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Heteroannulation through Copper Catalysis: A Novel Cyclization Leading to a Highly Regio- and Stereoselective Synthesis of 2-Substituted Benzothiazolines†

Bidisha Nandi and Nitya G. Kundu*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700032, India

ocngk@mahendra.iacs.res.in

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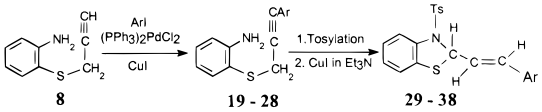
ABSTRACT



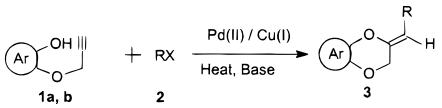
3-(2-Aminophenylthio)prop-1-yne 8 reacted with aryl iodides 9–18 under palladium–copper catalysis leading to the disubstituted alkynes 19–28 which after tosylation underwent a novel cyclization under copper catalysis to 2-substituted benzothiazolines 29–38. The expected 3-(arylidine)-2,3-dihydrobenzothiazines were not obtained.

Palladium-catalyzed reactions[1] have been of immense interest for both carboannulation[2] and heteroannulation processes.[3] Our own interest in this area has been in the use of terminal alkynes under palladium−copper catalysis to generate benzofused heterocyclic structures, with one heteroatom only, e.g. benzofurans,[4a] phthalides,[4b] quinolines,[4c] isoindolines,[4d] and isobenzofurans,[4e] structures which are an integral part of many naturally occurring and biologically active compounds.[5]

Subsequently, we have developed a variation of the above procedure to synthesize benzofused heterocyclic structures with two heteroatoms which would be of biological interest (Schemes 1 and 2).[6,7]

In continuation of those studies we felt that 3-(2-aminophenylthio)prop-1-yne **8** would react with aryl iodides

Scheme 1. Synthesis of (*Z*)-2-(Arylidene)-2,3-dihydro-1,4-benzodioxin and (*Z*)-2-(Arylidene)-2,3-dihydronaphtho[2,3-*b*]dioxin



1a, Ar = Phenyl
1b, Ar = Naphthyl
R = Aryl, Heteroaryl and Alkenyl

† This paper is dedicated to late Professor Phanindra Chandra Dutta, Head (1951−1977), Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700032, India, on the occasion of the Golden Jubilee Celebration of the department in January 2000.

(1) For general references, see: (a) Heck, R. F. *Org. React*. **1982**, *27*, 345. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*, Academic Press: London, 1985. (c) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev*. **1989**, *89*, 1433. (d) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.

(2) For selective references on carboannulation, see: (a) Ihle, N. C.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 560. (b) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. (c) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; McPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255. (d) Ma, S.; Negishi, E.-i. *J. Am. Chem. Soc.* **1995**, *117*, 6345. (e) Tietze, L. F.; Nobel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971.

(3) For selective references on heteroannulation, see: (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581. (b) Negishi, E.-i.; Coperet, C.; Ma, S.; Lion, S.-Y.; Lire, F. *Chem. Rev.* **1996**, *96*, 365. (c) Bouyssi, D.; Caviechioli, M.; Balme, G. *Synlett* **1997**, 944. (d) Roesch, K. R.; Larock, R. C. *J. Org. Chem*. **1998**, *63*, 5306. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem*.**1998**, *63*, 7652. Larock, R. C.; Han, X. *J. Org. Chem*. **1999**, *64*, 1875. Roesch, K. R.; Larock, R. C. *Org. Lett*. **1999**, *4*, 553. Larock, R. C. *J. Organomet. Chem*. **1999**, *576*, 111.

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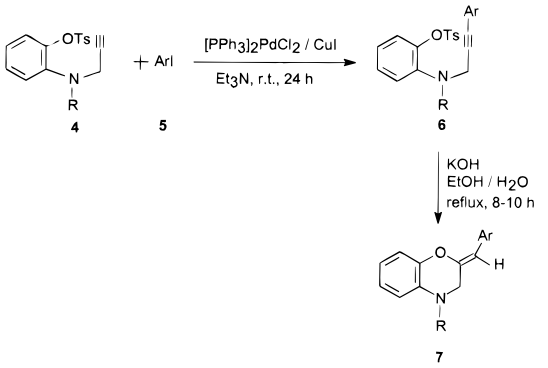
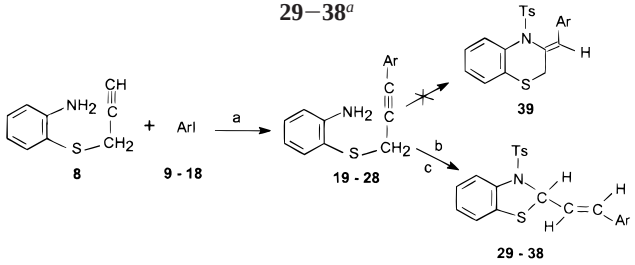
Scheme 2. Synthesis of (*Z*)-*N*-Aryl-2-arylidene-2,3-dihydrobenzo-1,4-oxazines



9−**18** under palladium−copper catalysis and subsequent cyclization would lead to 3-(arylidene)-2,3-dihydrobenzothiazines **39**. However, we found that the terminal alkyne **8** indeed reacted with the aryl iodides **9**−**18** to yield the disubstituted alkynes **19**−**28** which, however, in the form of the tosylates underwent a novel cyclization with cuprous iodide in triethylamine to 2-styryl-*N*-tosylbenzothiazolines **29**−**38** rather than to the expected 3-(arylidene)-2,3-dihydrobenzothiazines **39** (Scheme 3).

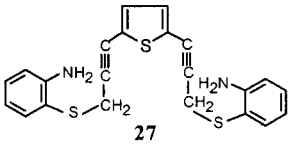
Scheme 3. Synthesis of 2-Styryl-*N*-tosylbenzothiazolines **29**−**38**[a]



[a] Reagents and conditions: (a) $(PPh_3)_2PdCl_2$ (3 mol %), CuI (6 mol %), Et_3N, CH_3CN, room temperature, 24 h; (b) *p*-TsCl, py, CH_2Cl_2, room temperature, 10 h; (c) CuI (40 mol %), Et_3N, THF, reflux, 36 h.

The reaction of aryl iodides **9**−**18** with alkyne **8** was carried out under very mild conditions by stirring the mixture at room temperature (25−30 °C) for 24 h in the presence of $(PPh_3)_2PdCl_2$ (3 mol %), CuI (6 mol %), and triethylamine-(4 equiv) in acetonitrile as solvent.[8] Bis-triphenylphosphine palladium chloride was found to be the catalyst of choice whereas cuprous iodide was found to be an essential cocatalyst. Carrying out the reaction in acetonitrile in the presence of triethylamine as a base gave the optimum yields (59−80%) (see Table 1) and reactions that were independent

Table 1. Reaction of 3-(2-Aminophenylthio)prop-1-yne **8** with Aryl Iodides **9**−**18** under Palladium−Copper Catalysis To Yield the Disubstituted Alkynes **19**−**28** (Scheme 3)

Entry	Aryl Iodides (ArI) (Ar)	Disubstituted Alkynes	Yield (%)
1	C_6H_5, **9**	**19**	73
2	1-naphthyl, **10**	**20**	68
3	3-ClC_6H_4, **11**	**21**	78
4	2-MeC_6H_4, **12**	**22**	77
5	4-MeC_6H_4,**13**	**23**	76
6	4-$MeOC_6H_4$, **14**	**24**	69
7	2-$MeOCOC_6H_4$, **15**	**25**	80
8	2-thienyl, **16**	**26**	71
9	5-iodo-2-thienyl, **17**	 **27**	59
10	2,4-dimethoxy pyrimidin-5-yl, **18**	**28**	73

of substitution on the aryl iodides. When 2,5-diiodothiophene **17** was used, the dialkynyl thiophene **27** was also obtained in good yield.

In contrast to our observations on the synthesis of 2-arylidene-2,3-dihydrobenzodioxins **3**, where palladium-catalyzed reactions and cyclization leading to the benzodioxins took place in a single step (Scheme 1), the cyclization of the disubstituted alkynes **19**−**28** did not take place in a single step under palladium−copper catalysis. We observed that the free amines **19**−**28** did not cyclize under various conditions. However, the corresponding tosylates could be cyclized with cuprous iodide (40 mol %) in the presence of triethylamine in tetrahydrofuran with a 36 h reflux.[9] As we have mentioned, cyclization did not lead to the expected benzothiazines **39** but surprisingly to the 2-substituted

(4) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 41. Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2815. (b) Kundu, N. G.; Pal, M. *J. Chem. Soc. Chem. Commun*. **1993**, 86. Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561. (c) Kundu, N. G.; Mahanty, J. S.; Das, P.; Das, B. *Tetrahedron Lett*. **1993**, *34*, 1625. Mahanty, J. S.; De, M.; Das, P.; Kundu, N. G. *Tetrahedron* ***1997***, *53*, 13397. (d) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435. (e) Khan, M. W.; Kundu, N. G. *Synlett* **1999**, 435.

(5) For references on naturally occurring and biologically active benzofurans, phthalides, quinolines, isoindolinones, and isobenzofurans, see references cited in 4a−e.

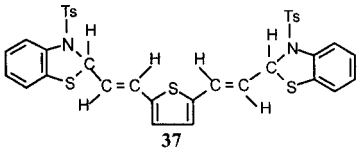
(6) Chowdhury, C.; Kundu, N. G. *Chem. Commun* **1996**, 1067. Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863.

(7) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, *11*, 1273.

(8) When the tosylate of **8** was used under similar conditions or with excess CuI (40 mol %), neither disubstituted alkynes **19**−**28** nor cyclic products **29**−**38** could be obtained.

(9) The use of less CuI led to lower yields—for example with **19**, use of 6 mol % of CuI gave 10% yield, similarly 20 mol % gave 30% yield, 30 mol % gave 45% yield, and 40 mol % gave 67% yield of **29**. Higher percentages of CuI led to a decline in yield. Also, the use of KOH in the cyclization step did not give any cyclic product, with the detosylated amines being recovered.

Table 2. Copper-Catalyzed Cyclization of the Tosylates of the Disubstituted Alkynes **19**−**28** to the 2-Substituted Benzothiazolines **29**−**38** (Scheme 3)

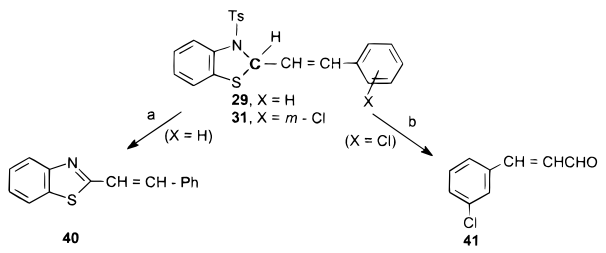
Entry	Tosylates of the Disubstituted Alkynes (Ar)	2-Styryl-N-tosyl benzothiazolines (29-38)	Yield(%)
1	C_6H_5, **19**	**29**	67
2	1-naphthyl, **20**	**30**	63
3	3-ClC_6H_4, **21**	**31**	76
4	2-MeC_6H_4, **22**	**32**	69
5	4-MeC_6H_4, **23**	**33**	80
6	4-$MeOC_6H_4$, **24**	**34**	66
7	2-MeOCO-C_6H_4,**25**	**35**	70
8	2-thienyl, **26**	**36**	75
9	5-iodo-2-thienyl, **27**	 **37**	76
10	2,4-dimethoxy pyrimidin-5-yl, **28**	**38**	80

benzothiazolines **29**−**38** in fairly good yields (Table 2). The structures of the benzothiazolines **29**−**38** follow from their analytical and spectroscopic data.[10] The presence of two vinylic hydrogens at δ 6.25 and 6.69 (J = 15 Hz) indicated the *E*-configuration of the double bond.

Additional evidences regarding the structures of the benzothiazolines follow (i) from the conversion of 2-styryl-*N*-tosylbenzothiazoline **29** to 2-styrylbenzothiazole **40**[11] (74%) by treatment with potassium *tert*-butoxide in DMF and (ii) from the conversion of 2-(*m*-chlorostyryl) benzothiazoline **31** to *m*-chlorocinnamaldehyde **41** (73%) by treatment with silver nitrate in Et_3N−phosphate buffer according to the procedure of Corey and Boger[12] (Scheme 4) and (iii) also from X-ray diffraction studies on **30**.[13]

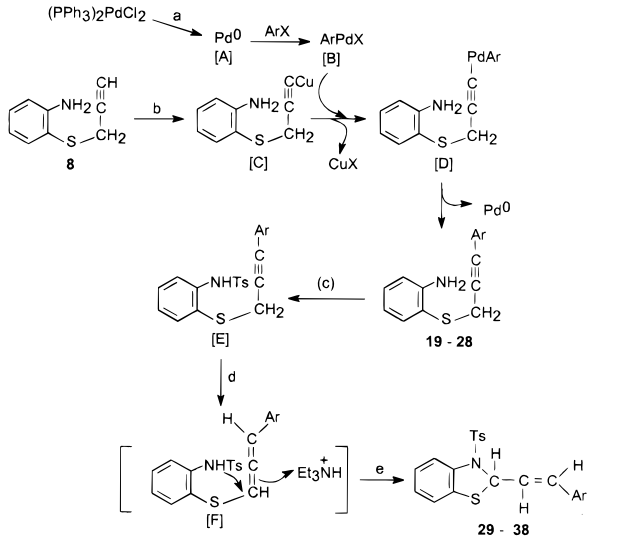
Mechanistically, the formation of benzothiazolines involves the following steps (as shown in Scheme 5): (i)

Scheme 4. Detosylation of **29** to 2-Styrylbenzothiazole **40** and Conversion of **31** to *m*-Chlorocinnamaldehyde **41**[a]



[a] Reagents and conditions: (a) K-OBu^t in DMF; (b) $AgNO_3$ in Et_3N−phosphate buffer (ph 7).

Scheme 5. Plausible Mechanism for the Formation of 2-Styrylbenzothiazolines[a]



[a] Reagents and conditions: (a) reduction of Pd^{II} to Pd^0 with alkynes and Et_3N; (b) CuI, Et_3N; (c) tosylation with *p*-TsCl-py; (d) isomerization to an allene with CuI, Et_3N; (e) nucleophilic attack on the allene (F) to generate the *N*-tosyl-2-styrylbenzothiazolines (**29**−**38**).

formation of ArPdX [B] through oxidative addition of Pd^0 [A] (generated from Pd^{II}) to ArX,[14] (ii) transmetalation of ArPdX with the Cu salt of **8** generating the alkynyl palladium species [D], (iii) extrusion of Pd^0 to yield the disubstituted alkynes **19**−**28**, (iv) tosylation of the free amine to [E], and (v) isomerization to the allenic intermediates[15] [F] which then cyclize to the (*E*)-2-styrylbenzothiazolines **29**−**38**.

In conclusion, we have described a palladium−copper-catalyzed reaction of 3-(2-aminophenylthio)prop-1-yne with a terminal acetylenic moiety with readily available aryl iodides. This has resulted in the formation of a number of disubstituted alkynes which under copper catalysis underwent an interesting rearrangement and subsequent cyclization to (*E*)-2-substituted benzothiazolines. Only five-membered heteroannulation took place when the styryl group at C-2 was in the *E*-configuration. No six-membered heteroannulated compounds were observed. We believe this is the first reported palladium−copper-catalyzed general procedure for

(10) Typical ^{1}H NMR data for compound **29** (300 MHz, $CDCl_3$, TMS, 25 °C): δ = 2.32 (s, 3H, $ArCH_3$), 6.2 (q, J_1 = 15 Hz, J_2 = 6 Hz, 1H, −C*H*═CHPh), 6.25 (d, J = 6 Hz, 1H.; −C*H*CH═CHPh), 6.69 (d, J = 15 Hz, 1H; −CH═C*H*Ph), 7.02−7.3 (m, 10H, ArH), 7.46 (d, J = 9 Hz, 2H, ArH), 7.72 (d, J = 9 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS, 25 °C): δ 21.516, 68.958, 120.87, 122.620, 125.321, 125.638, 126.853, 126.911, 127.367, 128.047, 128.374, 129.376, 130.650, 132.572, 134.539, 136.897, 144.243.

(11) Styrylbenzothiazole **40** was identical with an authentic sample (mp 111 °C) (synthesized according to the procedure of Brown D. M.; Kon, G. A. R. *J. Chem. Soc.* **1948**, 2147) by comparison of IR and ^{1}H NMR spectra.

(12) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5.

(13) To be reported in detail elsewhere.

(14) Sonogashira, K.; Tohda, Y.; Hagihara, Y. *Tetrahedron Lett.* **1975**, 4476.

(15) Theron, F.; Verry, M.; Vessiere, R. Rearrangement involving acetylenes. In *The chemistry of the carbon−carbon triple bond*, Part I, Chapter 10; Patai, S., Ed.; J. Wiley and Sons: Chichester, 1978; p 381.

the synthesis of various 2-substituted benzothiazolines. Also since benzothiazolines have profound biological activities,[16] we believe our method will be of interest to many synthetic organic and medicinal chemists as a new general method for the synthesis of 2-substituted benzothiazolines.[17,18]

Acknowledgment. Support has been provided by the Council of Scientific and Industrial Research, Government of India, New Delhi, under Grant 01(1385)/95/EMR-II to N.G.K.; B.N. was a JRF and then an SRF in the above project.

Supporting Information Available: Characterization data for products **29**, **31**, **40**, and **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For general references, see: Metzer, J. V. Thiazoles and their Benzo derivatives. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 6, p 235. (b) As antihypertensive, anticoagulant, and calcium agonist: Iwao, J.; Iso, I.; Oya, M. *Jpn. Kokai Tokyo Koho JP6183*, 175, *Chem. Abstr*. **1986**, *105*, 208865e. Yamamoto, K.; Fujita, K.; Tabasi, K.; Kawashima, Y.; Kato, E.; Oya, M.; Iso, T.; Iwao, J. *J. Med. Chem.* **1988**, *31*, 919. (c) As anticonvulsant, vasodilators, and blood platelet aggregation inhibitors: Santen Pharmaceutical Co. Ltd. *Jpn. Kokai, Tokyo Koho, JP 5967*, 27 [8467, 276]; *Chem. Abstr*. **1985**, *102*, 6464a. Ucar, H.; Vanderpoorten, K.; Cacciaguerra, S.; Spampinato, S.; Stables, J. P.; Depovere, P.; Isa, M.; Masereel, B.; Delarge, J.; Poupaert, J. H. *J. Med. Chem.* ***1998***, *41*, 1138. (d) As antifungal agents: Singh, R. V. *Main Group Metal Chem.* **1990**, *13*, 55; *Chem. Abstr*. **1992**, *116*, 2555. (e) Kanoongo, N.; Singh, R. V.; Tandon, J. P. *Ind. J. Chem., Sect. A* **1990**, *29A*, 560; *Chem. Abstr.* **1990**, *113*, 164355x.

(17) **General Experimental Conditions:** Aryl iodides **9**−**18** (3.6 mmol) in CH_3CN (5 mL) were stirred at rt with $(PPh_3)_2PdCl_2$ (3 mol %) and CuI (6 mol %) in the presence of Et_3N (14.4 mmol) under a nitrogen atmosphere for $^1/_2$ h. Acetylenic compound **8** (3.67 mmol) in CH_3CN (2 mL) was added, and the solution was stirred at rt for 24 h. After removal of solvent, the residue was extracted with $CHCl_3$ (2 × 25 mL) and H_2O (20 mL). The $CHCl_3$ layer was washed with H_2O (3 × 10 mL) and dried (anhydrous Na_2SO_4). After removal of solvent, the residue was chromatographed on silica gel (60−120 mesh), with the eluant being 5% ethyl acetate in light petroleum (60−80 °C), to yield the disubstituted alkynes **19**−**28**.

(18) **General Procedure for Cyclization:** The disubstituted alkynes were tosylated with *p*-TsCl (1.2 equiv) in the presence of pyridine (2.0 equiv) in CH_2Cl_2. The tosylates (0.76 mmol) were cyclized to benzothiazolines with CuI (40 mol %) in Et_3N (3.06 mmol) by being refluxed in THF (10 mL) for 36 h under an argon atmosphere. After removal of solvent, the residue was treated with H_2O (10 mL) and extracted with $CHCl_3$ (3 × 50 mL). The $CHCl_3$ extracts were combined, washed with H_2O (3 × 10 mL), and dried (anhydrous Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography on silica gel (60−120 mesh), with the eluant being 5% ethyl acetate in light petroleum (60−80 °C). Compound **29** was crystallized from chloroform−petroleum ether (60−80 °C), mp 154 °C.