Notes

Arylation of Ketone *N,N*-Dimethylhydrazones with (*π*-Chlorobenzene)chromium Tricarbonyl

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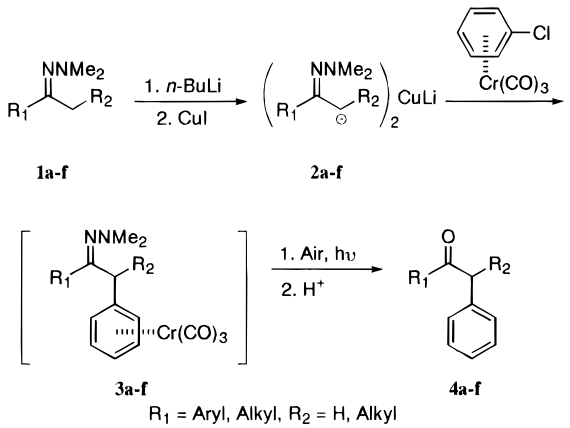
Summary: α-*Phenyl ketone* ***4*** *was obtained from N,N-dimethylhydrazone* ***1*** *by arylation with (π-chlorobenzene)chromium tricarbonyl in good yield.*

α-Aryl carbonyl compounds are important organic compounds. For example, ibuprofen, ketoprofen, suprofen, flubiprofen, indoprofen, fenoprofen, and naproxen are important commercial anti-inflammatory compounds.[1] However, although α-alkyl carbonyl compounds are easily prepared from carbonyl derivatives such as dimethylhydrazones by alkylation with alkyl halides,[2] aryl carbonyls could not be obtained by arylation with aryl halides under similar conditions.

On the other hand, (arene)tricarbonylchromium complexes, which were first described in 1958 by Fischer and Öfele,[3] have a multifarious potential for organic synthesis[4] and the chemistry of (arene)tricarbonylchromium has been the subject of intense investigation for many years. For example, Semmelhack reported the nucleophilic aromatic substitution by the anion of nitriles or esters using (*π*-chlorobenzene)chromium tricarbonyl.[5] Here, we report arylation of carbonyl derivatives, such as ketone *N,N*-dimethylhydrazone **1**, using (*π*-chlorobenzene)chromium tricarbonyl (Scheme 1). Ketone *N,N*-dimethylhydrazone **1** was conveniently prepared from ketone and *N,N*-dimethylhydrazine using trifluoroacetic acid as a catalyst in good yield (80−94%).

A typical procedure was as follows. After deprotonation of acetophenone *N,N*-dimethylhydrazone (**1a**) with lithium diisopropylamide (LDA) in THF, copper(I) iodide was added at −5 °C. The copper lithium azaenolate **2a** was trapped with (*π*-chlorobenzene)chromium tricarbonyl[6] at 70 °C, followed by decomplexation of the chromium tricarbonyl unit of **3a**, which was achieved by dissolution in diethyl ether, exposure to air and sunlight,[7] and hydrolysis by aqueous 2 *N* HCl. This afforded benzyl phenyl ketone (**4a**) in good yields (entry 1, Table 1).

Scheme 1



In this reaction, the key points were the preparation of the copper lithium azaenolate **2a** and the use of (*π*-chlorobenzene)chromium tricarbonyl. If a lithium salt of acetophenone *N,N*-dimethylhydrazone was used instead of **2a** (entry 2) or chlorobenzene was used instead of (*π*-chlorobenzene)chromium tricarbonyl (entry 3), the reaction did not proceed. Other results are listed in Table 1 (entries 4−8). Various α-phenyl ketones **4** were obtained from the copper lithium azaenolate **2** in good yields. When the copper lithium azaenolate was unstable (e.g., **2c**) at −5 °C, **4c** was only obtained in 6% yield. When this reaction was carried out at −78 °C, the yield of **4c** was low (24%) (entry 5).

Experimental Section

General Methods. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained on a JEOL ALPHA-400 spectrometer in $CDCl_3$ solvent and recorded in parts per million (ppm, δ) downfield from the internal TMS. Mass spectra were recorded on a Shimadzu GCMS-QP2000A spectrometer. Column chromatography was performed on Nacalai silica gel 60 (230−400 mesh), and thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates F_{254}. THF was dried and deoxygenated by distillation from potassium benzophenone under an argon atmosphere immediately before use. Benzene was purified by distillation over $CaCl_2$. *n*-Butyllithium as a

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(1) (a) Shen, T. Y. *Angew. Chem., Int. Ed. Engl.* **1972**, *6*, 460. (b) Lednicer, D.; Metscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1977; Vol. 1, pp 85, 267. *Ibid.* 1980; Vol. 2, p 63. (c) Hino, K.; Nakamura, H.; Nagai, Y.; Uno, H.; Nishimura, H. *J. Med. Chem.* **1983**, *26*, 222. (d) Giordano, C.; Castaldi, G.; Uggeri, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 413. (e) Rieu, J. P.; Boucherle, A.; Couse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095. (f) *The Merck Index*, 11th ed.; Merck: Rahway, NJ, 1989.

(2) Bergeiter, D. E.; Momongan, M. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 503 and references cited therein.

(3) Fischer, E. O.; Öfele, K. *Z. Naturforsch. B* **1958**, *13*, 458.

(4) Review: Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994; Chapter 10.

(5) Semmelhack, M. F.; Hall, H. T. Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7091.

(6) The (*π*-chlorobenzene)chromium tricarbonyl was prepared according to the established procedure, see: (a) Strohmeier, W. *Chem. Ber.* **1961**, *94*, 1961. (b) Nicholls, B.; Whitig, M. C. *J. Chem. Soc.* **1959**, 551.

(7) Davies, S. G.; Correia, L. M. A. R. B. *J. Chem. Soc., Chem. Commun.* **1993**, 1803.

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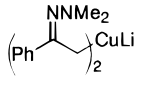
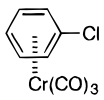
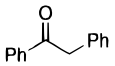
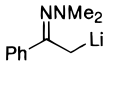
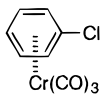
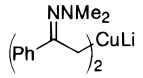
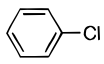
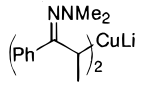
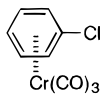
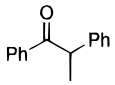
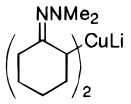
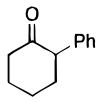
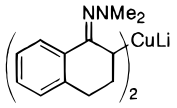
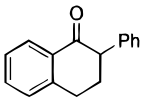
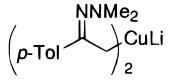
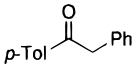
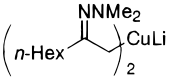
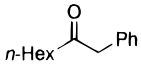
Table 1. Arylation of Ketone *N,N*-Dimethylhydrazone 1

Entry	Nu	ArX	Product **4**		Yield[a]
1				**4a**	64[b]
2			no reaction		
3			no reaction		
4				**4b**	75
5[c]				**4c**	24[b]
6				**4d**	80
7				**4e**	85
8				**4f**	72

[a] Isolated yields. [b] Yields were determined by GLC. [c] This reaction was carried out at −78 °C to room temperature.

ca. 1.6 M hexane solution was titrated with *sec*-butyl alcohol using *o*-phenanthroline as an indicator immediately before use. The other organic compounds were commercial products of the highest purity available. The yields of **4a** and **4c** were determined by GLC using biphenyl as an internal standard on a Shimazu capillary column, CBP1-W12-100.

General Procedure for the Preparation of *N,N*-Dimethylhydrazone 1. A mixture of ketone (40 mmol), *N,N*-dimethylhydrazine (50 mmol, 3.8 mL), trifluoroacetic acid (0.05 mL), and benzene (50 mL) was added to a flask equipped with a trap to remove water. The mixture was heated under reflux for 5 h, and then cooled to room temperature. The reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator, and the residue was purified by distillation under reduced pressure.

Acetophenone *N,N*-Dimethylhydrazone (1a). Yield 94%; bp 90 °C/4 mmHg; ^{1}H NMR δ 2.35 (s, 3H), 2.60 (s, 6H), 7.35−7.74 (m, 5H); MS *m*/*z* 162 (M^+, 98).

Propiophenone *N,N*-Dimethylhydrazone (1b). Yield 93%; bp 74 °C/1.5 mmHg; ^{1}H NMR δ 1.08 (t, 7.6 Hz, 3H), 2.57 (s, 6H), 2.90 (q, 7.6 Hz, 2H), 7.35−7.66 (m, 5H); MS *m*/*z* 176 (M^+, 67).

Cyclohexanone *N,N*-Dimethylhydrazone (1c). Yield 90%; bp 74.5 °C/17.5 mmHg; ^{1}H NMR δ 1.63−1.71 (m, 6H), 2.24 (t, 6.4 Hz, 2H), 2.44 (s, 6H), 2.51 (t, 6.1 Hz, 2H); MS *m*/*z* 140 (M^+, 73).

α-Tetralone *N,N*-Dimethylhydrazone (1d). Yield 80%; bp 129 °C/5 mmHg; ^{1}H NMR δ 1.88−1.94 (m, 2H), 2.60 (s, 6H), 2.78−2.84 (m, 4H), 7.10−7.27 (m, 3H), 8.13−8.16 (m, 1H); MS *m*/*z* 188 (M^+, 100).

4′-Methylacetophenone *N,N*-Dimethylhydrazone (1e). Yield 85%; bp 128 °C/15 mmHg; ^{1}H NMR δ 2.33 (s, 3H), 2.35 (s, 3H), 2.58 (s, 6H), 7.14−7.64 (m, 5H); MS *m*/*z* 176 (M^+, 100).

2-Octanone *N,N*-Dimethylhydrazone (1f). Yield 85%; bp 84 °C/15 mmHg; ^{1}H NMR δ 0.88 (t, 6.3 Hz, 3H), 1.26−1.35 (m, 6H), 1.44−1.54 (m, 2H), 1.94 (s, 3H), 2.44 (s, 6H); MS *m*/*z* 170 (M^+, 76).

General Procedure for Arylation of Ketone *N,N*-Dimethylhydrazone 1. To a THF (2.0 mL) solution of ketone *N,N*-dimethylhydrazone **1** (2.1 mmol) in a dried reaction flask was added *n*-BuLi in hexane (2.2 mmol, 1.38 mL) at −5 °C under an argon atmosphere. After 1 h, copper(I) iodide (1.1 mmol, 0.209 g) was added at this temperature. After 1 h, to a THF (3.0 mL) solution of (π-chlorobenzene)chromium tricarbonyl (1.0 mmol, 0.249 g) was added the copper lithium azaenolate **2** in THF at 70 °C. The mixture was continued to stir for 20 h, after which the mixture was cooled to room temperature. The reaction mixture was quenched with water and diluted with ether. The organic layer was washed with brine and dried over $MgSO_4$, followed by exposure to air and sunlight for 3 h. The filtrate was concentrated with a rotary evaporator. The residue was diluted with THF (20 mL), and aqueous 2 *N* HCl (30 mL) was added for hydrolysis. The reaction mixture was diluted with ether and water. The organic layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator, and the residue was purified by silica gel column chromatography or TLC (EtOAc:hexane = 8:1) to give α-phenylketone **4**.

Benzyl Phenyl Ketone (4a). ^{1}H NMR δ 4.29 (s, 3H), 7.25−8.03 (m, 10H); ^{13}C NMR δ 45.47, 126.86, 128.59, 128.62, 128.65, 129.44, 130.17, 133.14, 136.56, 197.64; MS *m*/*z* 196 (M^+, 2).

1,2-Diphenylpropan-1-one (4b). ^{1}H NMR δ 1.46 (d, 7.0 Hz, 3H), 4.61 (q, 7.0 Hz, 1H), 7.11−7.88 (m, 10H); ^{13}C NMR δ 18.47, 46.86, 125.86, 126.73, 127.44, 127.74, 131.74, 135.45, 140.44, 199.29; MS *m*/*z* 210 (M^+, 0.6).

2-Phenylcyclohexanone (4c). ^{1}H NMR δ 1.67−2.58 (m, 8H), 3.59−3.63 (m, 1H), 7.06−7.99 (m, 5H); ^{13}C NMR δ 26.16, 28.66, 35.94, 43.03, 58.23, 127.73, 129.19, 129.36, 139.58, 211.24; MS *m*/*z* 174 (M^+, 29).

2-Phenyl-1-tetralone (4d). ^{1}H NMR δ 2.40−2.49 (m, 2H), 3.00−3.18 (m, 2H), 3.80 (t, 7.9 Hz, 1H), 7.17−7.35 (m, 7H), 7.47−7.52 (m, 1H), 8.08−8.11 (m, 1H); ^{13}C NMR δ 28.86, 31.17, 54.39, 126.76, 126.91, 127.79, 128.42, 128.52, 128.77, 132.86, 133.42, 139.73, 144.05, 198.20; MS *m*/*z* 222 (M^+, 43).

Benzyl *p*-Tolyl Ketone (4e). ^{1}H NMR δ 2.39 (s, 3H), 4.25 (s, 2H), 7.19−7.35 (m, 7H), 7.86−7.97 (m, 2H); ^{13}C NMR δ 21.62, 45.39, 126.78, 128.62, 128.74, 129.30, 129.41, 134.09, 134.76, 143.95, 197.25; MS *m*/*z* 210 (M^+, 0.4).

1-Phenyl-2-octanone (4f). ^{1}H NMR δ 0.85 (t, 7.0 Hz, 3H), 1.21−1.27 (m, 6H), 1.54 (t, 7.3 Hz, 2H), 2.43 (t, 7.5 Hz, 2H), 3.67 (s, 2H), 7.19−7.34 (m, 5H); ^{13}C NMR δ 13.96, 22.42, 23.65, 28.73, 31.50, 41.95, 50.10, 126.89, 128.63, 129.35, 134.35, 208.59; MS *m*/*z* 205 (M^+ + H, 45).

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