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Microwave-Assisted Solventless Reaction of Iridium-Catalyzed Alkylation of Amines with Alcohols in the Absence of Base

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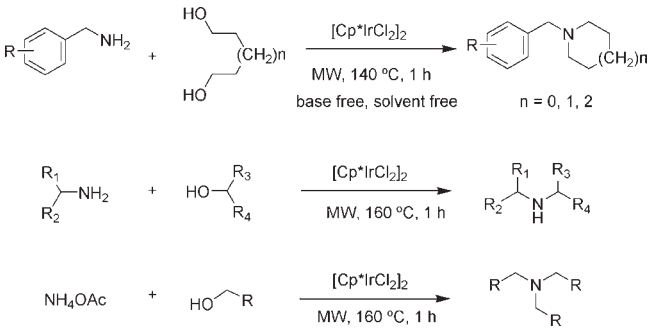
ABSTRACT



Microwave-assisted iridium catalyzed alkylation of amines with alcohols was undertaken under solvent-free and base-free conditions. Such alkylation reactions are green, atom-economic, and effective for mono-, di-, and triaklyation of amines. Good isolated yields were obtained for mono- and dialkylated amines using stoichiometric amounts of amines and alcohols, in the presence of 1 mol % $[Cp^*IrCl_2]_2$. Reasonable yields of trialkylated products were obtained using 4 equiv of alcohols.

Amines are a very important family of compounds in the pharmaceutical and chemical industries as well as in biology. The classic alkylation reaction of amines is achieved either by reaction with an alkyl halide or by reductive amination of an aldehyde and ketone. The former procedure can be problematic due to overalkylation and the toxic nature of many alkyl halides and related alkylating agents. The latter method requires the use of strong reducing reagents or dangerous hydrogen gas.[1] Very recently, direct catalytic alkylation with alcohols using a borrowed hydrogen concept emerged as an attractive green and atom-economical chemistry solution which generates only water as a byproduct.[2] Early examples of homogeneous catalyzed alkylations of amines by alcohols were published independently by Grigg[3] and Watanabe,[4] in 1981. Ruthenium[5] and

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(1) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2005.

(2) For recent reviews on borrowing hydrogen, see: (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, *38*, 753. (d) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (e) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611.

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(5) (a) Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T.-A. *J. Org. Chem.* **1996**, *61*, 4214. (b) Ganguly, S.; Roundhill, D. M. *Polyhedron* **1990**, *20*, 2517. (c) Huh, K.-T.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* **1988**, 449. (d) Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* **2007**, *48*, 3367. (e) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725. (f) Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263. (g) Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem.—Asian J.* **2007**, *2*, 403. (h) Tillack, A.; Hollmann, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881. (i) Del Zotto, A.; Baratta, W.; Sandri, M.; Verardo, G.; Rigo, P. *Eur. J. Inorg. Chem.* **2004**, 524. (j) Gunanathan, V; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661. (k) Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8126.

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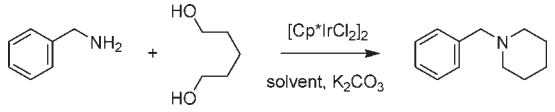
Table 1. Optimization of Conditions[a]



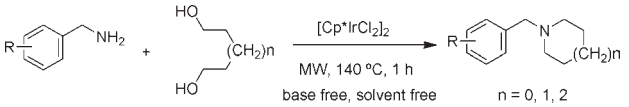
entry	sol.	base	conditions	conv[b]	yield[c]
1[d]	H_2O	None	140 °C, 1 h	10%	5%
2[d]	H_2O	None	140 °C, 10 h	90%	80%
3	H_2O	1%	MW, 130 °C, 1 h	80%	70%
4	H_2O	None	MW, 130 °C, 1 h	80%	70%
5[e]	H_2O	None	MW, 130 °C, 1 h	0%	0%
6	H_2O	None	MW, 140 °C, 1 h	85%	75%
7[d]	None	None	110 °C, 1 h	trace	trace
8[d]	None	None	110 °C, 10 h	50%	30%
9	None	None	MW, 110 °C, 1 h	5%	trace
10	None	None	MW, 130 °C, 0.5 h	10%	5%
11	None	None	MW, 140 °C, 1 h	100%	91%
12	None	1%	MW, 140 °C, 1 h	80%	70%
13	None	10%	MW, 140 °C, 1 h	75%	65%

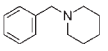
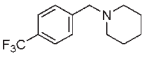
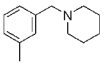
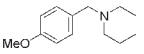
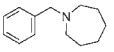
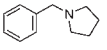
[a] Reaction conditions: benzylamine (1 mmol), 1,5-pentanediol (1 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), K_2CO_3 (0−10 mol %). [b] Conversion based on benzylamine. [c] Yield determined by HPLC. [d] Under conventional heating. [e] In the absence of iridium catalyst.

iridium catalysts[6,7] were subsequently reported as the most frequently used catalysts for the alkylation of amines by alcohols. Additionally, rhodium[8] and platinum[9] were also reported to be effective. $[Cp^*IrCl_2]_2$[10] was discovered to be a very efficient catalyst for alkylation of amines with alcohols. Other iridium catalysts such as $[Cp^*IrI_2]_2$,[11] $[IrCl(cod)]_2$,[12] and $[Cp^*Ir(NH_3)_3][Cl]_2$[13] were also reported to be efficient catalysts for iridium catalyzed alkylation of amines. These reactions are typically run in toluene under reflux for a long period of heating and require addition of base, e.g. potassium carbonate, which may form the iridium carbonate complex during the reaction. Although no base was needed in a few cases, a polar solvent and an extended period of heating were generally required.[11,13]

We are very interested in a green and atom-economical method for the preparation of amine. Recently, iridium catalysts were reported to be active in the solvent-free and microwave-assisted alkylation of C−C bond formation. Ruthenium catalyzed amine synthesis with alcohols under solvent-free microwave conditions was documented; however, extra ligand and an excess of alcohols were required. Herein we report an efficient, green, and atom-economical alkylation of amines with alcohols under solvent-free, base-free, and microwave conditions.

Table 2. Alkylation of Amines with Diols To Form N-Heterocycles[a]



entry	R	n	product	yield[b]
1	H	1		81%
2	*p*-CF_3	1		75%
3	*m*-Me	1		49%
4	*p*-MeO	1		46%
5	H	2		53%[c]
6	H	0		66%[c]

[a] Reaction conditions: amine (1 mmol), diol (1 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), MW, 140 °C, 1 h. [b] Isolated yield. [c] MW, 160 °C, 1 h.

Iridium complexes are generally more stable than rhodium complexes. $[Cp^*IrCl_2]_2$ was selected as the catalyst, and the N-alkylation of benzylamine with 1,5-pentanediol was employed as the model reaction for optimization of reaction conditions. The results are summarized in Table 1.

(6) For a very recent review, see: Suzuki, T. *Chem. Rev.* **2011**, *111*, 1825 and references cited therein.

(7) (a) Cami-Kobeci, G.; Williams, J. M. J. *Chem. Commun.* **2004**, 1072. (b) Cami-Kobeci, G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535. (c) Nordstrøm, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034. (d) Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth. Catal.* **2008**, *350*, 749. (e) Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661. (f) Prades, A.; Corberán, R.; Poyatos, M.; Peris, E. *Chem.—Eur. J.* **2008**, *14*, 11474. (g) Gnanamgari, D.; Sauer, E. L. O.; Schley, N. D.; Butler, C.; Incarvito, C. D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 321. (h) Blank, B.; Michlik, S.; Kempe, R. *Chem.—Eur. J.* **2009**, *15*, 3790. (i) Michlik, S.; Kempe, R. *Chem.—Eur. J.* **2010**, *16*, 13193.

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(11) (a) Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. Dev.* **2010**, *14*, 1046. (b) Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, 1541.

(12) (a) Blank, B.; Madalska, M; Kempe, R. *Adv. Synth. Catal.* **2008**, *350*, 749. (b) Blank, B.; Michlik, S.; Kempe, R. *Chem.—Eur. J.* **2009**, *15*, 3790.

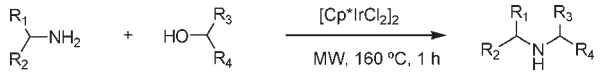
(13) Kawahara, R.; Fujita, K.-I.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108.

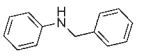
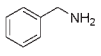
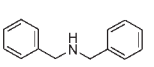
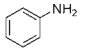
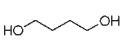
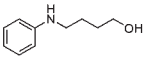
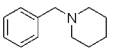
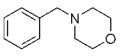
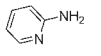
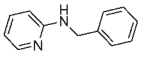
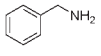
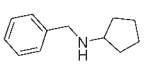
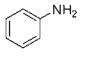
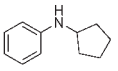
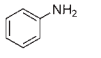
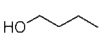
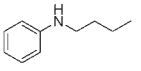
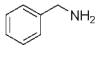
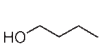
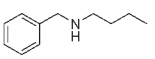
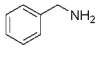
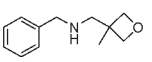
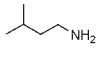
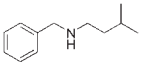
(14) (a) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 4375. (b) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023. (c) Anxionnat, B.; Pardo, D. G.; Ricci, G.; Cossy, J. *Org. Lett.* **2011**, *13*, 4084. (d) Lubinu, M. C.; De Luca, L.; Giacomelli, G.; Porcheddu, A. *Chem.—Eur. J.* **2011**, *17*, 82.

(15) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *J. Org. Chem.* **2011**, *76*, 2328. Iridium has been mentioned in the footnote to be effective; however, no details have been reported.

When water was used as solvent, under conventional heating, we observed that 1-benzylpiperidine was generated in about 5% yield at 140 °C for 1 h in the absence of base (entry 1, Table 1). Good conversion and yield were reached after 10 h of heating (entry 2, Table 1). The effectiveness of $[Cp^*IrCl_2]_2$ for the alkylation of amine encouraged us to test the microwave irradiated conditions. Good conversion and yield can be reached under microwave irradiation at 130 °C for 1 h both in the presence and in the absence of base (entries 3 and 4, Table 1). However, without the iridium catalyst, no desired product was generated (entry 5, Table 1). Improved conversion and yield were realized at 140 °C under microwave conditions.

Table 3. Alkylation of Amines with Various Alcohols[a]

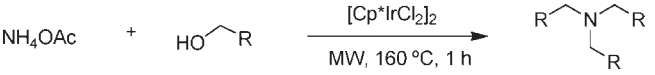


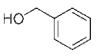
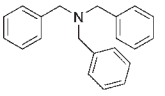
entry	amine	alcohol	product	yield[b]
1				77%
2				65%
3				55%
4				46%
5				46%
6				42%
7				53%
8				74%
9				54%
10				57%
11				58%
12				47%

[a] Reaction conditions: amine (1 mmol), alcohol (1 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), MW, 160 °C, 1 h. [b] Isolated yield.

The promising results promoted us to try a neat reaction under microwave conditions based on the assumption that a reduced amount of water will favor the conversion. When the reaction was undertaken in neat conditions at a relatively low reaction temperature (e.g., below 130 °C), neither conventional heating nor microwave irradiation afforded significant conversion (entries 7–10, Table 1). The optimized conditions for the iridium catalyzed amination was discovered to be a neat reaction without base at 140 °C for 1 h under microwave heating (entry 11, Table 1). In comparison, the addition of base was not beneficial (entries 12, and 13, Table 1). After suitable reaction conditions had been established, we wished to examine the scope and reliability of the synthesis of N-heterocycles by the reaction of different amines with suitable diols.[16] The results are summarized in Table 2. We were pleased to obtain good conversions and reasonable isolated yields of the corresponding *N*-benzyl-piperidine derivatives for both electron-rich and -deficient benzyl amines (entries 1–4, Table 2). For 7- and 5-membered N-heterocycles, a higher reaction temperature (160 °C) was required to reach complete conversion (entries 5 and 6, Table 2).

Table 4. Trialkylation of Amine Using NH_4OAc with Various Primary Alcohols[a]



entry	alcohol	product	yield[b]
1			77%
2			56%
3			41%

[a] Reaction conditions: ammonium acetate (1 mmol), alcohol (4 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), MW, 160 °C, 1 h. [b] Isolated yield.

With the success of dialkylation of amines with diols, we are very much interested in the possibility of monoalkylation of an amine with alcohol. To further evaluate the scope of the microwave-assisted neat reaction of the iridium catalyzed alkylation of amines with alcohols under base-free condition, a variety of amines and alcohols were exploited as the coupling partners. To ensure fast and complete conversion, the optimum reaction conditions

(16) (a) Fujita, K.-I.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525. (b) Prades, A.; Corberán, R.; Poyatos, M.; Peris, E. *Chem.—Eur. J.* **2008**, *14*, 11474.

were discovered to be microwave irradiation at 160 °C for 1 h. The results are collected in Table 3. Good isolated yields were obtained for the monoalkylation of alkylamine, arylamine, benzylamine, and heterocyclic amine, with a wide range of alcohols (Table 3).

Our focus next turned toward whether trialkylation of an amine was feasible. We examined the trialkylation of an amine with a benzyl alcohol using ammonium acetate as the amine source.[10e,f] The reactions were undertaken under microwave irradiation at 160 °C for 1 h. The results are summarized in Table 4. To ensure complete conversion and reasonable yields of the desired trialkylated products, 4 equiv of the primary alcohols were required.

In summary, we have communicated here an iridium catalyzed alkylation of amines with alcohols under microwave irradiation, solvent-free, and base-free conditions. $[Cp^*IrCl_2]_2$ is effective for mono-, di-, and trialkylation of amines with alcohols. Such green and atom-economical C−N bond forming reactions provide high efficiency and easy manipulation, possibly resulting in a superior process for the chemical and pharmaceutical industries.

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Supporting Information Available. Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.