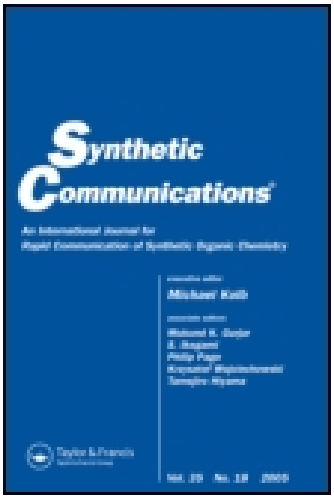

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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http://www.tandfonline.com/loi/lsyc20

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Published online: 29 Dec 2009.

To cite this article: Mohammad Bakherad, Ali Keivanloo, Mahmood Tajbakhsh & Taghi A. Kamali (2009) Synthesis of 6-Benzylimidazo[2,1-b][1,3]thiazole During Sonogashira Coupling, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:2, 173-178, DOI: 10.1080/00397910802573155

To link to this article: http://dx.doi.org/10.1080/00397910802573155

Synthetic Communications®, 40: 173–178, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802573155

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SYNTHESIS OF 6-BENZYLIMIDAZO[2,1-*b*][1,3]THIAZOLE DURING SONOGASHIRA COUPLING

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***The reaction of 2-amino-3-(2-propynyl)-1,3-thiazolium bromide* 2 *with various iodobenzenes* 3a–f *in the presence of palladium catalyst leads to the formation of 6-benzylimidazo[2,1-b][1,3]thiazoles* 4a–f.**

Keywords: Aryl iodide; imidazothiazole; Pd-catalyzed; Sonogashira coupling

INTRODUCTION

The imidazo[2,1-*b*]thiazole derivatives have been shown to possess antibacterial, antifungal, anthelmintic, antiviral, antiprotozoal, anti-inflammatory, anticonvulsant, anxiolytic, hypnotic, gastrointestinal, antiulcer, and immunomodulatory activities.[1–5] Compounds containing the imidazo[2,1-*b*][1,3]thiazole skeleton have been used as anthelmintic agents, antihypertensives, anti-inflammatories, immunosuppressive agents, fungicides, herbicides, antitumor agents, and cardiotonic agents.[6]

Considering the potent bioactivities of compounds possessing an imidazothiazole core, the development of a new strategy to synthesize 6-substituted imidazo[2,1-*b*][1,3]thiazoles efficiently attracted our attention.

Although several procedures have been developed for the synthesis of imidazo[2,1-*b*][1,3]thiazoles,[7] no examples involving arylation of imidazothiazole by Pd-Cu-catalayzed (Sonogashira coupling) reactions have been reported in the literature.

The Sonogashira reaction (i.e., the palladium and copper cocatalyzed coupling of terminal alkynes with aryl and vinyl halides) is one of the most widely used C-C bond formation reactions.[8] It provides an efficient route to aryl alkynes, which are interesting intermediates for the preparation of a variety of target compounds with applications ranging from natural products[9] and pharmaceuticals[10] to molecular organic materials.[11] Because of the utility of the products, the development of new catalyst systems has received considerable attention. Palladium-catalyzed reactions have been immensely practical for both carboannulation[12] and heteroannulation[13]

Received September 13, 2008.
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processes. In continuation of our recent studies[14] on the synthesis of fused heterocycles and the Pd-catalyzed reaction of acetylenes leading to heterocyclic compounds of biological significance, we became interested in developing a synthetic route to 6-substituted imidazo[2,1-*b*][1,3]thiazoles.

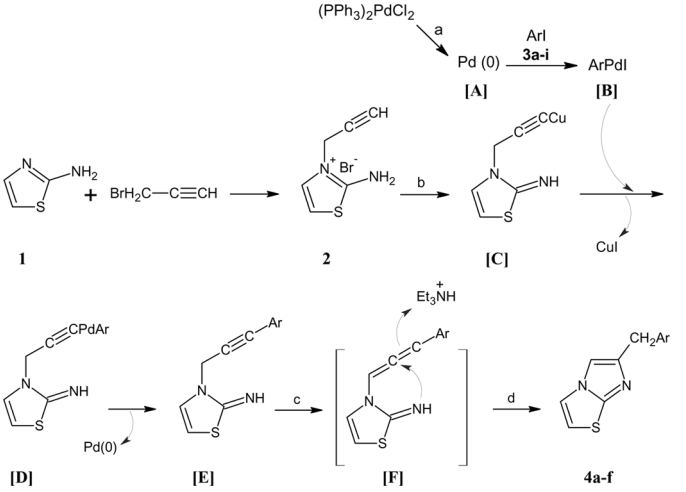
RESULTS AND DISCUSSION

In this article, we report that treatment of 2-amino-1,3-thiazole **1** with propargyl bromide in refluxing acetonitrile affords 2-amino-3-(2-propynyl)-1,3-thiazolium bromide **2** in good yield. The ^{1}H NMR spectrum of **2** showed a CH proton at 3.73 ppm, CH_2 protons at 5.03 ppm, and a single resonance for the NH_2 group at 9.78 ppm. This signal was removed on deuteration.

Compound **2** was treated in dimethylformamide (DMF) with aryl iodides **3a–f** and triethylamine in the presence of bis(triphenylphosphine)palladium(II) chloride and cuprous iodide at room temperature to give 6-substituted imidazo[2,1-*b*][1,3]thiazoles **4a–f** in moderate to high yields (Scheme 1, Table 1). The reactions were carried out under an argon atmosphere, and DMF and triethylamine were degassed prior to use.

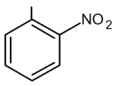
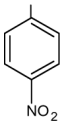
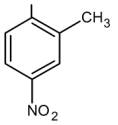
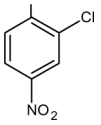
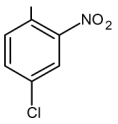
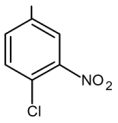
Mechanistically, the formation of 6-benzylimidazo[2,1-*b*][1,3]thiazoles involves the following steps (as shown in Scheme 1): (i) formation of ArPdI **[B]** through oxidative addition of Pd(0) **[A]** to ArI[15]; (ii) transmetallation of ArPdI with the Cu salt of **[C]**, generating the alkynyl palladium species **[D]**; (iii) extrusion of Pd(0) to yield the alkynes **[E]**; and (iv) isomerization to the allenic intermediates[16] **[F]** which then cyclize to products **4a–f**.

In conclusion, we have developed a successful palladium-catalyzed reaction for the synthesis of 6-benzylimidazo imidazo[2,1-*b*][1,3]thiazoles from readily available starting materials.



Scheme 1. Plausible mechanism for the formation of 6-benzylimidazo[2,1-*b*][1,3] thiazoles at room temprature. Reagents and conditions: (a) reduction of Pd(II) to Pd(0) with alkyne and Et_3N; (b) CuI, Et_3N; (c) isomerization to an allene with CuI, Et_3N; (d) nucleophilic attack on the allene (F) to generate the 2-benzylimidazo[2,1-*b*][1,3]thiazoles **4a–f**.

Table 1. Melting points and yields of 6-benzylimidazo[2,1-*b*][1,3]thiazoles **4a–f**

Product	Ar	Mp (°C)	Yield (%)
4a		224–225	72
4b		229–230	87
4c		254–255	85
4d		209–210	90
4e		231–232	95
4f		243–244	86

EXPERIMENTAL

Synthesis of 2-Amino-3-(2-propynyl)-1,3-thiazolium Bromide 2

A mixture of 2-aminothiazole **1** (2 g, 20 mmol) and propargyl bromide (2 mL, 24 mmol) in acetonitrile (10 mL) was heated under reflux for 1 h. The precipitate formed was filtered off and recrystallized from acetonitrile to afford the title compound. Yield 95%; mp 159–160°C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.73$ (t, $J = 2.4$ Hz, 1H, CH), 5.03 (d, $J = 2.3$ Hz, 2H, CH_2), 7.07 (d, $J = 4.5$ Hz, 1H, CH of thiazole), 7.50 (d, $J = 4.5$ Hz, 1H, CH of thiazole), 9.78 (s, 2H, NH_2); IR, υ (KBr disc): 3300, 3250, 2150 cm^{-1}; MS m/z 139 (M^+). Anal. calcd. for $C_6H_7BrN_2S$: C, 32.89; H, 3.22; N, 12.79; S, 14.63. Found: C, 32.65; H, 3.03; N, 12.55; S, 14.47.

Synthesis of 6-Substituted Imidazo[2,1-*b*][1,3]thiazoles 4a–f

A mixture of the aryl iodide **3a–f** (0.75 mmol), $(PPh_3)_2PdCl_2$ (0.05 mmol), CuI (0.1 mmol), and triethylamine (3 mmol) was stirred in DMF (5 mL) at room temperature under an argon atmosphere. 2-Amino-3-(2-propynyl)-1,3-thiazolium bromide **2** (1.27 mmol, 0.28 g) was then added, and the mixture was stirred at room temperature

for 18 h. After completion of the reaction, the resulting solution was concentrated in vacuo, and the crude product was subjected to silica-gel column chromatography using $CHCl_3$–CH_3OH (95:5) as the eluent to afford the pure product (Table 1).

6-(2-Nitrobenzyl)imidazo[2,1-*b*][1,3]thiazole 4a

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.25$ (s, 2H, CH_2), 6.95–7.96 (m, 6H, thiazol & ArH), 8.63 (s, 1H, CH of imidazole); IR, υ (KBr disc): 1520, 1340 cm^{-1}, MS m/z 259 (M^+). Anal. calcd. for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21; S, 12.37. Found: C, 55.32; H, 3.36; N, 16.40; S, 12.21.

6-(4-Nitrobenzyl)imidazo[2,1-*b*][1,3]thiazole 4b

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.18$ (s, 2H, CH_2), 7.25–8.15 (m, 6H, thiazol & ArH), 8.31 (s, 1H, CH of imidazole); IR, υ (KBr disc): 1525, 1340 cm^{-1}, MS m/z 259 (M^+). Anal. calcd. for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21; S, 12.37. Found: C, 55.37; H, 3.32; N, 16.45; S, 12.18.

6-(2-Methyl-4-nitrobenzyl)imidazo[2,1-*b*][1,3]thiazole 4c

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.50$ (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 7.22–8.06 (m, 5H, thiazol & ArH), 8.14 (s, 1H, CH of imidazole); IR, υ (KBr disc): 1530, 1345 cm^{-1}, MS m/z 273 (M^+). Anal. calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 57.31; H, 3.90; N, 15.51; S, 11.61.

6-(2-Chloro-4-nitrobenzyl)imidazo[2,1-*b*][1,3]thiazole 4d

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.28$ (s, 2H, CH_2), 7.24–8.28 (m, 5H, thiazol & ArH), 8.32 (s, 1H, CH of imidazole); IR, υ (KBr disc): 1525, 1340 cm^{-1}, MS m/z 293 (M^+), 295 ($M+2$). Anal. calcd. for $C_{12}H_8ClN_3O_2S$: C, 49.07; H, 2.75; N, 14.31; S, 10.92. Found: C, 49.29; H, 2.87; N, 14.20; S, 11.02.

6-(4-Chloro-2-nitrobenzyl)imidazo[2,1-*b*][1,3]thiazole 4e

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.34$ (s, 2H, CH_2), 7.26–7.93 (m, 5H, thiazol & ArH), 8.08 (s, 1H, CH of imidazole); IR, υ (KBr disc): 1520, 1340 cm^{-1}, MS m/z 293 (M^+), 295 ($M+2$). Anal. calcd. for $C_{12}H_8ClN_3O_2S$: C, 49.07; H, 2.75; N, 14.31; S, 10.92. Found: C, 48.88; H, 2.62; N, 14.47; S, 10.77.

6-(4-Chloro-3-nitrobenzyl)imidazo[2,1-*b*][1,3]thiazole 4f

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.13$ (s, 2H, CH_2), 7.25–7.95 (m, 5H, thiazol & ArH), 8.02 (s, 1H, CH of imidazole); IR, υ (KBr disc): 1530, 1350 cm^{-1}, MS m/z 293 (M^+), 295 ($M+2$). Anal. calcd. for $C_{12}H_8ClN_3O_2S$: C, 49.07; H, 2.75; N, 14.31; S, 10.92. Found: C, 49.23; H, 2.90; N, 14.45; S, 10.81.

ACKNOWLEDGMENTS

The authors thank the Research Council of Shahrood University of Technology for the support of this work.

REFERENCES

1. Howard, A. S. In *Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C. W. Rees, and E. V. F. Scriven, (Eds.); Pergamon Press: London, 1996; vol. 8, pp. 262–274.
2. Ismail, M. A.; Brun, R.; Wenzler, T.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. Novel dicationic imidazo[1,2-*a*]pyridines and 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridines as antiprotozoal agents. *J. Med. Chem.* **2004**, *47*, 3658–3664.
3. Gudmundsson, K. S.; Williams, J. D.; Drach, J. C.; Townsend, L. B. Synthesis and antiviral activity of novel erythrofuranosyl imidazo[1,2-*a*]pyridine C-nucleosides constructed via palladium coupling of iodoimidazo[1,2-*a*]pyridines and dihydrofuran. *J. Med. Chem.* **2003**, *46*, 1449–1455.
4. Geronikaki, A.; Babaev, E.; Dearden, J.; Dehaen, W.; Filimonov, D.; Galaeva, I.; Krajneva, V.; Lagunin, A.; Macaev, F.; Molodavkin, G.; Poroikov, V.; Pogrebnoi, S.; Saloutin, V.; Stepanchikova, A.; Stingaci, E.; Tkach, N.; Vlad, L.; Voronina, T. Design, synthesis, computational and biological evaluation of new anxiolytics. *Bioorg. Med. Chem.* **2004**, *12*, 6559–6568.
5. Amarouch, H.; Loiseau, P. R.; Bacha, C.; Caujolle, R.; Payard, M.; Loiseau, P. M.; Bories, C.; Gayral, P. Imidazo[2,1-*b*]thiazoles: Analogues du lévamisole. *Eur. J. Med. Chem.* **1987**, *22*, 463–466.
6. (a) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Lenaz, G.; Fato, R.; Bergamini, C.; Farruggia, G. Potential antitumor agents, 37: Synthesis and antitumor activity of guanylhydrazones from imidazo[2,1-*b*]thiazoles and from the new heterocyclic system thiazolo[2′,3′:2,3]imidazo[4,5-*c*]quinoline. *J. Med. Chem.* **2005**, *48*, 3085–3089; (b) Andreani, A.; Rambaldi, M.; Locatelli, A.; Bossa, R.; Fraccari, A.; Galatulas, I. Potential antitumor agents, 21: Structure determination and antitumor activity of imidazo[2,1-b]thiazole guanylhydrazones. *J. Med. Chem.* **1992**, *35*, 4634–4637; (c) Jaguelin, S.; Robert, A.; Gayral, P. Réaction des cyanoépoxydes avec le 2-mercaptobenzimidazole et la 2-aminothiazoline et évaluation biologique des produits formés. *Eur. J. Med. Chem.* **1991**, *26*, 51–57.
7. (a) Gürsoy, E.; Güzeldemirci, N. U. Synthesis and primary cytotoxicity evaluation of new imidazo[2,1-*b*]thiazole derivatives. *Eur. J. Med. Chem.* **2007**, *42*, 320–326; (b) Adib, M.; Mahdavi, M.; Noghania, M. A.; Mirzaei, P. Catalyst-free three-component reaction between 2-aminopyridines (or 2-aminothiazoles), aldehydes, and isocyanides in water. *Tetrahedron Lett.* **2007**, *48*, 7263–7265; (c) Kolavi, G.; Hegde, V.; Khazi, I. A. Intramolecular amidation: Synthesis of novel imidazo[2,1-*b*][1,3,4]thiadiazole and imidazo [2,1-*b*][1,3]thiazole fused diazepinones. *Tetrahedron Lett.* **2006**, *47*, 2811–2814.
8. (a) Sonogashira, K. Development of Pd–Cu-catalyzed cross-coupling of terminal acetylenes with sp^2-carbon halides. *J. Organomet. Chem.* **2002**, *653*, 46–49.
9. (a) Toyota, M.; Komori, C.; Ihara, M. A concise formal total synthesis of mappicine and nothapodytine B via an intramolecular hetero Diels–Alder reaction. *J. Org. Chem.* **2000**, *65*, 7110–7113; (b) Yoshimura, F.; Kawata, S.; Hirama, M. Synthetic study of kedarcidin chromophore: Atropselective construction of the ansamacrolide. *Tetrahedron Lett.* **1999**, *40*, 8281–8285; (c) Miller, M. W.; Johnson, C. R. Sonogashira coupling of 2-iodo-2-cycloalkenones: Synthesis of (+)- and (−)-Harveynone and (−)-tricholomenyn A. *J. Org. Chem.* **1997**, *62*, 1582–1585; (d) Sakai, A.; Aoyama, T.; Shioiri, T. Total synthesis

of vibsanol, a benzofuran-type lignan. *Tetrahedron Lett.* **1999**, *40*, 4211–4214; (e) Graham, A. E.; McKerrecher, D.; Davies, D. H.; Taylor, R. J. K. Sonogashira coupling reactions of highly oxygenated vinyl halides: The first synthesis of harveynone and *epi*-harveynone. *Tetrahedron Lett.* **1996**, *37*, 7445–7448.

10. (a) Nicolaou, K. C.; Dai, W.-M. Chemistry and biology of the enediyne anticancer antibiotics. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387–1416; (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. The chemistry of enediynes, enyne allenes, and related compounds. *Tetrahedron* **1996**, *52*, 6453–6518.
11. Wu, R.; Schumm, J. S.; Pearson, D. L.; Tour, J. M. Convergent synthetic routes to orthogonally fused conjugated oligomers directed toward molecular scale electronic device applications. *J. Org. Chem.* **1996**, *61*, 6906–6921.
12. (a) Ihle, N. C.; Heathcock, C. H. Palladium-catalyzed intramolecular alkyne–carbon monoxide-alkene insertion cascade for synthesis of α-methylenecyclopentenones. *J. Org. Chem.* **1993**, *58*, 560–563; (b) Larock, R. C.; Doty, M. J.; Cacchi, S. Synthesis of indenones via palladium-catalyzed annulation of internal alkynes. *J. Org. Chem.* **1993**, *58*, 4579–4583.
13. (a) Arcadi, A.; Cacchi, S.; Mainelli, F. Palladium-catalysed coupling of aryl and vinyl triflates or halides with 2-ethynylaniline: An efficient route to functionalized 2-substituted indoles. *Tetrahedron Lett.* **1989**, *30*, 2581–2584; (b) Roesch, K. R.; Larock, R. C. Synthesis of isoquinolines and pyridines via palladium-catalyzed iminoannulation of internal acetylenes. *J. Org. Chem.* **1998**, *63*, 5306–5607; (c) Larock, R. C.; Yum, E. K.; Refvik, M. D. Synthesis of 2,3-disubstituted indoles via palladium-catalyzed annulation of internal alkynes. *J. Org. Chem.* **1998**, *63*, 7652–7662; (d) Larock, R.; Can, X. Palladium-catalyzed cross-coupling of 2,5-cyclohexadienyl-substituted aryl or vinylic iodides and carbon or heteroatom nucleophiles. *J. Org. Chem.* **1999**, *64*, 1875–1887.
14. (a) Bakherad, M.; Isfahani, H. N.; Keivanloo, A.; Doostmohammadi, N. Pd-Cu-catalyzed heterocyclization during Sonogashira coupling: Synthesis of 2-benzylimidazo[1,2-*a*] pyridine. *Tetrahedron Lett.* **2008**, *49*, 3819–3822; (b) Bakherad, M.; Isfahani, H. N.; Keivanloo, A.; Sang, G. Synthesis of 2-benzylimidazo[2,1-*b*][1,3]benzothiazoles through palladium-catalyzed heteroannulation of acetylenic compounds. *Tetrahedron Lett.* **2008**, *49*, 6188–6191; (c) Heravi, M. M.; Kivanloo, A.; Rahimzadeh, M.; Bakavoli M.: Ghassemzadeh, M.; Neumüller, B. Regioselective synthesis of 6-benzylthiazolo-[3,2-*b*]1,2,4-triazoles during Sonogashira coupling. *Tetrahedron Lett.* **2005**, *46*, 1607–1610; (d) Heravi, M. M.; Keivanloo, A.; Rahimizadeh, M.; Bakavoli, M.; Ghassemzadeh, M. Pd–Cu-catalyzed heterocyclization during Sonogashira coupling: Synthesis of 3-benzylthiazolo[3,2-*a*]benzimidazole. *Tetrahedron Lett.* **2004**, *45*, 5747–5749.
15. Sonogashira, K.; Tohda, Y.; Hagihara, N. A convenient synthesis of acetylenes: Catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes, and bromopyridines. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
16. Theron, F.; Verry, M.; Vessiere, R. Rearrangement involving acetylenes. In *The Chemistry of the Carbon–Carbon Triple Bond, Part I*; S. Patai (Ed.); J. Wiley and Sons: Chichester, UK, 1978; Chapter 10, p. 381.