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Regioselective Synthesis of 3-Alkynyl-5-bromo-2-pyrones via Pd-Catalyzed Couplings on 3,5-Dibromo-2-pyrone

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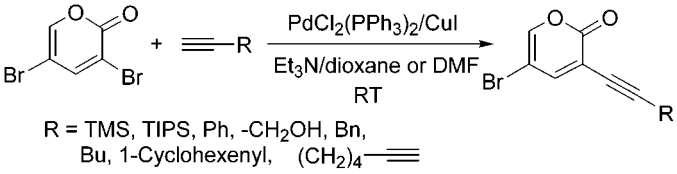
ABSTRACT



3,5-Dibromo-2-pyrone underwent facile Pd(0)-catalyzed coupling reactions with various alkynes to give rise to the corresponding 3-alkynyl-5-bromo-2-pyrones with good to excellent chemical yields and regioselectivity.

As structural subunits present in a variety of biologically active natural products[1] and as versatile synthetic building blocks,[2] 2-pyrones have gained much interest over the past few decades. There have been a number of reports in the literature on their chemical behaviors toward dienophiles, nucleophiles, and electrophiles in addition to their preparations.[3] Halogenated 2-pyrones are of particular interest, in that they would offer a convergent approach to the compounds containing 2-pyrone units. Halogenated 2-pyrones have been either used directly for transition metal catalyzed coupling reactions with aryltin and arylboronic acids or converted into tin-, boron-, zinc-, and copper-based organometallic reagents for couplings with electrophilic partners.[4]

We have recently reported a convenient synthetic method[5] for 3,5-dibromo-2-pyrone as well as its potency as an ambident diene.[6] Its ^{13}C NMR spectrum indicated that the two carbon centers with bromine atoms attached (C3 and C5 of 3,5-dibromo-2-pyrone) differ in their chemical shifts, implying that oxidative addition of Pd(0) could occur preferably at one carbon center (presumably the C3 position), leading to regioselective coupling reactions.[7] Second coupling reactions with other functionalities onto the remaining bromine group would thus provide, in principle, an easy

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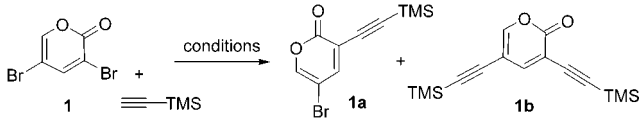
access to the multiply functionalized 2-pyrones. Herein, we report regioselective Sonogashira alkynylations of 3,5-dibromo-2-pyrone with various terminal alkynes to give rise to a series of 3-alkynyl-5-bromo-2-pyrone derivatives with good to excellent chemical yields and regioselectivity.

As seen in Table 1, summarizing some of the conditions we tested,[8] the $Pd(PPh_3)_2Cl_2/CuI/Et_3N$ system turned out to

Table 1. Sonogashira Couplings under Various Catalytic Systems[a]



catalyst system	solvent	total yields (%)	**1a**:**1b**
$Pd(PPh_3)_4/AsPh_3/Et_3N$	THF	56	89:11
$Pd(PhCN)_2Cl_2/CuI/(tBu)_3P/Et_3N$	dioxane	trace	
$Pd(PhCN)_2Cl_2/CuI/NaOtBu$	dioxane	trace	
$Pd(PPh_3)_2Cl_2/CuI/Et_3N$	THF	trace	
$Pd(PPh_3)_2Cl_2/CuI/Et_3N$	MeCN	trace	
$Pd(PPh_3)_2Cl_2/CuI/Et_3N$	DMF	72	85:15
$Pd(PPh_3)_2Cl_2/CuI/Et_3N$	dioxane	92	88:12

[a] All coupling reactions were conducted at rt with 1.2 equiv of TMS-acetylene.

be the best. The coupling reaction was highly dependent upon the type of solvents used. DMF and dioxane were better than THF and MeCN. Use of nucleophilic bases such as NaOtBu and Et_2NH resulted in the cleavage of the lactone unit. Thus, some of the superb literature conditions using these bases were not effective in our system. For example, only a trace amount of the coupled product was obtained under Buchwald and Fu's $Pd(PhCN)_2Cl_2/CuI/(tBu)_3P$ catalytic condition.[8b] Use of nonnucleophilic Et_3N in lieu of Et_2NH did not give much improvement.

The Sonogashira couplings with other terminal alkynes were conducted in both dioxane and DMF. For entries 1, 2, and 5, DMF and dioxane gave similar results, while for entries 6−8, dioxane was far better than DMF, giving much higher chemical yields and regioselectivity. The trend was, however, reversed in entries 3 and 4. Nonnucleophilic methyl propiolate did not undergo the coupling reactions. All new 3-alkynyl-5-bromo-2-pyrones **1a**−**8a** were fully characterized with ^1H and ^{13}C NMR, FT-IR, and high-resolution MS.[9]

Table 2. Regioselective Couplings of 3,5-Dibromo-2-pyrone with Various Terminal Alkynes

entry	alkyne	time(h)	solvent[a]	product	yield (%)[b]
1	TMS	0.5	A	**1a**	83
2	TIPS	0.5	A	**2a**	63
3	Ph	3	B	**3a**	91
4	OH	0.5	B	**4a**	70
5	Ph	12	A	**5a**	61
6	Bu	24	A	**6a**	91
7		30	A	**7a**	76
8	4	30	A	**8a**	84[c]

[a] A: dioxane; B: DMF. [b] Isolated yield. [c] 1,6-Octadiyne (5 equiv) was used.

Coupling reactions with 2.5 equiv of small terminal alkynes such as TMS-acetylene or propargyl alcohol generated the corresponding 3,5-dialkynyl-2-pyrones in 70−90% isolated yields (data not shown). Alkynes with large substituents, for example, entry 8, did not furnish the bis-alkynyl-2-pyrones, even when used in large excess.

These results indicate that the electron density on C3 in 3,5-dibromo-2-pyrone is greater than that on C5, from which we were able to finish the peak assignment of its ^{13}C NMR spectrum.

We carried out a few coupling reactions other than the Sonogashira on 3,5-dibromo-2-pyrone. Preliminary results showed that conventional Stille and Suzuki coupling reactions did not proceed as smoothly as Sonogashira couplings. Fortunately, 3,5-dibromo-2-pyrone underwent quite nice stannylation reactions with HMDT under the action of Pd catalysts. As shown below, 3,5-dibromo-2-pyrone was mono- or di-stannylated depending on the amount of HMDT and the type of solvent (Scheme 1). We obtained both mono-

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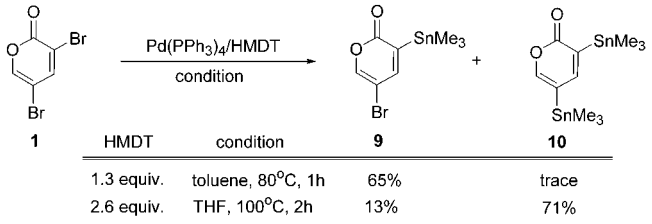
(9) Representative procedure: to a mixture of 580 mg of 3,5-dibromo-2-pyrone (2.28 mmol), 90 mg of $Pd(PPh_3)_2Cl_2$ (0.11 mmol), and 44 mg of CuI (0.24 mmol) in 30 mL of 1,4-dioxane were added 0.38 mL of Et_3N (2.74 mmol) and 269 mg of trimethylsilyl acetylene (2.74 mmol). After stirring for 0.5 h at rt under Ar, the reaction mixture was filtered through a plug of Celite and the filtered material was washed with ether. The filtrate was washed with H_2O, dried over $MgSO_4$, concentrated, and chromatographed (80:1 hexanes/EtOAc) to give 514 mg of **1a** (83% yield). **1a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, $J = 2.4$ Hz, 1H), 7.53 (d, $J = 2.4$ Hz, ^1H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 148.9, 147.6, 114.2, 104.6, 100.2, 96.5, −0.3; FT-IR ($CHCl_3$) 2927, 2856, 2379, 2163, 1741, 1204 cm^{-1}; HRMS (FAB+) m/z $(M + 1)^+$ calcd for $C_{10}H_{12}BrSiO_2$ 270.9790, found 270.9789.

Scheme 1. Stannylations of 3,5-Dibromo-2-pyrone

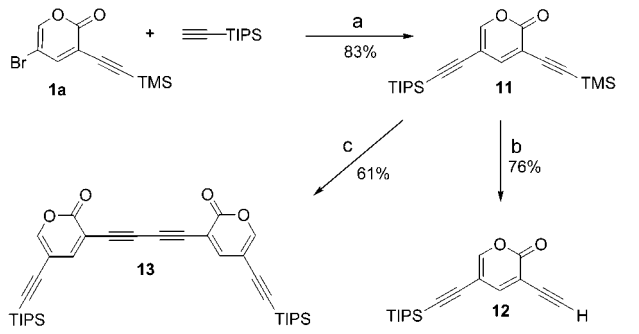


HMDT	condition	9	10
1.3 equiv.	toluene, 80°C, 1h	65%	trace
2.6 equiv.	THF, 100°C, 2h	13%	71%

(**9**) and bis-stannylated 2-pyrone (**10**) in 14% and 71% isolated yields, respectively, when the reaction mixture was heated with 2.6 equiv of HMDT in THF at 100 °C. Stannylation with 1.3 equiv of HMDT in THF at 80 °C gave the monostannylated 2-pyrone (**9**), but in 30% yield. When the reaction was conducted in toluene at 80 °C, however, only monostannylated 2-pyrone **9** was produced in 65% isolated yield. Again, C3 of 3,5-dibromo-2-pyrone underwent faster oxidative addition of Pd than C5. In fact, stannylation of 5-bromo-2-pyrone is quite sluggish as demonstrated by Meinwald et al.[4b] They heated a mixture of 5-bromo-2-pyrone and HMDT in THF at 80 °C for 30 h in the presence of $Pd(PPh_3)_4$ to give rise to 5-(trimethylstannyl)-2-pyrone in 68% yield. Both mono- **9** and bis-stannylated 2-pyrone **10** would be quite useful reagents for the generation of various other 2-pyrone derivatives under typical Stille conditions.

Second coupling reactions of 3-alkynyl-5-bromo-2-pyrones with other terminal alkynes with small substituents would provide doubly functionalized 3,5-dialknyl-2-pyrones. As shown in Scheme 2, **1a** underwent facile coupling reaction

Scheme 2. Modifications of 3-TMS-ethynyl-5-bromo-2-pyrone

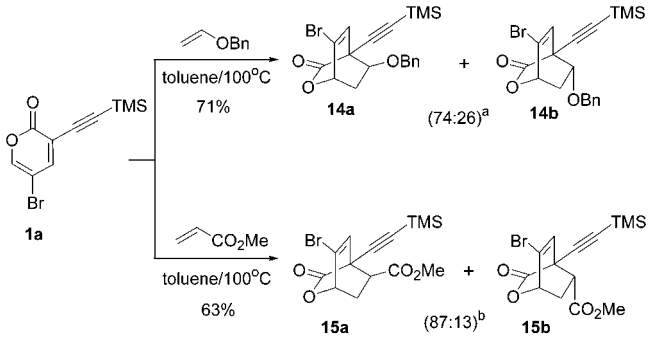


[a] $Pd(PPh_3)_2Cl_2$/CuI/Et_3N/dioxane/rt. [b] TBAF/THF-AcOH. [c] CuOTf·benzene/$CaCO_3$/dioxane/100 °C.

with TIPS-acetylene to give 3-TMS-ethynyl-5-TIPS-ethynyl-2-pyrone **11** in 83% yield. Selective removal of TMS over TIPS proceeded well with TBAF in a mixed solvent system of THF and acetic acid to provide **12**, which can be used for further functionalization. Cu(I)-catalyzed homocoupling of **11** furnished the structurally interesting dimeric 2-pyrone **13**,[10] bearing an internal diacetylene unit.

All 3-alkynyl-5-bromo-2-pyrones (**1a**−**8a**) prepared are potentially ambident dienes and, thus, capable of reacting with both electron-rich and electron-poor dienophiles. When heated in toluene, **1a** indeed underwent Diels−Alder cycloadditions with both benzyl vinyl ether and methyl acrylate to furnish the corresponding cycloadducts in reasonable chemical yields and *endo*/*exo* selectivity (Scheme 3).

Scheme 3. Diels−Alder Cycloadditions of 3-TMS-ethynyl-5-bromo-2-pyrone



[a] ^{1}H NMR ratio. [b] Isolated ratio.

These cycloadducts, especially *endo*-isomers, may find further usage as intermediates for the synthesis of various fused oxa- and carbocycles, upon transition metal catalyzed cyclizations.

In summary, we have found that 3,5-dibromo-2-pyrone underwent Sonogashira alkynylations with various terminal alkynes, regioselectively at the C3 position, to provide a series of synthetically useful 3-alkynyl-5-bromo-2-pyrones. We have also learned that 3,5-dibromo-2-pyrone can be stannylated either selectively on C3 or on both C3 and C5. In addition, some of the Sonogashira products can be further manipulated into other 2-pyrone derivatives by using the remaining bromine group as a handle as shown in Scheme 2. They are also potent ambident dienes, which can undergo Diels−Alder cycloadditions with both electron-deficient and electron-rich dienophiles to give rise to the stereochemically defined, functionally rich bicycloadducts as exemplified in Scheme 3. Thus, we expect these alkynyl-2-pyrones as well as stannylated 2-pyrones to have a wide spectrum of potential synthetic utility. Full details of 3-alkynyl-5-bromo-2-pyrones as ambident dienes as well as their applications for the synthesis of various fused oxa- and carbocyclic compounds will be reported elsewhere in due course.

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Supporting Information Available: Details of experimental procedures as well as compound characterizations for **1a**−**8a** and **9**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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