Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 8531–8534
Tetrahedron Letters

Palladium–copper catalysed heteroannulation of acetylenic compounds: an expeditious synthesis of isoindoline fused with triazoles☆

Chinmay Chowdhury,[a,*] Sukhendu B. Mandal[b] and Basudeb Achari[b]

[a]*Central Institute of Medicinal and Aromatic Plants, Process and Product Development, Kukrail Picnic Spot Road, P.O. CIMAP, Lucknow-226015, India*

[b]*Indian Institute of Chemical Biology, Medicinal Chemistry Division, 4, Raja S. C. Mullick Road, Kolkata-700032, India*

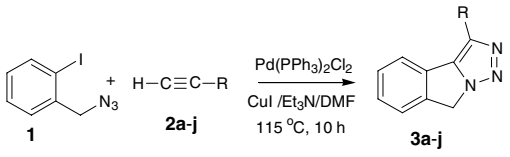
Received 27 July 2005; revised 28 September 2005; accepted 4 October 2005

Abstract—A convenient and general method for the synthesis of isoindoline fused with triazoles from *ortho*-iodobenzyl azide and acetylenes through palladium–copper catalysis is described.

Developing new synthetic methods for novel nitrogen-containing molecules has always been a frontier area of organic synthesis.[1] Among a large variety of compounds, isoindoline derivatives are of particular interest because of their diverse biological activities and clinical applications. The core ring structure is present in many heterocycles that have been shown to elicit a wide array of biological effects including NMDA receptor antagonism,[2a] modulation of estrogen[2b] and dopamine D_3 and D_4 receptors,[2c,d] inhibition of selective serotonin reuptake[2e] and anti-bacterial activity.[2f] Similarly, the 1,2,3-triazole nucleus is a structural motif found in large number of compounds possessing activities, such as anti-HIV,[3a] anti-microbial[3b] and anti-bacterial[3c] activities and has also found many applications in chemical industries.[3d] Fused triazoles have also found widespread use as anti-allergic agents[4a] and potent glycosidase inhibitors[4b] amongst others.[4c–e] Although a variety of approaches to isoindolines[5] and triazoles[6] have been described, to our knowledge the synthesis of isoindoline fused with triazoles which could perhaps be an important building block (or a novel pharmacophore), has not yet been reported.

As part of our continuing interest in the development of novel heterocyclic ring structures[7] of biological significance, the (3+2) cycloaddition strategy has promoted us to investigate the construction of isoindoline fused with triazoles in a single operation under palladium–copper catalysis. It is worth mentioning that the azido group has emerged as a useful chemical handle in synthetic chemistry and bioconjugate chemistry as well, soon after the discovery of its (3+2) cycloaddition with alkynes by Huisgen et al.[8] This classic reaction is even being carried out in living systems in order to understand the chemical biology.[9]

Here, we report that treatment of *ortho*-iodobenzyl azide[10] **1** with acetylene substrates **2a**–**j** in DMF in the presence of triethylamine and a catalytic amount of bis(triphenylphosphine)palladium(II) chloride and cuprous iodide furnished isoindolotriazoles **3a**–**j** in good yields (Scheme 1 and Table 1). Optimum yields were obtained when the reaction mixture was stirred at room temperature for 12 h followed by heating at 115 °C for 10 h. Heating gave some polymeric products, thus

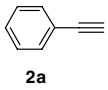
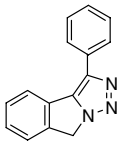
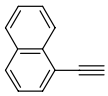
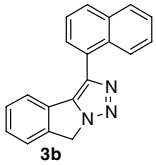
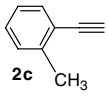
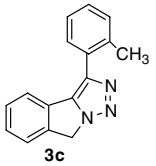
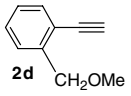
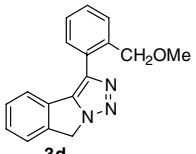
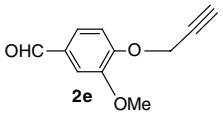
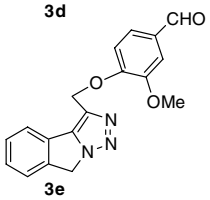
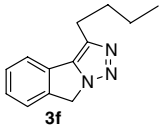
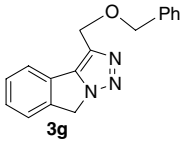
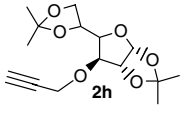
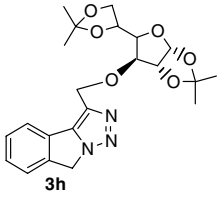
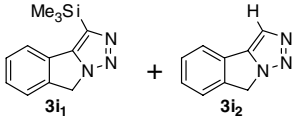
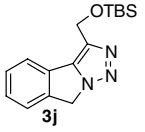


Scheme 1.

Keywords: Palladium and copper catalyst; Isoindoline; Triazole.
☆ CIMAP Communication No. 2005-44J.
* Corresponding author. Fax: +91 522 2357136; e-mail: cchinmay2@yahoo.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.10.006

Table 1. Palladium–copper catalysed heteroannulations of azides **1** with acetylenic compounds **2a–j** leading to isoindoline fused with triazoles **3a–j**

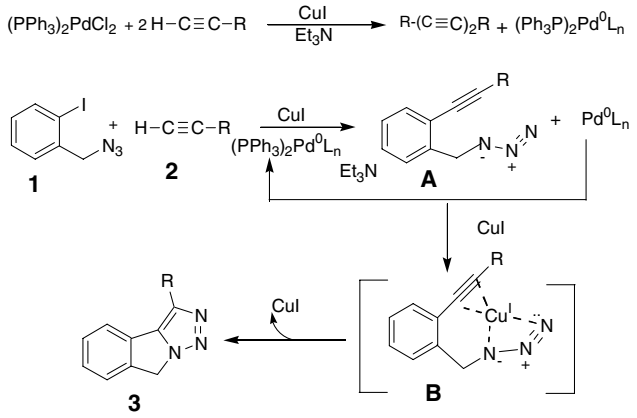
Entry	Acetylenes **2**	Products[a] **3**	Yields[b] (%)
1	 **2a**	 **3a**	58
2	 **2b**	 **3b**	61
3	 **2c**	 **3c**	60
4	 **2d**	 **3d**	63
5	 **2e**	 **3e**	28
6	$CH_3(CH_2)_3C{\equiv}CH$ **2f**	 **3f**	66
7	$PhCH_2OCH_2C{\equiv}CH$ **2g**	 **3g**	31
8	 **2h**	 **3h**	33
9[c]	$Me_3SiC{\equiv}CH$ **2i**	 **3i$_1$** + **3i$_2$**	57 (1:2)
10[d]	$TBSOCH_2C{\equiv}CH$ **2j**	 **3j**	59

[a] Satisfactory spectroscopic (^{1}H NMR, ^{13}C NMR, IR and mass) and analytical data were obtained for all the compounds synthesised.
[b] The yields (based on *o*-iodobenzyl azide **1**) are isolated yields of chromatographically pure materials.
[c] Partial desilylation took place under our reaction conditions.
[d] TBS represents *tert*-butyldimethylsilyl.

lowering the product yields. Heating at lower temperatures gave a mixture of the desired cyclised product **3** and the acyclic condensation product. The acyclic product (**A**, Scheme 2) may be an intermediate in the formation of product **3**. Bis(triphenylphosphine)palladium(II) chloride was found to be the catalyst of choice. Cuprous iodide was an essential co-catalyst. In the absence of either palladium catalyst or cuprous iodide no product was formed. This reaction was found to be equally applicable to both aromatic and aliphatic acetylenes. The acetylenic components **2** could also carry various substituents like methyl, methoxy, formyl, ether, *tert*-butyldimethylsilyl (TBS) and other moieties, without affecting the heteroannulation process (entries 3–5 and 10 in Table 1). The chiral sugar acetylene derivative **2h** was also found to be compatible (Table 1, entry 8). Partial desilylation of **2i** took place under our reaction conditions (Table 1, entry 9). The yields were generally found to be good except in the case of propargylated acetylenes (entries 5, 7 and 8). Modest yields, observed in these cases, could be attributable to a possible depropargylation reaction.[11]

The mechanism of the reaction may proceed according to Scheme 2. The catalytic cycle begins with the formation of an active Pd(0) species[7a,12] accompanied by the formation of an acetylenic dimer.[13] Next, coupling through a Sonogashira reaction[12] could lead to the formation of acylic product **A**. Presumably, the acyclic product **A** is converted to the cyclised product through copper-coordinated intermediate species **B**.[14] DMF, as a dipolar aprotic solvent, may also facilitate the intramolecular [3+2] cycloaddition of **B**.[15]

Thus, we have described the first successful palladium–copper catalysed reaction for the synthesis of isoindoline fused with triazoles from readily available starting materials. This reaction relies on carbon–carbon bond formation followed by cycloaddition of azide to the internal alkynes (generated in situ) under appropriate reaction conditions. Notably, cycloadditions of azide to the internal alkynes failed under click chemistry reaction conditions.[6a–c] Our newly developed method is operationally simple and we believe that this method will find applications in organic and medicinal chemistry as well.



Scheme 2. Proposed reaction mechanism.

General procedure: A mixture of *ortho*-iodobenzyl azide **1** (2 mmol), $(PPh_3)_2PdCl_2$ (0.07 mmol), CuI (0.14 mmol) and triethylamine (12 mmol) was stirred in DMF (14 ml) under an argon atmosphere for 1 h. The acetylenic compound **2** (2.5 mmol) was then added and the mixture stirred at room temperature for 12 h followed by heating at 115 °C for another 10 h. DMF was evaporated under reduced pressure and the residue was extracted with ethyl acetate (3×40 ml). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed in vacuo. The residue was purified by chromatography on silica gel (with 30–50% ethyl acetate in hexane as eluent) to obtain the desired product **3**. Thus, starting with **1** (518 mg, 2 mmol), and hex-1-yne **2f** (206 mg, 2.5 mmol), a colourless solid product **3f** (281 mg, 66%) was isolated. mp: 75–78 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.94 (t, $J = 7.3$ Hz, 3H), 1.39–1.51 (m, 2H); 1.76–1.86 (m, 2H), 2.99 (t, $J = 7.3$ Hz, 2H), 5.33 (s, 2H), 7.37–7.53 (m, 3H), 7.62 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.66, 22.13, 25.41, 31.44, 50.74, 120.60, 123.96, 127.50, 128.30, 128.52, 139.17, 140.50; IR (KBr) ν_{max} 3073, 2948, 2860, 1454, 1355, 1302 cm^{-1}, mass spectrum (FAB): $m/z = 214$ $(M+H)^+$, 198, 184, 170, 156, 142; Anal. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.23; H, 7.12; N, 19.73.

Acknowledgements

C.C. thanks Dr. Suman P. S. Khanuja, director of CIMAP, Lucknow, India, for constant encouragement of this work.

References and notes

1. Wohler's synthesis of urea can be considered the birth of organic synthesis: Wohler, F. *Ann. Phys. Chem.* **1828**, *12*, 253.
2. (a) Alanine, A.; Burner, S.; Buettelmann, B.; Heitz, N. M.; Jaeschke, G.; Pinard, E.; Wyler, R. Eur. Pat. Appl., EP10 90917, 2001; *Chem. Abstr.* **2001**, *134*, 280719b; (b) Bhagwat, S. S.; Gayo, L. M.; Stein, B.; Chao, Q.; Gangloff, A.; Mckie, J.; Rice, K. PCT Int. Appl., WO 0055137, 2000; *Chem. Abstr.* **2000**, *133*, 252323d; (c) Johnson, C. N.; Stemp, G. PCT Int. Appl., WO 0021950, 2000; *Chem. Abstr.* **2000**, *132*, 279110y; (d) Broughton, H. B.; Kulagowski, J. J.; Leeson, P. D.; Mawer, I. M. PCT Int. Appl., WO 9421628, 1994; *Chem. Abstr.* **1995**, *122*, 9863d; (e) Kapples, K. J.; Shutske, G. M. *J. Heterocycl. Chem.* **1997**, *34*, 1335–1338; (f) Yamada, M.; Hamamoto, S.; Hayashi, K.; Takaoka, K.; Matsukura, H; Yotsuji, M.; Yonezawa, K.; Ojima, K.; Takamatsu, T.; Taya, K.; Yamamoto, H.; Kiyoto, T.; Kotsubo, H. PCT Int. Appl., WO 9921849, 1999; *Chem. Abstr.* **1999**, *130*, 311706u.
3. (a) Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De-Clercq, C.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185–4194; (b) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J.

C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953–970; (c) Kume, M.; Kubota, T.; Kimura, Y.; Nakashimizu, H.; Motokawa, K.; Nakano, M. *J. Antibiot.* **1993**, *46*, 177–192; (d) Fan, W.-Q.; Katritzky, A. R.. In Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Comprehensive Heterocyclic Chemistry II; Elsevier Science: Oxford, 1996; Vol. 4, pp 1–126.

4. (a) Georgiev, V. S.; Loev, B.; Mack, R.; Musser, J. US Patent, US 4,276, 292, 1981; *Chem. Abstr.* **1981**, *95*, 132905v; (b) Tatsuta, K.; Ikeda, Y.; Miura, S. *J. Antibiot.* **1996**, *49*, 836–838; (c) Roma, G.; Dibraccio, M.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035; (d) Krülle, T. M.; De la Fuente, C.; Pickering, L.; Aplin, R. T.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3807–3820; (e) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2004**, *45*, 3725–3728.
5. (a) Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.* **1988**, *53*, 5381–5383; (b) Sun, Q.; Zhou, X.; Islam, K.; Kyle, D. J. *Tetrahedron Lett.* **2001**, *42*, 6495–6497; (c) Yamamoto, Y.; Nagata, A.; Itoh, K. *Tetrahedron Lett.* **1999**, *40*, 5035–5038; (d) Mance, A. D.; Borovicka, B.; Karaman, B.; Jakopcic, K. *J. Heterocycl. Chem.* **1999**, *36*, 1337–1341; (e) Kukkola, P. J.; Bilci, N. A.; Ikeler, T. J. *Tetrahedron Lett.* **1996**, *37*, 5065–5068; (f) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357–1364.
6. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237–1240; (c) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064; (d) Katritzky, A. R.; Zhang, Y.; Singh, S. K.; Steel, P. J. *Arkivoc* **2003**(xv), 47–64; (e) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897–3899; (f) Wang, Z.-X.; Qin, H.-L. *Chem. Commun.* **2003**, 2450–2451; (g) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Vander Eycken, E. *Org. Lett.* **2004**, *6*, 4223–4225.
7. (a) Chowdhury, C.; Kundu, N. G. *Chem. Commun.* **1996**, 1067–1068; (b) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863–1871; (c) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, 1273–1275; (d) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449–2467.
8. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598; (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1–176.
9. (a) Link, A. J.; Vink, M. K. S.; Tirrell, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 10598–10602; (b) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046–15047; (c) Tian, F.; Tsao, M.-L.; Schultz, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 15962–15963.
10. The starting material *ortho*-iodobenzyl azide **1** was prepared by heating ortho-iodobenzyl bromide (1.5 g, 5 mmol) and sodium azide (400 mg, 6.2 mmol) at 100 °C for 8 h in dry DMF (12 ml). After work-up and purification by chromatography on silica gel using 8% (v/v) ethyl acetate in hexane as eluent, the desired azide **1** was obtained in 82% yield.
11. Pal, M.; Parasuraman, K.; Yaleswarapu, K. R. *Org. Lett.* **2003**, *5*, 349–352.
12. (a) Sonogashira, K.; Tohda, Y.; Haghihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467–4470; (b) Sonogashira, K.. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 521–549.
13. In a few cases, dimers were isolated and characterised unambiguously by spectroscopic and analytical data.
14. Acyclic product **A** ($R = CH_2OTBS$) was isolated by carrying out the reaction at room temperature. Various experiments were then carried with **A** under various reaction conditions. Among them, the desired cycloaddition occurred when **A** was heated in DMF at 115 °C in the presence of triethylamine and a catalytic amount of cuprous iodide only. Without cuprous iodide starting material **A** was recovered.
15. Kadaba, P. K. *J Org. Chem.* **1976**, *41*, 1073–1075.