# Monophenylation of Morphinan-6-ones with Diphenyliodonium Iodide

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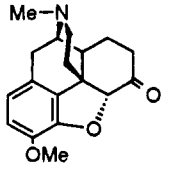
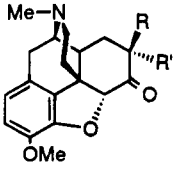
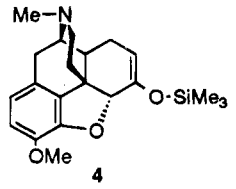
There are only a few methods available for direct arylation at the α-position of ketones.[1,2] Among these, diaryliodonium salts have been employed for the mono- and diarylation of activated ketones.[3–7] Most of these methods tend to afford diaryl ketones as the major product when the reaction was conducted with diphenyliodonium salts. More recently, the use of diphenyliodonium fluoride (**DIF**) was reported[8] to give mono- over diphenylated products. However, this method requires the formation of the silyl enol ether of the ketone and the preparation of **DIF** from diphenyliodonium iodide (**DII**). Here we report that hydrocodone (**1**) can be converted to 7-phenylhydrocodone (**2a**) in good yield simply by reacting its lithium enolate with commercially available **DII**.



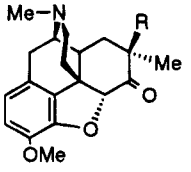

**1**




**2a** R = H, R' = Ph
**2b** R = Ph, R' = H
**3** R = R' = Ph




**4**




**5** R = H
**6** R = Ph

In initial studies, we employed the method of Chen and Koser[8] to phenylate hydrocodone (**1**). This involved the conversion of **1** to its trimethylsilyl enol ether **4** followed by treatment with **DIF**. The desired monophenylation product (**2a**) was obtained in low yield (11%) together with the diphenyl side product **3** (3%) and recovered starting material **1** (56%).

Because the recovery of a major amount of **1** suggested that a significant fraction of the silyl ether **4** had hydrolyzed prior to reacting with **DIF**, we decided to employ the lithium enolate of hydrocodone. This strategy was based on the fact that the fluoride counterion of **DIF** cleaves the silyl enol ether to generate the enolate which may be the reactive intermediate.[6,7,9] Indeed, the reaction of the lithium enolate of hydrocodone with **DII** afforded **2a** in good yield (71%) with only minor amounts of diphenylated side product **3** (4%) and the starting ketone **1** (10%).

The phenylation product **2a** possesses the 7α stereochemistry as indicated by the coupling constants $J_{7,8\alpha}$ = 13 Hz and $J_{7,8\beta}$ = 6 Hz. A positive proton NOE between H-7 and H-5 also is consistent with the assignment. This stereochemistry is expected if the phenyl group is placed in an energetically favored equatorial conformation, inasmuch as the C-ring of 6-keto opiates generally assumes a chair conformation.[10–13]

In following the reaction by TLC we noticed that an intermediate was a major component in the early stage of the reaction. This intermediate **2b** was slowly converted to **2a** during the course of the reaction, and rapidly during attempts at chromatographic purification. By following the course of the reaction with LC/MS, the intermediate ($t_R$ = 9 min) was found to possess the same molecular weight as **2a** ($t_R$ = 30 min.), which is consistent with the epimer **2b**. Due to the facile epimerization of **2b**, we were unable to isolate **2b** in pure form for further characterization.

In an effort to obtain additional evidence in support of the epimerization pathway, we investigated the phenylation of 7-methylhydrocodone (**5**). The reaction of the enolate of **5** with **DII** afforded only the β-phenyl epimer **6**. In this case, the kinetically-controlled stereochemistry is preserved because epimerization is precluded by the quaternary nature of C-7. The stereochemical assignment of C-7 was based on the positive proton NOE between H-5 (H-14 as well) and the ortho protons of the C-7 phenyl group.

This is consistent with the thermodynamically less favored epimer **2b** as the initial product and is reasonable in view of the fact that the β-face of the enolate is less hindered than the α-face (Figure 1). The kinetically formed 7β epimer **2b** would be expected to be less stable than **2a** because the 7-phenyl group assumes an axial-like orientation when ring C of the opiate is in a chair conformation. The diaxial interactions between the phenyl group and the C-ring protons can be eliminated either by conversion to a boat conformation or by epimerization via the enolate. The latter alternative is more likely in view of the greater thermodynamic stability of the chair over the boat conformation.

## Experimental Section

Diphenyliodonium iodide and anhydrous DMF were purchased from Aldrich Chemicals. Hydrocodone bitartrate was

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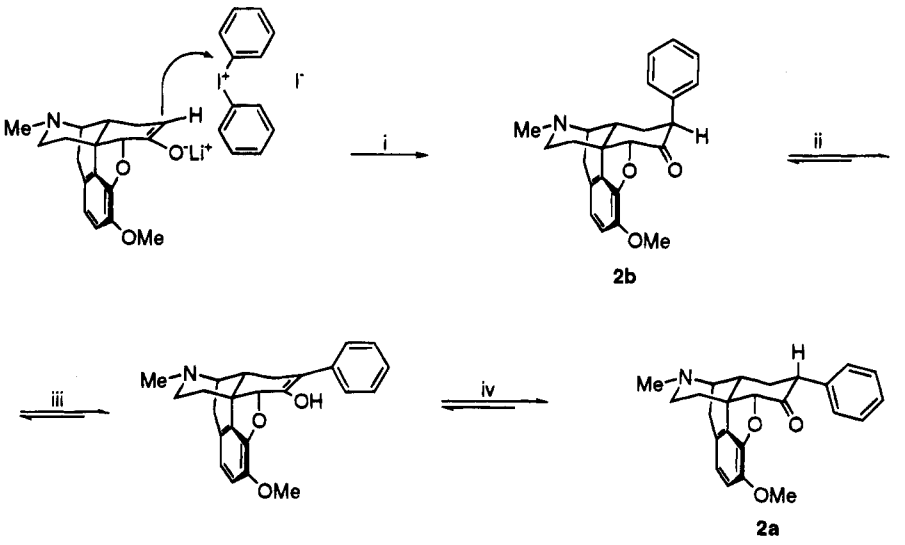


**Figure 1.** Proposed stereochemical pathway for the phenylation of hydrocodone enolate. (i) The approach of **DII** to the less hindered $\beta$ face of the enolate leads to the 6$\beta$ isomer which is epimerized via (ii) enolization and subsequent (iii) ketonization to the more thermodynamically stable 6$\alpha$ epimer.

obtained from Mallinckrodt and transformed to the free base. Column chromatography was performed with silica gel (200–400 mesh, Aldrich Chemicals). Spinning thin-layer chromatography was performed on silica gel (EM Science silica gel 60, PF254) using a Chromatotron (Harrison Research, Model 7924T, Palo Alto, CA). Chromatographic solvent systems are reported as volume/volume ratios. IR spectra were recorded on a Perkin-Elmer 281 spectrophotometer. NMR data were collected on a GE Omega 300 MHz spectrometer at room temperature (18–20 °C). The $\delta$ (ppm) scale was in reference to the deuterated solvent. Coupling constants are reported in Hz. Mass spectra were obtained on a Finnigan 4000 or a VG707EHF spectrometer. LC/MS was performed on a Sciex API III using a Ultrasphere column (Beckman, ODS, 5 $\mu$m, 2.0 mm × 15 cm). The mobile phase was $CH_3CN$–water (0% $CH_3CN$ to 60% $CH_3CN$ over 60 min) with trifluoroacetic acid (0.1%) using Beckman Solvent Module 126.

**Hydrocodone Trimethylsilylenol Ether (4).** Hydrocodone (300 mg, 1 mmol) was mixed with trimethylsilyl chloride (1.3 mmol), triethylamine (0.35 mL), and DMF (1 mL). The mixture was then stirred at 100 °C for 24 h. After filtration of insoluble material and washing with THF, the filtrate was then evaporated under reduced pressure to afford crude **4** (foam, 390 mg), which was used for the next reaction without further purification.[14] $^1$H NMR ($CDCl_3$): $\delta$ 6.61–6.73 (2d, $J$ = 8.1, 2H), 4.90–4.99 (dd, $J$ = 1.35, 6.31, 1H), 4.74 (d, $J$ = 1.35, 1H), 3.85 (s, 3H), 0.17 (s, 9H). MS (EI): $m/z$ 371 ($M^+$).

**Phenylation of Hydrocodone Trimethylsilylenol Ether (4) with Diphenyliodonium Fluoride (DIF).** To a THF (5 mL) solution of hydrocodone trimethylsilylenol ether (**4**) prepared from hydrocodone (300 mg, 1 mmol) was added **DIF** (480 mg, 1.6 mmol) in $CH_2Cl_2$ (5 mL) dropwise under argon over 20 min at room temperature. The reaction was monitored by TLC until the starting material had disappeared. After 10 min of stirring, the reaction was filtered and washed with THF. The solvent was removed under reduced pressure, and the residue was purified by spinning TLC (2 mm plate with ethyl acetate and acetone 95/5) to afford **2a** (foam, 45.3 mg, 11%), **3** (foam, 15.5 mg, 3.2%), and recovered **1** (170 mg, 56%). **2a.** $R_f$ 0.12 (acetone). $^1$H NMR ($CDCl_3$): $\delta$ 7.1–7.3 (m, 3H), 6.90–6.94 (m, 2H), 6.58–6.68 (2d, $J$ = 7.8, 2H), 4.78 (s, 1H), 3.84 (s, 3H), 3.64–3.67 (dd, $J$ = 13, 3.5, 1H), 3.21 (br, 1H), 3.04–3.08 (d, $J$ = 18.5, 1H), 2.80–2.82 (m, 1H), 2.59–2.61 (m, 1H), 2.45 (s, 3H), 3.34–2.38 (dd, $J$ = 6, 18.5, 1H), 2.13–2.25 (m, 2H), 2.01–2.05 (m, 1H), 1.86–1.89 (m, 1H), 1.63-1.70 (m, 1H). MS (EI): $m/z$ 375.2 ($M^+$). **3.** $R_f$ 0.68 (acetone). IR (KBr): 2931.2, 2839.8 (w), 2797.6 (w), 1771.9 (s), 1671.9 (s), 1497.8 (s), 1455.3 (s), 1384.4 (vs), 701.5 (s) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): $\delta$ 7.42–7.47 (t, $J$ = 7.2, 2H), 7.32–7.37 (t, $J$ = 7.2, 1H), 7.24–7.26 (d, $J$ = 7.2, 2H), 7.09–7.14 (m, 3H), 6.68–6.76 (2d, $J$ = 8.1, 2H), 6.61–6.64 (m, 2H), 5.01 (s, 1H), 3.94 (s, 3H), 3.23 (bs, 1H), 3.06-3.12 (d, $J$ = 18.3, 1H), 2.72–2.79 (m, 1H), 2.57–2.62 (dd, $J$ = 3.6, 13.8, 1H), 2.41–2.48 (m, 1H), 2.40 (s, 3H), 2.09–2.19 (m, 1H), 2.05–2.18 (m, 1H), 1.62–1.78 (m, 2H). $^{13}$C-NMR ($CDCl_3$): $\delta$ 207.76, 145.90, 143.60, 138.67, 130.23, 129.14, 128.86, 128.41, 128.30, 127.68, 127.33, 127.03, 126.69, 92.07, 63.43, 59.89, 57.70, 47.49, 47.16, 43.57, 38.43, 36.70, 35.54, 20.56. MS (EI): $m/z$ 451.0 ($M^+$).

**Phenylation of Hydrocodone (1) with Diphenyliodonium Iodide (DII).** Hexamethyldisilazane (0.45 mL, 2.1 mmol) was mixed with THF (5 mL) at −78 °C (dry ice in acetone). $n$-Butyllithium (0.64 mL, 1.6 mmol, 2.5 M in hexane) was added over a period of 5 min and stirred for 5 min. Hydrocodone (**1**) (324 mg, 1.08 mmol) in THF (10 mL) and 12-crown-4 (0.2 mL)[15] were then added, and the reaction mixture was stirred for 10 min. The resulting solution was quickly transferred to the mixture of **DII** (700 mg, 1.6 mmol) in DMF (45 mL) at −45 °C (dry ice in acetonitrile). This reaction mixture was stirred at −45 °C for 2 h, allowed to warm to room temperature, and stirred overnight. The reaction was quenched with water (15 mL), extracted with chloroform (3 × 30 mL), and dried ($MgSO_4$), and the solvent was removed. The residue was taken up with small amount of dichloromethane and applied to a Chromatotron plate (2 mm, silica gel) and eluted with first ethanol–chloroform (1/99) to afford **3** (38 mg, 7.8%) and then with ethanol–chloroform (9/91) to afford **2a** (290 mg, 71.6%).

In monitoring the reaction by TLC at early time intervals (0–6 h) epimer **2b** was detected, $R_f$ (silica gel GF254, acetone) **2a** 0.12, **2b** 0.66. At ~3 h reaction time, LC/MS indicated that **2a** ($M^+$ = 375) has retention time of 30 min, while **2b** ($M^+$ = 375) has a retention time of 9 min.

**7$\alpha$-Methyl-7$\beta$-phenylhydrocodone (6).** Hexamethyldisilazane (0.79 mL, 3.7 mmol) was mixed with THF (10 mL) at −78 °C (dry ice in acetone). $n$-Butyllithium (1.2 mL, 2.8 mmol, 2.4 M in hexane) was added over a period of 5 min and stirred for 5 min. 7$\alpha$-Methylhydrocodone[16] (**5**) (600 mg, 1.91 mmol) in THF (30 mL) was then added, and the reaction mixture was stirred for 10 min. The resulting solution was quickly transferred to the mixture of **DII** (990 mg, 2.4 mmol) in DMF (60 mL) at −45 °C (dry ice in acetonitrile). The mixture was stirred at −45 °C for 2 h, allowed to warm to room temperature, and stirred overnight. The reaction was quenched with water (40 mL) and then extracted with chloroform (3 × 40 mL). The chloroform extract was dried ($MgSO_4$), and the solvent was

(14) Attempts at purification resulted in the recovery of hydrocodone due to hydrolysis. The crude product (**4**) was determined to be ~78% pure by proton NMR integration.

(15) Without 12-crown-4, the phenylation reaction gives **2a** (56%) and **3** (10%).

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removed. The residue was chromatographed on a silica gel (60 g) column ($CHCl_3$–EtOH, 97/3) to afford **6** (foam, 0.55 g, 74%). $^1H$ NMR ($CDCl_3$): $\delta$ 7.15–7.39 (m, 5H), 6.61–6.72 (2d, $J$ = 7.8, 2H), 4.87 (s, 1H), 3.94 (s, 3H), 3.15–3.17 (m, 1H), 2.99–3.06 (d, $J$ = 18.3, 1H), 2.63–2.71 (m, 1H), 2.37–2.45 (m, 1H), 2.38 (s, 3H), 2.37–2.40 (m, 1H), 2.28–2.38 (m, 1H), 2.03–2.12 (m, 1H), 1.55–1.72 (m, 2H), 1.36–1.45 (t, $J$ = 8.7, 1H). $^{13}C$-NMR ($CDCl_3$): $\delta$ 20.44, 29.32, 35.58, 36.90, 38.44, 43.53, 47.54, 47.59, 54.60, 57.53, 59.80, 91.67, 115.47, 120.38, 126.82, 127.00, 127.75, 128.29, 130.13, 141.47, 143.60, 145.91, 209.91. MS (FAB): $m/z$ 390.2 (M + H).

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**Supplementary Material Available:** Proton NMR spectra of **2a**, **3**, **4**, and **6** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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