

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

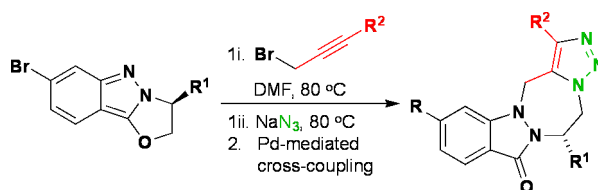
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ABSTRACT



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

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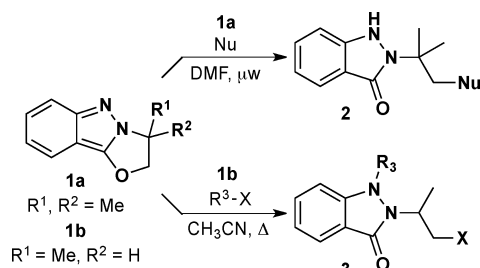
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novel molecules is their fusion of two heterocycles, each with well established biological activities. The indazolone scaffold is found in molecules possessing analgesic, antiangiogenic, anticancer, antihypertensive, anti-inflammatory, and antitumor 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 $\rightarrow$ 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

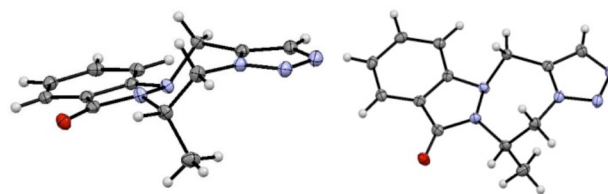
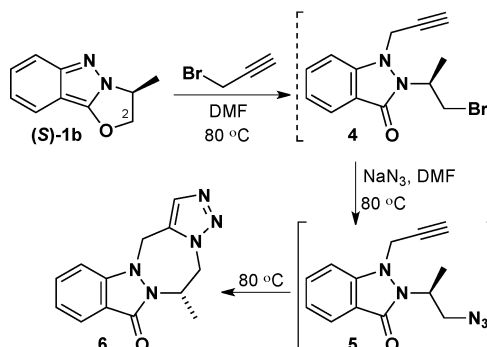


Figure 1. X-ray crystal structure of triazolotriazepinoindazolone **6**.

This encouraging result prompted us to investigate effecting (*S*)-**1b** $\rightarrow$ **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 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

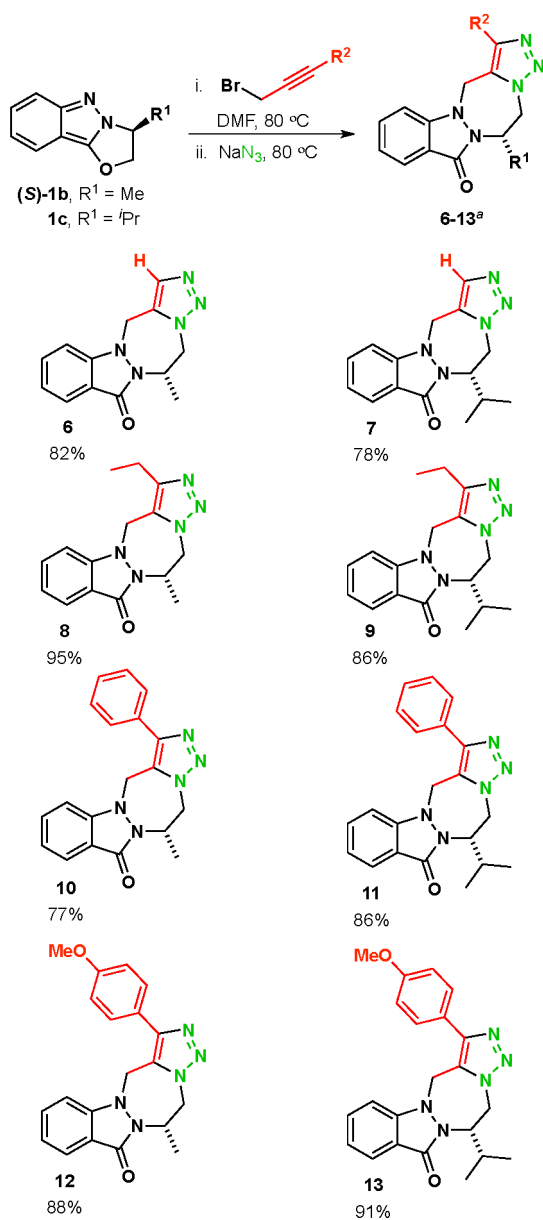
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(10) Reaction progress was monitored by TLC (SiO₂; 1:1 hexanes/EtOAc).

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

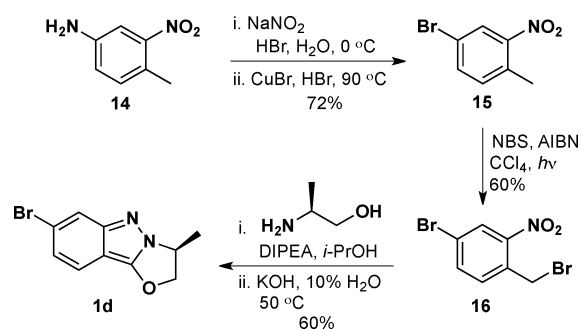


^a Isolated Yields.

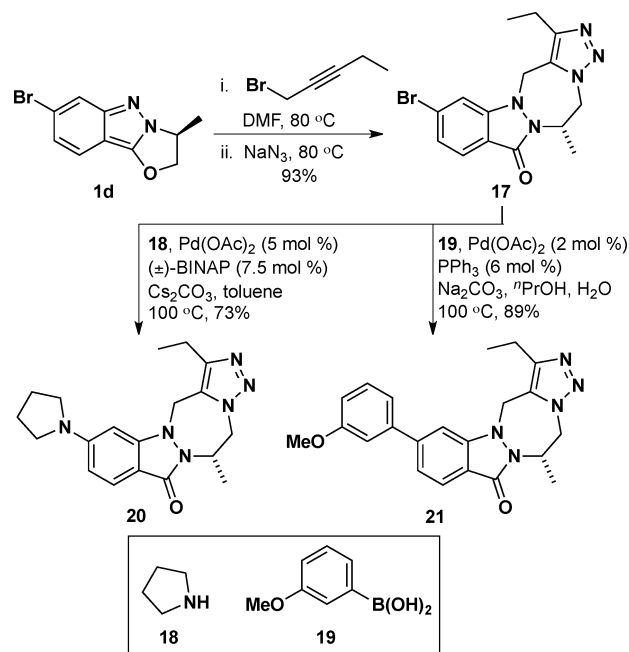
high-throughput biological screening, we next set out to diversify the output of this one-pot–three-step reaction by using palladium cross-coupling reactions on the benzo ring of the indazolone moiety. As outlined in Scheme 4, this was achieved by first preparing 7-bromooxazolino[3,2-*b*]indazole **1d**.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

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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) $-\text{CH}_2\text{Br} \rightarrow -\text{CH}_2\text{N}_3$ 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

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novel triazolotriazepinoindazolones as part of our commitment to the NIH MLSMR.

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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>.

The authors declare no competing financial interest.