Chemistry of Pentavalent Organobismuth Reagents. Regioselective α-Arylation of α,β-Unsaturated Carbonyls and Related Systems

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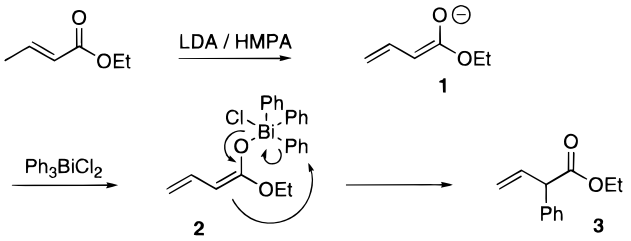
Introduction

The arylation of organic materials remains an arduous task for the synthetic chemist. Using bismuth reagents,[1] a wide range of functional groups can be arylated and, in some cases, alkylated. The effect of copper salts, or in some instances of metallic copper, permits the arylation of amines[2] and alcohols.[3] In appropriate examples, very hindered compounds can be prepared in good yields.[4] The anionic chemistry associated with pentavalent bismuth has also been extensively studied, showing once again that these derivatives are the reagents of choice for the arylation of compounds that contain a labile proton. Systematic studies demonstrated that β-dicarbonyls, phenols, enolizable ketones, and related compounds could be arylated with ease and often in good yields.[5] Indeed, triarylbismuth(V) has emerged as a particularly efficient aryl cation equivalent for the arylation of a wide variety of substrates under mild conditions.[6] Nevertheless, to the best of our knowledge, the bismuth-mediated arylation process has never been investigated on α,β-unsaturated systems. We report in the present paper that, upon treatment with LDA/HMPA (1.1 equiv) in THF and triphenylbismuth dichloride (1.1 equiv), α,β-unsaturated carbonyls and related systems undergo regioselective α-phenylation with concomitant deconjugation of the olefinic moiety (Scheme 1).

Scheme 1

Scheme 2



Results and Discussion

A postulated reaction mechanism is illustrated for the phenylation reaction of ethyl crotonate (Scheme 2). The first step involves the formation of the anionic species by LDA/HMPA.[7] This species can exist as the vinylogous enolate **1**, which then undergoes reaction with Ph_3BiCl_2. The existence of such an O−Bi bonded intermediate **2** has been well demonstrated in the case of phenols.[8] The subsequent rearrangement,[9] via collapse of the postulated intermediate, leads to the corresponding α-phenylated compound **3**. Complexation of the bismuth with the anionic oxygen could allow for the exclusive phenylation of the neighboring α-carbon atom. A radical phenylation process was unambiguously disproved by Barton and co-workers by conducting experiments on analogous systems in the presence of appropriate traps and by ESR studies.[10]

The overall yields are, in most cases, satisfactory. The reaction has successfully been extended to various substrates (see Table 1). As mentioned above, the phenylation reaction of ethyl crotonate led to the expected product with synchronous deconjugation of the double bond (entry 1). No reconjugation was observed under our conditions. However, if the reaction is run over an extended period of time (e.g., overnight instead of 2 h), the reconjugated product, ethyl 2-phenylcrotonate, becomes predominant. In an analogous manner, the reaction of ethyl 2-phenylcrotonate (entry 2) gave the expected hindered α-bisaryl ester.

The monophenylation of phorone (entry 3) employing stoichiometric amounts of both reagents (Bi and base) afforded a selective reaction; that is, the monoaryl ketone was formed preferentially over the diphenylated analogue

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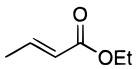
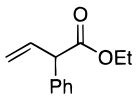
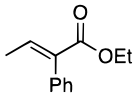
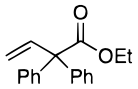
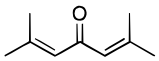
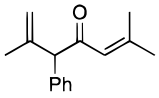
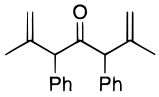
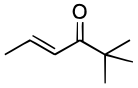
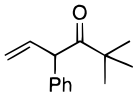
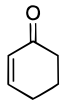
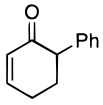
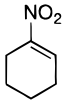
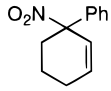
Table 1. Examples of Phenylation of α,β-Unsaturated Systems

entry	substrate	product	yield[a,d]
1			63
2			55
3			89
4			52[b, c]
5			66[c]
6			57
7			86[c]

[a] Isolated yields unless otherwise stated. [b] 2.2 equiv of LDA/HMPA/Ph_3BiCl_2. [c] ^1H NMR yield. [d] The mass balance was accounted for as the unreacted starting material.

(>95:5). Surprisingly, we observed the introduction of a second aryl group at the α′ position when 2 equiv of reagent was utilized (entry 4), although one might have expected that the acidity of the adjacent α proton would be enhanced by the presence of the first aryl group and therefore give rise to a tetrasubstituted α-carbon atom.

The process works equally well on hindered ketones such as 2,2-dimethylhex-4-en-3-one (entry 5) but is not successful for cyclohexenone (entry 6) where the classical C-6 arylation is priviledged. The procedure was also applied to 1-nitrocyclohex-1-ene using triethylamine as base in CH_2Cl_2 (without HMPA). The deconjugated arylated product was obtained in 86% yield (entry 7). However, the allylic nitro proved to be especially labile and was subjected to partial decomposition during column chromatography over silica, as already observed by others.[11]

In some cases (entries 4 and 5), the final product comigrates on silica with Ph_3Bi, which results from dismutation of Ph_2BiCl. A strongly acidic workup with acetic acid/catalytic trifluoroacetic acid permitted the conversion of Ph_3Bi into insoluble $(AcO)_3Bi$.[12] This allowed the removal, from the reaction mixture, of the apolar triphenylbismuth. This procedure tends, unfortunately, to decrease the isolated yield of product.

In conclusion, we have shown that pentavalent bismuth reagents selectively α-arylate selected α,β-unsaturated esters, ketones, and related substrates in the presence of a suitable base. The reaction proceeds with deconjugation of the double bond.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover microscope and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz using residual $CHCl_3$ (7.25 ppm) and $CDCl_3$ (77 ppm) as internal standard, respectively. Flash column chromatography was performed on Baxter S/P brand silica gel (60 Å, 230−400 mesh). All reactions were performed under Ar in a flame-dried flask using anhydrous THF (dried by distillation over sodium) or CH_2Cl_2 (dried by distillation over CaH_2). Reagents were purchased from Aldrich Chemical Co. except (*E*)-2,2-dimethylhex-4-en-3-one that was synthesized according to literature procedures.[13]

A General Procedure for the Arylation of α,β-Unsaturated Carbonyl Systems Is Given for the Phenylation of Ethyl Crotonate (Entry 1). At −78 °C, to a solution of LDA (0.55 mL of a 2 M solution in heptane/THF/ethylbenzene, 1.1 equiv) and freshly distilled HMPA (0.19 mL, 1.1 equiv) in 10 mL of anhydrous THF is added dropwise ethyl crotonate (0.114 g, 1 mmol, 1 equiv). The solution is stirred at −78 °C for 20 min. Ph_3BiCl_2 is then added in one portion, and the mixture is allowed to warm to rt. After 2 h, the reaction is quenched with 10% NH_4Cl, and the aqueous layer is extracted twice with Et_2O. The combined organic layers are washed twice with H_2O, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude is purified on silica (eluent, hexanes/Et_2O, 95/5) to yield the desired phenylated product:[14] oil, 0.120 g, 63%; ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 4.30 (d, J = 8.1 Hz, 1H), 5.15 (d, J = 17.1 Hz, 1H), 5.21 (d, J = 9.9 Hz, 1H), 6.22 (ddd, J = 8.1 Hz, J = 9.9 Hz, J = 17.1 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 55.8, 60.9, 117.3, 127.2, 127.9, 128.6, 135.8, 138.1, 172.2.

2,2-Diphenyl-3-butenoic Acid Ethyl Ester (Entry 2): oil, 0.141 g, 55%; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 4.24 (q, J = 7.2 Hz, 2H), 4.57 (dd, J = 1.2 Hz, J = 17.4 Hz, 1H), 5.37 (dd, J = 1.2 Hz, J = 10.8 Hz, 1H), 6.82 (dd, J = 17.4 Hz, J = 10.8 Hz, 1H), 7.17 (m, 4H), 7.28 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 13.9, 61.4, 64.4, 117.8, 127.0, 127.8, 129.4, 141.0, 141.1, 173.5; HRMS calcd for $C_{18}H_{18}O_2$ (M^+) 267.1385, found 267.1381.

2,6-Dimethyl-3-phenylhept-1,5-dien-4-one (Entry 3): oil, 0.190 g, 89%; ^1H NMR ($CDCl_3$) δ 1.76 (s, 3H), 1.85 (s, 3H), 2.16 (s, 3H), 4.40 (s, 1H), 4.72 (s, 1H), 5.01 (s, 1H), 6.10 (s, 1H), 7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.7, 22.4, 27.7, 66.6, 114.4, 123.9, 126.9, 128.3, 129.3, 137.3, 143.7, 156.3, 198.2; HRMS calcd for $C_{15}H_{19}O$ 215.1436, found 215.1418.

2,6-Dimethyl-3,5-diphenylhept-1,6-dien-4-one (Entry 4). The reaction is run on a 1 mmol scale using 2.2 equiv of LDA/HMPA and 2.2 equiv of Ph_3BiCl_2. Elimination of the apolar Ph_3Bi is achieved by treatment of the mixture of phenylated product/Ph_3Bi obtained after silica gel chromatography with CH_3COOH/CF_3COOH (20/1, 0.16 mL) in THF and under reflux for 2 h. After filtration, evaporation of the solvents, and chromatography on silica (eluent, hexanes/Et_2O: 96/4), the arylated product is obtained as a 1/1 meso (a) and *dl* (b) mixture: oil, 0.096 g, 34%; ^1H NMR ($CDCl_3$) δ 1.66 (s, $3H_a$), 1.73 (s, $3H_b$), 4.53 (s, $1H_a$), 4.55 (s, $1H_b$), 4.62 (s, $1H_a$), 4.81 (s, $1H_b$), 4.98 (s, $1H_a$), 5.03 (s, $1H_b$), 7.08 (m, $4H_{a+b}$), 7.26 (m, $16H_{a+b}$); ^{13}C NMR ($CDCl_3$) δ 22.2 (a), 22.3 (b), 64.9 (a + b), 114.6 (a + b), 127.2 (a), 127.3 (b), 128.4 (a + b) 129.1 (a), 129.3 (b), 136.4 (a), 136.5 (b), 143.0 (a + b), 205.2 (a), 205.4 (b); HMRS calcd for $C_{21}H_{22}NaO$ $(M + Na)^+$ 313.1569, found 313.1561.

2,2-Dimethyl-4-phenylhex-5-en-3-one[15] **(Entry 5).** To remove the contaminating Ph_3Bi, the reaction is worked up and purified as described above to yield 0.079 g of pure product: oil, 39%; ^1H NMR ($CDCl_3$) δ 1.13 (s, 9H), 4.85 (d, J = 8.4 Hz, 1H),

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5.07 (m, 2H), 6.14 (ddd, J = 17.1 Hz, J =10.2 Hz, J = 8.4 Hz, 1H), 7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.3, 45.5, 56.7, 116.0, 126.9, 128.1, 128.6, 138.3, 138.7.

6-Phenylcyclohex-2-en-1-one (Entry 6): white solid, mp 68−69 °C (lit.[16] mp 65−67 °C), 0.098 g, 57%; ^{1}H NMR ($CDCl_3$) δ 2.29 (m, 2H), 2.47 (m, 2H), 3.61 (t, J = 8.1 Hz, 1H), 6.16 (dt, J = 10.2 Hz, J = 1.8 Hz, 1H), 7.03 (dt, J = 10.2 Hz, J = 3.9 Hz, 1H), 7.16 (m, 2H), 7.30 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 25.4, 30.6, 53.3, 126.8, 128.2, 128.4, 130.2, 139.3, 149.9, 199.1.

1-Nitro-1-phenylcyclohex-2-ene (Entry 7). To a solution of 1-nitrocyclohex-1-ene (0.056 g, 0.44 mmol, 1 equiv) in 2 mL of anhydrous CH_2Cl_2 are added, at 0 °C, Ph_3BiCl_2 (0.248 g, 1.1 equiv) and, dropwise, NEt_3 (0.068 mL, 1.1 equiv). The reaction is stirred for 2 h at rt. The solvent is evaporated under reduced pressure, and the crude is taken into ether. The precipitate is filtered over neutral alumina. After evaporation of the solvent, the crude is purified by chromatography on silica (eluent, hexanes/Et_2O, 95/5) to yield the desired phenylated compound: oil, 0.018 g, 20%; ^{1}H NMR ($CDCl_3$) δ 1.53−1.72 (m, 2H), 2.08−2.21 (m, 3H), 2.85−2.93 (m, 1H), 6.24 (m, 1H), 6.38 (d, J = 10.2 Hz, 1H), 7.33−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.0, 24.6, 34.5, 91.6, 125.5, 125.9, 128.3, 128.6, 134.4, 140.4.

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Supporting Information Available: Reproductions of ^{1}H and ^{13}C NMR spectra of compounds described in entries **2**−**4** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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