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Heteroannulation through copper catalysis: a novel cyclisation leading to an unusual formation of 2-aroylquinoxalines

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Abstract

N-[(3′-Aryl)prop-2′-ynyl]-*N*,*N*′-1,2-phenylene di-*p*-tosylamides, **15**–**22**, underwent an unusual ring closure with potassium carbonate (2 equiv.) and copper(I) iodide (10 mol%) in DMF at 100°C for 24 h to yield 2-aroylquinoxalines (**23**–**30**) instead of the expected 2-alkylidene-1,4-di-tosyl-1,2,3,4-tetrahydroquinoxalines (**31**).

Keywords: copper catalysis; quinoxalines.

Palladium-catalysed reactions[1] have been of great significance in carboannulation[2] and heteroannulation[3] processes. Our own efforts in this area have been the use of terminal alkynes under palladium–copper catalysis[4] to generate a number of heterocyclic structures, e.g. benzofurans,[5] phthalides,[6] quinolines,[7] isoindolinones,[8] flavanones,[9] benzodioxanes,[10] benzoxazines,[11] benzodioxepines[12] and benzoxazepines,[12] which usually follow the expected cyclisation processes. Recently, however, we reported some unusual reactions where 2-substituted benzothiazolines (**3**) were formed from 3-(2-aminophenylthio)prop-1-yne (**1**) due to the use of excess copper(I) iodide in the cyclisation step (Scheme 1a).[13] Similarly the use of excess CuI in the arylation step of the terminal alkynes (**4**) together with the palladium catalyst led to novel depropargylation and *S*-arylation reactions leading to diaryl sulfides[14] (**5**) (Scheme 1b).

In the present letter we report some unusual reactions during cyclisation of alkynes under copper catalysis. The terminal alkyne (**6**) underwent the usual *C*-arylation reaction with aryl iodides (**7**–**14**) in the presence of $(PPh_3)_2PdCl_2$ (3 mol%), CuI (8 mol%), triethylamine (5 mmol) in acetonitrile at room temperature for 24 h to yield the disubstituted alkynes (**15**–**22**) in moderate to good yields. These were then cyclised with CuI (10 mol%) in the presence of K_2CO_3

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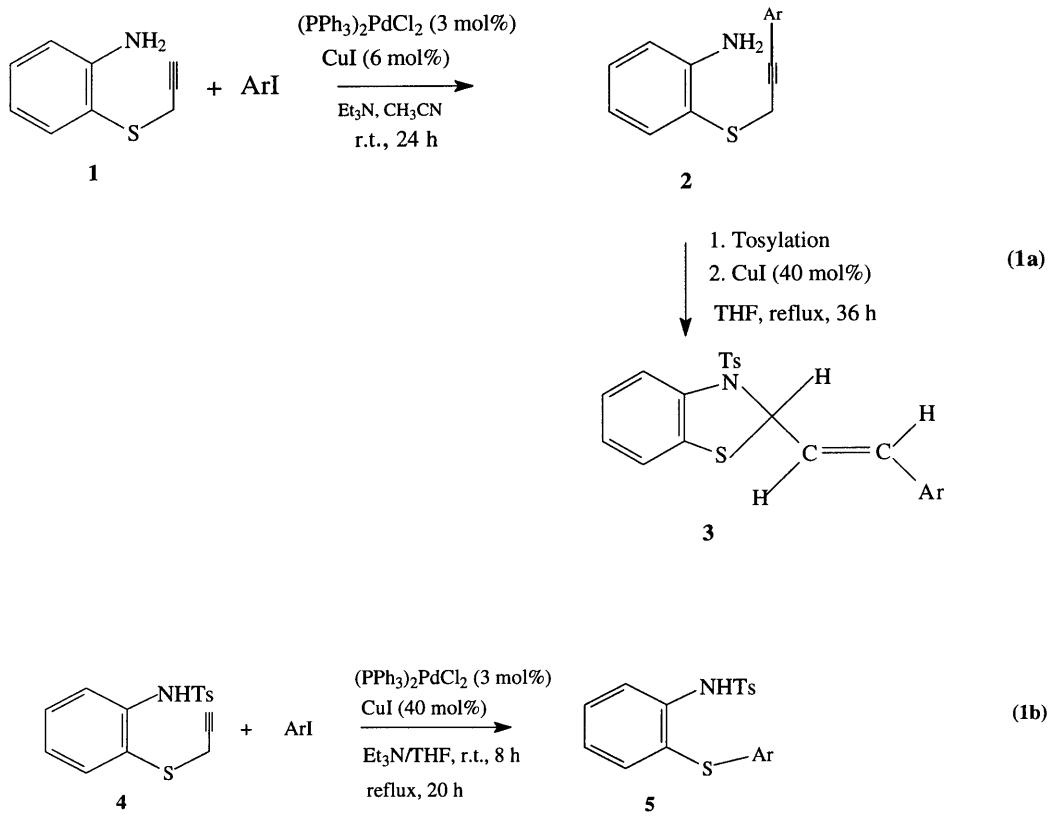
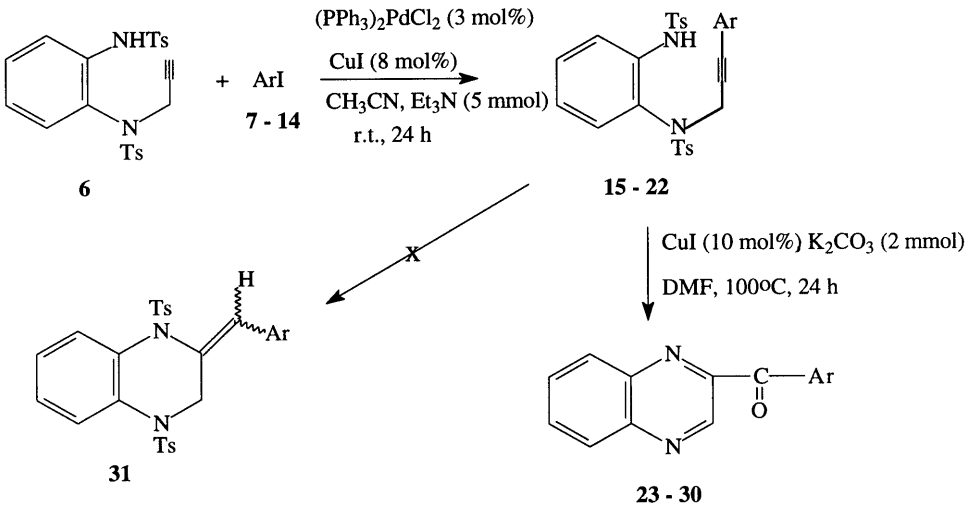


Scheme 1.

in DMF by heating at 100°C for 24 h. But interestingly, instead of the expected 2-alkylidene-1,2,3,4-tetrahydroquinoxaline **31**, the 2-aroylquinoxalines (**23**–**30**) were formed in good yields (Scheme 2, Table 1).



Scheme 2.

Table 1
Synthesis of 2-aroyl quinoxalines (**23**–**30**) through copper-catalysed reactions (Scheme 2)

Entry	Aryl iodides (Ar)	Disubstituted alkynes (%)[a]	2-Aroyl quinoxalines (%)[b]
1	Phenyl (**7**)	**15** (43)	**23** (46)
2	1-Naphthyl (**8**)	**16** (59)	**24** (44)
3	C_6H_4Cl-*m* (**9**)	**17** (60)	**25** (60)
4	C_6H_4Me-*p* (**10**)	**18** (60)	**26** (53)
5	C_6H_4Me-*o* (**11**)	**19** (55)	**27** (50)
6	C_6H_4OMe-*p* (**12**)	**20** (41)	**28** (40)
7	C_6H_4OMe-*o* (**13**)	**21** (52)	**29** (49)
8	2-Thienyl (**14**)	**22** (65)	**30** (45)

[a] Yields are based on **6**.
[b] Yields are based on the corresponding disubstituted alkynes.

The palladium-catalysed reactions of the terminal alkyne **6** leading to the disubstituted alkynes (**15**–**22**) needed both bistriphenylphosphine palladium(II) chloride as the catalyst and CuI as the co-catalyst. The absence of either of them did not lead to the products. However, in the cyclisation process yielding the 2-aroylquinoxalines (**23**–**30**), only CuI was needed and was found to be essential. The absence of CuI did not give any cyclic product. Similarly, K_2CO_3 was found to be essential for the reaction. Its replacement with Et_3N failed to yield the cyclic products (**23**–**30**). All the products were characterised by C,H,N analysis, and IR, UV and NMR data.[15,16] *Typical experimental condition are as follows*: ArI (1.5 mmol), $(PPh_3)_2PdCl_2$ (3 mol%), CuI (8 mol%) and Et_3N (5 mmol) were stirred in acetonitrile (5 ml) for 1 h, compound **6** (1 mmol) was added and the mixture was stirred at rt for 24 h. After removal of solvent at low pressure, the residue was extracted with chloroform (3×50 ml), washed with water (3×50 ml) and dried over Na_2SO_4. After removal of the solvent and chromatographic purification on neutral alumina (25% ethyl acetate in light petroleum, bp 60–80°C as the eluent), the disubstituted alkynes (**15**–**22**) were obtained as solids.

*Synthesis of 2-aroylquinoxalines (**23**–**30**)*: The disubstituted alkynes (**15**–**22**) (1 mmol) were dissolved in DMF (5 ml) and stirred with anhydrous K_2CO_3 (2 mmol) for 3–4 h to form the salts. CuI (10 mol%) was then added and the mixture was further stirred at rt for 1 h and then heated at 100°C for 24 h. DMF was removed under low pressure and the residue in $CHCl_3$ (3×50 ml) was washed with H_2O (3×50 ml), dried over Na_2SO_4 and solvent removed. The crude product was purified by column chromatography on neutral alumina (10% ethylacetate in light petroleum, bp 60–80°C as the eluent) to yield the 2-aroylquinoxalines (**23**–**30**) as solids, which were further purified by crystallisation from ethanol.

In conclusion, we describe a novel cyclisation procedure under copper catalysis where instead of the expected 2-alkylidene-1,2,3,4-tetrahydroquinoxalines a number of 2-aroylquinoxalines were formed in good to excellent yields. Although a number of classical methods[17] are available for the synthesis of quinoxalines, we believe ours is the first successful and efficient copper-catalysed procedure for the synthesis of 2-substituted quinoxalines under relatively mild conditions. Also, since the quinoxalines are of immense biological significance,[18] the procedure described here could be of great value to many investigators active in this area.

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15. For compound **17**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.37 (3H, s, Ar–CH_3), 2.39 (3H, s, Ar–CH_3), 3.48 (1H, d, $J=18$ Hz, H_a of CH_2), 4.58 (1H, d, $J=18$ Hz, H_b of CH_2), 6.84–7.88 (17H, m, Ar–H and NH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.94, 22.01, 42.46, 84.44, 85.07, 122.96, 137.26, 144.32,145.02; DEPT-135: δ 42.18 (inverted-CH_2); IR (KBr): ν_{max} 3273, 1598, 1500; UV (chloroform) λ_{max} 244 nm ($\log \varepsilon = 4.468$). Anal calcd for $C_{29}H_{25}N_2S_2O_4Cl$: C, 61.65; H, 4.42; N, 4.96. Found: C, 61.47; H 4.61; N, 4.76%.
For compound **25**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–8.26 (8H, m, Ar–H), 9.51 (1H, s, Ar–C_3–H); ^{13}C NMR ($CDCl_3$ 75.5 MHz): δ 129.81–148.3, 191.32; DEPT-135: absence of 191.32; mass spectra: m/z 270, 268 (M^+), 240, 233, 205, 139, 111, 102, 75, 51; IR (KBr) ν_{max} 1670, 1590, 1567; UV (ethanol): λ_{max} 253 ($\log \varepsilon = 4.385$), 309 ($\log \varepsilon = 4.442$) nm; anal calcd for $C_{15}H_9N_2OCl$: C, 67.03; H, 3.35; N, 10.42. Found: C, 67.26; H, 3.53; N, 10.38%.
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