A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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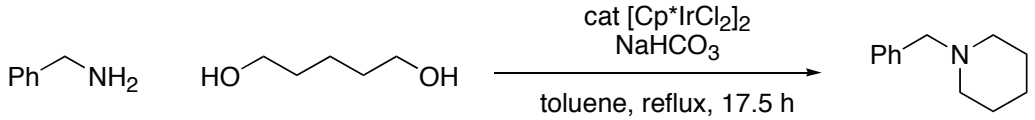
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.083.0217
Organic Syntheses, Vol. 83, p. 217-221 (2006); Coll. Vol. 11, p. 697-701 (2009).

IRIDIUM-CATALYZED *N*-HETEROCYCLIZATION OF PRIMARY AMINES WITH DIOLS: *N*-BENZYLPIPERIDINE



Submitted by Ken-ichi Fujita,[1a] Youichiro Enoki, and Ryohei Yamaguchi.[1b]
Checked by Gustavo Moura-Letts and Dennis P. Curran.[1c]

1. Procedure

N-Benzylpiperidine (Note 1). A 100-mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, a rubber septum, and a reflux condenser with a bubbler-sealed outlet is charged with di-μ-chloro-dichlorobis(η^5-pentamethylcyclopentadienyl)diiridium $[Cp^*IrCl_2]_2$ (199 mg, 0.25 mmol) (Note 2) and sodium bicarbonate (41 mg, 0.48 mmol) (Note 3) under an argon atmosphere. Addition of 10 mL of toluene (Note 4) by syringe to the flask affords an orange suspension. Benzylamine (10.70 g, 10.91 mL, 99.86 mmol) (Note 5) is added by syringe through the rubber septum over 10 sec. During the addition, the color of the suspension changes to yellow. Then 1,5-pentanediol (10.39 g, 10.45 mL, 99.76 mmol) (Note 5) is added by syringe through the septum over 30 sec. Under an argon flow, the rubber septum is replaced with a glass stopper. The black suspension (Note 6) is heated at reflux in an oil bath (oil bath temperature: 120 °C) for 17.5 h, then the reaction mixture is cooled to room temperature (Note 7). The reflux condenser is removed, and a short-path vacuum distillation apparatus is mounted to the flask. Distillation at 21.0 mmHg yields a fraction boiling between 123–125 °C; the clear, very pale yellow liquid is *N*-benzylpiperidine (14.20–14.30 g, 81–82% based on 1,5-pentanediol) (Notes 8, 9).

2. Notes

1. This is a modification of a published procedure.[2]
2. The submitters prepared the iridium complex di-μ-chloro-dichlorobis(η^5-pentamethylcyclopentadienyl)diiridium according to

the literature method.[3] They also report that the commercially available complex from Aldrich Chemical Company, Inc. or Strem Chemicals, Inc. can be substituted. The checkers purchased the catalyst from Strem.

3. Sodium bicarbonate (EP) was purchased from Wako Pure Chemical Industries, Ltd. (submitters) or Fisher Scientific (checkers) and used as received.

4. Toluene (GR) was purchased from Wako Pure Chemical Industries, Ltd. (submitters) or Aldrich (checkers) and distilled from sodium benzophenone ketyl under an argon atmosphere before use.

5. Benzylamine (GR, >99%) and 1,5-pentanediol (EP, >97%) were purchased from Tokyo Kasei Kogyo Co., Ltd. (submitters) or Aldrich (checkers) and used as received.

6. The submitters reported that the mixture remained yellow, but the checkers observed that it turned black after about 5 min.

7. At this time, a small quantity of water was observed in the bottom of the flask.

8. The submitters reported that the distillate was colorless. The checkers observed that the clear, very pale yellow liquid could be redistilled to provide a clear, colorless liquid, if desired. Alternatively, in a separate run where special care was taken to collect only clear distillate, 13.30 g (76%) product was obtained.

9. The spectral data and elemental analysis are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (m, 2 H), 1.56 (m, 4 H), 2.36 (m, 4 H), 3.46 (s, 2 H), 7.31–7.23 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.3, 25.9, 54.4, 63.8, 126.7, 127.9, 129.0, 138.6; IR (thin film) 3062, 2934, 2852, 2684, 1493, 1369, 1154, 1113 cm^{-1}; EIMS *m/z*: 91(100), 175(95), 98(92), 84(91), 65(75), 176(58). Purity (>99.5%) was assessed by Gas Chromatography (GC) with a retention time (R_t) of 11.16 min: (Agilent 19091Z-413E, HP-1 Methyl siloxane, 0.32mm x 30m x 0.25μm; temperature 50 °C, ramp 10°/min to 350 °C).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

N-Heterocyclic compounds are important intermediates in medicinal chemistry, material chemistry, and synthetic organic chemistry. In particular, pyrrolidine, piperidine and morpholine derivatives are present in large classes of biologically active natural products. For the past several decades, much effort has been devoted to development of efficient methods for the synthesis of these *N*-heterocycles. Recently, a variety of transition metal-catalyzed reactions for the synthesis of *N*-heterocyclic compounds have been disclosed and reviewed.[4,5] From an environmental point of view, *N*-heterocyclization of primary amines with diols is an attractive method because an *N*-heterocyclic product can be obtained from easily available starting materials in one pot without generation of wasteful or harmful byproducts (H_2O is the only byproduct). Although some ruthenium-catalyzed systems for *N*-heterocyclization of primary amines with diols have been reported, most of them require high reaction temperature (>150 °C) and applicable substrates are rather restricted.[6-9]

The method outlined here represents a convenient and environmentally benign *N*-heterocyclization of primary amines with diols catalyzed by a Cp*(C_5Me_5) iridium complex. The reaction can be conducted under relatively mild conditions (reflux in toluene as a solvent), and it does not generate any wasteful byproducts. Additional examples of the $[Cp^*IrCl_2]_2$-catalyzed *N*-heterocyclization of primary amines with diols are shown in the Table.[2] Using this protocol, a variety of pyrrolidine, piperidine, and morpholine derivatives can be synthesized in good to excellent yields. A seven-membered cyclic amine (azepane) can be also synthesized in a satisfactory yield (entry 2).

Table. Cp*Ir Complex-Catalyzed *N*-Heterocyclization of Primary Amines with a Variety of Diols[a]

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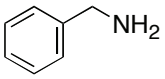
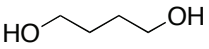
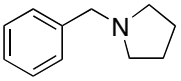
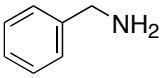
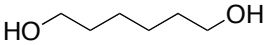
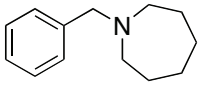
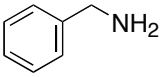
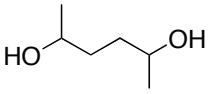
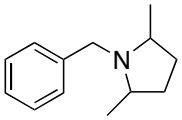
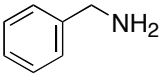
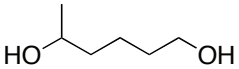
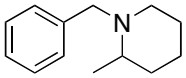
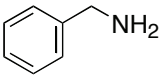
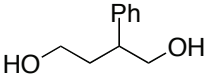
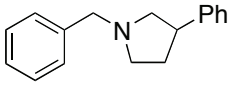
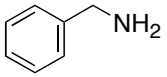
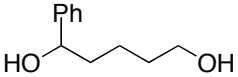
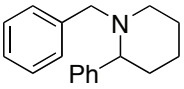
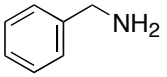
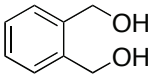
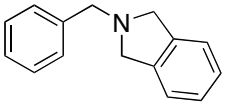
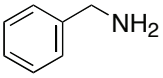
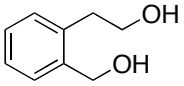
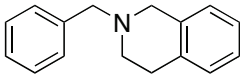
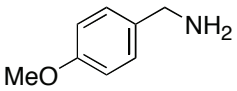
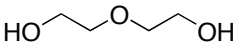
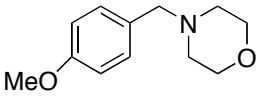
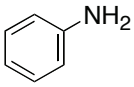
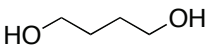
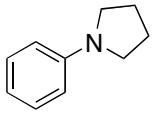
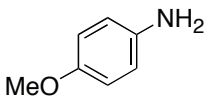
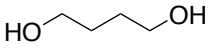
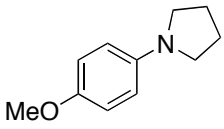
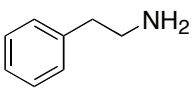
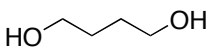
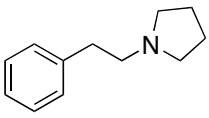
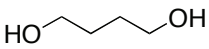
1			1.0	72	
2[c]			2.0	73	
3[d]			1.0	94[e]	
4			1.0	79	
5			2.0	90	
6			4.0	78[f]	
7[g,h]			2.0	63	
8			2.0	76	
9			2.0	76	
10[i,j]			5.0	70	
11[i]			5.0	90	
12			4.0	73	
13	n-$C_8H_{17}NH_2$		4.0	81[f]	nC_8H_{17} 

[a]The reaction was carried out at 110 °C for 17 h with amine (3.0 mmol), diol (2.0 mmol), $[Cp^*IrCl_2]_2$ (1.0 –5.0 % Ir), and $NaHCO_3$ (same number of equiv as Ir catalyst) in toluene (1 mL). [b]Isolated yield. [c] Toluene (3 mL) was used. [d]Na_2CO_3 was used as base. [e]*Cis/trans* = 73/27 (determined by ^1H NMR analysis. [f]GC yield. [g]Amine (2.0 mmol) was used. [h]Base was not added. [i]Reaction temperature was 130 °C. [j]Reaction time was 40 h.

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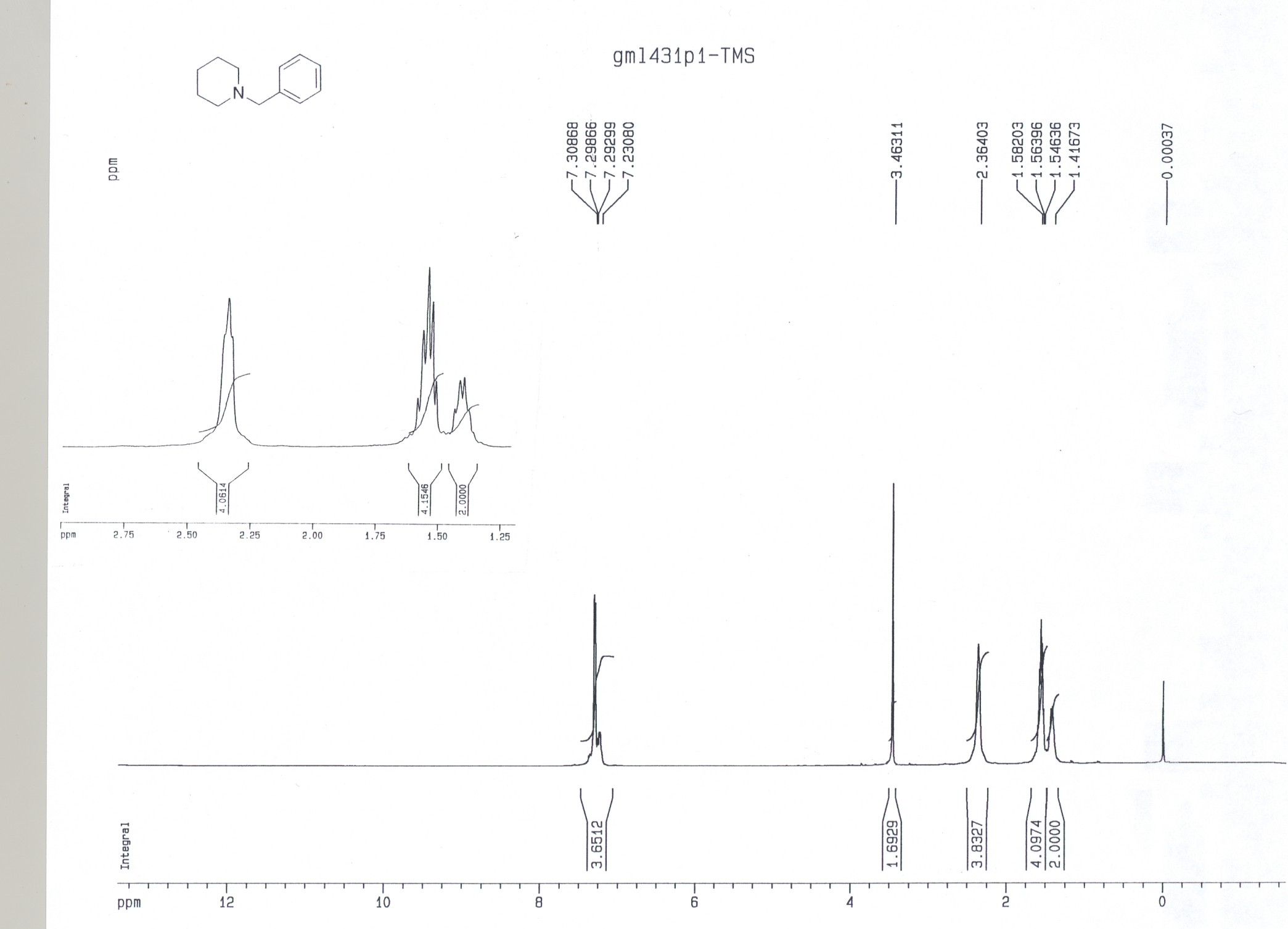
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Di-μ-chloro-dichlorobis(η^5-pentamethylcyclopentadienyl)diiridium [$Cp^*IrCl_2]_2$ Iridium, di-μ-chlorodichlorobis[(1,2,3,4,5-η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl]di-; (12354-84-6)
1,5-Pentanediol; (111-29-5)
Benzylamine: Benzenemethanamine; (100-46-9)
N-Benzylpiperidine: Piperidine, 1-(phenylmethyl)-; (2905-56-8)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7.29866
7.29299
7.23080
3.46311
2.36403
1.58203
1.56396
1.54636
1.41673
0.00037
Integral
4.0614
4.1546
2.0000
ppm
2.75
2.50
2.25
2.00
1.75
1.50
1.25
Integral
3.6512
1.6929
3.8327
4.0974
2.0000
ppm
12
10
8
6
4
2
0