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Bismuth-based cyclic synthesis of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid *via* the oxyarylcarboxy dianion, $(O_2CC_6H_2{}^tBu_2O)^{2-}$†

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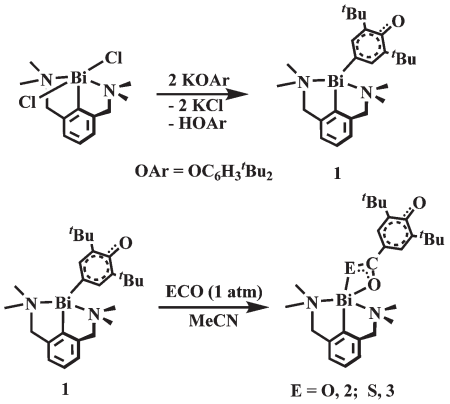
3,5-Di-*tert*-butyl-4-hydroxybenzoic acid can be made under mild conditions in a cyclic process from carbon dioxide and 3,5-di-*tert*-butyl-4-phenol using bismuth-based C–H bond activation and CO_2 insertion chemistry starting with the Bi^{3+} complex, Ar′$BiCl_2$, of the NCN pincer ligand, Ar′ = 2,6-$(Me_2NCH_2)_2C_6H_3$. Complexes of the recently discovered oxyaryl dianion, $(C_6H_2{}^tBu_2$-3,5-O-4$)^{2-}$, and the oxyarylcarboxy dianion, $[O_2C(C_6H_2{}^tBu_2$-3,5-O-4$)]^{2-}$, are intermediates in the process. Further studies of the oxyarylcarboxy dianion in Ar′Bi$[O_2C(C_6H_2{}^tBu_2$-3,5-O-4$)$-κ^2O,O'], show that it undergoes decarboxylation upon reaction with I_2 and it reacts with trimethylsilyl chloride to produce the trimethylsilyl ether of the trimethylsilyl ester of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid and the Ar′$BiCl_2$ starting material.

Recent synthetic studies of bismuth aryloxide chemistry have led to a series of new dianionic ligands, specifically the oxyaryl $(C_6H_2{}^tBu_2$-3,5-O-4$)^{2-}$, oxyarylcarboxy $[O_2C(C_6H_2{}^tBu_2$-3,5-O-4$)]^{2-}$, and oxyarylthiocarboxy $[OSC(C_6H_2{}^tBu_2$-3,5-O-4$)]^{2-}$ dianions that contain both an oxo group and aryl, carboxy or thiocarboxy components.[1,2] As shown in Scheme 1, these dianionic ligands are accessible by the reaction of the NCN phenyl pincer complex of bismuth dichloride, Ar′$BiCl_2$ [Ar′ = 2,6-$(Me_2NCH_2)_2C_6H_3$], with potassium 2,6-di-*tert*-butylphenolate, KOAr.[1,2] Precedent for the bismuth-based C–H bond activation in the first reaction in Scheme 1, which provides the synthetic access to these dianionic ligands, can be found in the use of bismuth in catalytic oxidation and ammoxidation of propene to form acrolein and acrylonitrile in the SOHIO process.[3–6] In those catalytic processes, bismuth is thought to perform the hydrogen abstraction necessary for the propene activation.[3] The mild CO_2 activation in the second reaction in Scheme 1 was the first observation of CO_2 insertion into a bismuth carbon bond.[2]



Scheme 1 Synthesis of complexes containing oxyaryl (**1**), oxyarylcarboxy (**2**), and oxyarylthiocarboxy (**3**) dianions.

Exploration of the utility of these reactions and the new dianionic ligands in synthesis has revealed that this C–H and CO_2 activation chemistry can be used in a cyclic manner to make 3,5-di-*tert*-butyl-4-hydroxybenzoic acid. This carboxylic acid is used in biomedical applications as a precursor to antiviral compounds[7] and to cyclooxygenase inhibitors.[8] Although it is not an expensive chemical, the published syntheses, which are largely in the patent literature,[7–10] typically functionalize the parent phenol with carbon dioxide by heating (80–210 °C) under high pressure (5–15 atm) with exposure to strong base.[9,10]

The process described below demonstrates that bismuth, a metal rarely used in catalysis or CO_2 activation, can effect this synthesis in a cyclic manner at ambient temperatures under an atmosphere of carbon dioxide. We also report the facile decarboxylation reaction of the oxyarylcarboxy intermediate in the cycle, Ar′Bi$[O_2C(C_6H_2{}^tBu_2$-3-5-O-4$)$-κ^2O,O'], to show the reversible nature of this bismuth-centered CO_2 chemistry and the use of the oxyarylcarboxy dianion complex to make a silyl ether silyl ester in one step.

The first two reactions in Scheme 1 provide the oxyarylcarboxy dianion complex, Ar′Bi$[O_2C(C_6H_2{}^tBu_2$-3-5-O-4$)$-κ^2O,O'],

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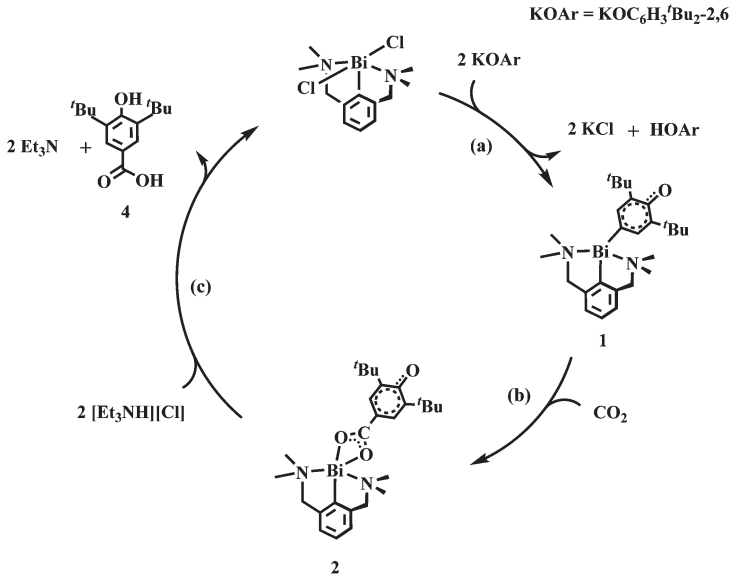
†Electronic supplementary information (ESI) available: Experimental data; ^1H NMR and ^{13}C NMR of compound **6**, and ^1H NMR of **2** and one equiv. of $[Et_3NH][Cl]$.



Scheme 2 Reaction cycle for (a) C–H bond activation, (b) CO_2 insertion, and (c) protonation to make 3,5-di-*tert*-butyl-4-hydroxybenzoic acid using Ar′$BiCl_2$ catalytically.

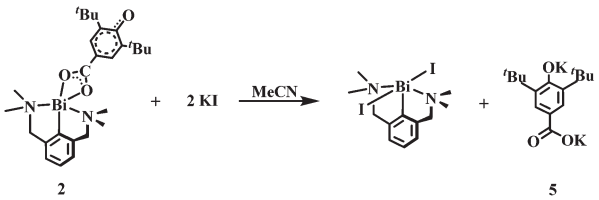
2, which contains the conjugate base of the target compound, 3,5-di-*tert*-butyl-4-hydroxybenzoic acid, **4**.[11–13] Double protonation of **2** can be effected by $[Et_3NH][Cl]$ in a reaction that reforms Ar′$BiCl_2$, the starting material in Scheme 1. As shown in Scheme 2, this sequence constitutes a cyclic process for the formation of **4** in which the $(Ar'Bi)^{2+}$ unit is used catalytically. The net reaction is given in eqn (1).

$$2KOAr + CO_2 + 2[Et_3NH][Cl] \rightarrow 4 + 2KCl + 2Et_3N + HOAr \quad (1)$$

The isolated yields of the individual reactions starting with the formation of **1** are (a) 61%, (b) 73% and (c) 88%, which combine for an overall yield of 39% for **4** with respect to bismuth. If the carboxylic acid is synthesized in a stepwise manner, but without isolating the intermediates, a final overall yield of 73% for **4** with respect to bismuth can be achieved. Ar′$BiCl_2$ is recovered in comparable yield. The identity and purity of **4** was demonstrated by GC-MS and ^{1}H and ^{13}C NMR spectroscopy.[13]

Since the reagents, $[Et_3NH][Cl]$ and KOAr, react to form 2,6-di-*tert*-butylphenol and KCl, and since $[Et_3NH][Cl]$ protonates **1** to form [Ar′Bi($C_6H_2{}^tBu_2$-3,5-OH-4)][Cl], which does not insert CO_2,[2] the sequence in Scheme 2 must be done in a cyclic stepwise manner rather than as a continuous catalytic process. In addition, there is spectroscopic evidence (Fig. S3†) that the first equivalent of $[Et_3NH][Cl]$ reacts with **2** to form an intermediate such as Ar′Bi(Cl)[$O_2C(C_6H_2{}^tBu_2$-3-5-OH-4)] that is susceptible to deprotonation by KOAr to regenerate **2**. Unfortunately this compound always formed as a mixture with Ar′$BiCl_2$ and could not be isolated. The cyclic nature of the reaction facilitates the isolation of the product, since it is the only hexane soluble compound in the final reaction, (c).

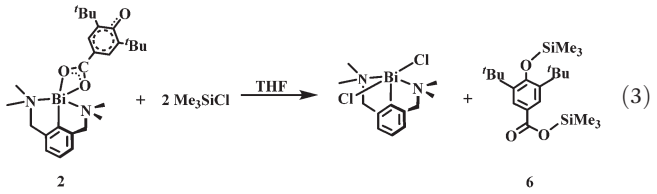
An alternative route to **4** has been explored using potassium iodide to cleave the oxyarylcarboxy dianion, eqn (2). This



(2)

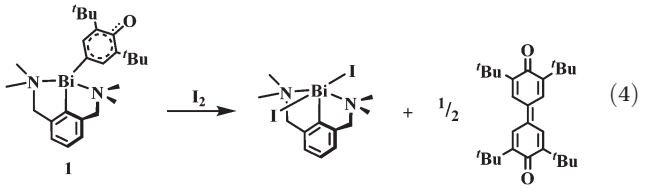
generates the dipotassium salt of **4**, namely dipotassium 3,5-di-*tert*-butyl-4-oxidobenzoate, **5**, and the NCN pincer diiodide, Ar′BiI_2.[14] Protonation of the dipotassium salt, **5**, with two equiv. of $[Et_3NH][Cl]$ formed **4** in 70% overall yield. However, conversion of the NCN pincer diiodide, Ar′BiI_2, back to the oxyarylcarboxy complex, **2**, was surprisingly more difficult than that of the dichloride. The reaction of Ar′BiI_2 and KOAr, analogous to the 4 h synthesis of **1**[1,2] from Ar′$BiCl_2$, reaches completion only after 18 h. Hence, this KI route is not preferable to Scheme 2.

The oxyaryl complex **1** was reported to react with one and two equiv. of R_3SiX reagents (R = Me, Ph; X = CN, N_3, Cl) to produce, in step-wise fashion, Ar′Bi(X)($C_6H_2{}^tBu_2$-3,5-OSiR_3-4) and Ar′BiX_2, respectively.[2] The analogous reaction of 1 equiv. of trimethylsilyl chloride with the oxyarylcarboxy complex **2** did not produce an analogous isolable Ar′Bi(Cl)($O_2CC_6H_2{}^tBu_2$-3,5-OSiMe_3-4) product. However, reaction of **2** with an excess of Me_3SiCl produced Ar′$BiCl_2$ and the trimethylsilyl ether of the trimethylsilyl ester of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid, *i.e.*, trimethylsilyl 3,5-di-*tert*-butyl-4-(trimethylsilyloxy)-benzoate, **6**, eqn (3). Compound **6** was characterized by NMR and IR spectroscopy and mass spectrometry in agreement with its formulation in eqn (3).



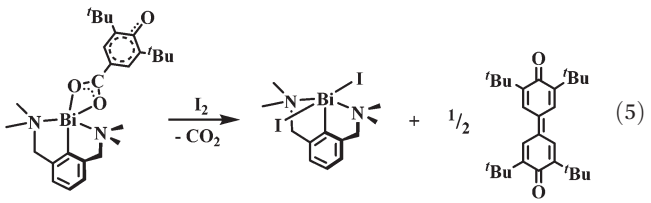
2 6 (3)

The oxyaryl dianion complex **1** was previously reported to react with one equiv. of I_2, to yield the known bismuth diiodide, Ar′BiI_2,[14] and the product of coupling the aryl groups, (3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone), eqn (4).[15,16]



1 (4)

An analogous reaction was performed with compound **2** to further explore the chemistry of the new oxyarylcarboxy dianionic ligand. Surprisingly, this reaction quickly yielded the same products observed in eqn (4), namely Ar′BiI_2 and the coupled aryl product, eqn (5). These products required the oxyarylcarboxy ligand to undergo decarboxylation. To test this, the reaction was performed with the ^{13}C labeled analog, **2**-$^{13}CO_2$, in a sealed J. Young NMR tube. Free $^{13}CO_2$ was observed by ^{13}C NMR spectroscopy, confirming the rapid decarboxylation of the dianionic ligand in eqn (5).



2 (5)

In conclusion, the C–H bond activation accessible from the bismuth NCN pincer complex, Ar′$BiCl_2$, can be combined with CO_2 activation and subsequent protonation to provide a cyclic route to 3,5-di-*tert*-butyl-4-hydroxybenzoic acid. The bismuth-based cycle requires only ambient temperature and 1 atm of CO_2 rather than a heated reaction under CO_2 pressure as previously reported and demonstrates the viability of using bismuth in CO_2 based processes. The oxyarylcarboxy dianion that is central to this cycle can be converted in one step to a silyl ether silyl ester derivative of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid and it is easily decarboxylated with I_2.

Acknowledgements

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