

# Monoalkylation of Acetonitrile by Primary Alcohols Catalyzed by Iridium Complexes

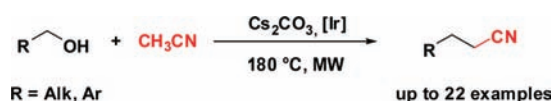
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## ABSTRACT



The monoalkylation of acetonitrile by primary alcohols was achieved in a one-pot sequence in the presence of iridium catalysts. A diversity of nitriles has been obtained from aryl- and alkyl-methanols in excellent yield.

Nitriles are useful compounds as they can be transformed easily to amides, carboxylic acids, aldehydes, ketones, amines, etc. The monoalkylation of acetonitrile represents a challenge since the formation of the bis-alkylated nitrile is often observed.<sup>1</sup> This alkylation is generally performed by generating the anion using a substoichiometric amount of base followed by the addition of an alkyl halide.<sup>2</sup> The other procedure is the use of

cyanomethylcopper (generated by treatment of acetonitrile with *n*-BuLi, followed by the addition of CuI) which reacts according to an SN<sub>2</sub>' process with an allyl bromide to produce the monoallylated acetonitrile.<sup>3</sup> All the known methods to achieve the monoalkylation of acetonitrile were realized by using alkyl halides which are toxic. Alternatively, it has been demonstrated that [Ir]- and [Ru]-complexes can serve as efficient catalysts for hydrogen transfer from alcohols to aldehydes,<sup>4</sup> and this process has been used to realize the alkylation of **activated nitriles<sup>5</sup> and esters.<sup>6</sup>** In this case, the alkylating reagent is an alcohol which is less toxic and more easily accessible than an alkyl halide. Furthermore, the only byproduct of the reaction is water.

Here, we report that **nonactivated** nitriles, such as acetonitrile, can be monoalkylated in good to excellent yields by utilizing primary alcohols and iridium complexes. In order to optimize the monoalkylation of acetonitrile **1** by

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(1) (a) Berlan, J.; Delmas, H.; Duée, I.; Duche, J. L.; Vuiglio, L. *Synth. Commun.* **1994**, *24*, 1253–1260. (b) For a review of nitrile alkylations, see: Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Organic Reactions*, Vol. 31; John Wiley & Sons, Inc.: 1984; pp 1–364.

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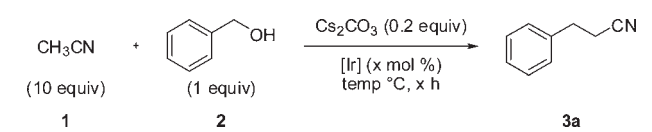
(4) For examples, see: (a) Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* **2001**, *6*, 4710–4712. (b) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72–73. (c) Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7*, 4017–4019. (d) Matsu-ura, T.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2006**, *71*, 8306–8308. (e) Burling, S.; Paine, B. M.; Nama, D.; Brown, V. S.; Mahon, M. F.; Prior, T. J.; Pregosin, P. S.; Whittlesey, M. K.; Williams, J. M. J. *J. Am. Chem. Soc.* **2007**, *129*, 1987–1995. (f) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 73–75. (g) Maeda, K.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 689–696. (h) Aramoto, H.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2009**, *74*, 628–633. (i) Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15018–15111.

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alcohols, benzyl alcohol **2** was chosen as the alkylating agent and different conditions were tested (Table 1). At first, acetonitrile **1** (10 equiv) and benzyl alcohol **2** (1 equiv) were treated with  $\text{Cs}_2\text{CO}_3$  (0.2 equiv) in the presence of  $[\text{IrCp}^*\text{Cl}_2]_2$  (2 mol %) for 16 h at 150 or 180 °C (Table 1, entries 1 and 2). Under these conditions, it was observed that the reaction was slow, the conversion of **2** was incomplete (35% to 80%), and the yield in **3a** was moderate (30% to 71%). It was noticed that, under similar conditions, the replacement of  $[\text{IrCp}^*\text{Cl}_2]_2$  by the less expensive catalyst  $[\text{IrcodCl}]_2$  led to similar results (Table 1, entries 3 and 4). It is worth noting that a complete conversion of **2** was observed after 3 days and, under these conditions, the isolated yield in **3a** was 89% and no polyalkylation of acetonitrile was observed. In order to accelerate the metal-catalyzed reaction, microwave irradiation was performed.<sup>5c,7</sup> With 2–5 mol % of catalyst, at 180 °C after 9 h, the conversion of **2** was not complete (75–88%) and the yield in **3a** was modest (Table 1, entries 5 and 6). When  $[\text{IrcodCl}]_2$  was added in two portions with an interval of 30 min, the conversion of **2** was increased to 90% (Table 1, entry 7) and the yield in **3a** was increased to 70% (Table 1, entry 8) even with  $2 \times 1$  mol % of catalyst. The best yield of **3a** was obtained when **1** and **2** were preheated in the presence of  $\text{Cs}_2\text{CO}_3$  (0.2 equiv), and after 20 min, 1 mol % of  $[\text{IrcodCl}]_2$  was added. Then, the reaction mixture was again heated under microwave irradiation, and 20 min later, 1 mol % of  $[\text{IrcodCl}]_2$  was added

**Table 1.** Optimization of the Monoalkylation of Acetonitrile by Benzyl Alcohol

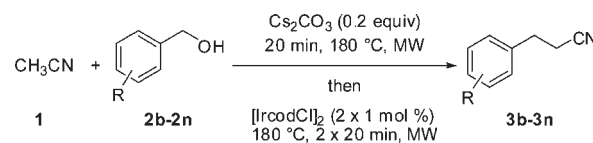


entry	cat. [Ir] (x mol %)	temp	t	$\tau_c$ of <b>2</b> <sup>a</sup>	yield in <b>3a</b>
1	$[\text{IrCp}^*\text{Cl}_2]_2$ (2 mol %)	150 °C	16 h	35%	30% <sup>a</sup>
2	$[\text{IrCp}^*\text{Cl}_2]_2$ (2 mol %)	180 °C	16 h	80%	71% <sup>a</sup>
3	$[\text{IrcodCl}]_2$ (2 mol %)	180 °C	16 h	79%	61% <sup>a</sup>
4	$[\text{IrcodCl}]_2$ (2 mol %)	180 °C	3 d	100%	89% <sup>b</sup>
5	$[\text{IrcodCl}]_2$ (2 mol %)	180 °C	1 h	60%	—
		MW	9 h	75%	48% <sup>b</sup>
6	$[\text{IrcodCl}]_2$ (5 mol %)	180 °C	1 h	50%	—
		MW	9 h	88%	55% <sup>b</sup>
7	$[\text{IrcodCl}]_2$ ( $2 \times 2.5$ mol %)	180 °C	$2 \times 30$ min	90%	73% <sup>b</sup>
		MW			
8	$[\text{IrcodCl}]_2$ ( $2 \times 1$ mol %)	180 °C	$2 \times 30$ min	90%	70% <sup>b</sup>
		MW			
9 <sup>c</sup>	$[\text{IrcodCl}]_2$ ( $2 \times 1$ mol %)	180 °C	$2 \times 20$ min	100%	90% <sup>b</sup>
		MW			

<sup>a</sup> Determined by GC/MS. <sup>b</sup> Isolated yield. <sup>c</sup> **1** and **2** were preheated with  $\text{Cs}_2\text{CO}_3$  at 180 °C during 20 min.

and the reaction mixture was heated for an additional 20 min. Under these latter conditions, the conversion of **2** was complete and **3a** was isolated in 90% yield (Table 1, entry 9).<sup>8</sup>

**Table 2.** Generalization to Substituted Benzylic Alcohols

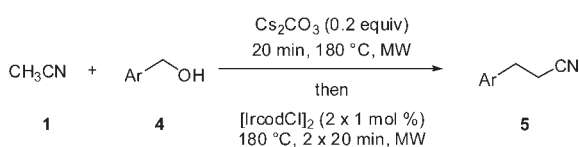


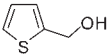
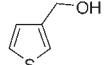
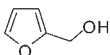
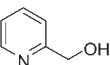
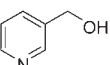
entry	alcohol <b>2</b>	nitrile <b>3</b> (yield <sup>b</sup> )
1 <sup>a</sup>	<b>2b</b>	<b>3b</b> (86%)
2 <sup>a</sup>	<b>2c</b>	<b>3c</b> (70%)
3 <sup>a</sup>	<b>2d</b>	<b>3d</b> (78%)
4	<b>2e</b>	<b>3e</b> (74%)
5	<b>2f</b>	<b>3f</b> (0%)
6	<b>2g</b>	<b>3g</b> (0%)
7	<b>2h</b>	<b>3h</b> (67%)
8	<b>2i</b>	<b>3i</b> (74%)
9	<b>2j</b>	<b>3j</b> (65%)
10	<b>2k</b>	<b>3k</b> (79%)
11	<b>2l</b>	<b>3l</b> (81%)
12	<b>2m</b>	<b>3m</b> (71%)
13	<b>2n</b>	<b>3n</b> (0%)
14	<b>2o</b>	<b>3o</b> (0%)

<sup>a</sup> 3 mol % were necessary to perform a complete conversion of **2**. <sup>b</sup> Isolated yields.

These optimized reaction conditions (Table 1, entry 9) proved to be quite general as the yields in **3** (Table 2) were good when different benzylic alcohols were used (up to 86%). The alkylation of acetonitrile **1** can be performed with benzylic alcohols substituted by electron-donating groups (**2b–2e**). However, the substitution of the aromatic ring of the benzylic alcohols by electron-withdrawing groups (**2f** and **2g**) did not afford the desired alkylated nitriles (**3f** and **3g**). Substitution of the aromatic ring of **2** by a fluorine atom (**2h–2j**) or by a chloride atom (**2k–2m**) led to **3h–3m** in good yield; in contrast, compounds **3** were not observed when a bromide or an iodide was present on the aromatic ring of the benzylic alcohols **2** (**2n** and **2o**).<sup>9</sup>

**Table 3.** Alkylation by Heteroaryl-methanols



entry	alcohol <b>4</b>	nitrile <b>5</b> (yield <sup>b</sup> )
1	<b>4a</b> 	<b>5a</b> (85%)
2	<b>4b</b> 	<b>5b</b> (76%)
3	<b>4c</b> 	<b>5c</b> (75%)
4 <sup>a</sup>	<b>4d</b> 	<b>5d</b> (69%)
5 <sup>a</sup>	<b>4e</b> 	<b>5e</b> (68%)

<sup>a</sup> 3 mol % were necessary to perform a complete conversion of **4**.  
<sup>b</sup> Isolated yields.

Heteroaryl-methanols such as **4** can be involved in the alkylation of acetonitrile. The results are reported in Table 3. Pyridine, furan, and thiophene were tolerated as

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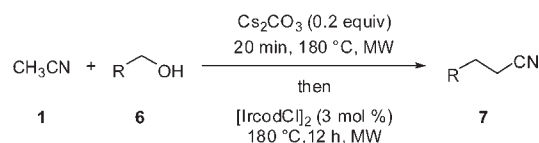
(8) The reaction can be performed without microwave irradiation; however by using this later, the reaction was accelerated.

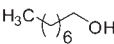

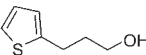
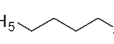

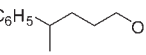
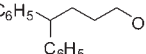
(9) The cleavage of the C–Br and C–I bonds was observed.

the alkylation of acetonitrile by **4** produced the corresponding nitriles **5** in good yields (Table 3).

It was also possible to use **nonactivated** primary alcohols such as **6** as they allowed the **monoalkylation** of acetonitrile. Thus, although preheating was still required, [IrcodCl]<sub>2</sub> (3 mol %) was added at once and the reaction mixture was heated at 180 °C for 12 h under microwave irradiation. When acetonitrile was heated with octanol **6a**, the corresponding nitrile **7a** was isolated in 60% yield. Nitriles **7b–7d** were synthesized in good yields (52–80%) by utilizing the corresponding alkyl alcohols **6b–6d**, and diol **6e** was converted to the bis-nitrile **7e** in 74% yield. This reaction is very sensitive to steric hindrance as  $\gamma$ -substituted alcohol **6f** was transformed to the corresponding nitrile in poor yield and **6g** led to a complex mixture of nonidentified compounds (Table 4, entries 6 and 7).

**Table 4.** Alkylation of Acetonitrile by Aliphatic Alcohols



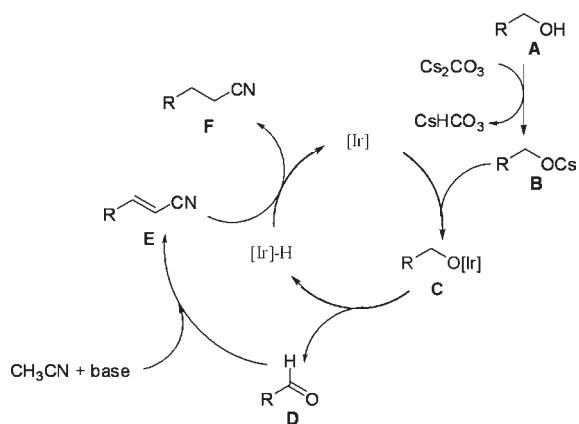
entry	alcohol <b>6</b>	nitrile <b>7</b> (yield <sup>a</sup> )
1	<b>6a</b> 	<b>7a</b> (60%)
2	<b>6b</b> 	<b>7b</b> (80%)
3	<b>6c</b> 	<b>7c</b> (52%)
4	<b>6d</b> 	<b>7d</b> (66%)
5	<b>6e</b> 	<b>7e</b> (74%)
6	<b>6f</b> 	<b>7f</b> (30%)
7	<b>6g</b> 	<b>7g</b> (0%) mixture of non identified products

<sup>a</sup> Isolated yields.

The reaction may be explained by the mechanism reported in Scheme 1 inspired by previously published mechanisms.<sup>5</sup> At first, it seems important to generate a cesium alcoholate (**B** from **A**) to get good yields in the

(10) The necessity of the presence of both alcohol and Cs<sub>2</sub>CO<sub>3</sub> in the first step has been studied.

**Scheme 1.** Proposed Mechanism



monoalkylated acetonitrile.<sup>10</sup> The alcoholate **B** can then react with the iridium complex to produce an iridium

intermediate **C** which goes through a  $\beta$ -elimination to produce aldehyde **D** which undergoes a base-catalyzed aldol condensation with acetonitrile to form  $\alpha,\beta$ -unsaturated nitrile **E**. This latter reacts with the Ir-hydride to give **F**, and the iridium complex is then regenerated. More detailed mechanistic studies are presently performed and will be reported in due time.

**Acknowledgment.** B.A. thanks Sanofi-Aventis for a grant, and Sanofi-Aventis is gratefully acknowledged for financial support. Dr. K. Rossen (Sanofi-Aventis) is acknowledged for his comments

**Supporting Information Available.** Experimental procedure and characterization data and NMR spectra of compounds **3**, **5**, and **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.