Regioselectivity in the Sonogashira coupling of 4,6-dichloro-2-pyrone†

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The Sonogashira cross-coupling of 4,6-dichloro-2-pyrone with terminal acetylenes proceeds in good yields and high regioselectivity for the 6-position; dibenzylidene acetone (dba) type ligands play a non-innocent role in reactions mediated by $Pd(dba)_2/PPh_3$; theoretical studies indicate that C-6 oxidative addition is favoured both kinetically and thermodynamically.

The 2-pyrone motif (**1**) is ubiquitous in many natural products, displaying beneficial and exploitable therapeutic potential (Fig. 1).[1] Non-natural substituted 2-pyrones, prepared *via* cross-coupling reactions of **2** (Negishi, Sonogashira, Stille, and Suzuki, *etc.*),[2] are effective inhibitors of specific types of human ovarian carcinoma (A2780) and human chronic myelogenous leukemia (K562) cell lines (in an *in vitro* cell culture system).[3] 4-Alkynyl variants of **2** also exhibit pronounced solvatochromism in fluorescence, which is expected to aid the identification of their mode of action.[4] Transition metal carbonyl complexes containing the 2-pyrone ring-system, which are η^1-carbonyl-[5] and η^4-diene-coordinated,[6] undergo Suzuki coupling; interestingly, the latter complexes possess useful carbon monoxide-releasing ability which could be used in vasorelaxation and inflammatory diseases.[7]

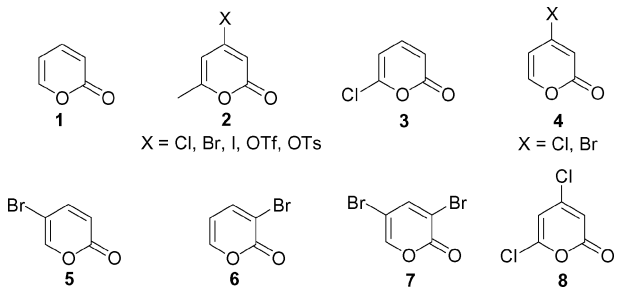

Fig. 1 Readily available halogenated 2-pyrones.

Recently, the application of halogenated 2-pyrones (**2**–**7**) has been of considerable interest to us and several other research groups. The cross-coupling reactions of **3** and **4** have been investigated by ourselves,[8] Bellina and co-workers,[9] and Kalinin *et al*.[10] Cho and co-workers have reported extensively on the cross-coupling reactions of 5-bromo- and 3-bromo-2-pyrones (**5** and **6**), as well as 3,5-dibromo-2-pyrone **7**.[11] Compound **7** undergoes regioselective Stille coupling reactions with aryl-, heteroaryl- and vinyl-stannanes to produce various 3-substituted-5-bromo-2-pyrones, where remarkable Cu(I) effects are observed, resulting in a switch in regioselectivity for the 5-position in the presence of stoichiometric amounts of Cu(I).[12] Generally, coupling occurs at the 3-position for Sonogashira coupling,[13] Suzuki coupling[14] and amination reactions.[15]

Other halogenated 2-pyrones in cross-coupling processes include 5-iodo-6-substituted-2-pyrones[16] and 3-bromo-5-iodo-2-pyrones.[17] Meinwald and co-workers have coupled 3-methyl-5-bromo-2-pyrone to an alkylzinc reagent, which was a key step in the synthesis of the cockroach sex pheromone, supellapyrone [5-(2′*R*,4′*R*-dimethylheptanyl)-3-methyl-2-pyrone].[18]

Herein, we detail investigations into the regioselective Sonogashira couplings of 4,6-dichloro-2-pyrone **8**, a remarkably versatile 2-pyrone.[19] Some unusual observations and side-reactions are discussed.

One of the remarks made by Cho and co-workers for the underlying reasons for selective cross-coupling at the 3-position of **7** was the difference in electron density at C3 *versus* C5 ($\Delta\delta$ = 13.8).[11–15] The ^{13}C NMR spectrum of **7** clearly indicates that C3 is more deshielded than C5 (Fig. 2).

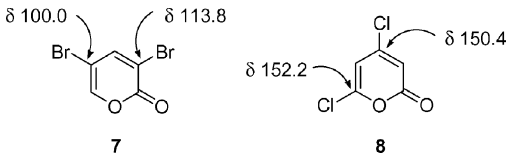

Fig. 2 ^{13}C NMR chemical shifts in **7** and **8**.

However, the small difference between C4 and C6 in **8** ($\Delta\delta$ = 1.8) implies that a regioselective coupling with this substrate ought to be difficult; nevertheless, **8** was predicted to be as reactive as **7** based on latent polarity. Given the potential high value of the alkynylated products from **8** *vide supra*, the Sonogashira coupling of **8** with phenylacetylene under various conditions was studied (Scheme 1 and Table 1). Three primary products were expected: 4-chloro-6-(2-phenylethynyl)-2-pyrone **9a**, 6-chloro-4-(2-phenylethynyl)-2-pyrone **10a** and 4,6-bis(2-phenylethynyl)-2-pyrone **11a**. Mindful of the known side-reactions[8] of Et_3N (used as a base in Sonogashira coupling) with 6-chloro-2-pyrone **3** we did expect to detect the amine adducts derived from **8** (*i.e.* compound **12**) as well as 1,3-diyne products (*e.g.* **13a**) resulting from oxidative dimerisation (note: the use of DBU, DABCO or common mineral bases results in negligible reaction).

Under the first set of conditions tested, **9a** was the major cross-coupled product, formed in 69% yield (entry 1).‡ § This was accompanied by **11a** in 5% yield and the amine adduct **12** in 9% yield. Compound **12** was shown by UV spectroscopy to be formed by a non-palladium-mediated background reaction in an identical solvent system (and concentration of Et_3N) to that used

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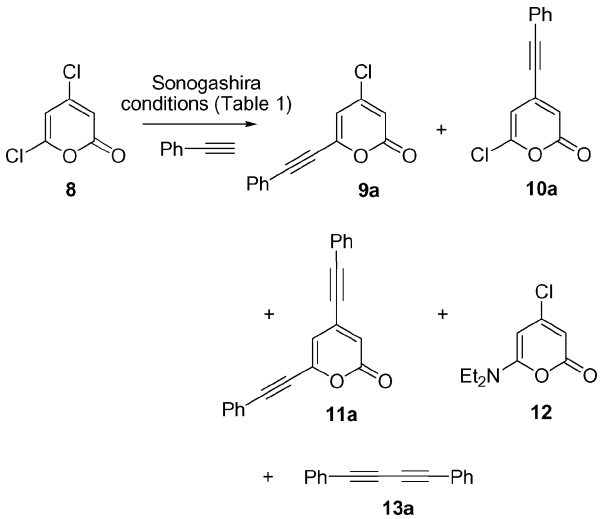
† Electronic supplementary information (ESI) available: characterisation and theoretical data. See DOI: 10.1039/b518232h

Table 1 Sonogashira alkynylation of **8** under various reaction conditions

Entry	Reaction conditions	Product % yield		
		9a	**11a**	**12**
1	$Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (3 mol%), Et_3N (3 equiv.), toluene, PhC≡CH (1.1 equiv.), 25 °C, 21 h	69	5	9
2	As for entry 1, in a glove-box (O_2 < 5 ppm; H_2O < 10 ppm)	68	10	5
3	As for entry 1, using 3 equiv. PhC≡CH	71	14	0
4	As for entry 3, in a glove-box	67	18	0
5	As for entry 1, 60 °C	55	0	17
6	As for entry 5, with no added CuI	37	0	16
7	$Pd(dba)_2$ (5 mol%), PPh_3 (10 mol%), CuI (3 mol%), Et_3N (3 equiv.), toluene, 25 °C, PhC≡CH (1.1 equiv.), 21 h[a]	34	7	5
8	As for entry 7, in a glove-box[b]	41	10	8
9	As for entry 7, 60 °C	0	19	48
10	As for entry 9, with no added CuI	0	0	45

[a] Compound **13a** was formed in 5% yield. [b] Compound **13a** was formed in 8% yield.



Scheme 1 Sonogashira coupling of 4,6-dichloro-2-pyrone **8**.

in Sonogashira cross-coupling (Fig. 3 and 4). The kinetics indicate that the reaction is first order with respect to **8**.

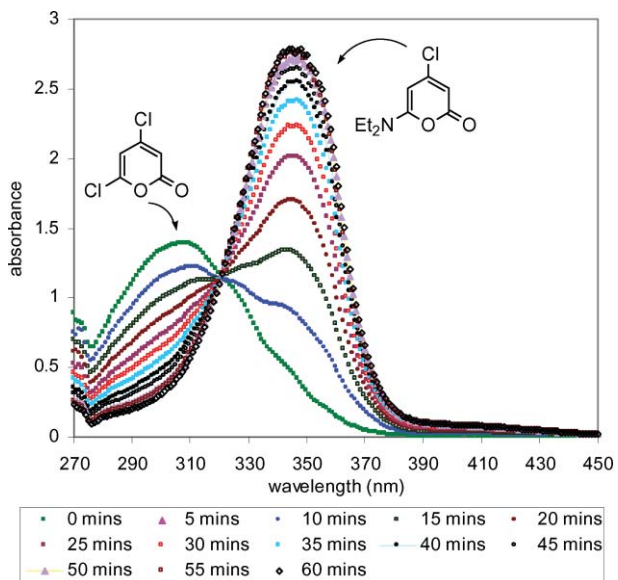


Fig. 3 Decay of **8** in a toluene–Et_3N (4%) solvent mixture as monitored by UV spectroscopy.

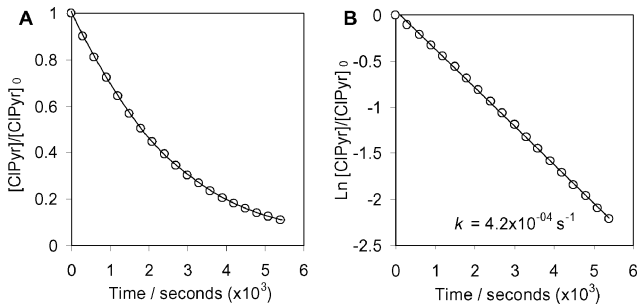


Fig. 4 Kinetics for the reaction of **8** (ClPyr) in a toluene–Et_3N (4%) solvent mixture.

Small quantities of **13a** (3–5%) were formed in all reactions using $Pd(PPh_3)_2Cl_2$ as a precatalyst.¶ This can be balanced against the pre-reduction of $Pd(PPh_3)_2Cl_2$ with copper(I) phenylacetylide to give the active catalyst $Pd(0)(PPh_3)_n$. The identical reaction conducted in a glove-box gave similar results (entry 2). The global yields of **9a** and **11a** were slightly higher in this latter reaction. In the presence of 3 equiv. of phenylacetylene, the yield of **9a** was 71%, with the yield of **11a** increasing to 14% (entry 3). The formation of **12** was not observed in this reaction. A similar distribution was seen in the identical reaction conducted in a glove-box (entry 4). At 60 °C, a lower yield of **9a** and higher yield of **12** was seen (entry 5). In the absence of CuI at 60 °C the reaction was less efficient (entry 6).

Alkynylation was also assessed using a palladium(0) source (entry 7). Thus, PPh_3 was added to $Pd(dba)_2$ to generate $Pd(PPh_3)_2$-η^2-dba *in situ* under identical conditions to the reaction employing $Pd(PPh_3)_2Cl_2$ (entry 1). The reaction was sluggish, with **9a** produced in 34% yield, with both **11a** and **12** observed. However, the formation of **13a** raised the possibility that hydrodechlorination was taking place or that adventitious O_2 was promoting oxidative dimerisation. To address the latter issue, the identical reaction was run in a glove-box (entry 8). The yield of **9a** was slightly improved, although **13a** increased to 8% yield. We were unable to detect 4-chloro-2-pyrone by GC–MS (a potential product of hydrodechlorination). Increasing the temperature to 60 °C increased the yield of **11a**, with **12** being the dominant product (entry 9). In the absence of CuI, **12** was produced exclusively (entry 10). It therefore appears that the dba ligand is non-innocent in these reactions. Intrigued by the extent of dba involvement, and the hydrodechlorination side-reaction, a stoichiometric reaction

of $Pd(PPh_3)$-η^2-dba with **8** in C_7D_8 (0.023 M) was monitored by ^{31}P NMR spectroscopy (Fig. 5), providing a snap-shot of the initial oxidative addition step in the catalytic cycle. The oxidative addition product, $Pd(PPh_3)$-η^2-dba and $Pd(PPh_3)_2Cl_2$ were all detected after 20 min at 25 °C. The formation of the latter complex, in part, accounts for the formation of **13a** under glove-box conditions using a palladium(0) precatalyst source.[20]

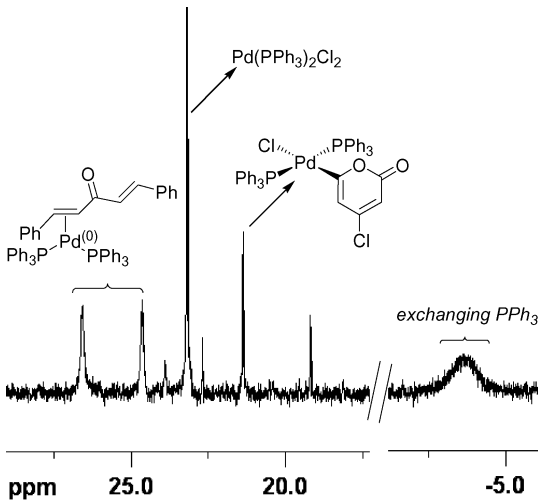
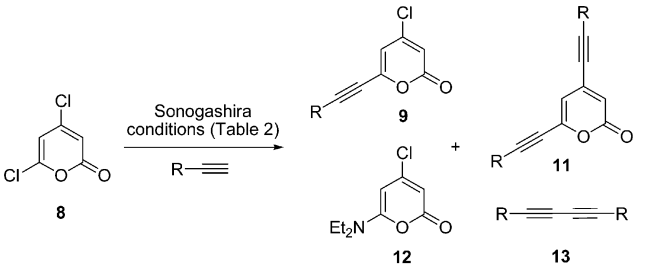


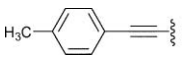
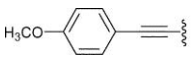
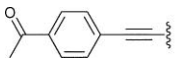
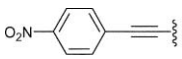
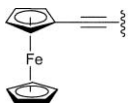
Fig. 5 Snap-shot of the reaction of $Pd(PPh_3)_2$-η^2-dba with **8** in C_7D_8 at 25 °C by ^{31}P NMR spectroscopy (202 MHz).

Using the best conditions (entry 1, Table 1), a series of other terminal alkynes was cross-coupled with **8** (Table 2), which in all cases were regioselective for the 6-position. 1-Pentyne and 1-hexyne reacted with **8** to give **9b** and **9c** in reasonable yields, respectively (entries 1 and 2). Trimethylsilylacetylene produced **9d** in better yield when used in excess with respect to **8** (entry 3). Several *para*-substituted aryl terminal alkenes reacted with **8** with varying success. For example, with 4-methoxyphenylacetylene the yield of the coupled product **9f** was 70% (entry 5), whereas 4-acetophenylacetylene gave the coupled product **9g** in 50% (entry 6). In the presence of excess terminal alkyne, the yield of the coupled product dropped substantially. Moreover, oxidative dimerisation was a serious side-product in this reaction, although somewhat curiously the background reaction (to give **12**) did not occur. 4-Nitrophenylacetylene gave the coupled product **9h** in poor yield (entry 7). However, the more hindered 1-ethynylferrocene reacted well with **8** to give the coupled product **9i** in very good yield (entry 8). It is of interest that these cross-coupled products exhibit fluorescence properties.[21]

Theoretical studies. Preliminary density functional theory calculations at the B3LYP level (see ESI† for the computational details and for Cartesian coordinates of the calculated structures) facilitate an understanding of the origin of the regioselectivity, which clearly derives from the oxidative addition step. Here, a PMe_3 ligand was employed to model the larger PPh_3 ligand. The oxidative addition leading to palladium(II) intermediate **I** is more favorable than **II**, both kinetically and thermodynamically (Fig. 6). Here, the α-oxygen appears to act like a π-donor ligand, stabilising the developing positive charge on the carbon in **TS-I**. The **TS-II** structure does not bear this additional stabilisation. We

Table 2 Sonogashira alkynylation of **8** with various terminal alkynes



Entry	Product (R =)	Conditions[a]	Product % yield 9	11	12	13
1	$CH_3(CH_2)_2C\equiv C-$ **9b**	**A**	47	0	21	—
		B	49	19	18	—
2	$CH_3(CH_2)_3C\equiv C-$ **9c**	**A**	67	3	3	—
		B	76	8	7	—
3	$TMSC\equiv C-$ **9d**	**A**	19	14	9	—
		B	53	14	9	—
4	 **9e**	**A**	48	0	4	—
		B	54	5	6	—
5	 **9f**	**A**	70	13	0	5
6	 **9g**	**A**	50	0	0	15
		B	20	14	0	31
7	 **9h**	**A**	35	15	0	4
8	 **9i**	**A**	75	5	0	5
		B	60	11	4	5

[a] **A**: $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (3 mol%), Et_3N (3 equiv.), toluene, RC≡CH (1.1 equiv.), 25 °C, 21 h; **B**: as for **A**, using 3 equiv. RC≡CH.

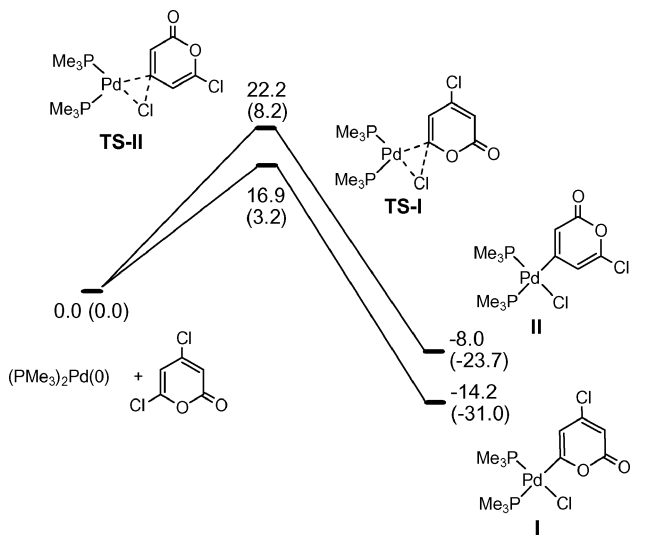


Fig. 6 Energy profiles for the two possible pathways in the oxidative addition of 4,6-dichloro-2-pyrone **8** with $(PMe_3)_2Pd(0)$. The relative free energies and reaction energies (in parentheses) are given in kcal mol^{-1}.

anticipate that this type of electron delocalisation also influences the reactivity of the carbon–palladium bond in **I**.

In summary, we have detailed reaction conditions that facilitate the rather tricky Sonogashira alkynylation of 4,6-dichloro-2-pyrone **8**. Side-reactions of **8** with Et_3N are a problem that can be suppressed by careful selection of the palladium catalyst/precatalyst source. The dba ligands from $Pd(dba)_2$ clearly hinder the cross-coupling reactions of **8**. This outcome appears to be more convoluted than the simple situation where dba ligates and lowers the concentration of $(PPh_3)_nPd(0)$ in the catalytic cycle,[22] and potentially hints at a secondary role for this ligand. The high regioselectivity seen at the 6-position in **8** shows that a certain degree of caution is required when using ^{13}C NMR chemical shifts to predict the reactivity of halogenated 2-pyrones. It is of particular note that cross-coupling at the 4-position in **8** is not observed. The fact that dialkynylation is possible suggests that the 4-chloro substituent is more activated in the mono-alkynylated products **9** relative to **8** (under the described reaction conditions). In due course, the biological effects and fluoresecence properties of the novel cross-coupled products will be reported.

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Notes and references

‡ Quantitative ^1H NOE (500 MHz) and ^1H–^{13}C HMBC experiments confirm the C6-substitution pattern. The regiochemistry was also confirmed by an independent synthesis of 6-(2-phenylethynyl)-2-pyrone;[9] the spectroscopic data for 4-(2-phenylethynyl)-2-pyrone[8] were used for comparison purposes.

§ *General procedure for Sonogashira cross-coupling*: to a degassed solution containing **8** (0.38 mmol, 1 equiv.) and the terminal acetylene (0.42 mmol, 1.1 equiv) in dry toluene (2 mL) under a nitrogen atmosphere, was added Et_3N (0.16 ml, 1.15 mmol, 3 equiv.), followed by $Pd(PPh_3)_2Cl_2$ (1.3 mg, 1.9 μmol, 5 mol%) and CuI (0.2 mg, 1.1 μmol, 3 mol%). The solution was allowed to stir for 21 h at 25 °C. After this time, the mixture was concentrated *in vacuo* and the resultant oil purified by column chromatography on silica-gel using hexane–ethyl acetate mixtures (9 : 1 to 7 : 3), which gave the cross-coupled products as crystalline solids or viscous oils. *Representative data*: 4-chloro-6-(phenylethynyl)-2-pyrone (**9a**) was isolated as a yellow crystalline solid. Mp 97–98 °C; δ_H (400 MHz, $CDCl_3$) 7.52 (m, 3H), 7.40 (m, 2H), 6.51 (d, 1H, ^4J = 1.7 Hz) 6.41 (d, 1H, ^4J = 1.7 Hz); δ_C (400 MHz, $CDCl_3$) 160.6, 144.3, 138.4, 132.0, 128.6, 121.0, 120.5, 117.5, 112.0, 95.9, 81.3; ν_{max} (CH_2Cl_2) 2210 (C≡C), 1728 (C=O), 1618 (C=C), 1531; LRCI *m/z* 231 (MH^+, 100), 248 ($M + NH_4^+$, 73); HRCI *m/z* exact mass calc. for $C_{13}H_{11}NO_2Cl$ ($M + NH_4^+$): 248.04785. Found: 248.04780. 4,6-Dichloro-2-pyrone (**8**) was prepared according to the procedure described by Afarinkia *et al.* in 65% yield as a pale white solid.[19] Mp 44–46 °C, lit. 43–45 °C; δ_H (400 MHz, $CDCl_3$) 6.31 (s, 2H); LRCI *m/z* 164 (M^+, 55), 129 ($M^+ - Cl$, 100). 4-Chloro-6-(*N*-diethylamino)-2-pyrone (**12**) was isolated as a viscous oil (see Tables 1 and 2 and text for yields); δ_H (400 MHz, $CDCl_3$) 5.45 (d, 1H, ^4J = 1.6 Hz), 5.18 (d, 1H, ^4J = 1.6 Hz), 3.39 (q, 4H, ^3J = 7.1 Hz), 1.23 (t, 6H, ^3J = 7.1 Hz); δ_C (100 MHz, $CDCl_3$) 160.6, 134.6, 127.7 93.6, 82.3, 42.7, 12.5; ν_{max} (CH_2Cl_2) 1726 (C=O), 1585 (C=C), 1531; LRCI *m/z* 202 (MH^+, 100), 218 ($M + NH_4^+$, 60); HRCI *m/z* exact mass calc. for $C_9H_{13}NO_2Cl$ (MH^+): 202.06348. Found: 202.06344. Further characterisation data can be found in the Electronic Supplementary Information.

¶ It was established that use of a catalyst system of either $Pd(OAc)_2/PPh_3$ (1 : 3) or $Pd(OAc)_2$, the so-called ligand-free conditions, proved ineffective in cross-coupling **8** with several terminal acetylenes under a variety of conditions (solvent, base and temperature, including changes in global Pd concentration).

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