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SYNTHESIS OF SUBSTITUTED CYCLOBUTENEDIONES BY THE PALLADIUM CATALYZED CROSS-COUPLING OF HALOCYCLOBUTENEDIONES WITH ORGANOSTANNANES.

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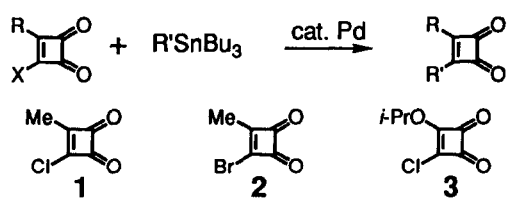
Abstract. Halo-substituted cyclobutenediones undergo palladium catalyzed cross-coupling with organostannanes providing a mild method for the synthesis of substituted cyclobutenediones.

The development of new techniques for the synthesis of substituted cyclobutenediones has become increasingly important with the recent advent of powerful methods of quinone[2,-11] and alkylidene-cyclopentenone[4, 8, 12-15]synthesis based on thermal and transition metal induced transformations of cyclobutenedione adducts prepared by 1,2-addition of unsaturated nucleophiles. As a complement to traditional methods for the construction of substituted cyclobutenediones via the addition of organolithium nucleophiles to squaric acid esters,[16, 17]we have recently documented the versatility of tri-*n*-butylstannyl substituted cyclobutenediones[18]and cyclobutenedione monoketals[19] for the introduction of a broad array of substitutents onto the cyclobutenedione core via palladium catalyzed cross-coupling technology. In order to complete this aspect of our study of practical methods for the synthesis of substituted cyclobutenediones, we document herein the reverse reaction, the use of halo-substituted cyclobutenediones as cross-coupling reaction partners with organostannane reagents (Eqn. 1), a reaction that should find ample use in the synthesis of highly functionalized cyclobutenediones. Very recently, a few 3,4-dialkynyl-3-cyclobutene-1,2-diones were prepared by the addition of alkynyl organometallics to 3,4-dichloro-3-cyclobutene-1,2-dione.[20]

Eqn. 1



1 2 3

Three halocyclobutenedione substrates were chosen for study, 3-chloro-4-methyl-3-cyclobutene-1,2-dione, **1**,[21] and 3-bromo-4-methyl-3-cyclobutene-1,2-dione, **2**,[22] both readily prepared from 3-hydroxy-4-methyl-3-cyclobutene-1,2-dione by reaction with the appropriate oxalyl halide, and 3-chloro-4-isopropoxy-3-cyclobutene-1,2-dione, **3**, prepared in 62% yield by treatment of 3,4-dichlorocyclobutenedione[23] with one equivalent of isopropanol in methylene chloride followed by addition of 1 equivalent of Et_3N.[24] The halocyclobutenediones **1** and **2** were treated with a variety of organotin reagents under traditional Stille cross-coupling conditions (2% $(PhCH_2)ClPd(PPh_3)_2$ / THF / 50 °C) and the results are listed in the Table.[25] In general, bromocyclobutenedione **2** was more effective than the chloro analog, **1**, in the cross-coupling with organostannanes, the reaction being complete in shorter times with higher yields resulting in most cases. Although infrared and ^1H NMR spectra of compounds **4g** and

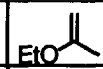
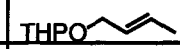
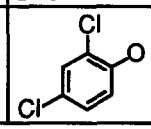
4h were in accord with the assigned structures, both compounds decomposed on standing, and satisfactory combustion data could not be obtained. $PhSSnBu_3$ reacted with both halocyclobutenediones 1 and 2 in the absence of palladium catalyst to give product 4i (Table, entry 9), but palladium significantly catalyzed the reaction (67% in 20 h versus 80% in 8 h for 1 and 86% in 20 h versus 88% in 3 h for 2). Allyl-tri-*n*-butylstannane did not give product with either substrate under the conditions employed.

In order to generalize further the use of the halocyclobutenedione–organostannane cross-coupling protocol, 3-chloro-4-isopropoxycyclobutene-1,2-dione, 3, was treated with a variety of organostannanes. This less reactive halocyclobutenedione did not cross-couple efficiently with the organostannanes in the Table (except for entries 9 and 10) under the traditional conditions (2% $(PhCH_2)ClPd(PPh_3)_2$ / THF / 50 °C); however, the use of cocatalytic CuI (5%) and $(PhCH_2)ClPd(PPh_3)_2$ (5%) in CH_3CN at 70 °C induced an efficient reaction.[25] The benefit of cocatalytic CuI on the Stille cross-coupling reaction has been documented previously.[18] As above, although both $PhSSnBu_3$ and 2,4-dichlorophenoxy-tri-*n*-butylstannane reacted with 3 in the absence of catalyst to give the corresponding substituted cyclobutenedione 5, the reactions were facilitated by the presence of metal catalysts (Table, entries 9 and 10). Compound 5i was formed in 80% in 20 h in the absence of palladium, and in 87% yield in 3 h in the presence of 5% $PhCH_2)ClPd(PPh_3)_2$. The reaction of 2,4-dichlorophenoxystannane (entry 10) took 72 h to produce 15% of 5j in the absence of catalyst, but gave product in 30% yield after 72 h when 5% $(PhCH_2)ClPd(PPh_3)_2$ was introduced into the reaction and in 68% in 24 h when 5% cocatalytic CuI was also added.

Experimental procedures for the synthesis of 4a and 5e are typical. *Synthesis of 4a*: 3-Chloro-4-methyl-3-cyclobutene-1,2-dione (0.211 g, 1.62 mmol) and phenyltri-*n*-butyltin (0.590 g, 1.61 mmol) were dissolved in 8 mL of THF under a nitrogen atmosphere at room temperature. $(PhCH_2)ClPd(PPh_3)_2$ (0.024 g, 2 mol%) was added and the mixture was heated to 50 °C with stirring and was monitored by tlc for disappearance of phenyltri-*n*-butyltin (20h, SiO_2, 1:5 ethyl acetate / hexane; $PhSnBu_3$: $R_f = 0.80$, product: $R_f = 0.20$). The solvent was removed on a rotary evaporator and the residue was purified by chromatography on silica gel to give 0.193 g (70%) of 4a as a yellow solid: mp 101-102 °C (CH_2Cl_2 / hexane); IR (CH_2Cl_2, cm^{-1}): 3050, 2950, 1780, 1765, 1590, 1335; ^1H NMR ($CDCl_3$, 300MHz): δ 8.03-8.00 (m, 2H), 7.60-7.50 (m, 3H), 2.65 (s, 3H); MS Calcd. for $C_{11}H_8O_2$: 172.0542. Found: 172.0542. Analogous reaction of 3-bromo-4-methyl-3-cyclobutene-1,2-dione (0.349 g, 1.99 mmol) with phenyl tributyltin (0.730g, 1.99 mmol) gave 85% of 4a (0.292g). *Synthesis of 5e*: 3-Chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione (0.318 g, 1.82 mmol) and 2-(trimethylsilyl)ethynyl tributyltin (0.708 g, 1.81 mmol) were dissolved in 10 ml of CH_3CN, $(PhCH_2)ClPd(PPh_3)_2$ / CuI (1:1) (0.087 g, 5 mol%) was added and the reaction was heated to 70 °C for 10 h. The solvent was removed on rotary evaporator and the residue was purified by chromatography on silica gel (SiO_2, 1:5 EtOAc / hexane, R_f=0.27) to give 0.244 g (57%) of 5e as a yellow solid: mp 35-36 °C (CH_2Cl_2 / hexane); IR (CH_2Cl_2, cm^{-1}): 2960, 1785, 1760, 1585, 1378, 1325; ^1H NMR ($CDCl_3$, 300MHz): δ 5.37 (hept, J = 6Hz, 1H), 1.50 (d, J = 6Hz, 6H), 0.26 (s, 9H). Anal. Calcd. for $C_{12}H_{16}O_3Si$: C, 60.99; H, 6.82. Found: C, 61.04; H, 6.84.

Table. Palladium Catalyzed Cross-Coupling of 3-Halo-4-substituted-cyclobutenediones with Organostannanes.[a]

1, X = Cl; 2, X = Br — 3 — 4 — 5

Entry	R	Product, % yield, reaction time from 1	from 2	from 3
1	Ph	4a, 70, 20 h	4a, 85, 6 h	5a, 87, 20 h
2	4-Me-Ph	4b, 81, 20 h	4b, 83, 10 h	5b, 76, 20 h
3	4-Cl-Ph	----	4c, 81, 15 h	----
4	2-thienyl	4d, 65, 15 h	4d, 73, 13 h	----
5	TMS–C≡C	4e, 56, 20 h	4e, 57, 20 h	5e, 57, 10 h
6	*n*-Bu–C≡C	4f, 50, 20 h	4f, 55, 20 h	5f, 58, 10 h
7		4g[b], 62, 10 h	----	5g[b], 70, 20 h
8		4h[b], 61, 20 h	----	5h, 49, 20 h
9	PhS	4i, 80, 8 h	4i, 88, 3 h	5i, 87, 3 h
10		----	----	5j, 68, 24 h

[a] $PhSnBu_3$, p-$MeC_6H_4SnBu_3$, and p-$ClC_6H_4SnBu_3$ were prepared according to the procedure of Azizan, et. al.[26] (2-Thienyl)$SnBu_3$ was prepared according to the procedure of Gopinantham, et. al.[27] *n*-BuC≡C$SnBu_3$ and $Me_3SiC{\equiv}CSnBu_3$ were prepared according to the procedure of Bottaro, et. al.[28] 1-Tetrahydropyranyloxy-3-prop-2-enyltri-*n*-butyltin was prepared according to the procedure of Corey and Williams.[29] (1-Ethoxy)vinyltri-*n*-butyltin and phenyl tri-*n*-butyltin sulfide were purchased from Aldrich Chemical Company. Tri-*n*-butyltin 2,4-dichlorophenolate was purchased from P & B Research Chemicals. [b] Although spectroscopic data were consistent with the indicated structures, satisfactory combustion analysis data could not be obtained

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22. Preparation of 3-bromo-4-methyl-3-cyclobutene-1,2-dione, **2**. Following the procedure for the preparation of **1** (reference 21), reaction of 3-hydroxy-4-methyl-3-cyclobutene-1,2-dione (1.525 g, 13.6 mmol) with 6.80 mL (1.0 equiv.) of $(COBr)_2$ (2.0 M in CH_2Cl_2) gave 3-bromo-4-methyl-3-cyclobutene-1,2-dione (1.739 g, 73%) as a yellow oil: bp 78-81 °C / 0.5 mm Hg; IR (CH_2Cl_2, cm^{-1}): 2980, 1865, 1810, 1785, 1582, 1340; ^1H NMR ($CDCl_3$, 300MHz): δ 2.40 (s, 3H).
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