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SYNTHESIS OF PIPERAZINE DERIVATIVES BY Cp*Ir COMPLEX-CATALYZED *N*-ALKYLATIVE REACTIONS OF ETHANOLAMINES

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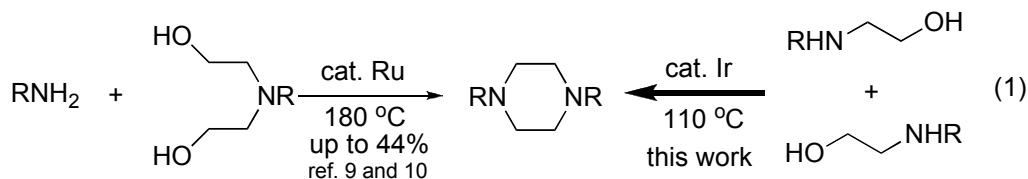
Abstract – A new method for the synthesis of piperazine derivatives catalyzed by a Cp*Ir complex has been developed. Cp*Ir complex-catalyzed *N*-alkylative homocoupling reactions of *N*-benzylethanolamines give *N,N'*-dibenzylpiperazine derivatives. For example, the reaction of *N*-benzylethanolamine in the presence of [Cp*IrCl₂]₂ (2.5 mol%) and NaHCO₃ (15 mol%) in toluene at 110 °C for 17 h gives *N,N'*-dibenzylpiperazine in 66% yield. Cp*Ir complex-catalyzed *N*-alkylative cross coupling reactions of Boc-protected diethanolamines with benzylamine also give *N*-benzyl-*N'*-Boc-piperazine derivatives in moderate to good yields.

INTRODUCTION

Piperazine and its derivatives are synthetically important and valuable because of their roles as indispensable structures of a variety of pharmaceutical compounds.¹ For example, some of piperazine derivatives having benzyl substituent on nitrogen are known to be promising as anticancer agents or peptidomimetic drugs.^{1a,c} Generally, synthesis of piperazines has been carried out by heterocyclization using primary amines and bis(haloalkyl)amines,² reductive coupling of diimines,³ and reduction of keto- or diketopiperazines.⁴ In such reactions, formation of wasteful byproducts (hydrogen chloride or metal salt) and/or use of strong reductant can not be avoided.

Recently, we and other groups have developed atom-economical catalytic systems for carbon-nitrogen bond formation using amines and alcohols, which are based on the high catalytic performance of iridium^{5,6} and ruthenium^{6,7} complexes in hydrogen transfer reactions. In such catalytic reactions, only water is generated as a stoichiometric co-product. When this methodology is extended to the synthesis

of piperazine, two strategies can be considered.⁸ The first one is the double *N*-alkylation of primary amines with diethanolamines (the left arrow in eq 1). This type of reaction was actually studied by Watanabe *et al.*⁹ and van Koten *et al.*¹⁰ Several *N*-arylpiperazines were synthesized by the catalytic system using ruthenium complexes. However, these reactions had to be conducted under harsh conditions (180 °C), and the yields of the piperazines were relatively low (<44%).



In this paper, we wish to report the synthesis of piperazines according to the second strategy (i.e. double *N*-alkylative homocoupling of ethanolamines, the right arrow in eq 1). By using a Cp*Ir catalyst (Cp* = pentamethylcyclopentadienyl), the reaction proceeds under relatively mild conditions (110 °C) to give a series of benzylpiperazine derivatives. We also disclose an effective catalytic system according to the first one (the left arrow in eq 1), in which use of Cp*Ir catalyst makes them possible to lower the reaction temperature and to improve the yields.

RESULTS AND DISCUSSION

First, we investigated the homocoupling reaction of *N*-benzylethanolamine (**1a**) giving *N,N'*-dibenzylpiperazine (**2a**) catalyzed by [Cp*IrCl₂]₂ under various conditions (Table 1). When the reaction of **1a** was carried out at 110 °C for 17 h in toluene in the presence of [Cp*IrCl₂]₂ (2.5 mol%) as a catalyst, **2a** was formed in 20% yield (entry 1). The reaction was considerably accelerated by the addition of a weak base (entries 2-5). When the reaction was carried out in the presence of 15 mol% of NaHCO₃, the yield of **2a** increased up to 66% (entry 2). Other weak bases, such as Na₂CO₃, NaOAc, and K₂CO₃ were also effective (entries 3-5), while stronger bases Cs₂CO₃ and NaO^tBu were not (entries 6 and 7). When the reaction was carried out using a smaller amount of catalyst (1.0 mol%), the yield of **2a** was lowered (entry 8). The reaction could be conducted under the solvent-free conditions, resulting in a slightly low yield (entry 9). The optimum reaction temperature was 110 °C: the reactions at higher (130 °C) or lower (90 °C) gave inferior results (entries 10 and 11).

On the basis of the optimization of the catalytic conditions, the homocoupling reactions of a series of *N*-benzylethanolamines having functional groups on aromatic ring were conducted. The results are summarized in Table 2. Methyl, methoxy, chloro, bromo, and trifluoromethyl substituents were tolerant in the present heterocyclization system to give the corresponding piperazine derivatives in moderate to good yields.¹¹

Table 1. *N*-Alkylative Homocoupling of *N*-Benzylethanolamine (**1a**) Catalyzed by Cp*Ir Complex under Various Conditions^a

c1ccccc1CNCCO **1a**
 $\xrightarrow[\text{toluene, 110 } ^\circ\text{C, 17 h}]{\text{cat. [Cp}^*\text{IrCl}_2\text{]}_2, \text{ base}}$
c1ccccc1CN(CCNc2ccccc2)c3ccccc3 **2a**

entry	Ir catalyst (mol%)	base (mol%)	yield (%) ^b
1	2.5	none	20
2	2.5	NaHCO ₃ (15)	66
3	2.5	Na ₂ CO ₃ (15)	56
4	2.5	NaOAc (15)	54
5	2.5	K ₂ CO ₃ (15)	36
6	2.5	Cs ₂ CO ₃ (15)	7
7	2.5	NaOtBu (15)	1
8	1.0	NaHCO ₃ (6)	42
9 ^c	2.5	NaHCO ₃ (15)	57
10 ^d	2.5	NaHCO ₃ (15)	54
11 ^e	2.5	NaHCO ₃ (15)	51

^aThe reaction was carried out with **1a** (1.0 mmol), [Cp*IrCl₂]₂ (0.025 mmol), and base (0.15 mmol) in toluene (0.1 mL) at 110 °C for 17 h. ^bDetermined by GC. ^cWithout solvent. ^dAt 90 °C. ^eAt 130 °C.

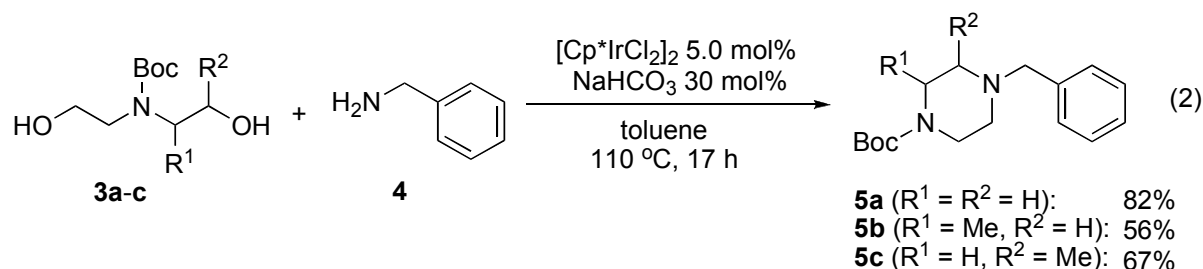
Table 2. *N*-Alkylative Homocoupling of Several *N*-Benzylethanolamines (**1a-g**) Catalyzed by [Cp*IrCl₂]₂ / NaHCO₃ System^a

ArCNCCO **1a-g**
 $\xrightarrow[\text{toluene, 110 } ^\circ\text{C, 17 h}]{[\text{Cp}^*\text{IrCl}_2\text{}]_2 \text{ 2.5 mol\%, NaHCO}_3 \text{ 15 mol\%}}$
ArCN(CCNc1ccccc1)Ar **2a-g**

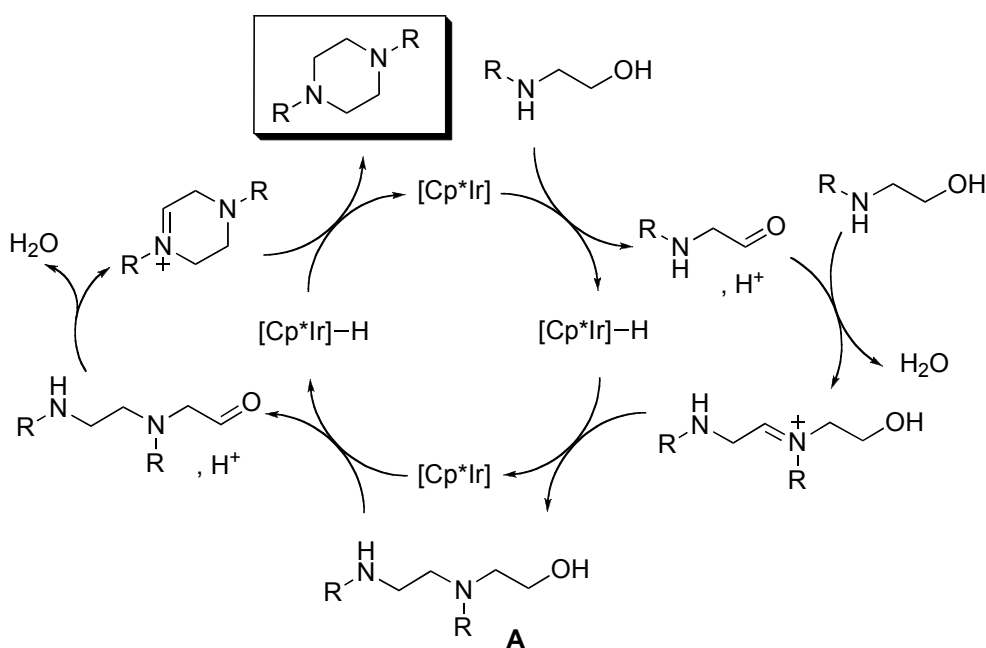
entry	substrate	product	yield (%) ^b
1	1a R = H	2a	(66)
2	1b R = 4-Me	2b	45
3	1c R = 2-Me	2c	47
4	1d R = 4-OMe	2d	53
5	1e R = 4-Cl	2e	49
6	1f R = 4-Br	2f	63
7	1g R = 4-CF ₃	2g	54

^aThe reaction was carried out with **1** (1.0 mmol), [Cp*IrCl₂]₂ (0.025 mmol), and NaHCO₃ (0.15 mmol) in toluene (0.1 mL) at 110 °C for 17 h. ^bIsolated yield. The value in parentheses indicates GC yield.

Furthermore, we examined the cross coupling reactions of Boc-protected diethanolamines (**3a-c**) with benzylamine (**4**) on the basis of the strategy shown in the left side in eq 1. These reactions gave *N*-benzyl-*N'*-Boc-piperazine derivatives (**5a-c**) under relatively mild conditions (110 °C) in moderate to high yields (eq 2).



In the previous papers, we have proposed mechanisms for intermolecular *N*-alkylation of primary amines with alcohols,^{5b,g} intramolecular *N*-alkylation of amino alcohols,^{5a} and cycloalkylation of primary amines with diols^{5c,e} catalyzed by a Cp*Ir complex. On the basis of those, a possible mechanism for the present *N*-alkylative homocoupling of ethanolamines is described in Scheme 1. The first stage of the reaction would involve an intermolecular carbon-nitrogen bond formation through hydrogen transfer processes and condensation to afford a diaminoethanol intermediate **A**. Subsequent intramolecular carbon-nitrogen bond formation would give a piperazine product.



Scheme 1

In summary, we have developed a new method for the synthesis of piperazine derivatives catalyzed by a Cp*Ir complex using ethanolamines as starting materials. Furthermore, we have disclosed an effective

catalytic system using Cp*Ir complex for the double *N*-alkylation of primary amines with diethanolamines to afford piperazines.

EXPERIMENTAL

General: All reactions and manipulations were carried out under an atmosphere of argon by means of standard Schlenk techniques. ^1H and ^{13}C NMR spectra were recorded on JEOL A-500 and EX-270 spectrometers. Gas chromatography (GC) analyses were performed on a Shimadzu GC-14A gas chromatograph and on a GL-Sciences GC353B gas chromatograph with a capillary column (Shimadzu CBP1-M25-025 or GL-Science TC-17). Column chromatography was carried out by using Wako-gel C-200. Solvents were dried by using standard procedures and distilled prior to use. The catalyst $[\text{Cp}^*\text{IrCl}_2]_2$ was prepared according to the literature method.¹²

General procedure for the *N*-alkylative homocoupling of *N*-benzylethanolamine (1a**) giving *N,N'*-dibenzylpiperazine (**2a**) catalyzed by Cp*Ir complex shown in Table 1:** Under an atmosphere of argon in a heavy-walled glass reactor, **1a** (1.0 mmol), $[\text{Cp}^*\text{IrCl}_2]_2$ (0.025 mmol, 2.5 mol%), base (0.15 mmol, 15 mol%), and toluene (0.1 mL) were placed. The reactor was sealed, and the mixture was stirred at 110 °C for 17 h. The yield of **2a** was determined by GC analysis using decane as an internal standard.

General procedure for the *N*-alkylative homocoupling of *N*-benzylethanolamines (1a-g**) giving *N,N'*-dibenzylpiperazine derivatives (**2a-g**) catalyzed by Cp*Ir complex shown in Table 2:** Under an atmosphere of argon in a heavy-walled glass reactor, **1** (1.0 mmol), $[\text{Cp}^*\text{IrCl}_2]_2$ (0.025 mmol, 2.5 mol%), base (0.15 mmol, 15 mol%), and toluene (0.1 mL) were placed. The reactor was sealed, and the mixture was stirred at 110 °C for 17 h. After analysis by GC, the products were isolated by silica-gel column chromatography (eluent: hexane-EtOAc).

N,N'-Dibenzylpiperazine (**2a**): ^{13}C NMR (270 MHz, CDCl_3): δ 7.35-7.20 (m, 10H), 3.51 (s, 4H), 2.48 (s, 8H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 138.2, 129.2, 128.2, 127.0, 63.1, 53.1.

N,N'-Bis(*p*-methylbenzyl)piperazine (**2b**): ^1H NMR (270 MHz, CDCl_3): δ 7.19 (d, J = 8 Hz, 4H), 7.10 (d, J = 8 Hz, 4H), 3.46 (s, 4H), 2.46 (s, 8H), 2.32 (s, 6H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 136.5, 135.0, 129.2, 128.8, 62.7, 53.0, 21.0. Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.19; H, 8.71; N, 9.15.

N,N'-Bis(*o*-methylbenzyl)piperazine (**2c**): ^1H NMR (270 MHz, CDCl_3): δ 7.26-7.20 (m, 2H), 7.14-7.07 (m, 6H), 3.43 (s, 4H), 2.44 (s, 8H), 2.34 (s, 6H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 137.4, 136.6, 130.1, 129.7, 126.9, 125.4, 60.8, 53.3, 19.2. Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.48; H, 9.01; N, 9.37.

N,N'-Bis(*p*-methoxybenzyl)piperazine (**2d**): ^1H NMR (270 MHz, CDCl_3): δ 7.21 (d, J = 9 Hz, 4H), 6.84

(d, $J = 9$ Hz, 4H), 3.79 (s, 6H), 3.44 (s, 4H), 2.45 (s, 8H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 158.9, 130.6, 128.5, 113.6, 61.9, 55.1, 52.1. Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.37; H, 7.99; N, 8.40.

N,N'-Bis(*p*-chlorobenzyl)piperazine (**2e**): ^1H NMR (270 MHz, CDCl_3): δ 7.28–7.21 (m, 8H), 3.45 (s, 4H), 2.44 (s, 8H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 136.7, 132.6, 130.3, 128.3, 62.1, 52.9. Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_2$: C, 64.48; H, 6.01; N, 8.36. Found: C, 64.18; H, 6.04; N, 8.21.

N,N'-Bis(*p*-bromobenzyl)piperazine (**2f**): ^1H NMR (270 MHz, CDCl_3): δ 7.42 (d, $J = 9$ Hz, 4H), 7.18 (d, $J = 9$ Hz, 4H), 3.44 (s, 4H), 2.44 (s, 8H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 137.2, 131.2, 130.7, 120.7, 62.2, 52.9. Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{Br}_2\text{N}_2$: C, 50.97; H, 4.75; N, 6.60. Found: C, 50.94; H, 4.67; N, 6.45.

N,N'-Bis(*p*-trifluoromethylbenzyl)piperazine (**2g**): ^1H NMR (270 MHz, CDCl_3): δ 7.56 (d, $J = 8$ Hz, 4H), 7.44 (d, $J = 8$ Hz, 4H), 3.56 (s, 4H), 2.48 (s, 8H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 142.5, 129.3 (q, $J = 32$ Hz), 129.2, 125.5 (q, $J = 4$ Hz), 124.2 (q, $J = 270$ Hz), 62.4, 53.1. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{F}_6\text{N}_2$: C, 59.70; H, 5.01; N, 6.96. Found: C, 59.63; H, 5.00; N, 7.02.

General procedure for the *N*-alkylative cross coupling of Boc-protected diethanolamines (3a-c) with benzylamine (4) giving *N*-benzyl-*N'*-Boc-piperazine derivatives (5a-c) catalyzed by Cp^*Ir complex shown in Eq 2: Under an atmosphere of argon in a heavy-walled glass reactor, **3** (0.50 mmol), **4** (1.5 mmol), $[\text{Cp}^*\text{IrCl}_2]_2$ (0.025 mmol, 5.0 mol%), base (0.15 mmol, 30 mol%), and toluene (0.1 mL) were placed. The reactor was sealed, and the mixture was stirred at 110 °C for 17 h. After analysis by GC, the products were isolated by silica-gel column chromatography (eluent: hexane-EtOAc).

tert-Butyl 4-benzyl-1-piperazinecarboxylate (**5a**):¹⁴ ^1H NMR (270 MHz, CDCl_3): δ 7.35–7.25 (m, 5H), 3.51 (s, 2H), 3.42 (t, $J = 5$ Hz, 4H), 2.38 (t, $J = 5$ Hz, 4H), 1.45 (s, 9H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 154.8, 137.8, 129.1, 128.2, 127.1, 79.5, 63.0, 52.8, 28.4.

tert-Butyl 2-methyl-4-benzyl-1-piperazinecarboxylate (**5b**):¹⁵ ^1H NMR (270 MHz, CDCl_3): δ 7.33–7.24 (m, 5H), 4.18 (m, 1H), 3.80 (d, $J = 13$ Hz, 1H), 3.46 (m, 1H), 3.11 (m, 1H), 2.75 (d, $J = 11$ Hz, 1H), 2.58 (d, $J = 11$ Hz, 1H), 2.11 (dd, $J = 11, 4$ Hz, 1H), 2.00 (m, 1H), 1.47 (s, 9H), 1.24 (d, $J = 7$ Hz, 3H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 154.8, 138.4, 128.7, 128.2, 127.0, 79.3, 62.8, 57.4, 53.2, 28.4, 15.9.

tert-Butyl 3-methyl-4-benzyl-1-piperazinecarboxylate (**5c**):¹⁶ ^1H NMR (270 MHz, CDCl_3): δ 7.34–7.23 (m, 5H), 4.00 (d, $J = 14$ Hz, 1H), 3.67–3.62 (m, 2H), 3.18 (d, $J = 14$ Hz, 1H), 3.10–3.02 (m, 1H), 2.88 (br, 1H), 2.66–2.61 (m, 1H), 2.48–2.37 (m, 1H), 2.10–2.04 (m, 1H), 1.45 (s, 9H), 1.12 (d, $J = 6$ Hz, 3H); ^{13}C NMR (67.8 MHz, CDCl_3): δ 154.7, 138.7, 128.9, 128.2, 126.9, 79.4, 58.0, 53.1, 50.0, 28.4, 15.3.

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