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Heteroannulation through copper catalysis: a novel and highly regio- and stereoselective cyclisation of alkynes leading to (*E*)-2-(2-arylvinyl)quinazolinones

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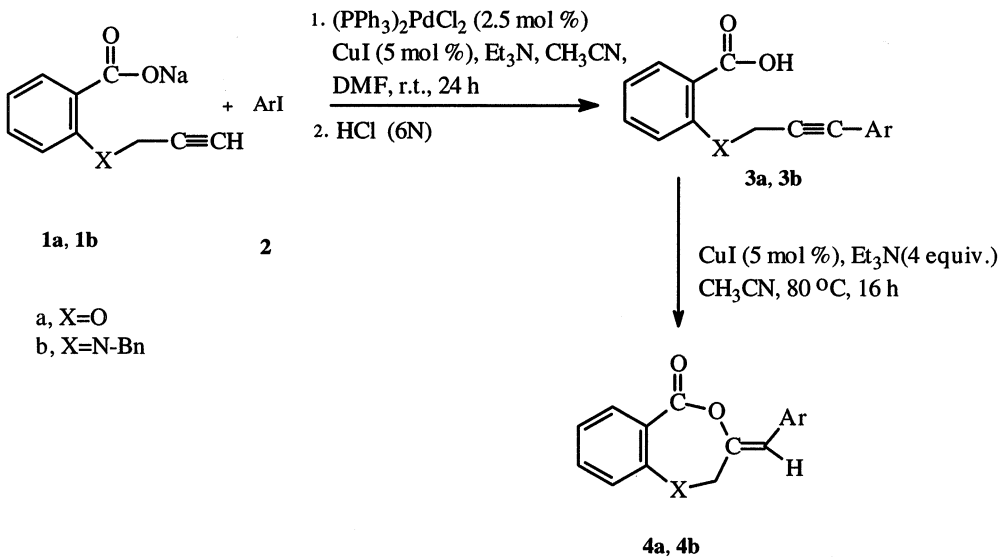
Abstract—2-[*N*-Alkyl(benzyl)-*N*-(prop-2′-ynyl)]aminobenzamides **5** reacted with aryl iodides **2** under palladium–copper catalysis to yield disubstituted alkynes **6**–**13**, which underwent a novel cyclisation in the presence of CuI, K_2CO_3, *n*-Bu_4NBr in acetonitrile to yield (*E*)-1-alkyl(benzyl)-3-aryl-2-(2-arylvinyl) quinazolin-4-ones **14**–**21** in excellent yields instead of the expected benzodiazepinones **22**.

Palladium-catalysed heteroannulation reactions have been of remarkable importance in developing heterocyclic structures.[1] We have shown that terminal alkynes could be utilised for palladium-catalysed heteroannulation leading to various benzofused heterocycles, e.g. benzofurans,[2] phthalides,[3] quinolines and quinolones,[4] benzodioxans,[5] isoindolinones,[6] benzoxazines,[7] and flavanones.[8] Recently, we reported[9] a highly regio- and stereoselective synthesis of (*Z*)-3-arylidene-2,3-dihydro-5*H*-1,4-benzodioxepin-5-ones **4a** and (*Z*)-3-arylidene-2,3-dihydro-5*H*-4,1-benzoxazepin-5-ones **4b** through palladium–copper catalysed reactions, where in the final step a copper-catalysed *exo*-dig attack by a carboxylate anion on the disubstituted alkynes took place (Scheme 1).

In continuation of those studies, we became interested in developing other heterocyclic structures containing



Scheme 1.

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two heteroatoms through copper-catalysed cyclisation of disubstituted alkynes, and in this letter we report our results in this area. 2-[*N*-Benzyl(methyl)-*N*-(prop-2′-ynyl)]aminobenzamide **5** reacted with aryl iodides **2** in the presence of bis(triphenylphosphine)palladium chloride as a catalyst, cuprous iodide as a co-catalyst and triethylamine as a base in acetonitrile at room temperature for 16 hours leading to the disubstituted alkynes (**6**–**13**).[10] The disubstituted alkynes could then be cyclised with CuI (20 mol%), K_2CO_3, *n*-Bu_4NBr in CH_3CN at 80°C for 24 hours. Surprisingly, however, we observed that instead of the expected benzodiazepinones **22**, generated by an *exo*-dig nucleophilic attack on the alkynes (**6**–**13**), the quinazolinones (**14**–**21**) (presumably arising from a novel alkyne–allene rearrangement and nucleophilic attack on the terminal carbon of the allene intermediate) were obtained in good yields (Table 1). Both CuI and *n*-Bu_4NBr were needed for the success of the cyclisation reaction.[11] The CuI method of cyclisation was found to be highly regio- and stereoselective yielding the quinazolinones predominantly having *E*-stereochemistry around the vinylic group.

The structure of the quinazolinones follow from their ^1H and ^{13}C NMR spectra.[12] A typical reaction procedure is as follows: a mixture of 2-iodothiophene (136 mg, 0.65 mmol), $(Ph_3P)_2PdCl_2$ (11 mg, 0.016 mmol), CuI (6 mg, 0.03 mmol) and triethylamine (330 mg, 3.25 mmol) was stirred in acetonitrile (9 ml) at rt for 30 min under an argon atmosphere. The acetylenic compound **5a** (180 mg, 0.65 mmol) dissolved in acetonitrile (3 ml) was added slowly and the reaction mixture was allowed to stir at room temperature for 16 h. After removal of solvent under reduced pressure, the residue was worked-up with chloroform (50 ml) and water (3×25 ml). The residue obtained after removal of chloroform was then purified by column chromatography on silica gel (60–120 mesh) using chloroform–light petroleum (60–80°C) (3:1) as eluent to yield the disubstituted alkyne **7** (175 mg) in 75% yield. A mixture of the above disubstituted alkyne (130 mg, 0.36 mmol), CuI (14 mg, 0.07 mmol), K_2CO_3 (125 mg, 0.90 mmol) and *n*-Bu_4NBr (116 mg, 0.36 mmol) in acetonitrile (9 ml) was refluxed for 24 h under an argon atmosphere. After removal of solvent under reduced pressure, the residue was worked-up with chloroform (40 ml) and water (3×25 ml). The residue obtained from the chloroform layer was then purified by column chromatography on neutral alumina using chloroform–light petroleum (60–80°C) (3:1) as eluent: the quinazolinone **15** (80 mg, 61%) was obtained as a colourless solid, mp 198–199°C.

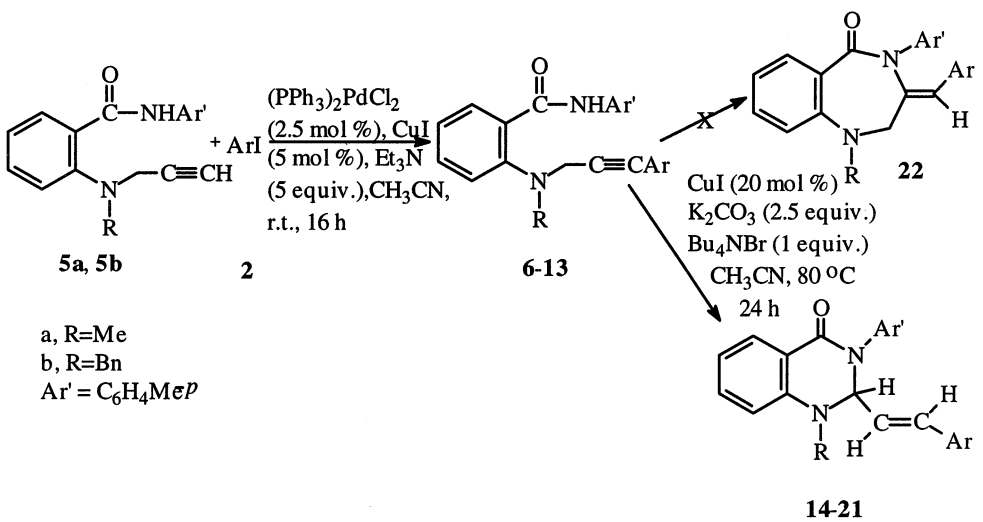
Table 1. Copper-catalysed cyclisation of disubstituted alkynes (**6**–**13**) to quinazolinones (**14**–**21**) (Scheme 2)

Entry	N–R	Aryl iodides (Ar) **2**	Disubstituted alkynes[c] (%)[a] **6**–**13**	Quinazolinones[c] (%)[b] **14**–**21**
1	Me (**5a**)	C_6H_4Me-*o* (**2a**)	**6** (76)	**14** (67)
2	Me (**5a**)	2-Thienyl (**2b**)	**7** (75)	**15** (61)
3	Me (**5a**)	2,4-Dimethoxy pyrimidin-5-yl (**2c**)	**8** (79)	**16** (65)
4	Me (**5a**)	$C_6H_4CO_2Me$-*o* (**2d**)	**9** (90)	**17** (69)
5	Bn (**5b**)	C_6H_4Me-*o* (**2a**)	**10** (72)	**18** (63)
6	Bn (**5b**)	2-Thienyl (**2b**)	**11** (73)	**19** (67)
7	Bn (**5b**)	2,4-Dimethoxy pyrimidin-5-yl (**2c**)	**12** (91)	**20** (62)
8	Bn (**5b**)	$C_6H_4CO_2Me$-*o* (**2d**)	**13** (89)	**21** (61)

[a] Yields are based on **2**.

[b] Yields are based on the corresponding disubstituted alkynes.

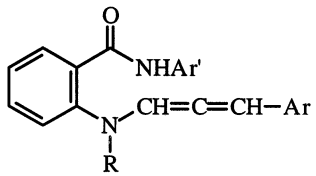
[c] All new compounds have been fully characterised by IR, ^1H, ^{13}C NMR and elemental analyses.



Scheme 2.

The mechanism of the reaction can be envisaged to involve the following steps: (a) The conversion of **5** (through its copper-salt) to **6–13** through Sonogashira–Hagihara coupling is well established;[13] (b) a rearrangement of **6–13** to allene intermediates (**A**) took place involving alkyne–allene rearrangement in the propargyl group attached to the nitrogen atom;[14] (c) subsequent nucleophilic attack by the amide nitrogen on the terminal carbon (next to the *N*-atom) of the allenes would result in the quinazolinones **14–21**.

Structure of Intermediate **A**



Thus, we have described a very interesting and useful procedure for the conversion of a substituted terminal alkyne through palladium-catalysed reactions and subsequent copper-catalysed cyclisation to quinazoline derivatives. The method is very mild, requires inexpensive starting materials and reagents and is very easy to operate. We believe this is the first reported synthesis of quinazolines through copper-catalysed cyclisation. Since quinazolines are of wide natural occurrence[15] and of great biological importance,[16] our method will constitute a general and important method for the synthesis of substituted quinazoline derivatives.

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10. Both bis(triphenylphosphine)palladium(II) chloride and CuI were found to be essential for the *C*-arylation reaction.
11. 20 mol% of CuI was found to be the optimum needed for the cyclisation reaction.
12. Typical ^{1}H NMR data for compound **15** (300 MHz, $CDCl_3$, TMS): 2.35 (3H, s, $ArCH_3$), 2.94 (3H, s, -NCH_3), 5.13 (1H, d, $J=7.8$ Hz, N_2CH), 6.18 (1H, dd, $J_1=7.8$ Hz, $J_2=15.6$ Hz, -CH=CAr), 6.57 (1H, d, $J=15.6$ Hz, =CHAr), 6.67 (1H, d, $J=8.1$ Hz, ArH), 6.89–6.93 (3H, m, ArH), 7.15–7.28 (5H, m, ArH), 7.40–7.43 (1H, m, ArH), 8.05 (1H, dd, $J_1=1.8$ Hz, $J_2=7.8$ Hz, ArH). ^{13}C NMR (75 MHz $CDCl_3$, TMS): δ 21.52, 36.06, 81.52, 112.91, 117.62, 119.19, 122.56, 125.78, 127.22, 127.56, 127.63, 127.90, 129.77, 130.26, 134.43, 137.42, 138.52, 140.71, 147.23, 162.63. DEPT (75 MHz, $CDCl_3$, TMS): δ 21.23, 35.77, 81.23, 112.62, 118.90, 122.27, 125.49, 126.93, 127.27, 127.35, 127.62, 129.48, 129.97, 134.14. IR (KBr): ν_{max} 1647, 1632, 1605 cm^{-1}. Calcd for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77%. Found: C, 73.16; H, 5.68; N, 7.97%.
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