BCSJ

Selective Direct N-Alkylation of Amines with Alcohols using Iron(III) Phthalocyanine Chloride under Solvent-Free Conditions

Maki Minakawa,* Masataka Okubo and Motoi Kawatsura*


M. Minakawa

Department of Chemistry, College of Humanities and Science, Nihon University, Sakurajosui, Setagaya-ku, Tokyo 156-8550

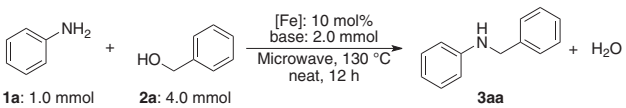
E-mail: minakawa@chs.nihon-u.ac.jp
Received: June 23, 2015; Accepted: August 26, 2015; Web Released: September 4, 2015

Direct N-alkylation of amines with alcohols in the presence of iron(III) phthalocyanine chloride as a catalyst in solvent-free conditions under microwave irradiation afforded the corresponding *N*-alkylamines in moderate to high yield with excellent selectivity.

Direct N-alkylation of amines with alcohols is an attractive and environmentally friendly alternative to conventional methodology, such as alkylation of amine with alkyl halides. The conventional procedure is problematic due to overalkylation and the toxic nature of alkylating reagents.[1] The direct N-alkylation of amines with alcohols is less hazardous and more atom economical because the only by-product is water. In the reaction a generally accepted mechanism, a so-called borrowing-hydrogen methodology,[2] involves dehydrogenation of alcohols to provide carbonyl compounds, which are converted to imines, and the subsequent reduction of imines by transition metal hydrides to give *N*-alkylamines. The most common metals used for the catalytic N-alkylation of amines with alcohols are Ru[3] and Ir.[4] Recently, catalysts derived from other metals, such as Au,[5] Ag,[6] Cu,[7] Ni,[8] Rh,[9] Pd,[10] and Fe[11] have also been explored. However, Fe-catalyzed N-alkylation of amines with alcohols has remained a challenging topic.[11] In this paper, we described the selective and efficient N-alkylation of amines with alcohols using iron catalysis in solvent-free conditions under microwave irradiation. This reaction employed $[Fe^{III}(Pc)]Cl$ (Pc: phthalocyaninato), an inexpensive commercial compound that is typically used as an industrial additive for ink and rubber manufacturing. The $[Fe^{III}(Pc)]Cl$ showed good catalytic activity for the direct N-alkylation of amines with alcohols.

In initial studies, we tested several iron-catalyzed reaction conditions for the direct N-alkylation of aniline with benzyl alcohol (Table 1). The N-alkylation of aniline (**1a**) with benzyl alcohol (**2a**) using $FeCl_3$ (10 mol %) and ^{t}BuOK as a base in solvent-free conditions under microwave irradiation at 130 °C for 12 h gave *N*-benzylaniline (**3aa**) in 59% isolated yield (Entry 1). The N-alkylation using $FeCl_2$ afforded the desired product **3aa** in 38% yield (Entry 2). The reaction with different bases (^{t}BuONa, KOH, K_2CO_3, or Cs_2CO_3) in the presence of $FeCl_3$ resulted in lower yield of the desired product (Entries 3–6). Therefore, we selected ^{t}BuOK as a base for further evaluation. After screening several Fe catalysts, it was found that the N-alkylation of aniline (**1a**) with benzyl alcohol (**2a**) using $[Fe^{III}(Pc)]Cl$ (10 mol %) as a catalyst afforded the desired product **3aa** in 91% yield (Entry 10). The N-alkylation with 10 mol % of $[Fe^{II}(Pc)]$ gave **3aa** in 31% yield under similar conditions (Entry 11). The reaction was ineffective in the absence of Fe catalyst (Entry 12).[12] Although Singh et al. reported an efficient N-alkylation of amines with alcohols using $[Fe^{II}(Pc)]$ catalyst for preparation of benzoimidazoles, benzothiozoles, and benzoxazoles, the $[Fe^{III}(Pc)]Cl$ was more effective than $[Fe^{II}(Pc)]$ under our conditions in the N-alkylation of aniline (**1a**) with benzyl alcohols (**2a**).[11b] A slower reaction was observed without microwave irradiation (Entry 13). The reaction with 0.5 mmol of ^{t}BuOK under similar conditions gave 51% of **3aa** (Entry 14). Although the efficient N-alkylation of amine with a catalytic amount of ^{t}BuOK was reported,[6c,13] an excess amount of ^{t}BuOK was needed in our reaction conditions. The reaction for 6 h under similar conditions afforded a reduced yield (66%) of **3aa** (Entry 15).

Table 1. Optimization of conditions[a)]



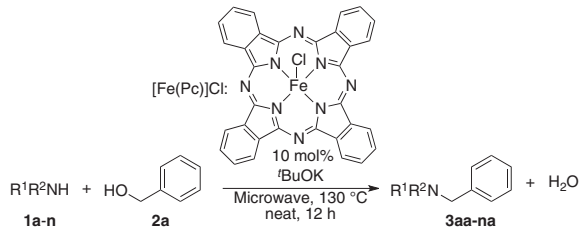
1a: 1.0 mmol **2a**: 4.0 mmol **3aa**

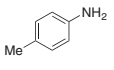
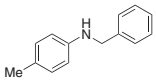
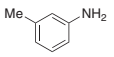
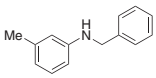
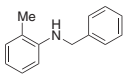
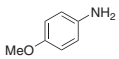
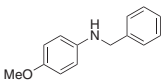
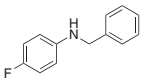
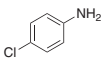
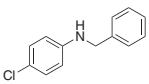
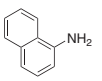
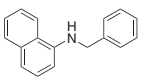
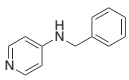
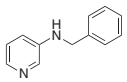
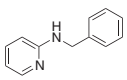
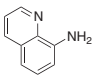
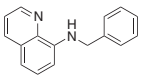
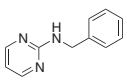
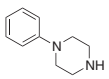
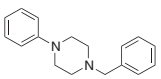
Entry	[Fe]	Base	Yield/%[b)]
1	$Fe^{III}Cl_3$	^{t}BuOK	59
2	$Fe^{II}Cl_2$	^{t}BuOK	38
3	$Fe^{III}Cl_3$	^{t}BuONa	7
4	$Fe^{III}Cl_3$	KOH	11
5	$Fe^{III}Cl_3$	K_2CO_3	5
6	$Fe^{III}Cl_3$	Cs_2CO_3	9
7	$[Fe^{III}(acac)_3]$	^{t}BuOK	58
8	$Fe^{III}F_3$	^{t}BuOK	60
9	$[Fe^{II}(C_5H_5)_2]$	^{t}BuOK	27
10	$[Fe^{III}(Pc)]Cl$[c)]	^{t}BuOK	91
11	$[Fe^{II}(Pc)]$[c)]	^{t}BuOK	31
12		^{t}BuOK	21
13[d)]	$[Fe^{III}(Pc)]Cl$[c)]	^{t}BuOK	48
14[e)]	$[Fe^{III}(Pc)]Cl$[c)]	^{t}BuOK	51
15[f)]	$[Fe^{III}(Pc)]Cl$[c)]	^{t}BuOK	66

a) Reaction conditions: **1a** (1.0 mmol), **2a** (4.0 mmol), Fe catalyst (10 mol %, based on aniline), and base (2.0 mmol) in solvent-free conditions under microwave irradiation at 130 °C for 12 h under N_2 atmosphere. b) Isolated yield. c) Pc: phthalocyaninato. d) Without microwave irradiation (oil bath). e) 0.5 mmol of ^{t}BuOK was used. f) Reaction time: 6 h.

We next examined the Fe-catalyzed N-alkylation of various amines **1b**–**1n** with benzyl alcohol (**2a**) under the optimized reaction conditions (Table 2). The formation of *N*-alkylamines from 4-methylaniline (**1b**), 3-methylaniline (**1c**), and 2-methylaniline (**1d**), with **2a** carried out under similar conditions to give *N*-benzyl-4-methylaniline (**3ba**; 80%), *N*-benzyl-3-methylaniline (**3ca**; 84%), and *N*-benzyl-2-methylaniline (**3da**; 59%), respectively (Entries 1–3). The reaction of 4-meth-

Table 2. N-Alkylation of various amines with benzyl alcohol[a)]

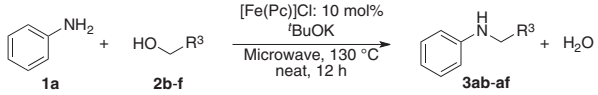


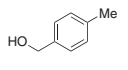
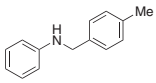
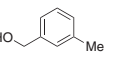
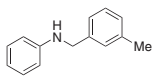
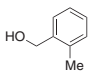
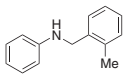
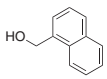
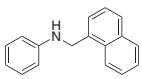
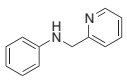
Entry	Amine		Product		Yield[b)]/%
1		**1b**		**3ba**	80
2		**1c**		**3ca**	84
3		**1d**		**3da**	59
4		**1e**		**3ea**	64
5[c)]		**1f**		**3fa**	69
6		**1g**		**3ga**	36
7[d)]		**1h**		**3ha**	97
8		**1i**		**3ia**	86
9[e)]		**1j**		**3ja**	86
10		**1k**		**3ka**	64
11		**1l**		**3la**	94
12[c)]		**1m**		**3ma**	59
13[d),f)]		**1n**		**3na**	82

a) Reaction conditions: **1** (1.0 mmol), **2** (4.0 mmol), [Fe(Pc)]Cl (10 mol %, based on amine), and ^{t}BuOK (2.0 mmol) under microwave irradiation in solvent-free conditions at 130 °C for 12 h under N_2 atmosphere. b) Isolated yield. c) 110 °C. d) 170 °C. e) 150 °C. f) 24 h.

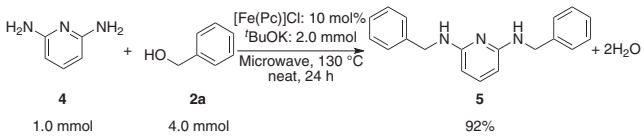
oxyaniline (**1e**) afforded *N*-alkylamine **3ea** in 64% isolated yield under similar conditions (Entry 4). Electron-poor anilines **1f** and **1g** with **2a** were converted to **3fa** and **3ga** in 69% and 36% yield, respectively (Entries 5 and 6).[14] The reaction of 1-naphthylamine (**1h**) with **2a** led to the formation of *N*-alkylamine **3ha** in 97% yield (Entry 7). Heteroaryl amines **1i**–**1m** similarly reacted with **2a** to afford amines **3ia**–**3ma** in 59–94% yield (Entries 8–12). The reaction of 1-phenylpiperazine (**1n**) with **2a** was also carried out to provide 1-benzyl-4-phenylpiperazine **3na** in 82% yield (Entry 13). No overalkylation reactions were observed in all cases by GC-MS analysis. Unfortunately, the reaction of primary alkyl amines with benzyl alcohol was not effective under the reaction conditions.

Table 3. N-Alkylation of aniline with various alcohols[a)]



Entry	Alcohol		Product		Yield[b)]/%
1		**2b**		**3ab**	65
2		**2c**		**3ac**	85
3		**2d**		**3ad**	96
4		**2e**		**3ae**	89
5		**2f**		**3af**	92

a) Reaction conditions: **1** (1.0 mmol), **2** (4.0 mmol), [Fe(Pc)]Cl (10 mol %, based on amine), and ^{t}BuOK (2.0 mmol) in solvent-free conditions under microwave irradiation at 130 °C for 12 h under N_2 atmosphere. b) Isolated yield.

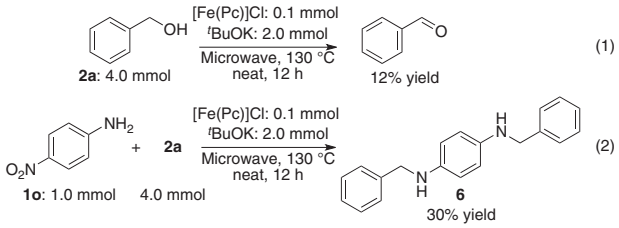


Scheme 1. N-Alkylation of diamines.

Moreover, N-alkylation of aniline (**1a**) with various alcohols was performed as shown in Table 3. The reaction of **1a** with 4-methylbenzyl alcohol (**2b**), 3-methylbenzyl alcohol (**2c**), and 2-methylbenzyl alcohol (**2d**) proceeded to give the corresponding *N*-benzylated amine (**3ab**–**3ad**) in 65–96% yield (Entries 1–3). The N-alkylation of **1a** with (1-naphthyl)methanol (**2e**) gave *N*-benzylated amine **3ae** in 89% yield (Entry 4). The reaction of **1a** with 2-pyridine methanol (**2f**) afforded **3af** in 92% yield (Entry 5). In the reaction of **1a** with phenethyl alcohol, no reaction was observed under similar conditions.

Furthermore, the reaction of the diamine **4** with benzyl alcohol (**2a**) afforded the compound **5** in 92% yield under similar conditions (Scheme 1). This type of subunit has an important role in process of self-assembly.[7c,15]

Simple mechanistic studies are shown in Scheme 2. Under the optimal conditions without amine, benzyl alcohol (**2a**) was converted to benzaldehyde (eq 1). In addition, the reaction of 4-nitrobenzyl amine (**1o**) with **2a** afforded diamine product **6** (eq 2). The result showed that the nitro group did not survive under the conditions.[16] Although Fe-catalyzed N-alkylation via S_N2-type mechanism also reported,[11c] the results suggested that



Scheme 2. Mechanistic studies.

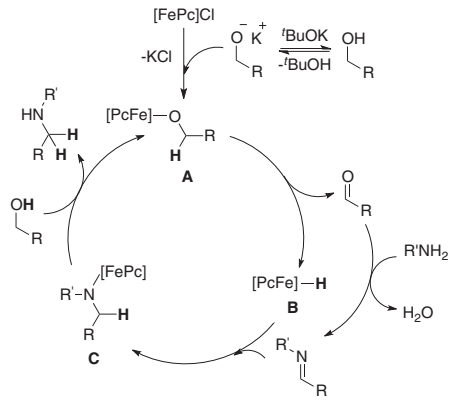


Figure 1. A possible catalytic cycle.

the reaction proceeded through a hydrogen borrowing mechanism. Because a smaller amount of base led to lower yield of desired product under similar reaction conditions, the reaction may be promoted by Meerwein–Pondorf–Verley (MPV) reduction.[12] Although the mechanism for the present reaction is not completely clear yet, a possible catalytic cycle is shown in Figure 1.[7c,10a,11a] Reaction of the in situ-formed potassium alkoxide with [Fe(Pc)]Cl generates the iron alkoxide species **A**. The iron species **A** leads to the catalytic oxidation of an alcohol to the corresponding carbonyl compound with the generation of a hydrido iron species **B**.[17] The carbonyl intermediate readily reacts with amine to afford an imine compound. Then addition of the hydrido iron **B** to a C=N bond occurs to give an iron species **C**. The species **C** reacts with an alcohol to give product and regenerate the alkoxo iron complex **A**. In conclusion, we developed the N-alkylation of amines with alcohols using iron(III) phthalocyanine chloride under solvent-free conditions. Various aromatic amines with benzyl alcohols were applicable to give the corresponding *N*-alkylamines in moderate to high yield. It should be noted that the present N-alkylation proceeded with excellent selectivity for mono-alkylation under solvent-free conditions.

Supporting Information

Experimental procedure, compound characterization, and ^{1}H and ^{13}C NMR spectra are available free of charge on J-STAGE.

References

1 T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753.

2 Recent Reviews: a) Y. Obora, *ACS Catal.* **2014**, *4*, 3972. b) S. Pan, T. Shibata, *ACS Catal.* **2013**, *3*, 704. c) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1853. d) J. Norinder, A. Börner, *ChemCatChem* **2011**, *3*, 1407.

3 Recent Ru catalyst: a) S. P. Shan, T. T. Dang, A. M. Seayad, B. Ramalingam, *ChemCatChem* **2014**, *6*, 808. b) S. Demir, F. Coşkun, I. Özdemir, *J. Organomet. Chem.* **2014**, *755*, 134. c) D. Weickmann, W. Frey, B. Plietker, *Chem.—Eur. J.* **2013**, *19*, 2741. d) S. Agrawal, M. Lenormand, B. Martín-Matute, *Org. Lett.* **2012**, *14*, 1456. e) F. E. Fernández, M. C. Puerta, P. Valerga, *Organometallics* **2012**, *31*, 6868. f) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *J. Org. Chem.* **2011**, *76*, 2328. g) R. Cano, D. J. Ramón, M. Yus, *J. Org. Chem.* **2011**, *76*, 5547.

4 Recent Ir catalyst: a) D. Wang, X.-Q. Guo, C.-X. Wang, Y.-N. Wang, R. Zhong, X.-H. Zhu, L.-H. Cai, Z.-W. Gao, X.-F. Hou, *Adv. Synth. Catal.* **2013**, *355*, 1117. b) A. Wetzel, S. Wöckel, M. Schelwies, M. K. Brinks, F. Rominger, P. Hofmann, M. Limbach, *Org. Lett.* **2013**, *15*, 266. c) A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou, B. Martín-Matute, *Chem.—Eur. J.* **2012**, *18*, 14510. d) F. Li, H. Shan, L. Chen, Q. Kang, P. Zou, *Chem. Commun.* **2012**, *48*, 603. e) H. Ohta, Y. Yuyama, Y. Uozumi, Y. M. A. Yamada, *Org. Lett.* **2011**, *13*, 3892. f) W. Zhang, X. Dong, W. Zhao, *Org. Lett.* **2011**, *13*, 5386. g) I. Cumpstey, S. Agrawal, K. E. Borbas, B. Martín-Matute, *Chem. Commun.* **2011**, *47*, 7827. h) R. Kawahara, K. Fujita, R. Yamaguchi, *Adv. Synth. Catal.* **2011**, *353*, 1161.

5 Recent Au catalyst: a) H. Yang, R. Mao, C. Luo, C. Lu, G. Cheng, *Tetrahedron* **2014**, *70*, 8829. b) N. Zotova, F. J. Roberts, G. H. Kelsall, A. S. Jessiman, K. Hellgardt, K. K. M. Hii, *Green Chem.* **2012**, *14*, 226. c) T. Ishida, R. Takamura, T. Takei, T. Akita, M. Haruta, *Appl. Catal., A* **2012**, *413–414*, 261. d) L. He, Y. Qian, R.-S. Ding, Y.-M. Liu, H.-Y. He, K.-N. Fan, Y. Cao, *ChemSusChem* **2012**, *5*, 621. e) C.-H. Tang, L. He, Y.-M. Liu, Y. Cao, H.-Y. He, K.-N. Fan, *Chem.—Eur. J.* **2011**, *17*, 7172.

6 Recent Ag catalyst: a) H. Liu, G.-K. Chuah, S. Jaenicke, *J. Catal.* **2012**, *292*, 130. b) K. Shimizu, K. Shimura, M. Nishimura, A. Satsuma, *RSC Adv.* **2011**, *1*, 1310. c) X. Cui, Y. Zhang, F. Shi, Y. Deng, *Chem.—Eur. J.* **2011**, *17*, 1021.

7 Recent Cu catalyst: a) F. Santoro, R. Psaro, N. Ravasio, F. Zaccheria, *RSC Adv.* **2014**, *4*, 2596. b) M. Dixit, M. Mishra, P. A. Joshi, D. O. Shah, *Catal. Commun.* **2013**, *33*, 80. c) A. Martínez-Asencio, D. J. Ramón, M. Yus, *Tetrahedron* **2011**, *67*, 3140.

8 Ni catalyst: a) K. Shimizu, S. Kanno, K. Kon, S. M. A. H. Siddiki, H. Tanaka, Y. Sakata, *Catal. Today* **2014**, *232*, 134. b) K. Shimizu, N. Imaiida, K. Kon, S. M. A. H. Siddiki, A. Satsuma, *ACS Catal.* **2013**, *3*, 998. c) K. Shimizu, K. Kon, W. Onodera, H. Yamazaki, J. N. Kondo, *ACS Catal.* **2013**, *3*, 112.

9 Rh catalyst: P. Satyanarayana, G. M. Reddy, H. Maheswaran, M. L. Kantam, *Adv. Synth. Catal.* **2013**, *355*, 1859.

10 Pd catalyst: a) T. T. Dang, B. Ramalingam, S. P. Shan, A. M. Seayad, *ACS Catal.* **2013**, *3*, 2536. b) Y. Zhang, X. Qi, X. Cui, F. Shi, Y. Deng, *Tetrahedron Lett.* **2011**, *52*, 1334.

11 Fe catalyst: a) A. J. Rawlings, L. J. Diorazio, M. Wills, *Org. Lett.* **2015**, *17*, 1086. b) M. Bala, P. K. Verma, U. Sharma, N. Kumar, B. Singh, *Green Chem.* **2013**, *15*, 1687. c) Y. Zhao, S. W. Foo, S. Saito, *Angew. Chem., Int. Ed.* **2011**, *50*, 3006. d) C. Gonzalez-Arellano, K. Yoshida, R. Luque, P. L. Gai, *Green Chem.* **2010**, *12*, 1281. e) R. Martínez, D. J. Ramón, M. Yus, *Org. Biomol. Chem.* **2009**, *7*, 2176.

12 Q. Xu, Q. Li, X. Zhu, J. Chen, *Adv. Synth. Catal.* **2013**, *355*, 73.

13 K. Iida, T. Miura, J. Ando, S. Saito, *Org. Lett.* **2013**, *15*, 1436.

14 Dehalogenated product **3aa** was obtained in Entries 5 (10% yield) and 6 (17% yield), respectively. In the case of 4-CF_3-aniline, trace amount of product **3** was observed under the similar conditions.

15 J.-W. Park, J.-H. Park, C.-H. Jun, *J. Org. Chem.* **2008**, *73*, 5598.

16 X. Cui, Y. Deng, F. Shi, *ACS Catal.* **2013**, *3*, 808.

17 H. Nakazawa, M. Itazaki, *Top. Organomet. Chem.* **2011**, *33*, 27.