*-BuOK using [Ir(OH)(cod)]$_2$ as a catalyst. This method provides a very clean and atom-economical convenient direct route to substituted nitriles, which are very important raw materials in organic and industrial chemistry.

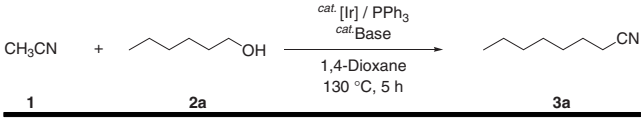
Nitriles are an important class of compounds and widely used in the production of fine chemicals.[1] In particular, linear nitriles are industrially important compounds which possess excellent biodegradability.[2] Thus, it is important to develop a simple synthetic method for nitriles. In general, alkyl nitriles are prepared by the nucleophilic substitution of alkyl halides with cyanide ions.[3] The main disadvantage of this method is the formation of undesirable waste salts. Aromatic nitriles can be obtained by the Sandmayer reaction and gas-phase ammoxidation.[3] Alternative procedures are dehydration of amides or aldoximes,[4] conversion of alcohols, aldehydes, and carboxylic acids to nitriles using various reagents,[5] and direct conversion of amines.[6] However, these methods have major drawbacks: for example, they require hazardous reagents, multistep reactions, or require severe reaction conditions. Recently, Mizuno and coworkers reported the Ru-catalyzed liquid-phase aerobic oxidative synthesis of nitriles directly from alcohols and ammonia.[7]

One-carbon elongation of alkyl chains of alcohols with acetonitrile to higher nitriles, is also an alternative key transformation in organic synthesis.[8] Acetonitrile is also an important feedstock in the chemical industry and large amounts of acetonitrile are coproduced in the SOHIO acrylonitrile process (30–40 kg of acetonitrile were produced per 1000 kg of acrylonitrile).[1] The development of a novel method for preparing substituted nitriles from acetonitrile would therefore be highly beneficial from industrial and atom-economical points of view. The conventional method for the formation of substituted nitriles consists of the reaction of acetonitrile with an aldehyde in the presence of a stoichiometric amount of base, giving α,β-unsaturated nitriles, followed by hydrogenation.[9]

It is well known that Ir and Ru complexes serve as efficient catalysts for hydrogen transfer from alcohols to aldehydes;[10] this can be used in the α-alkylation of ketones, activated methylenes, and esters,[10,11] and in the β-alkylation (Guerbet reaction) of alcohols.[10,12] Hydrogen transfer is also used in coupling reactions of alcohols with 2-alkynes to give homoallylic alcohols and α,β-unsaturated ketones by our group.[13]

If the alkylation of acetonitrile with alcohols could be achieved, this strategy would provide a very attractive route to substituted nitriles. In this paper, we disclose a novel method for the preparation of substituted nitriles by Ir-catalyzed α-alkylation of acetonitrile using primary/secondary alcohols or diols as alkylating agents (eq 1).[14,15]

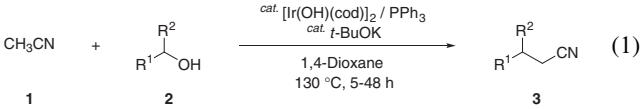
Table 1. Ir-catalyzed reaction of acetonitrile (**1**) with 1-hexanol (**2a**) under various conditions[a]



1 2a 3a

Entry	Ir catalyst	Base	Yield/%[b] 3a
1	[Ir(OH)(cod)]$_2$	*t*-BuOK	70 (66)
2	[Ir(OMe)(cod)]$_2$	*t*-BuOK	60
3	[IrCl(cod)]$_2$	*t*-BuOK	4
4	[IrCl(coe)$_2$]$_2$	*t*-BuOK	n.d.[c]
5	[Cp*IrCl$_2$]$_2$	*t*-BuOK	n.d.[c]
6[d]	IrCl$_3$·3H$_2$O	*t*-BuOK	n.d.[c]
7[d]	[Ir(cod)$_2$]$^+$BF$_4^-$	*t*-BuOK	n.d.[c]
8	[Ir(OH)(cod)]$_2$	KOH	50
9	[Ir(OH)(cod)]$_2$	Cs_2CO_3	4
10	[Ir(OH)(cod)]$_2$	None	n.d.[c]
11[e]	[Ir(OH)(cod)]$_2$	*t*-BuOK	6
12[f]	[Ir(OH)(cod)]$_2$	*t*-BuOK	61
13[g]	[Ir(OH)(cod)]$_2$	*t*-BuOK	2
14[h]	[Ir(OH)(cod)]$_2$	*t*-BuOK	3
15[i]	[Ir(OH)(cod)]$_2$	*t*-BuOK	3
16[j]	[Ir(OH)(cod)]$_2$	*t*-BuOK	30
17[k]	[Ir(OH)(cod)]$_2$	*t*-BuOK	46

[a]Conditions: **1** (10 mmol) was allowed to react with **2a** (1 mmol) in the presence of an Ir catalyst (0.05 mmol), PPh_3 (0.15 mmol), and a base (0.10 mmol) in 1,4-dioxane (1 mL) at 130 °C for 5 h. [b]GC yields based on **2a** used. The number in parenthesis shows isolated yield. [c]Not detected by GC. [d]Ir catalyst (0.10 mmol) was used. [e]*t*-BuOK (0.05 mmol) was used. [f]*t*-BuOK (0.20 mmol) was used. [g]MeCN (1 mmol) was used. [h]Reaction performed without a ligand. [i]PCy_3 (0.15 mmol) was used as the ligand. [j]dppe (0.075 mmol) was used as the ligand. [k]PPh_3 (0.10 mmol) was used as the ligand.



1 2 3 (1)

The reaction of acetonitrile (**1**) with *n*-hexanol (**2a**) was chosen as a model reaction and carried out under various conditions (Table 1). For instance, the reaction of **1** with **2a** in the presence of [Ir(OH)(cod)]$_2$ (5 mol %), PPh_3 (15 mol %), and *t*-BuOK (10 mol %) in 1,4-dioxane at 130 °C for 5 h in a pressure tube produced octanenitrile (**3a**) in 70% yield (Entry 1). When [Ir(OMe)(cod)]$_2$ was employed as the catalyst, **3a** was obtained in a slightly lower yield (Entry 2), and other selected Ir complexes such as [IrCl(coe)$_2$]$_2$, [Cp*IrCl$_2$]$_2$, IrCl$_3$·3H$_2$O, and

$[Ir(cod)_2]^+BF_4^-$ showed low or no catalytic activities (Entries 3–7). As expected, no **3a** was formed in the absence of an Ir complex. The alkylation was extensively influenced by the base employed. Strong bases such as *t*-BuOK and KOH were found to be suitable bases (Entries 1 and 8). However Cs_2CO_3 was inert in this alkylation, and no reaction was induced in the absence of a base (Entries 9 and 10). The addition of smaller amounts of *t*-BuOK resulted in considerably decreased yields of **3a** (Entry 11). When the amount of *t*-BuOK was increased, **3a** was obtained in a slightly lower yield (Entry 12). These results indicate that this reaction was efficiently promoted by the addition of a catalytic amount (10 mol %) of a base, and *t*-BuOK was found to be the most suitable base. Another important feature of the present reaction was the ratio of **1** to **2a**. Among the substrate ratios examined, the best result was obtained using an excess (10 equiv) of **1** with respect to **2a**. This significantly affected the yield of **3a** (Entry 1 vs. Entry 13). In this reaction, the highest catalytic activity was attained using $[Ir(OH)(cod)]_2$ in combination with triphenylphosphine (PPh_3) as a ligand. Other selected phosphine ligands such as tricyclohexylphosphine (Cy_3P) and bidentate phosphine ligands such as 1,2-bis(diphenylphosphino)ethane (dppe) were found to have low catalytic activities (Entries 15 and 16). The optimized reaction temperature was 130 °C, and the reaction at 100 °C resulted in a considerable decrease (11%) in the yield of **3a**. Among the solvents examined, 1,4-dioxane was found to be the best solvent. Under the reaction conditions in Entry 1, Table 1, the yields of **3a** in various solvents were as follows: *p*-xylene 58%, *n*-octane 28%, DMSO 13%, toluene 8%, and solvent-free conditions 47%.

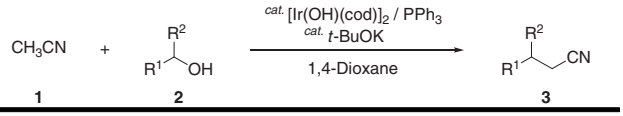
Table 2 shows the alkylation of **1a** with various alcohols under the same conditions as in Entry 1, Table 1. The reaction of **1a** with aliphatic alcohols, i.e., *n*-butanol (**2b**), *n*-octanol (**2c**), and *n*-hexadecanol (**2d**), afforded the corresponding nitriles, **3b**, **3c**, and **3d**, in 55%, 72%, and 80% yields, respectively (Entries 1–3). Similarly, **1** was efficiently alkylated with cyclohexylmethanol (**2e**) to give **3e** in good yield (83%) (Entry 4). The alkylation of **1a** with various 4-substituted benzyl alcohols, **2f**–**2i**, gave rise to the corresponding phenethyl cyanides, **3f**–**3i**, in high to excellent yields (77–95%) (Entries 5–8). 2-Naphthylmethanol (**2j**) gave the corresponding product **3j** in substantial yield (Entry 9).

In contrast to the previously reported α-alkylation reactions developed by our group, the present reaction proceeded with *secondary alcohols* as substrates (Entries 10–14).[11a–11e] In the case of the reaction with α,ω-diol **2p** under microwave irradiation, α,ω-dinitrile **3p** was formed in 51% yield (Entry 15).

The reaction mechanism may be explained by the following pathway (Scheme 1). The α-alkylation reaction is thought to proceed by sequential reactions, involving three key steps, similar to the mechanism proposed in a recent review:[10] (i) hydrogen transfer from alcohol **2** to an Ir complex, giving aldehyde **A** and an Ir–hydride intermediate **B**,[10,16] (ii) a base-catalyzed aldol condensation between the resulting acetonitrile **1** to form α,β-unsaturated ketone **C**, and (iii) hydrogenation of **C** by an Ir–hydride complex generated during the course of the reaction, leading to the α-alkylated nitrile **3**.

In conclusion, we developed a novel method for the Ir-catalyzed alkylation of acetonitrile with alcohols, providing a clean and atom-economical industrial route to various substituted nitriles.[17]

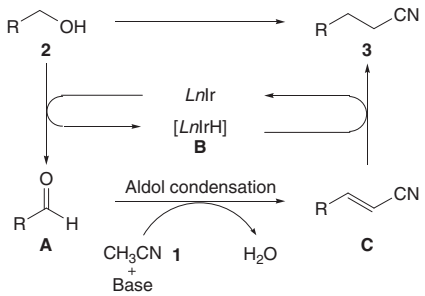
Table 2. Ir-catalyzed reaction of acetonitrile (**1**) and primary and secondary alcohols **2**[a]



1 2 3

Entry	Alcohol **2**		**2**	**3**	Yield/%[b]
	R^1	R^2			
1	n-C_3H_7	H	**2b**	**3b**	55
2[c]	n-C_7H_{15}	H	**2c**	**3c**	72
3[d]	n-$C_{15}H_{31}$	H	**2d**	**3d**	80
4[e]	c-C_6H_{11}	H	**2e**	**3e**	83
5	C_6H_5	H	**2f**	**3f**	77
6	p-CH_3-C_6H_4	H	**2g**	**3g**	94
7	p-t-Bu-C_6H_4	H	**2h**	**3h**	95
8[e]	p-CH_3O-C_6H_4	H	**2i**	**3i**	92
9	2-Nap	H	**2j**	**3j**	83
10[f,g,h]	n-C_4H_9	CH_3	**2k**	**3k**	76
11[f,g,h]	c-C_6H_{11}-OH		**2l**	**3l**	82
12[f,g,h]	C_6H_5-$(CH_2)_2$	CH_3	**2m**	**3m**	88
13[f,i,j]	C_6H_5	CH_3	**2n**	**3n**	69
14[f,i,k]	C_6H_5	C_6H_5	**2o**	**3o**	48
15[l]	OH-$(CH_2)_{10}$-OH		**2p**	**3p**	51

[a]Conditions: same as Entry 1, Table 1. [b]Isolated yields. [c]For 7 h. [d]For 36 h. [e]For 15 h. [f]$[Ir(OH)(cod)]_2$ (0.10 mmol) and PPh_3 (0.4 mmol) were used. [g]*t*-BuOK (0.20 mmol) was used. [h]For 24 h. [i]For 48 h. [j]*t*-BuOK (0.30 mmol) was used. [k]*t*-BuOK (0.40 mmol) was used. [l]Reaction carried out at 200 °C for 7 min under microwave irradiation. Microwaves were irradiated using a Biotage Initiator™ in 2 mL vial. Power varied automatically between 0–100 W to maintain temperature.



Scheme 1. Plausible reaction mechanism.

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