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Regioselective Stille coupling reactions of 3,5-dibromo-2-pyrone with various aryl and vinyl stannanes

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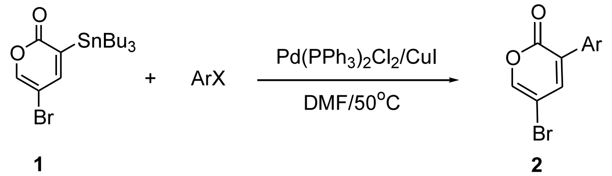
Abstract—3,5-Dibromo-2-pyrone underwent facile regioselective Stille coupling reactions with aryl, heteroaryl and vinyl stannanes to produce various 3-substituted, 5-bromo-2-pyrones. Addition of a catalytic amount of CuI greatly increased the selectivity and chemical yield of the desired 3-aryl-5-bromo-2-pyrone. Second Stille coupling reactions on the resulting 3-aryl-2-pyrones gave rise to a series of potentially useful 2-pyrones with two different functionalities at C3 and C5 position in good to excellent isolated yields. 2-Pyrones with pyridyl groups at C3 position can undergo Lewis acid catalyzed Diels–Alder cycloaddition reactions with benzyl vinyl ether. © 2002 Elsevier Science Ltd. All rights reserved.

In connection with our current interest in 3,5-dibromo-2-pyrone, which stems from its ambident dienyl character,[1–7] we have studied various other transition metal catalyzed coupling reactions on this compound. Recently, we have reported Pd-catalyzed regioselective alkynylations and stannylations of 3,5-dibromo-2-pyrone.[1] Also reported was that the resulting 3-(trimethylstannyl)-5-bromo-2-pyrone underwent Stille coupling reactions with various aryl halides to furnish a series of previously unknown 3-aryl-5-bromo-2-pyrones in a highly regioselective manner.[2] With this method, we were able to prepare a wide variety of synthetically useful 3-substituted-5-bromo and 3,5-disubsituted-2-pyrones (Scheme 1).

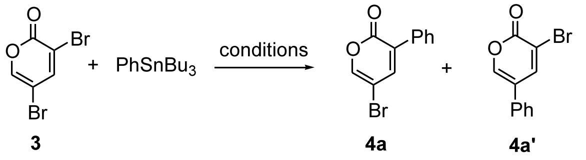


Scheme 1. Stille couplings of 3-(trimethylstannyl)-5-bromo-2-pyrone with various aryl halides.

Although quite useful, this approach requires a separate preparation of 3-trimethylstannyl-5-bromo-2-pyrone for the synthesis of 3-substituted, 5-bromo-2-pyrones. In addition, the stannylated 2-pyrone was not effective in the couplings with heteroaryl halides such as 2-bromopyridine, 2-bromothiophene and 2-bromofuran. For synthetic inconvenience and aforementioned ineffectiveness, we have studied direct Stille coupling reactions of 3,5-dibromo-2-pyrone with various stannyl reagents.

Herein, we wish to report regioselective Stille coupling reactions of 3,5-dibromo-2-pyrone with aryl, heteroaryl and vinyl stannanes. A set of experiments showed that the condition B gave best results in terms of chemical yields and regioselectivity (Table 1). Addition of a catalytic amount of CuI (10 mol%) greatly increased the regioselectivity and chemical yield of the desired 3-phenyl-5-bromo-2-pyrone (**4a**).

Table 1. Stille coupling reaction of 3,5-dibromo-2-pyrone with tributylphenyltin under different reaction conditions



	Condition	**4a** (%)	**4a**′ (%)
A	$Pd(PPh_3)_4$/toluene/100°C/30 min	81	16
B	$Pd(PPh_3)_4$/CuI/toluene/100°C/30 min	94	Trace
C	$Pd(PhCN)_2Cl_2/AsPh_3$/NMP/20°C/5 h	60	Trace
D	$Pd(PPh_3)_4$/THF/100°C/40 min	64	11
E	$Pd_2(dba)_3$/THF/100°C/4 h	30	5

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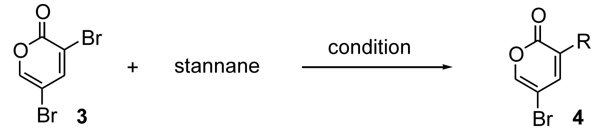
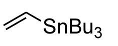
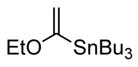
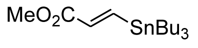
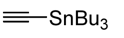
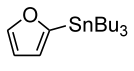
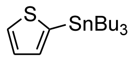
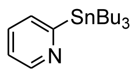
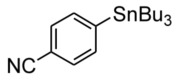
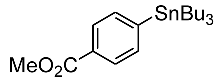
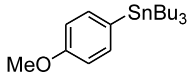
Table 2. Stille couplings with various other stannanes



entry	stannane	condition	product	yield
1		**C** (6 h)	**4b**	57%
2		**B** (30 min)	**4c**	50%
3		**B** (2 h)	**4d**	34%
4		**B** (10 min)	**4e**	52%
5		**B** (20 min)	**4f**	61%
6		**B** (20 min)	**4g**	72%
7		**B** (10 min)	**4h**	51%
8		**B** (1 h)	**4i**	80%
9		**B** (1.5 h)	**4j**	79%
10		**B** (7 h)	**4k**	61%

Under the condition B, we undertook coupling reactions with various other aryl, heteroaryl and vinyl stannyl reagents (Table 2).[8]

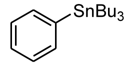
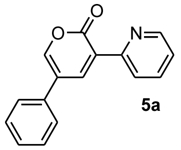
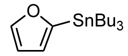
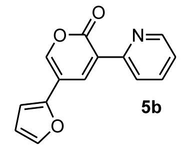
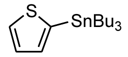
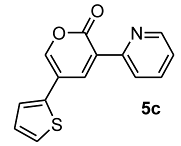
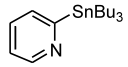
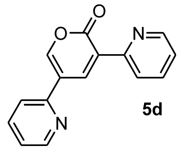
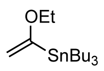
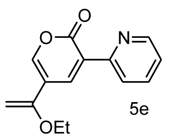
The coupling reaction with vinyltin (entry 1) gave virtually no coupling product under the condition B, but did proceed under the condition C to give **4b** in 57% yield.

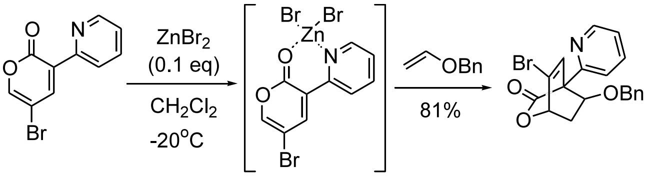
As mentioned previously, 3-(trimethylstannyl)-5-bromo-2-pyrone is not effective in the coupling reactions with 2-bromopyridine, 2-bromothiophene and 2-bromofuran. Use of 3,5-dibromo-2-pyrone as electrophilic partner in this way gave much better results, providing the corresponding 3-heteroaryl-5-bromo-2-pyrones in 51–72% isolated yields (entries 5, 6, and 7).

Second coupling reactions of the resulting 3-substituted-5-bromo-2-pyrones generated a series of structurally interesting 2-pyrones bearing two different groups in 50–79% isolated yields (Table 3), much better than the similar cases in the literature where 5-bromo-2-pyrone was coupled with vinyl or aryl stannanes in 41–43% yields.[9]

All the products shown in the Table 2 are potentially ambident dienes, capable of undergoing Diels–Alder cycloadditions with either electron poor or rich dienophiles.[2] Of particular interest is that 2-pyrone derivatives with 2-pyridine substituent at 3-position can undergo Diels–Alder cycloadditions with electron rich dienophiles in the presence of Lewis acids. As shown in Scheme 2 as a representative case, the product **4h** underwent Zn^{+2} catalyzed Diels–Alder cycloaddition

Table 3. Stille coupling reactions of **4h** with selected aryl halides

entry	aryl halide	condition	product	yield
1		A (2 h)	 **5a**	59%
2		A (1 h)	 **5b**	79%
3		A (7 h)	 **5c**	50%
4		A (0.5 h)	 **5d**	52%
5		A (3 h)	 5e	50%



4h **5** **6a**

Scheme 2. $ZnBr_2$ catalyzed Diels–Alder cycloaddition of 3-(2-pyridyl)-5-bromo-2-pyrone with benzyl vinyl ether.

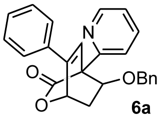
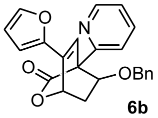
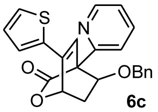
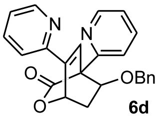
with benzyl vinyl ether to furnish the *endo*-cycloadduct **6a** as an essentially single product in 81% yield after 48 h at −20°C. No cycloaddition was, however, observed with electron deficient methyl acrylate under the same reaction conditions, understandable based on electronic requirement.

Mono-coordinating BF_3 etherate did not give the cycloadduct. The cycloaddition proceeds in a catalytic manner, presumably through the intermediate **5**. The 2-pyrones **4f** and **4g** were much poorer diene, perhaps due to their inability to form tight Zn-chelates. After 12 h at rt, they gave the corresponding cycloadducts in 30–40% yields under the identical conditions.

The di-substituted 2-pyrones **5a–d** also underwent yet smooth Zn^{+2} catalyzed cycloadditions with benzyl vinyl ether, providing the *endo*-cycloadducts **6a–d** with no detectable *exo*-adducts produced (Table 4).[10]

In summary, we have found that 3,5-dibromo-2-pyrone underwent highly regioselective Stille coupling reactions with various aryl, heteroaryl and vinyl stannanes to furnish 3-substituted, 5-bromo-2-pyrones. Subsequent second Stille couplings on the resulting 2-pyrones generated 3,5-disubstituted 2-pyrones.[11] 2-Pyrones with pyridyl group at C3 position undergo diastereospecific Zn^{+2} catalyzed Diels–Alder cycloadditions with electron rich benzyl vinyl ether, but not with electron deficient methyl acrylate. We are currently screening various chiral ligands for their asymmetric Diels–Alder reactions.

Table 4. $ZnBr_2$ catalyzed Diels–Alder cycloadditions of **5a–d** with benzyl vinyl ether

entry	diene	condition	product	endo:exo	yield
1	**5a**	rt (48h)	 **6a**	100:0	64%
2	**5b**	rt (48h)	 **6b**	100:0	73%
3	**5c**	rt (48h)	 **6c**	100:0	73%
4	**5d**	rt (48h)	 **6d**	100:0	55%

Acknowledgements

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References

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6. Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* **2001**, *42*, 1065.
7. Cho, C.-G.; Kim, Y.-W.; Kim, W.-K. *Tetrahedron Lett.* **2001**, *42*, 8193.
8. Typical procedure: A mixture of 30 mg (0.12 mmol) of 3,5-dibromo-2-pyrone, 52 mg (0.14 mmol) of tributylphenyltin, 7 mg (5 mol%) of $Pd(PPh_3)_4$, 2 mg (10 mol%) of CuI and 1 mL of toluene was heated at 100°C for 0.5 h. Upon cooling to rt, the reaction mixture was treated with saturated KF (aq.), diluted with Et_2O, and filtered through a plug of Celite. The filtrate was dried over $MgSO_4$, concentrated and purified by column chromatography (hexanes:EtOAc, 20/1) provided 28 mg of **1a** in 94% yield.
9. (a) Danieli, B.; Lesma, G.; Martinelli, M.; Passarella, D.; Peretto, I.; Silvani, A. *Tetrahedron* **1998**, *54*, 14081; (b) Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693.
10. Typical procedure: A mixture of 35 mg (0.14 mmol) of **4h**, 38 mg (2 equiv.) of benzyl vinyl ether, 3 mg (10 mol%) of $ZnBr_2$ in CH_2Cl_2 was stirred for 48 h at −20°C. The reaction mixture was concentrated and purified by column chromatography (hexanes:EtOAc) to provide 44 mg of **6a** in 81% yield.
11. All new 2-pyrone derivatives prepared were fully characterized with ^1H, ^{13}C NMR, FT-IR and HRMS.