Published in final edited form as:

Org Lett. 2012 August 3; 14(15): 3870–3873. doi:10.1021/ol3015804.

A One-pot–Three-step Route to Triazolotriazepinoindazolones from Oxazolino-2*H*-indazoles

Wayne E. Conrad[†], Kevin X. Rodriguez[†], Huy H. Nguyen[†], James C. Fetting[†], Makhuf J. Haddadin^{*,§}, and Mark J. Kurth^{*,†}

Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616, United States and Department of Chemistry, American University of Beirut, Beirut, Lebanon

Abstract

A one-pot–three-step method has been developed for the conversion of oxazolino-2*H*-indazoles into triazolotriazepinoindazolones with three points of diversity. Step one of this process involves a propargyl bromide-initiated ring opening of the oxazolino-2*H*-indazole (available by the Davis-Beirut reaction) to give an *N*¹-(propargyl)-*N*²-(2-bromoethyl)-disubstituted indazolone, which then undergoes $-\text{CH}_2\text{Br} \rightarrow -\text{CH}_2\text{N}_3$ displacement (step two) followed by an uncatalyzed intramolecular azide-alkyne 1,3-dipolar cycloaddition (step three) to form the target heterocycle. Employing 7-bromooxazolino-2*H*-indazole allows for further diversification through, for example, palladium-catalyzed coupling chemistry, as reported here.

The generation of libraries of structurally complex and diverse small molecules for high-throughput screening is a vitally important, integral part in the drug discovery process.¹ Two powerful methods for generating structural complexity are cycloaddition reactions and one-pot–multistep methods.² Herein, we present a one-pot–three-step transformation exploiting propargyl bromide-initiated ring opening and a subsequent intramolecular azide-alkyne 1,3-dipolar cycloaddition (IAAC),³ which converts oxazolino-2*H*-indazoles into novel triazolotriazepinoindazolone heterocycles wherein a 1,2,5-triazepine is fused to both an indazolone and a triazole.

In previous reports, we have shown that oxazolino-2*H*-indazoles, available via the Davis-Beirut reaction,⁴ can be converted into *N*²-substituted indazolones by treatment with various nucleophiles⁵ or *N*¹, *N*²-disubstituted indazolones by treatment with various electrophiles⁶ (Scheme 1). The chemistry reported here combines this electrophilic indazole $\rightarrow$ indazolone reaction with an IAAC to provide an efficient route to triazolotriazepinoindazolones {e.g., 12,13-dihydro[1,2,3]triazolo-[1',5':5,6][1,2,5]triazepino[1,2-*a*]indazol-10(4*H*)-ones}. An interesting aspect of these novel molecules is their fusion of two heterocycles, each with well established biological activities. The indazolone scaffold is found in molecules

haddadin@AUB.edu.lb; mjkurth@ucdavis.edu.

[†]University of California.

[§]American University of Beirut.

Supporting Information Available Full experimental details and characterization data (¹H NMR, ¹³C NMR, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

possessing analgesic, antiangiogenic, anti-cancer, antihypertensive, anti-inflammatory, and anti-tumor activities⁷ and the 1,2,3-triazole scaffold is known to express anti-allergic, anticonvulsant, antifungal, anti-HIV, antimicrobial, and antiviral activities.^{3a,8} Triazepines, while less fully evaluated, are reported to have antibacterial, antifungal, antioxidant, and immuno-suppressive activities.⁹

To launch the current investigation into a propargyl bromide-initiated ring opening and subsequent intra-molecular azide-alkyne 1,3-dipolar cycloaddition transformation, we first prepared the requisite indazolone from oxazolino-2*H*-indazole (**S**)-**1b** by treating it with propargyl bromide; *N*¹-Alkylation to the oxazolo[3,2-*b*]indazol-5-ium bromide followed by nucleophilic (Br⁻) attack at C2 delivered **4** (Scheme 2). We speculated that from **4**, subsequent bromide → azide conversion would position the system for an uncatalyzed intramolecular azide-alkyne cycloaddition to afford triazolotriazepinoindazolone **6**.

In the event, addition of sodium azide to **4** in DMF at 80 °C converted bromide **4** to triazolotriazepinoindazolone **6** in 69% yield from **4**. The structure of **6** was established by X-ray crystallography, which, as illustrated in Figure 1, also revealed an intriguing biplanar conformation for the indazolone and triazole heterocycles.

This encouraging result prompted us to investigate effecting (**S**)-**1b** → **6** as a one-pot–three-step transformation. We were indeed pleased to find that treating a 0.1M solution of (**S**)-**1b** with propargyl bromide (1.5 equiv.) at 80 °C led smoothly to the disappearance (TLC)¹⁰ of (**S**)-**1b** and formation of **4** (18 h). At this point, addition of sodium azide (1.6 equiv.) with continued heating at 80 °C for 16 h caused a clean conversion of **4** to **6**, most likely via the intermediacy of **5**. This one-pot–three-step protocol delivered **6** in 82% yield.

With this protocol in hand, we turned to an investigation of the scope of this operationally simple, one-pot method for the construction of triazolo-, triazepino-, and indazolone-fused heterocycles. As outlined in Scheme 3, this one-pot–three-step method accommodates both terminal and internal alkynes. Regarding the latter, alkyl- as well as electron-neutral and electron-rich internal aryl-substituted propargyl bromide analogs all perform equally well. Attempts at employing internal alkynes conjugated to electron-poor aryl groups (*p*-CN, *p*-CF₃) resulted in the formation of a complicated reaction mixture.

As a part of our commitment to the NIH Molecular Libraries Small Molecule Repository (MLSMR) for high-throughput biological screening, we next set out to diversify the output of this one-pot–three-step reaction by using palladium cross-coupling reactions on the benzo- ring of the indazolone moiety. As outlined in Scheme 4, this was achieved by first preparing of 7-bromooxazolino- [3,2-*b*]indazole **1d**. Sandmeyer reaction of aniline **14** delivered aryl bromide **15** and subsequent benzylic bromination using NBS and catalytic AIBN gave 4-bromo-1-(bromomethyl)-2-nitrobenzene (**16**). Applying our standard one-pot Davis-Beirut reaction to this dibromide along with (**S**)-2-amino-1-propanol gave 7-bromoindazole **1d** in 60% yield.

Employing **1d** in a one-pot–three-step intramolecular azide-alkyne cycloaddition reaction along with 1-bromo-2-pentyne delivered the targeted 6-bromotriazolotriazepinoindazolone **17** in 93% yield (Scheme 5). With the stage thus set, the aryl bromide moiety of **17** was employed in two demonstrative palladium cross-coupling reactions; Buchwald-Hartwig amination¹¹ of **17** with pyrrolidine delivered **20** in 73% yield and Suzuki cross-coupling¹² with 3-methoxyphenylboronic acid gave **21** in 89% yield. Importantly, the triazolotriazepinoindazolones depicted in Schemes 3 and 5 have physical properties that are in accordance with Lipinski's rule-of-five for drug-likeness; for example, logP values range between 1.18 and 4.25.¹³

In summary, we have developed a methodology that provides ready access to triazolotriazepinoindazolones from oxazolino-2*H*-indazoles. The key steps in this one-pot-three-step protocol are (i) propargyl bromide-initiated ring opening of the oxazolino-2*H*-indazole (available by the Davis-Beirut reaction), (ii) $-\text{CH}_2\text{Br} \rightarrow -\text{CH}_2\text{N}_3$ displacement, and (iii) uncatalyzed intramolecular azide-alkyne 1,3-dipolar cycloaddition. We have also shown that palladium catalyzed cross-coupling reactions can be exploited to further diversify these previously unreported heterocycles. By exploiting this reactivity, we have synthesized a set of novel triazolotriazepinoindazolones as part of our commitment to the NIH MLSMR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Science Foundation (CHE-0910870) and the National Institutes of Health (GM089153) for generous financial support of this work and the National Science Foundation (Grant 0840444) for the Dual source X-ray diffractometer. W.E.C. acknowledges the United States Department of Education for a GAANN fellowship. We also thank Ms. Kelli M. Farber in our laboratory for assistance in the collection of HRMS data.

References

1. a) Tan DS. *Nat Chem Biol.* 2005; 1:74–84. [PubMed: 16408003] b) Walters WP, Namchuk M. *Nat Rev Drug Discovery.* 2003; 2:259–66.
2. Dandapani S, Marcaurelle LA. *Curr Opin Chem Biol.* 2010; 14:362–70. [PubMed: 20409744]
3. For a review, see: Majumdar KC, Ray K. *Synthesis.* 2011; 23:3767–83. For recent examples, see: Arigela RK, Mandadapu AK, Sharma SK, Kumar B, Kundu B. *Org Lett.* 2012; 14:1804–07. [PubMed: 22440058] Donald JR, Martin SF. *Org Lett.* 2011; 13:852–55. [PubMed: 21275426] Oliva AI, Christmann U, Font D, Cuevas F, Ballester P, Buschmann H, Torrens A, Yenes S, Pericàs MA. *Org Lett.* 2008; 10:1617–19. [PubMed: 18348569]
4. (a) Avila B, Solano DM, Haddadin MJ, Kurth MJ. *Org Lett.* 2011; 13:1060–63. [PubMed: 21294577] (b) Solano DM, Butler JD, Haddadin MJ, Kurth MJ. *Org Synth.* 2010; 87:339–49. (c) Butler JD, Solano DM, Robins LI, Haddadin MJ, Kurth MJ. *J Org Chem.* 2008; 73:234–40. [PubMed: 18052193] (d) Mills AD, Maloney P, Hassanein E, Haddadin MJ, Kurth MJ. *J Comb Chem.* 2007; 9:171–77. [PubMed: 17206845] (e) Mills AD, Nazer MZ, Haddadin MJ, Kurth MJ. *J Org Chem.* 2006; 71:2687–89. [PubMed: 16555821] (f) Kurth MJ, Olmstead MM, Haddadin MJ. *J Org Chem.* 2005; 70:1060–62. [PubMed: 15675871]
5. (a) Donald MB, Conrad WE, Oakdale JS, Butler JD, Haddadin MJ, Kurth MJ. *Org Lett.* 2010; 12:2524–27. [PubMed: 20438102] (b) Oakdale JS, Solano DM, Fettinger JC, Haddadin MJ, Kurth MJ. *Org Lett.* 2009; 11:2760–63. [PubMed: 19505119]
6. Conrad WE, Fukazawa R, Haddadin MJ, Kurth MJ. *Org Lett.* 2011; 13:3138–41. [PubMed: 21612219]
7. a) Cappelli A, Nannicini C, Gallelli A, Guiliani G, Velenti S, Mohr GP, Anzini M, Mennuni L, Ferrari F, Caselli G, Giordani A, Peris W, Makovec F, Giorgi G, Vomero S. *J Med Chem.* 2008; 51:2137–46. [PubMed: 18318468] b) Huang LJ, Shih ML, Chen H-S, Pan S-L, Teng CM, Lee F-Y, Kuo SC. *Bioorg Med Chem.* 2006; 14:528. c) Wang H, Han H, Von Hoff DD. *Cancer Res.* 2006; 66:9722–9730. [PubMed: 17018631] e) Kawanishi N, Sugimoto T, Shibata J, Nakamura K, Masutani K, Ikuta M, Hirai H. *Bioorg Med Chem Lett.* 2006; 16:5122–5126. [PubMed: 16876403] f) Fletcher SR, McIver E, Lewis S, Burkamp F, Leech C, Mason G, Boyce S, Morrison D, Richards G, Sutton K, Jones AB. *Bioorg Med Chem Lett.* 2006; 16:2872–76. [PubMed: 16563760] Cerecetto H, Gerpe A, Gonzalez M, Aran VJ, Ocha de Ocariz C. *Mini-Rev Med Chem.* 2005; 5:869–78. [PubMed: 16250831] Abouzid KAM, El-Abhar HS. *Arch Pharmacol Res.* 2003; 26:1–8.

8. a) Kharb R, Sharma PC, Yar MS. *J Enzyme Inhib Med Chem*. 2011; 26:1–21. [PubMed: 20583859]
b) Brodie MJ, Rosenfeld WE, Vasquez B, Sachdeo R, Perdomo C, Mann A, Arroyo S. *Epilepsia*. 2009; 50:1899–1909. [PubMed: 19490053]
9. a) Gupta M, Paul S, Gupta R. *Eur J Med Chem*. 2011; 46:631–35. [PubMed: 21185625] b) Sankaran M, Kumarasamy C, Chokkalingam U, Mohan PS. *Bioorg Med Chem Lett*. 2010; 20:7147–51. [PubMed: 20947350] c) Khalil AM, Berghot MA, Gouda MA. *Eur J Med Chem*. 2009; 44:4448–54. [PubMed: 19570595] d) Ryng S, Zimecki M, M czynski M, Chodackzek G, Koci ba M. *Pharmacol Rep*. 2005; 57:195–202. [PubMed: 15886418]
10. Reaction progress was monitored by TLC (SiO₂; 1:1::hexanes: EtOAc).
11. (a) Wolfe JP, Buchwald SL. *J Org Chem*. 2000; 65:1144–57. [PubMed: 10814066] (b) Wolfe JP, Wagwaw S, Marcoux JF, Buchwald SL. *Acc Chem Res*. 1998; 31:805–18.(c) Hartwig JF. *Angew Chem Int Ed*. 1998; 37:2046–67.
12. (a) Callam CS, Lowary TL. *J Chem Ed*. 2001; 78:947–48.(b) Huuf BE, Koeing TM, Mitchell D, Stanzak MA. *Org Syn*. 1997; 75:53–56.(c) Miyuara N, Suzuki A. *Chem Rev*. 1995; 95:2457–83.
13. (a) Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. *Adv Drug Delivery Rev*. 1997; 23:3–25. (b) Hann MM, Oprea TI. *Curr Opin Chem Biol*. 2004; 8:255–63. [PubMed: 15183323]

Figure 1.
X-ray crystal structure of triazolotriazepinoindazolone **6**.

Scheme 1.
Nucleophilic and Electrophilic Ring Opening of oxazolino-2*H*-indazoles

Scheme 2.

Proposed pathway for the one-pot-three-step synthesis of triazolotriazepinoindazolones.

^a Isolated Yields.

Scheme 3.

One-pot–three-step synthesis of variously substituted triazolotriazepinoindazolones.

^a Isolated Yields.

Scheme 4. Synthesis of precursors of 7-bromo-Oxazolino[3,2-*b*]Indazole **1d**.

Scheme 5.
Synthesis and palladium cross-coupling reactions of 6-bromotriazolotriazepinoindazolone **17**.