ORGANIC LETTERS

2012
Vol. 14, No. 15
3870–3873

A One-Pot−Three-Step Route to Triazolotriazepinoindazolones from Oxazolino-2*H*-indazoles

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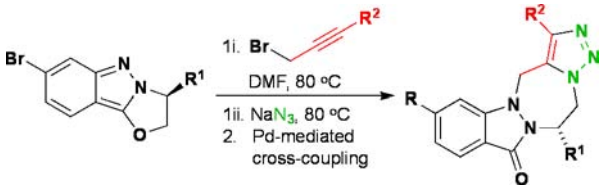
Received June 7, 2012

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 $-CH_2Br \rightarrow -CH_2N_3$ 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 nucleophiles[5] or N^1,N^2-disubstituted indazolones by treatment with various electrophiles[6] (Scheme 1). The chemistry reported here combines this electrophilic indazole → 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

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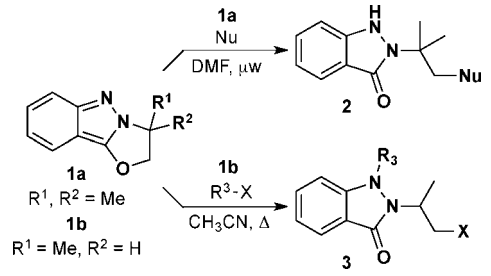
10.1021/ol3015804
Published on Web 07/23/2012

novel molecules is their fusion of two heterocycles, each with well established biological activities. The indazolone scaffold is found in molecules possessing analgesic, antiangiogenic, anticancer, antihypertensive, anti-inflammatory, and antitumor activities,[7] and the 1,2,3-triazole scaffold is known to express antiallergic, anticonvulsant, antifungal, anti-HIV, antimicrobial, and antiviral activities.[3a,8] Triazepines, while less fully evaluated, are reported to have antibacterial, antifungal, antioxidant, and immunosuppressive activities.[9]

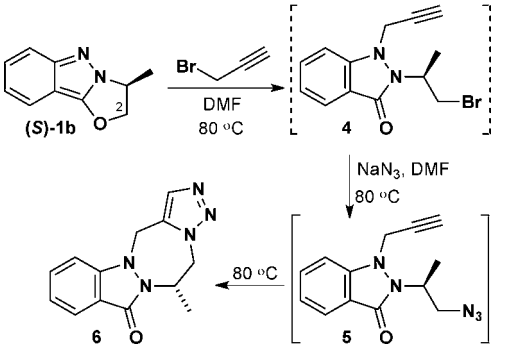
Scheme 1. Nucleophilic and Electrophilic Ring-Opening of Oxazolino-2*H*-indazoles



To launch the current investigation into a propargyl bromide initiated ring opening and subsequent intramolecular 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.

Scheme 2. Proposed Pathway for the One-Pot−Three-Step Synthesis of Triazolotriazepinoindazolones



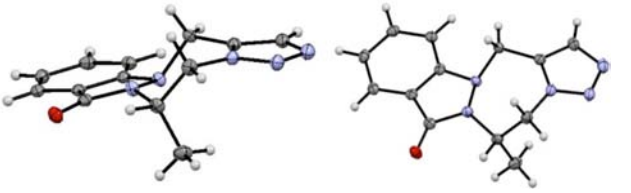


Figure 1. X-ray crystal structure of triazolotriazepinoindazolone **6**.

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 0.1 M 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 heterocyles. 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*-CF_3) 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

(7) (a) Cappelli, A.; Nannicini, C.; Gallelli, A.; Guiliani, G.; Velenti, S.; Mohr, G. P.; 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. (b) Huang, L.-J.; Shih, M.-L.; Chen, H.-S; Pan, S.-L; Teng, C.-M.; Lee, F.-Y; Kuo, S.-C. *Biorg. Med. Chem.* **2006**, *14*, 528. (c) Wang, H.; Han, H.; Von Hoff, D. D. *Cancer Res.* **2006**, *66*, 9722–9730. (e) Kawanishi, N.; Sugimoto, T.; Shibata, J.; Nakamura, K.; Masutani, K.; Ikuta, M.; Hirai, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5122–5126. (f) Fletcher, S. R.; McIver, E.; Lewis, S.; Burkamp, F.; Leech, C.; Mason, G.; Boyce, S.; Morrison, D.; Richards, G.; Sutton, K.; Jones, A. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2872–76. Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; Ocha de Ocariz, C. *Mini-Rev. Med. Chem.* **2005**, *5*, 869–78. Abouzid, K. A. M.; El-Abhar, H. S. *Arch. Pharmacal. Res.* **2003**, *26*, 1–8.

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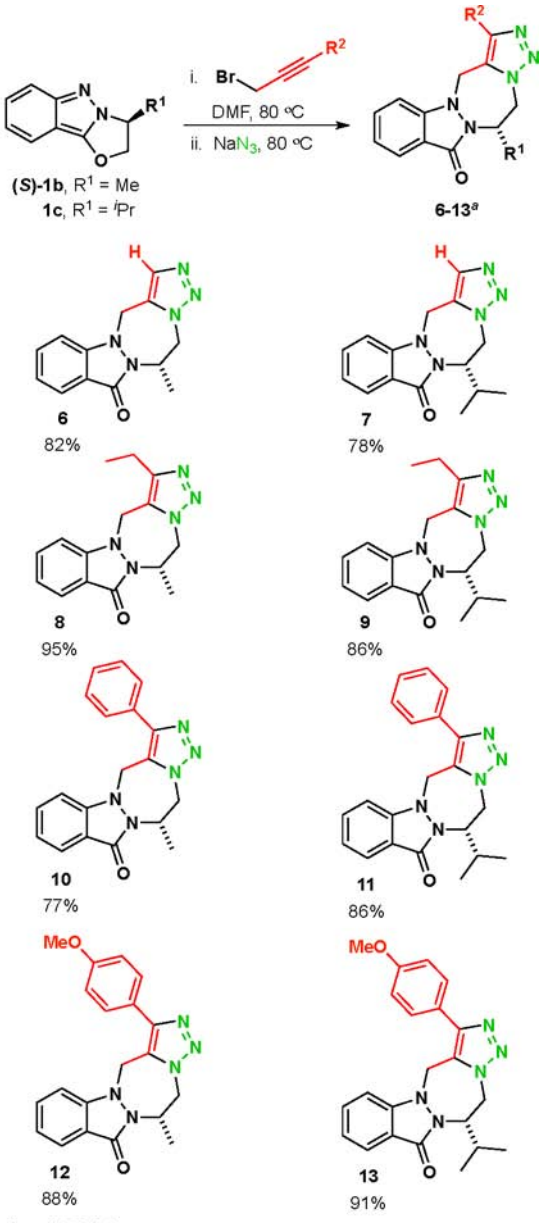
(10) Reaction progress was monitored by TLC (SiO_2; 1:1 hexanes/EtOAc).

Scheme 3. One-Pot–Three-Step Synthesis of Variously Substituted Triazolotriazepinoindazolones

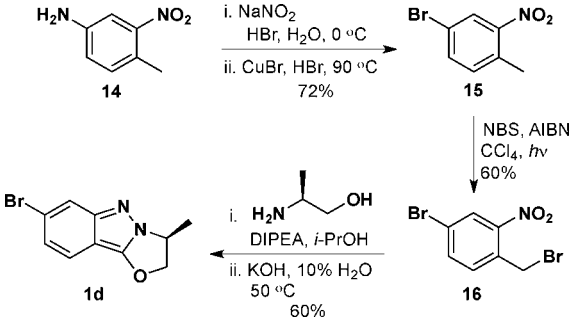


[a] Isolated Yields.

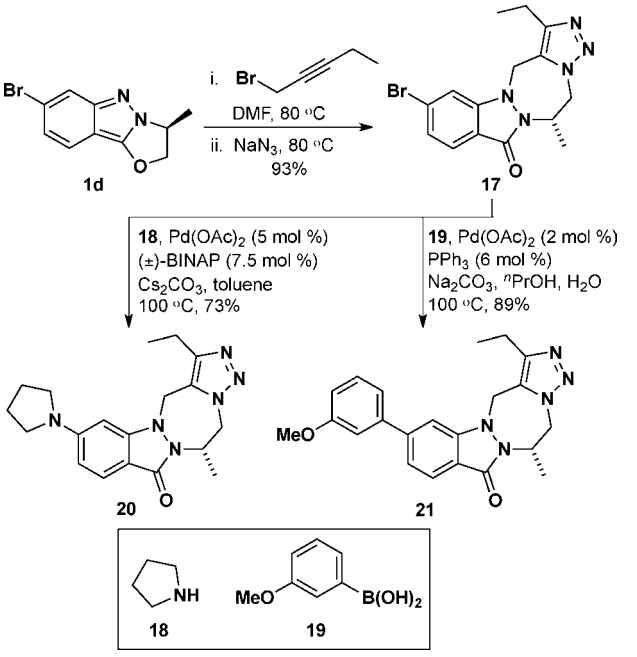
high-throughput biological screening, we next set out to diversify the output of this one-pot–three-step reaction by using palladium cross-coupling reactions on the benzo ring of the indazolone moiety. As outlined in Scheme 4, this was achieved by first preparing 7-bromooxazolino-[3,2-*b*]indazole **1d**. 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-

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**



2-pentyne delivered the targeted 7-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 amination[11] of **17** with pyrrolidine delivered **20** in 73% yield, and Suzuki cross-coupling[12] with 3-methoxyphenylboronic acid gave **21** in 89% yield. Importantly, the triazolotriazepinoindazolones depicted in Schemes 3 and 5 have physical properties

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that are in accordance with Lipinski's rule-of-five for drug-likeness; for example, log *P* 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) $-CH_2Br \rightarrow -CH_2N_3$ 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.

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Acknowledgment. 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.

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

The authors declare no competing financial interest.