A New Atom-Economical and Selective Synthesis of Secondary and Tertiary Alkylamines by Means of Cp*Iridium Complex Catalyzed Multiple N-Alkylation of Ammonium Salts with Alcohols without Solvent

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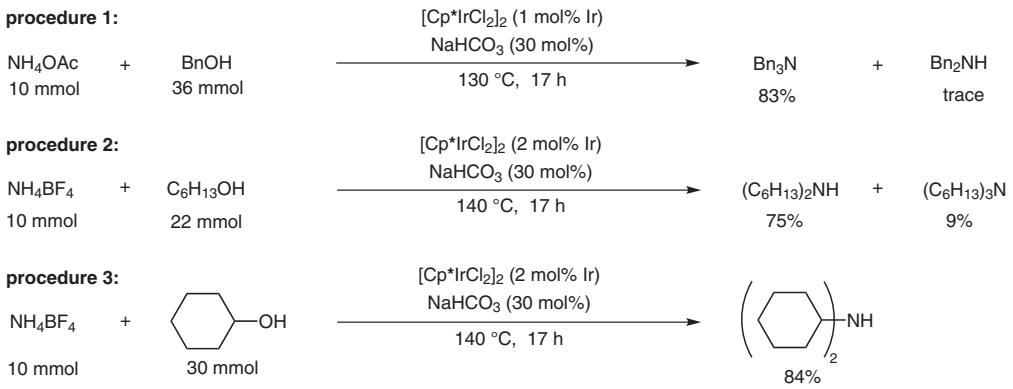
Abstract: A new atom-economical and selective synthetic method for secondary and tertiary alkylamines has been achieved by means of (pentamethylcyclopentadienyl)iridium (Cp*Ir) complex catalyzed multiple N-alkylations of ammonium salts with primary and secondary alcohols without solvent.

Key words: ammonium salt, alcohol, amine, N-alkylation, iridium complex



Scheme 1

Introduction

Amines are a very important class of fundamental organic compounds in a variety of biological, medicinal, agrochemical, and material chemistry. Consequently, considerable efforts have been made to develop versatile and efficient synthetic methodologies for these compounds.[1]

Recently, we have reported atom-economical catalytic systems for the synthesis of secondary and tertiary amines by the N-alkylation of primary and secondary amines with alcohols and diols catalyzed by a (pentamethylcyclopentadienyl)iridium (Cp*Ir) complex,[2] in which the high catalytic performance of Cp*Ir complexes for hydrogen transfer reactions is essential.[3] Ammonia or simple salts are attractive nitrogen sources for the synthesis of amines and there have been some reports on homogeneous catalytic systems using it as the substrate.[4–7] Thus, the utilization of ammonia or its simple salts as nitrogen sources has been an important objective in catalytic organic chemistry. The reported catalytic systems so far have described the synthesis of primary alkyl- and arylamines, as well as secondary and tertiary arylamines, while, to the best of our knowledge, there has been no report on the selective catalytic synthesis of di- and trialkylamines from ammonia or its simple salts.[8] Herein, we wish to report practical procedures for the selective synthesis of secondary and tertiary alkylamines by the Cp*Ir complex catalyzed atom-economical multiple N-alkylation of ammonium salts with primary and secondary alcohols without solvent.[9]

The three representative procedures for practical synthetic methods for tertiary and secondary amines from ammonium salts and alcohols are shown in Scheme 1: (1) procedure 1 demonstrates the exclusive preparation of tribenzylamine (a tertiary amine) by Cp*Ir-catalyzed tri-N-alkylation of ammonium acetate with benzyl alcohol (a primary alcohol), (2) procedure 2 shows the selective preparation of dihexylamine (a secondary amine) by Cp*Ir-catalyzed di-N-alkylation of ammonium tetrafluoroborate with hexan-1-ol (a primary alcohol), and (3) pro-

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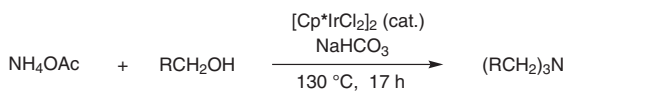
Table 1 Preparation of Trialkylamines by Cp*Ir-Catalyzed N-Alkylation of Ammonium Acetate with Primary Alcohols



Entry	R	$[Cp^*IrCl_2]_2$ (mol% Ir)	Yield[a] (%)
1[b]	Ph	1.0	83
2[b]	4-MeC_6H_4	2.0	87
3[b]	4-$MeOC_6H_4$	1.0	76
4[b]	4-ClC_6H_4	2.0	77
5[c,d]	4-BrC_6H_4	3.0	77
6[c]	3-BrC_6H_4	3.0	89
7[c]	4-$F_3CC_6H_4$	3.0	84
8[c]	4-$MeO_2CC_6H_4$	3.0	70
9[c,d]	4-PhC_6H_4	3.0	83
10[e]	$(CH_2)_4Me$	5.0	60
11[f]	$(CH_2)_2$*i*-Pr	5.0	55
12[f]	CH_2*t*-Bu	5.0	66
13[f]	CH_2CH_2Ph	5.0	73

[a] Isolated yield.
[b] NH_4OAc (10 mmol), alcohol (36 mmol), $NaHCO_3$ (30 mol%).
[c] NH_4OAc (1 mmol), alcohol (3.6 mmol), $NaHCO_3$ (6 mol%).
[d] Toluene (1.0 mL) was added as a solvent.
[e] NH_4OAc (10 mmol), alcohol (50 mmol), $NaHCO_3$ (30 mol%); at higher temperature (140 °C).
[f] NH_4OAc (1 mmol), alcohol (5 mmol), $NaHCO_3$ (30 mol%); at higher temperature (140 °C).

cedure 3 shows the exclusive preparation of dicyclohexylamine (a secondary amine) by Cp*Ir-catalyzed di-N-alkylation of ammonium tetrafluoroborate with cyclohexanol (a secondary alcohol).

Scope and Limitations

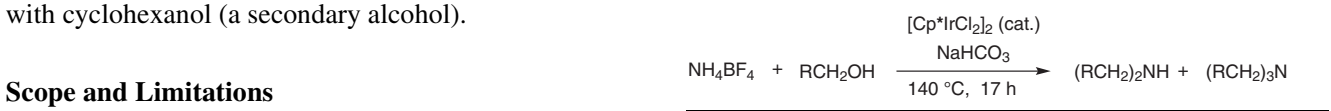
When the reaction of ammonium acetate (10 mmol) and benzyl alcohol (3.6 equiv) in the presence of $[Cp^*IrCl_2]_2$ (1 mol% Ir) and sodium bicarbonate (30 mol%) without solvent was conducted at 130 °C for 17 hours with vigorous stirring as shown in Scheme 1, procedure 1, tribenzylamine was obtained in 83% isolated yield by simple Kugelrohr distillation (Table 1, entry 1). After several experiments, we found that the use of a large reaction flask and vigorous stirring are important to obtain a high yield of tribenzylamine, otherwise a considerable amount of dibenzylamine is produced. Other examples are shown in Table 1.

In the reactions with benzylic alcohols, the triple N-alkylations proceed smoothly to afford tertiary amines in good to high yields (Table 1, entries 1–9), while the reactions with aliphatic alcohols required five equivalents of the alcohol and higher reaction temperatures (140 °C) to obtain good yields of products (Table 1, entries 10–13). Several functional groups such as chloro, bromo, and methoxycarbonyl, can be tolerated in these reactions (Table 1, entries 4–8). It has been also found that higher yields are obtained by using a larger amount (30 mol%) of base ($NaHCO_3$) in large-scale reactions of ammonium acetate with benzylic alcohols, although we have already reported that 6 mol% of sodium bicarbonate is used in smaller scale reactions.

Although ammonium acetate has been found to be the good ammonium source as mentioned above for procedure 1, it is very difficult to prepare secondary amines even when using two equivalents of an alcohol. For example, the reaction of ammonium acetate with hexan-1-ol (2.2 equiv) gave trihexylamine (35%) along with a trace amount of dihexylamine. Next we examined several ammonium salts and found that the reaction of ammonium tetrafluoroborate resulted in the selective formation of secondary amines along with small amounts of tertiary amines (Scheme 1, procedure 2). The results are summarized in Table 2. In these reactions, the higher temperature (140 °C) and use of a sealed reaction flask or a pressure bottle are recommended to obtain high selectivity and yield.

In the reactions of ammonium tetrafluoroborate with secondary alcohols, secondary amines are produced exclusively probably due to steric hindrance (Scheme 1, procedure 3). The results are summarized in Table 3. The reactions with cyclic and aliphatic secondary alcohols give the corresponding secondary amines. An excess of alcohol (1.5 equiv) was used to obtain higher yields. In the reaction with the acid-sensitive alcohol, 1-phenylethanol, the use of ammonium acetate instead of ammonium tetrafluoroborate gave better results (Table 3, entry 4).

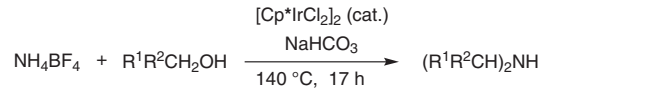
Table 2 Selective Preparation of Dialkylamines by Cp*Ir-Catalyzed N-Alkylation of Ammonium Tetrafluoroborate with Primary Alcohols

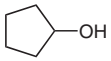
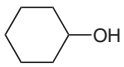
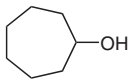


Entry	R	$[Cp^*IrCl_2]_2$ (mol% Ir)	Yield[a] (%) $(RCH_2)_2NH$	Yield[a] (%) $(RCH_2)_3N$
1[b]	$(CH_2)_4Me$	2.0	75	9
2[c]	$(CH_2)_6Me$	3.0	66	8
3[c]	$(CH_2)_2$*i*-Pr	3.0	98	2
4[c]	CH_2*t*-Bu	2.0	78	2
5[c]	Bn	3.0	50	9

[a] GC yield.
[b] NH_4BF_4 (10 mmol), alcohol (22 mmol), $NaHCO_3$ (30 mol%).
[c] NH_4BF_4 (1.0 mmol), alcohol (2.2 mmol), $NaHCO_3$ (30 mol%).

Table 3 Preparation of Dialkylamines by Cp*Ir-Catalyzed N-Alkylation of Ammonium Tetrafluoroborate with Secondary Alcohols



Entry	Alcohol	$[Cp^*IrCl_2]_2$ (mol% Ir)	Yield[a] (%)
1[b]		3.0	81
2[b]		2.0	84
3[c]		3.0	78
4[c,d]	PhCH(OH)Me	3.0	77[e]
5[c]	$Me(CH_2)_5CH(OH)Me$	3.0	54[f]

[a] Isolated yield.
[b] NH_4BF_4 (10 mmol), alcohol (30 mmol), $NaHCO_3$ (30 mol%).
[c] NH_4BF_4 (1.0 mmol), alcohol (3.0 mmol), $NaHCO_3$ (30 mol%).
[d] NH_4OAc was used instead of NH_4BF_4.
[e] Ratio *meso*/*dl* 62:38 (^{1}H NMR).
[f] A mixture of diastereomers.

In summary, we have developed a new atom-economical and selective synthetic method for secondary and tertiary alkylamines by (pentamethylcyclopentadienyl)iridium (Cp*Ir) complex catalyzed multiple N-alkylation of ammonium salts with primary and secondary alcohols.

All reactions and manipulations were carried out in a glovebox or using standard Schlenk techniques under an atmosphere of N_2 or argon. ^{1}H and ^{13}C NMR spectra were recorded on Jeol A-500 and EX-270 spectrometers. Gas chromatography (GC) analyses were performed on a GL-Sciences GC353B gas chromatograph with a capillary column (GL-Sciences TC-17). Column chromatography was carried out by using Florisil. Solvents were dried by standard procedures and distilled prior to use. The catalyst $[Cp^*IrCl_2]_2$ was prepared according to the literature method.[10] All other reagents are commercially available and were used after distillation.

Procedure 1
Tribenzylamine;[2d,11] Typical Procedure
To a 100-mL flask under an atmosphere of argon was added NH_4OAc (766 mg, 9.94 mmol), $[Cp^*IrCl_2]_2$ (40 mg, 0.050 mmol, 1.0 mol% Ir), and $NaHCO_3$ (250 mg, 2.97 mmol, 30 mol%). $PhCH_2OH$ (3.797 g, 35.1 mmol) was added by syringe and the flask was sealed with a glass stopper. The mixture was stirred at r.t. for 30 min and then at 130 °C for 17 h. Then, aq 2 M NaOH (20 mL) was added to the mixture and the product was extracted with CH_2Cl_2 (45 mL). Evaporation of the solvent followed by Kugelrohr distillation (200 °C/0.4 mbar) gave the product; yield: 2.358 g (83%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.43–7.19 (m, 15 H), 3.56 (s, 6 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.6, 128.7, 128.2, 126.8, 57.9.

Trihexylamine;[12] Typical Procedure
To a 100-mL flask under an atmosphere of argon was added NH_4OAc (762 mg, 9.89 mmol), $[Cp^*IrCl_2]_2$ (199 mg, 0.250 mmol, 5.0 mol% Ir), and $NaHCO_3$ (251 mg, 3.00 mmol, 30 mol%). Hexan-1-ol (5.145 g, 50.4 mmol) was added by syringe and the flask was sealed with a glass stopper. The mixture was stirred at r.t. for 30 min and then at 140 °C for 17 h. Then, aq 2 M NaOH (20 mL) was added to the mixture and the product was extracted with CH_2Cl_2 (45 mL). Evaporation of the solvent followed by Kugelrohr distillation (180 °C/133 mbar) gave the product; yield: 1.599 g (60%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.43–2.36 (t, *J* = 7 Hz, 6 H), 1.51–1.21 (m, 24 H), 0.98–0.85 (t, *J* = 7 Hz, 9 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 54.3, 31.9, 27.3, 27.1, 22.6, 14.0.

Procedure 2
Dihexylamine;[12a,13] Typical Procedure
To a heavy-walled glass tube (15 mL) under an atmosphere of argon was added NH_4BF_4 (1.050 g, 10.0 mmol), $[Cp^*IrCl_2]_2$ (80 mg, 0.10 mmol, 2.0 mol% Ir), and $NaHCO_3$ (252 mg, 3.00 mmol, 30 mol%). Hexan-1-ol (2.254 g, 22.1 mmol) was added by syringe and the glass tube was sealed with a Teflon stopper. The mixture was stirred at r.t. for 30 min and then at 140 °C for 17 h. Then, aq 2 M NaOH (20 mL) was added to the mixture and the product was extracted with CH_2Cl_2 (45 mL). The GC yields of dihexylamine and trihexylamine were 75% and 9%, respectively. Evaporation of the solvent followed by column chromatography (Florisil, hexane) gave a mixture of dihexylamine and trihexylamine (1.567 g). From this mixture, pure dihexylamine was isolated by further column chromatography (Florisil, hexane); yield: 1.01 g (55%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.62–2.55 (t, *J* = 7 Hz, 4 H), 1.50–1.29 (m, 16 H), 0.90–0.85 (t, *J* = 7 Hz, 6 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 50.1, 31.7, 30.1, 27.0, 22.5, 13.9.

Procedure 3
Dicyclohexylamine;[9,14] Typical Procedure
To a 100-mL flask under an atmosphere of argon was added NH_4BF_4 (1.050 g, 10.0 mmol), $[Cp^*IrCl_2]_2$ (81 mg, 0.10 mmol, 2.0 mol% Ir), and $NaHCO_3$ (251 mg, 2.99 mmol, 30 mol%). Cyclohexanol (3.015 g, 30.1 mmol) was added by syringe and the flask was sealed with a glass stopper. The mixture was stirred at r.t. for 30 min and then at 140 °C for 17 h. Then, aq 2 M NaOH (20 mL) was added to the mixture and the product was extracted with CH_2Cl_2 (45 mL). Evaporation of the solvent followed by Kugelrohr distillation (175 °C/133 mbar) gave the product; yield: 1.529 g (84%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.55 (m, 2 H), 1.88–1.83 (m, 4 H), 1.75–1.69 (m, 4 H), 1.63–1.57 (m, 2 H), 1.33–0.95 (m, 10 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 52.5, 33.9, 25.7, 24.8.

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