Novel Heteroannulation through Copper Catalysis: a Highly Regio- and Stereoselective Synthesis of 2-Substituted 3,1-Benzoxathiinones

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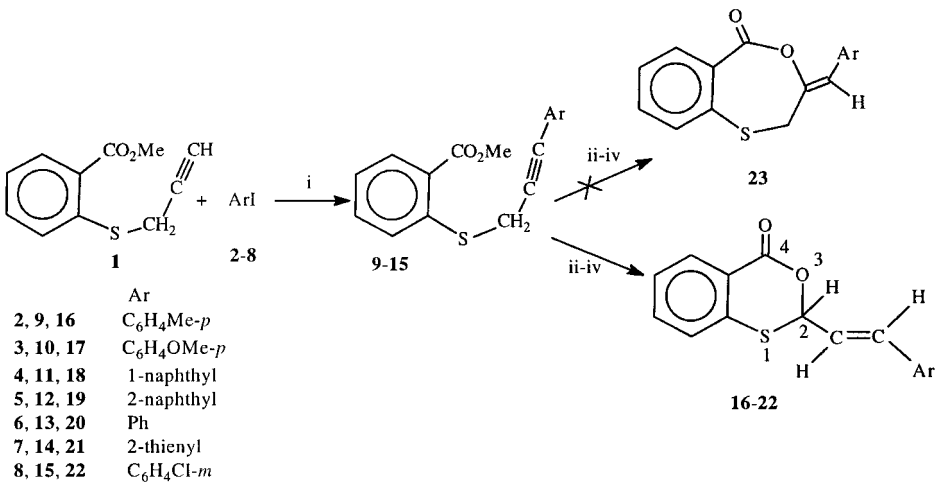
Abstract: A highly regio- and stereoselective method, comprising a cuprous iodide-catalysed cyclisation as a key step, gives an easy access to *(E)*-2-(2-arylvinyl)-3,1-benzoxathiin-4-ones **16-22**.

Key words: copper catalysis, 3,1-benzoxathiinones

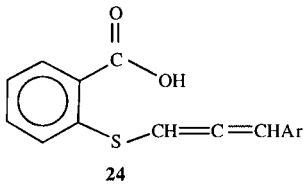
Palladium-catalysed reactions[1,2] have been of great significance in C-C bond formation and extensively used in the last few decades for carboannulation[3] and heteroannulation[4] processes. We have utilised the palladium-catalysed reactions of aryl halides with a nucleophilic group at the ortho-position and terminal alkynes to generate various benzofused heterocyclic structures.[5] In a different strategy, by using prop-2-ynyloxy or prop-2-ynylamino aromatic compounds with an ortho-nucleophilic group and aryl iodides under palladium-copper-catalysed conditions and subsequent cyclisation of the disubstituted alkynes generated, we could easily synthesise benzo-fused heterocyclic structures with two heteroatoms, e.g. substituted benzodioxans, [6a] benzoxazines,[6b] benzodioxepinones and benzoxazepinones.[6c] In continuation of these studies, we recently found that 3-(2-aminophenylthio)prop-1-yne could successfully be arylated with aryl iodides under palladium-copper catalysis to the corresponding disubstituted alkynes which, however, underwent a novel cyclisation with cuprous iodide to 2-substituted benzothiazolines.[7]

In order to explore further the scope of copper mediated cyclisation in the heteroannulation processes, we have recently reacted 3-(2-carbomethoxyphenylthio)prop-1-yne **1** with aryliodides **2-8** under palladium-copper catalysis to generate the disubstituted alkynes **9-15** in excellent yields (70-84%). The alkynes were then hydrolysed to the corresponding acids, which on cyclisation with cuprous iodide (20 mol%), Et_3N (2 equiv.) in THF under reflux for 24 hours yielded the *(E)*-2-(2-arylvinyl)-3,1-benzoxathiin-4-ones **16-22** in good yields (61-70%) instead of the expected 3-alkyl (aryl)idene-4,1-benzoxathiepin-5-ones **23**. No



	Ar
2, 9, 16	C_6H_4Me-*p*
3, 10, 17	C_6H_4OMe-*p*
4, 11, 18	1-naphthyl
5, 12, 19	2-naphthyl
6, 13, 20	Ph
7, 14, 21	2-thienyl
8, 15, 22	C_6H_4Cl-*m*

Reagents (i) $(PPh_3)_2PdCl_2$ (3.5 mol%); CuI (6 mol%); Et_3N; CH_3CN (ii) 5 mol dm^{-3} methanolic KOH (iii) HCl (1:1) (iv) CuI (20 mol%), Et_3N, THF.



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Scheme

Table Palladium-catalysed arylation of **1** and the subsequent copper-catalysed cyclisation leading to 2-(2-arylvinyl)-3,1-benzoxathiin-4-ones **16-22**

Entry	Aryliodides (Ar)	Disubstituted alkynes, **9-15**,[h] yield (%)	2-(2-Arylvinyl)-3,1-benzoxathiin-4-ones, **16-22**[h] yield (%)
1[a,b]	**2**	(77)	**16** (63)
2[a,c]	**2**	**9** (77)	-
3[a,d]	**2**	**9** (77)	**16** (25)
4[a,e]	**2**	**9** (77)	**16** (62)
5[a,f]	**2**	**9** (77)	**16** (37)
6[a,g]	**2**	**9** (77)	**16** (62)
7[a,b]	**3**	**10** (76)	**17** (70)
8[a,b]	**4**	**11** (75)	**18** (65)
9[a,b]	**5**	**12** (84)	**19** (68)
10[a,b]	**6**	**13** (77)	**20** (63)
11[a,b]	**7**	**14** (70)	**21** (61)
12[a,b]	**8**	**15** (78)	**22** (63)

[a]Typical reaction for arylation, e.g. synthesis of compound **9**. A mixture of *p*-iodotoluene (2.4 mmol) and 3-(2-carbomethoxyphenylthio)prop-1-yne **1** (2.4 mmol) was stirred with $(PPh_3)_2PdCl_2$ (0.08 mmol), CuI (0.14 mmol) and triethylamine (9.6 mmol) in acetonitrile (10 ml) at room temperature for 20 h in an argon atmosphere. After the removal of solvent and triethylamine, the residue was treated with water (5 ml) followed by extraction with $CHCl_3$ (3 × 20 ml). The organic layer was washed with water (5 ml), dried (anh. Na_2SO_4) and the crude product was purified by column chromatography on silica gel (60-120 mesh) with the eluent being $CHCl_3$/ light petroleum (60-80^{0}C) (1:1; v/v) to furnish **9** as a light yellow solid.

[b]Synthesis of 2-(2-arylvinyl)-3,1-benzoxathiin-4-ones, e.g. synthesis of compound **16**; the disubstituted alkyne **9** (1.0 mmol) was stirred with a methanolic solution of potassium hydroxide (5 mol dm^{-3}; 20 ml) at room temperature for 2 h. After the removal of methanol under reduced pressure, the residue was diluted with water (5 ml), acidified with dilute HCl (1:1) and extracted with diethyl ether (3 × 20 ml). The combined organic layer was washed with water (5 ml) and dried (anh. Na_2SO_4). The crude product obtained was then heated under reflux with CuI (0.2 mmol) and Et_3N (2.24 mmol) in THF (15 ml) in an argon atmosphere for 24 h. After removal of solvent and Et_3N, the residue was purified by column chromatography on silica gel (60-120 mesh) with the eluent being $CHCl_3$/light petroleum(60-80^{0}C) (1:1) to furnish **16** as a pale yellow solid.

[c]CuI (zero mol%), Et_3N (2 equiv.) in cyclisation step iv.

[d]CuI (10 mol%), Et_3N (2 equiv.).

[e]CuI (30 mol%), Et_3N (2 equiv.).

[f]CuI (40 mol%), Et_3N (2 equiv.).

[g]CuI (20 mol%), Et_3N (2.5 equiv.).

[h]Satisfactory spectroscopic data (IR and ^{1}H NMR) were obtained for all the compounds synthesised : typical data, **9**, mp 92 °C; IR ν_{max} 1705, 1585.4, 1566.1, 1508.2 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$)δ_H 2.3 (s, 1H, $ArCH_3$), 3.88 (s, 2H, S-CH_2), 3.9 (s, 3H, $COOCH_3$), 7.05 (d, 2H, *J* 8.1 Hz, ArH), 7.16-7.26 (m, 3H, ArH), 7.45-7.55 (m, 2H, ArH), 7.98 (d, 1H, *J* 7.5 Hz, 1.2 Hz, ArH). **16**, light yellow solid, mp 89 °C; IR ν_{max} 1728.1, 1589.2, 1512.2 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.35 (s, 3H, $ArCH_3$), 6.22 (d, 1H, J = 6.3 Hz, S-C*H*), 6.36 (dd, 1H, J_1 = 15.9 Hz, J_2 = 6.3 Hz, C*H*=CHAr), 6.92 (d, 1H, J = 15.9 Hz, CH=C*H*Ar), 7.16 (d, 2H, J = 7.8 Hz, Ar*H*), 7.31-7.37 (m, 4H, Ar*H*), 7.5 (td, 1H, J_1 = 9 Hz, J_2 = 1.2 Hz, Ar*H*), 8.2 (d, 1H, *J* 8.1 Hz, Ar*H*). Elemental analyses were satisfactory.

compounds of *(Z)*-configuration or 7-membered heterocycles were obtained. The structures were established from spectroscopic data [see under Table; compound **16**, δ_H 6.36 (dd, 1H, *J* 15.9 Hz, 6.3 Hz, C*H*=CHAr), 6.92 (d, 1H, *J* 15.9 Hz, CH=C*H*-Ar)]. Both cuprous iodide and triethylamine were found to be essential reagents needed for the cyclisation step. Absence of either of them did not yield any benzoxathiinones. Also, 20 mol% of CuI (entry 1) was found to be the optimum amount needed for the cyclisation. Any less or more amount of the catalyst led to decline in yields (entries 2-5). Similarly, 2 equivalents of Et_3N was found to be the optimum (entries 1 and 6) for the reaction.

Mechanistically, it appears that the disubstituted alkynes underwent rearrangement to the allenic intermediates[8] **24**. A nucleophilic attack by the carboxylate ion generated on the terminal carbon (next to the sulfur atom) of the allenic group[9] gives rise to the *(E)*-2-(2-arylvinyl)-3,1-benzoxathiin-4-ones **16-22**. Thus, we have described a very general and highly regio- and stereoselective procedure for the synthesis of 2-substituted-3,1-benzoxathiin-4-ones. In the literature[10] only a few methods are available for the synthesis of these interesting heterocyclic structures. Also, 2-(2-arylvinyl)-3,1-benzoxathiinones are of potential biological interest (e.g. as possible enzyme inhibitors) because of the presence of various active functionalities (e.g. vinyl, lactone and sulfur moieties) in the molecular domain. Thus, we believe the procedure we have described will be of considerable interest to many organic and medicinal chemists.

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(8) Allenic intermediates **24** were formed in all cases due to alkaline hydrolysis of **9-15**. The crude allenes were used for cyclisation to benzoxathiinones **16-12**. An allenic compound **24** (Ar = 2-naphthyl) was isolated and characterised fully from the alkaline hydrolysis of **12**, mp 154 °C. IR. (KBr) ν_{max} 1932.5, 1678, 1596.9, 1585.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.49(d, 1H, J = 6 Hz, S-C*H*=C=CH), 6.62 (d, 1H, J = 6Hz, S-CH=C=C*H*) 7.24 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz,Ar*H*), 7.44-7.53 (m, 4H, Ar*H*), 7.66-7.71 (m, 2H, Ar*H*), 7.77-7.81 (m, 3H, Ar*H*), 8.08(dd, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 89.59, 97.98, 124.99, 125.24, 126.44, 126.76, 126.9, 127.02, 127.99, 128.1, 128.17, 128.78, 130.69, 132.16, 132.78, 133.27, 133.89,, 141.57, 168.67, 209.36. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ_C 89.3, 97.69, 124.7, 124.95, 126.15, 126.47, 126.61, 126.72, 127.81, 127.88, 128.5, 131.87, 132.5

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