Unusual α-Methylation of Alkoxyaryl Ketones with Higher Order Methyl Cuprate and Lithium Bromide

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Pseudopterosins A and E, 1 and 2, are members of a group of strongly antiinflammatory and analgesic agents that are marine metabolites from Caribbean sea whips of the genus Pseudopterogorgia.2 These two compounds have shown the most promise as therapeutic agents for inflammation, each exceeding the potency of the drug industry standard indomethacin.2a,d,e Several groups have investigated the substitution of the acetate (or trichloroacetate) of the corresponding alcohol 5 with the higher order dimethylcyanocuprate7 in the presence of lithium bromide (LiBr) or with simple lithium dimethylcuprate in the presence of LiBr or BF3 etherate. We describe herein the unusual course of this reaction and that of other analogues of (alkoxyaryl)ketones, namely, an α-methylation of the ketone.

We first tested the methylation reaction in a model system, namely, 6-methoxytetrahydro-1-naphthal.8 Prepared in 99% yield by reduction of 6-methoxy-1-tetralone with LiAlH4. The acetate9 and trichloroacetate of 8 could be easily formed but gave mainly the product of E1 elimination, namely, the dihydroxynaphthalene.10 on treatment with methyllithium (or methylcuprate) and Lewis acids. We next investigated phosphate as a leaving group. Addition of n-butyllithium to the alcohol 8 at −78 °C in THF followed by addition of 1 equiv of diethyl chlorophosphite with stirring for 10 min presumably afforded the corresponding phosphate. This very labile benzylic phosphate was not isolated but rather treated directly with excess methylmagnesium bromide. Under these conditions, again only a small amount of coupling was observed. However, when the n-butyllithium was added to a mixture of 8, diethyl chlorophosphite, and excess methyl Grignard reagent, we isolated a 68% yield of the desired methylated product 9.11 We found that the use of 5 equiv of the higher order cuprate 7 in place of the Grignard reagent gave a higher overall yield (79%) of 9 with some of the dihydroxynaphthalene also being formed. Other leaving groups were also tested in this process without great success. The corresponding triflates or mesylates were too unstable and gave mainly the E1 elimination product under all conditions tried. Having demonstrated that the conversion of a benzylic alcohol into a benzylic methyl group was possible under these conditions, we turned our attention directly to the key pseudopterosin substrate. Treatment of the alcohol 5 with acetyl chloride or trichloroacetyl chloride gave the


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corresponding acetate and trichloroacetate in good yield. Reaction of these esters with excess (5 equiv) of the higher order cuprate 7 (prepared from low halide MeLi) and 2 equiv of LiBr with stirring at −78 °C for 5 h slowly afforded a new compound in each case. After the reaction was allowed to warm gradually to 25 °C and was stirred overnight at 25 °C, workup furnished the unexpected product of α-methylation of the ketone, namely, 10ab.

Under the best conditions, the isolated yield of this unusual product was 75% (10a, X = H, 52%; 10b, X = Cl 75%). This product of α-methylation, 10a, was also obtained in 43% yield when lithium dimethylcuprate was used in the presence of LiBr or BF3 etherate with the acetate.

Since this is an abnormal mode of reaction for ketones with higher order cuprates, we decided to examine somewhat the scope of the process. Simple alkyl ketones, e.g., 4-tert-butyldiphenoxane, do not give any α-methylation, and simple alkyl aryl ketones, e.g., α-tetralone, 1-indanone, and acetophenone, give no more than trace amounts of α-methylation. In these cases, in addition to mostly recovered starting material, some tertiary alcohol (from 1,2-addition of methyl to the ketone) is also isolated, especially when BF3 etherate is used as the Lewis acid. The reaction seems to require the presence of an alkyl group on the aromatic ring para to the carbonyl group. Thus 6-methoxy-1-tetralone 11a gave the α-methylated ketone 12a in 68% yield, 4-methoxyacetophenone 11b afforded 12b in 35% yield, and 5-methoxy-1-indanone 11c gave 12c in 13% yield (no attempts have been made to optimize these yields). However, a tert alkyl group did not promote the reaction, e.g., 3′-methoxyacetophenone 11d did not give the α-methylated product 12d. If the lithium bromide is omitted from the reaction mixture, no α-methylation is observed, even with the alkoxaryl ketones. Other lithium salts, e.g., lithium perchlorate, did not give any alkylation. Other Lewis acidic additives (e.g., BF3:Et2O) have given some α-methylation but the results have not been reproducible, except for LiBr.

We do not have a good hypothesis as to the mechanism for this methylation. Presumably the alkyl group increases the basicity of the carbonyl so that it can form a more stable complex with the lithium cation, which might lead more readily to an enol (or enolate) than in the simple aryl ketones. However, it is unclear how an enol (or enolate) and a higher order cuprate (both electron-rich species) could combine to produce an α-methyl ketone. The most likely hypothesis still seems somewhat unlikely. Oxidation of the bromide ion to bromine followed by bromination of the endol (or enolate) would give the α-bromo ketone, which might well produce the α-methyl ketone on reaction with either the lower or higher order cuprate. This would explain the lack of reaction with lithium perchlorate, since there is no source of positive halogen to generate the required α-halo ketone. When the reaction is run, a small amount of black solid metal can be seen in the flask and a large amount of brownish-red (copper-colored) metallic material coats the flask’s walls, implying a reduction of the cuprate species. However, even given all of this circumstantial evidence, there is no obvious source of oxidant in this reaction (more than a catalytic amount is needed since the yields of α-methylation can be quite high and the reaction is run under an argon atmosphere), so this hypothesis is not yet assured. Further mechanistic speculation awaits more experimental work.

In summary, we have observed a novel α-methylation of alkoxaryl ketones with higher order cuprates in the presence of lithium bromide. Since there are many excellent methods for α-methylation of ketones in high yield, this process is not useful synthetically but is of interest mechanistically.

**Experimental Section**

**General.** All temperatures and boiling points (bp) are uncorrected, and reactions were carried out under argon with the exclusion of moisture. Dichloromethane and pyridine were distilled from CaH2. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl radical. Boron trifluoride-etherate (BF3:Et2O) was stirred over CaH2, distilled (67 °C at 43 mmHg) with an excess of diethyl ether (Et2O), and stored at −23 °C under N2. Chromatography was conducted on 230–400 mesh silica gel.

1H and 13C NMR were recorded on a Bruker AM200 or ARX500 spectrometer with tetramethylsilane as external standard. IR spectra were recorded on a Nicolet 510 FT-IR, Nicolet 205 FT-IR, or a Perkin-Elmer series 1600 spectrometer. Mass spectra were obtained on a VG Autospec and are given for the molecular ion unless otherwise stated.

**General Procedure for Higher Order Cuprate Preparation.** In a dry one neck flask was placed highly dried CuCN (under high vacuum for 10 h at 100 °C). The vessel was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (1 mL/mmol CuCN) was introduced via syringe, and the slurry was cooled to −78 °C. To the slowly stirring suspension was added the organolithium species (2 equiv relative to CuCN) dropwise. The heterogeneous mixture was allowed to warm gradually until complete dissolution resulted (may require 0 °C) and was then cooled to −78 °C (may get turbid at high concentration). The substrate was then introduced either as a solution in THF or as a neat liquid, and the mixture was stirred at the appropriate temperature until starting material was consumed. Reactions were routinely followed by TLC. Following completion, the reaction was quenched with a mixture composed of 10% concentrated NH4OH in saturated aqueous NH4Cl solution and allowed to stir at room temperature for 2–3 h.

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Standard extractive workup followed by chromatographic purification afforded the results.

6-Methoxytetrahydro-1-naphthol (8). To a solution of LiAlH₄ (95%, 2.6 g, 0.01 mol) in THF (200 mL) was added gradually with stirring 6-methoxy-1-tetralone (17.6 g, 0.01 mol) at 25 °C. The mixture was stirred for 18 h at reflux, then cooled to 0 °C, and quenched with cold water. After stirring for 6 h, the mixture was extracted with ether, dried (MgSO₄), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the known19 1H-naphthol (8).

79%.

Tetrahydro-6-methoxy-1-methyl-naphthalene (9) (with MeMgBr). To a solution of the lithiated alcohol [prepared from 6-methoxy-1-naphthalen-1-one (11 mg, 0.036 mmol) in THF (2 mL)] was added diethyl chlorophosphate (3 equiv) and then methylene chloride. The organic layer was washed with saturated NaHCO₃ and brine, dried (MgSO₄), and concentrated in vacuo. Flash chromatography of the residue on silica gel (10% ether in petroleum ether) gave the known21 1H-naphthyl acetate: 1H NMR (200 MHz, CDCl₃) 3.8 (3H, s), 5.85 (1H, d, J = 8.5 Hz). 3,4-Dihydro-6-methoxynaphthalene: 1H NMR (200 MHz, CDCl₃) 3.8 (3H, s), 5.85—5.94 (1H, m), 6.4 (1H, m), 6.69 (2H, m), 6.94 (1H, d, J = 9 Hz).

Tetrahydro-6-methoxy-1-methyl-naphthalen-9(1H)-one (9) (with MeCNLi). In a dry one neck flask was placed highly dried CuCN (450 mg, 2.6 mmol) in THF (5 mL) was added dropwise the solution of lithium 6-methoxytetrahydro-1-naphthoxide [prepared from 6-methoxy-1-tetralone (47 mg, 0.26 mmol)] upon treatment with 2.5 M n-BuLi (0.1 mL) followed dropping MeCNLi (5 equiv) at ~78 °C. The reaction mixture was allowed to warm gradually to room temperature and stirred for over night. The reaction mixture was quenched by the addition of cold water, extracted with ether, dried (MgSO₄), and concentrated in vacuo. Flash chromatography of the residue on silica gel (10% ether in petroleum ether) gave the known21 1H-naphthyl acetate: 1H NMR (200 MHz, CDCl₃) 3.8 (3H, s), 5.85—5.94 (1H, m), 6.4 (1H, m), 6.69 (2H, m), 6.94 (1H, d, J = 9 Hz).

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and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (2 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the methyllithium lithium bromide complex (1.5 M MeLi·LiBr, 0.7 mL, 1 mmol) dropwise. The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution was introduced 4-methoxycacetophenone 11b (150 mg, 1 mmol), and the reaction was stirred for 2 h at −78 °C. It was then allowed to warm to 25 °C gradually and stirred for 2 days more. The reaction was quenched with a mixture composed of 10% concentrated NH₄OH in saturated aqueous NH₄Cl solution and allowed to stir at room temperature for 3 h. It was then extracted with ether, dried (MgSO₄), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the well-known 4'-methoxypropionophenone 12b (58 mg, 0.353 mmol, 35.3%): 1H NMR (200 MHz, CDCl₃) δ 1.21 (3H, t, J = 7.3 Hz), 2.29 (2H, q, J = 7.2 Hz), 3.87 (1H, s), 6.93 (2H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.8 Hz); 13C NMR (125 MHz, CDCl₃) δ 199.5, 163.3, 130.2, 130.0, 113.7, 55.5, 31.4, 8.5; IR (neat) 3495 (CO overtone), 3055, 1680 (CO) cm⁻¹; MS (m/e) 164 (M⁺), 135, 107. 5-Methoxy-2-methyl-1-indanone (12c). In a dry one neck flask was placed highly dried CuCN (450 mg, 5 mmol). The flask was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (5 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the methyllithium (1.0 M MeLi, 10 mL, 10 mmol) dropwise and then LiBr (200 mg). The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution was introduced 5-methoxy-1-indanone 11c (81 mg, 0.5 mmol), and the reaction was stirred for 2 h at −78 °C. It was then allowed to warm to 25 °C gradually and stirred for 2 days more. The reaction was quenched with a mixture composed of 10% concentrated NH₄OH in saturated aqueous NH₄Cl solution and allowed to stir at room temperature for 3 h. It was then extracted with ether, dried (MgSO₄), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the known 5-methoxy-2-methyl-1-indanone 12c (12 mg, 0.068 mmol, 13.6%): 1H NMR (200 MHz, CDCl₃) δ 1.29 (3H, d, J = 7.3 Hz), 2.26–2.73 (2H, m), 3.28–3.42 (1H, dd; d = 8.5, 8.2 Hz), 3.88 (3H, s) 6.89 (2H, d, J = 8 Hz), 7.69 (1H, d, J = 8.2 Hz); 13C NMR (125 MHz, CDCl₃) δ 207.9, 166.0, 157.0, 129.7, 125.7, 115.3, 109.7, 55.6, 42.1, 35.1, 16.6; IR (neat) 3495 (overtone of CO), 3071, 1702 (CO) cm⁻¹; MS (m/e) 176 (M⁺), 161, 133. Acknowledgment. We thank Sung Kyun Kwan University for a fellowship and the Agricultural Research Division of American Cyanamid Company for financial support. We also thank Professor Bruce Lipshutz (University of California, Santa Barbara) for helpful advice and discussions.

Supporting Information Available: Proton NMR spectra of compounds 5, 9, 10a and 10b (and their precursors), and 12abc and carbon NMR spectra of 5 and 12abc. This material is available free of charge via the Internet at http://pubs.acs.org.