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Stille couplings of 3-(trimethylstannyl)-5-bromo-2-pyrone for the syntheses of 3-aryl-5-bromo-2-pyrones and their ambident dienyl characters

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Abstract—3-(Trimethylstannyl)-5-bromo-2-pyrone underwent facile Stille coupling reactions with aryl halides to produce various 3-substituted 5-bromo-2-pyrones. The resulting 3-aryl-2-pyrone derivatives underwent both normal and inverse electron demand Diels–Alder cycloadditions depending on the type of the dienophiles being reacted. © 2002 Elsevier Science Ltd. All rights reserved.

Substituted 2-pyrones are important structural subunits present in a number of naturally occurring products.[1] Also as versatile synthetic building blocks, they have been used for the syntheses of many useful molecules.[2] In many cases, they have interesting physiological activities and have thus drawn much attention for their synthesis.[3] Due to the labile internal ester bond, however, direct substitutions onto the 2-pyrone ring have been scarcely reported.[4]

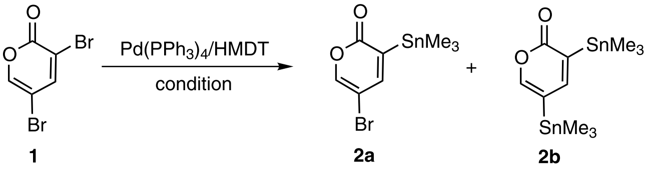
We have recently reported that 3,5-dibromo-2-pyrone undergoes Sonogashira coupling reactions with various terminal alkynes, regioselectively at the C3 position.[5] In addition, trimethyltin group could be introduced either selectively at the C3 or both C3 and C5 positions, depending on the reaction conditions (Table 1).

Those stannylated 2-pyrones, readily separable with column chromatography, would be useful reagents for the introduction of various functionalities onto the pyrone rings to produce structurally diverse 3-substituted and 3,5-disubstituted 2-pyrones.

Herein, we report the Stille coupling reactions of **2a** with various aryl and hetero-aryl halides for the synthesis of a series of previously unknown 3-aryl-5-bromo-2-pyrone derivatives. Noteworthy is that all of the 3-substituted-5-bromo-2-pyrones are potent ambident dienes endowed from the presence of the bromine atom at the C5 position.[6]

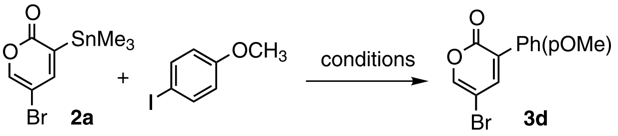
The coupling reactions of **2a** were investigated under various catalytic conditions as summarized in Table 2.

Table 1. Stannylations of 3,5-dibromo-2-pyrone



HMDT	Conditions	**2a** (%)	**2b** (%)
1.2 equiv.	Toluene, 80°C, 4 h	67	6
2.5 equiv.	THF, 100°C, 2 h	13	71

Table 2. Stille couplings of **2a** under various conditions



Entry	Conditions[a]	Yield (%)
1	$Pd(PPh_3)_4$/toluene/100°C, 24 h	33
2	$Pd(PPh_3)_2Cl_2$/DMF/50°C, 3 h	45
3	$Pd(PPh_3)_2Cl_2$/CuI/DMF/50°C, 3 h	73
4	$Pd(PPh_3)_2Cl_2$/CuI/MeCN/50°C, 8 h	35
5	$Pd(PPh_3)_2Cl_2$/CuI/THF/50°C, 10 h	50

[a] In all reactions, 5 mol% of Pd catalysts were used.

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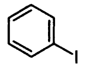
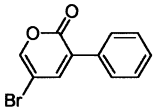
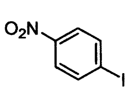
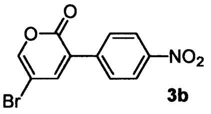
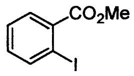
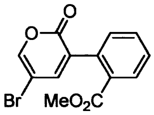
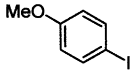
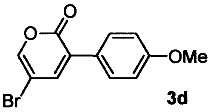
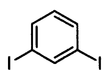
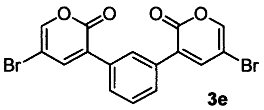
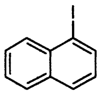
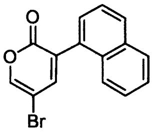
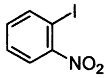
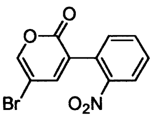
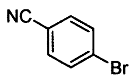
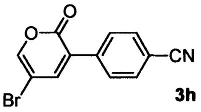
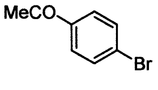
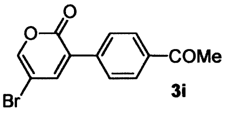
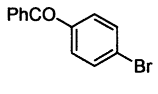
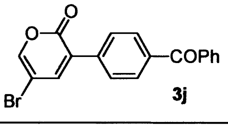
As it turned out, the condition in entry 3 was best suited for our Stille coupling reaction. The presence of catalytic amount of Cu^{+1} led to substantial increases of the rates and chemical yields.[7] Use of less polar solvents such as MeCN and THF did not give much improvement. Table 3 summarizes the results on the Stille couplings of **2a** with various aryl halides using 5 mol% of Pd catalyst.

Oxidative additions of Pd(0) at C5 of 3-(trimethyltin)-5-bromo-2-pyrone (**2a**) were sufficiently slow to suppress otherwise problematic oligomerizations. The couplings with both electron rich and deficient aryl halides were well proceeded, but not with aryl triflate under the literature conditions. Couplings with hetero-aryl halides provided 3-heteroaryl-5-bromo-2-pyrones, in moderate yields as shown in Table 4.

Table 3. Stille couplings of **2a** with selected aryl halides

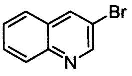
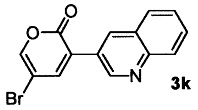
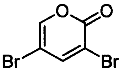
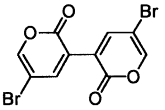
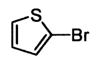
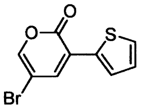
entry	aryl halide	condition	product	yield
1		A (2h)	 **3a**	92%
2		A (3h)	 **3b**	76%
3		A (4h)	 **3c**	69%
4		A (3h)	 **3d**	73%
5		A (2h)	 **3e**	50%
6		A (0.5h)	 **3f**	45%
7		B (72h)	 **3g**	64%
8		B (36h)	 **3h**	73%
9		B (25h)	 **3i**	63%
10		B (11h)	 **3j**	70%

(A) $Pd(PPh_3)_2Cl_2$/CuI/DMF/50°C, (B) $Pd(PPh_3)_4$/toluene/100°C

The bis-stannylated 2-pyrone **2b** also underwent facile Stille coupling reactions with various aryl halides. The reaction at the C5 position was significantly slower than at C3. As shown below, either mono-coupled **4a** or bis-coupled product **4b** can be obtained as a major product by controlling reaction time and temperature (Table 5). Second couplings at C5 of **4a** would generate other structurally interesting 2-pyrones containing two different aryl groups.

In the essence, all the coupled products are potentially ambident dienes due to the presence of the bromine atom at C5 position. As shown in Scheme 1, 3-phenyl-5-bromo-2-pyrone **1a** underwent both normal and inverse electron demand Diels–Alder cycloadditions, reacting with both methyl acrylate and benzyl vinyl ether to provide the corresponding cycloadducts with good to excellent diastereoselectivity and chemical yields.

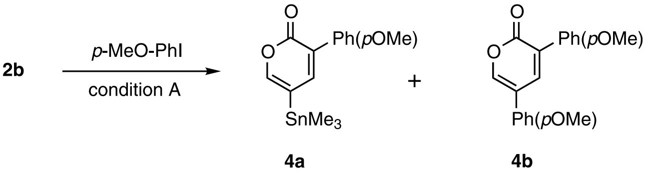
Table 4. Couplings with hetero-aryl halides

entry	aryl halide	condition[a]	product	yield
11		B (20h)	 **3k**	41%
12		A (0.5h)	 **3l**	63%
13		B (24h)	 **3m**	42%

(a) 5 mol% Pd catalysts were used

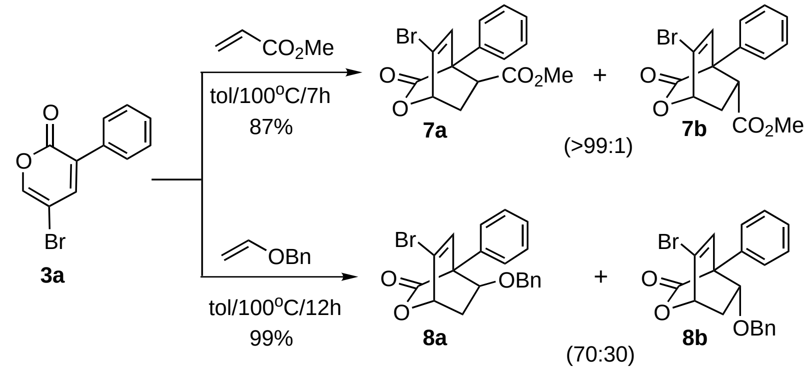
(A) $Pd(PPh_3)_2Cl_2$/CuI/DMF/50°C, (B) $Pd(PPh_3)_4$/toluene/100°C

Table 5. Synthesis of mono- or bis-aryl-2-pyrones



4a **4b**

Reaction time (h)	Temp. (°C)	Yield (%)	
		4a	**4b**
8	50	59	Trace
48	100	17	67

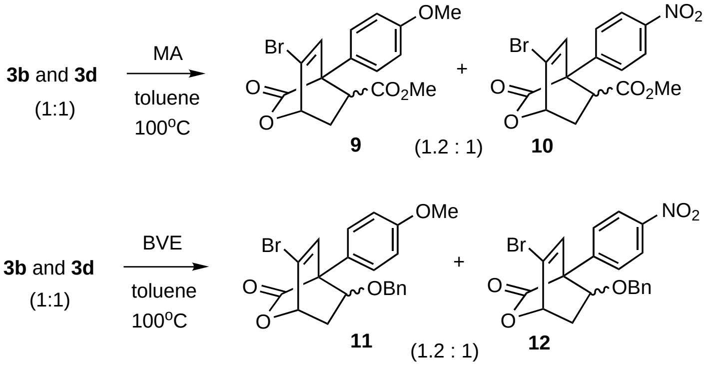


Scheme 1. Diels–Alder cycloadditions of **3a** with MA and BVE.

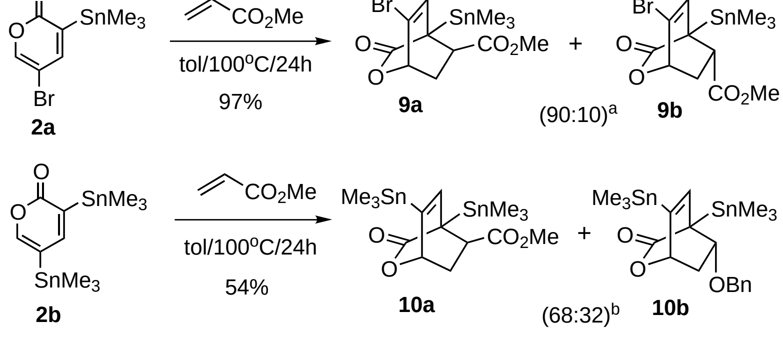
Introduction of proper functional groups on the aryl groups may modulate their dienyl characters. Thus, in principle, electron donating substituents on the aryl group may shift the resulting 2-pyrones to favor normal electron demand Diels–Alder cycloadditions over the other, and vice versa. A few competition experiments, however, showed that the shifts were only minimal as seen in Scheme 2. In these experiments, an equimolar mixture of **3b** and **3d** was heated with 3 equiv. of dienophile; methyl acrylate (MA) and benzyl vinyl ether (BVE), respectively. The reactions were halted before the completion.

The stannylated 2-pyrones themselves may function as dienes. As presented in Scheme 3, they indeed underwent Diels–Alder cycloadditions with methyl acrylate to produce the corresponding stannylated bicyclolactones. Only a trace amount of the cycloadducts were detected from the reactions with electron-rich, benzyl vinyl ether, even after heating for 4 days.

In summary, we have shown that 3-(trimethylstannyl)-2-pyrone readily prepared from regioselective stannylation of 3,5-dibromo-2-pyrone underwent facile Stille coupling reactions with various aryl and hetero-aryl



Scheme 2. Competitive Diels–Alder cycloadditions of **3b** and **3d**.



(a) ^{1}H NMR ratio; (b) Isolated ratio

Scheme 3. Diels–Alder cycloadditions of **2a** and **2b**.

halides to furnish various 3-substituted-5-bromo-2-pyrones. Second coupling reactions would generate 2-pyrones substituted with two different aryl groups. The resulting products cycloadded with both electron deficient and rich dienophiles. We are currently investigating other transition metal-catalyzed coupling reactions on 3,5-dibromo-2-pyrone including aminations and amidations as well as synthetic applications of the resulting products.

Acknowledgements

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