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Nucleophilic Substitution of Oxazino-/Oxazolino-/Benzoxazin-[3,2-*b*]indazoles: An Effective Route to 1 *H*-Indazolones

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Abstract

A variety of nucleophiles – thiolates, alkoxides, amines, iodide, and cyanide – react with oxazino-, oxazolino-, and benzoxazin[3,2-*b*]indazoles under microwave conditions to yield a diverse set of 2-substituted 1 *H*-indazolones. The synthetic utility of these indazoles is further demonstrated by ANRORC (Addition of the Nucleophile, Ring Opening, and Ring Closure) reactions to yield isomeric pyrazoloindazolones by a process wherein iodide acts first as a nucleophile and subsequently as a leaving group.

The indazole ring and its derivatives have been reported to exhibit analgesic,¹ antitumor,² anticancer,³ anti-inflammatory,⁴ and anti-fertility activity.⁵ Of the two indazole isomers, 2*H*-indazoles are much less explored than 1*H*-indazoles.⁶ As a continuation of our interest in the chemistry of 2*H*-indazoles and the related 1*H*-indazolones,⁷ we set out to synthesize a series of 1*H*-indazolone derivatives as part of our commitment to the National Institute of General Medical Sciences (NIGMS) for the creation of pilot-scale libraries.

We recently reported that treatment of 2-(2-nitro-benzylamino)propan-1-ol (**1b**) with KOH in 10% aqueous *i*-PrOH results in a one-pot, bis-heterocyclization to oxazolino[3,2-*b*]indazole **2b**.⁸ In contrast, treatment of 2-(2-nitrobenzylamino)ethanol (**1a**) with KOH in 70% aqueous MeOH produces 2-(2-methoxyethyl)-1*H*-indazol-3(2*H*)-one (**3a**). We subsequently discovered that treating indazole **2b** with MeOH/KOH causes it to undergo ‘dealkylative’ ring-opening to give 2-(1-methoxypropan-2-yl)-1*H*-indazol-3(2*H*)-one (**3b**), suggesting that **1a** delivered **3a** via the intermediacy of indazole **2a** (Scheme 1).

Herein, we report a study of indazole-based nucleophilic ring-opening reactions on substrates **2c**, **5**, and **6**. Indazole derivatives **2c**, **5**, and **6**⁹ were prepared by a one-pot alkylation/bis-heterocyclization process starting from 1-(bromomethyl)-2-nitrobenzene, whereas indazole **4** was prepared by an analogous, but stepwise, process (Scheme 2). Treating indazole **4** with sodium ethanethiolate under microwave conditions (155 °C, 10 min) delivered the anticipated dealkylated indazolone **7** in 62% unoptimized yield and

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

presumably ethyl(methyl)-sulfide.¹⁰ With this initial result in hand, we began a detailed study of the indazole-based nucleophilic ring-opening reaction of indazoles **2c**, **5**, and **6**.

As illustrated in Table 1, a variety of nucleophiles were investigated in the reaction with **6**, including thiolates, alkoxides, amines, and iodide. The yields of these reactions varied between fair to nearly quantitative and several reactivity trends were observed. In addition, solvent optimization was conducted. Variable and generally moderate reactivity were observed in MeOH, THF, or MeCN. However, DMF gave the best and most consistent results under microwave conditions. Comparable results were generally obtained using DMSO as solvent.

This nucleophile study began with indazolobenzox-azine **6**. Thiolate, alkoxy, and 1°-amine nucleophiles produced 1*H*-indazolones **8** – **14** in fair to good yield. Despite the benzylic nature of the breaking C,O-bond, **6** proved unreactive towards several other nucleophiles (diisopropyl amine, isocyanate, isothiocyanate, azide, and methyl Grignard).

An interesting result came from the reaction of indazole **6** with KI. As depicted in Scheme 3, iodide opens the benzoxazine heterocycle as anticipated to presumably give potassium 2-(2-(iodo-methyl)phenyl)-3-oxo-2,3-dihydroindazol-1-ide which, by a subsequent intramolecular *N*-alkylation, cyclizes to indazolo[2,1-*a*]indazol-6(12*H*)-one (**15'**). This **6** → **15'** conversion proceeds by an ANRORC (Addition of the Nucleophile, Ring Opening, and Ring Closure) reaction.¹⁰

With these encouraging results in hand, we turned to a study of the nucleophile-initiated chemistry of 5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (**2c**); the results are outlined in Table 2. Indazole **2c** was found to be more reactive toward nucleophilic attack and, in most cases, delivered the ring-opened product in higher yield compared to **6**.¹¹

We observed no apparent reaction upon treatment of indazole **2c** with KI – although the results with indazole **6** would suggest that, most probably, **2c** does open to intermediate **23'**. However, confronted with an *N*-alkylative cyclization to a 4-membered ring, we postulate that **23'** instead cyclizes back to **2c** via an *O*-alkylation reaction (Scheme 4).

Based on the assumption that **2c** and **23'** are in equilibrium in the presence of KI under thermal conditions, we speculated that **2c** could be effectively opened with less reactive nucleophiles via the intermediacy of **23'**. To test this, stoichiometric KI was added to the reaction mixture to form transient intermediate **23'**, which was subsequently intercepted by the secondary nucleophile to give the ring-opened 1*H*-indazolone (rather than cyclizing back to indazole **2c**). This modified Finkelstein method¹² enabled the production of indazolones **24** and **25** in fair yields (Table 2, entries 9 and 10).

We next investigated nucleophilic addition to 3,4-dihydro-2*H*-[1,3]oxazino[3,2-*b*]indazole (**5**), the results of which are outlined in Table 3. Indazole **5** displayed reactivity between that of **2c** and **6**. Like **6**, indazole **5** reacts with potassium iodide to give an *N*-alkylated final product (**34'**; see Scheme 5) by an ANRORC process. Likewise, when potassium iodide was added to the reaction in attempt to synthesize indazolones **30**, **35**, and **36**, the ANRORC process was favored yielding **34'** rather than the targeted indazolones.

Another interesting result was observed in the reaction of indazole **5** with alkoxides (Table 3, entries 5 and 6). Whereas **2c** and **6** gave the targeted ether-containing indazolone, **5** gave elimination products **38** and **39** (see Scheme 5). In this transromation, alkoxides – even 1°-alkoxides – react with **5** as a base presumably to give sodium 2-allyl-2*H*-indazol-3-olate. Under these basic conditions, a subsequent isomerization from allyl to vinyl amide¹³

delivers an (E)-**38**/(Z)-**39** mixture in 57% combined yield (3:2 non-thermodynamic ratio, respectively).

In light of this **5** → **38/39** result, we also investigated the alkoxide-mediated chemistry of oxazolino[3,2-*b*]-indazoles **2b** and **2d** (see Scheme 6). Indazole **2b**, like **2c**, very cleanly gives oxazolino opening and produces indazolone–ether **40** in excellent yield. In contrast, indazole **2d** gives no addition product, producing only enamides **38** and **39** in a 9:1 thermodynamic ratio, respectively, in 99% combined yield.

In summary, we have demonstrated that nucleophilic ring-opening of oxazolo- and oxazino[3,2-*b*]indazoles can lead to novel 2-substituted-1*H*-indazolones that via other methods are difficult to access. A simple route to a variety of 2-substituted-1*H*-indazolones is reported. In addition, an unexpected example of the ANRORC reaction was realized. Further investigation as to the scope and application of this ANRORC reaction will be the focus of future reports.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Nucleophilic opening of oxazolo[3,2-*b*]indazoles.

Scheme 2. Dealkylative indazole $\rightarrow$ indazolone conversion.

Scheme 3.
Potassium iodide mediated ANRORC reaction of **6**.

Scheme 4.
Potassium iodide reaction with indazole **2c**.

Scheme 5.
ANRORC and elimination reactions with indazole 5.

Scheme 6. Alkoxide-mediated chemistry of indazoles **2b** and **2d**.

Table 1Nucleophilic ring-opening of indazole **6**.

entry	nucleophile	indazolone	yield
1	CH ₃ CH ₂ SNa	8	77%
2	C ₆ H ₅ SNa	9	99%
3	HO(CH ₂) ₂ SNa	10	74%
4	CH ₃ (CH ₂) ₇ ONa	11	52%
5	<i>n</i> -C ₅ H ₉ ONa	12	35%
6	<i>i</i> PrNH ₂	13	NR
7*	C ₆ H ₅ NH ₂	14	58%
8	KI	15	<i>see</i> Scheme 5

NR
No Reaction.*
140 °C for 30 min.

Table 2Nucleophilic ring-opening of indazole **2c**.

entry	nucleophile	indazolone	yield	yield w/KI
1	CH ₃ CH ₂ SNa	16	85%	
2	C ₆ H ₅ SNa	17	99%	
3	HO(CH ₂) ₂ SNa	18	95%	
4	KCN	19	38%	58%
5	CH ₃ (CH ₂) ₇ ONa	20	88%	
6	<i>n</i> -C ₅ H ₉ ONa	21	80%	
7*	<i>i</i> PrNH ₂	22	59%	61%
8	KI	23	see Scheme 4	
9	O=C=NK	24	NR	44%
10	NaN ₃	25	NR	48%
11	H ₃ CMgBr	26	NR	

* 170 °C for 120 min.

NR No Reaction.

Table 3Nucleophilic ring-opening of indazole **5**.

entry	nucleophile	indazolone	yield
1	CH ₃ CH ₂ SNa	27	53%
2	C ₆ H ₅ SNa	28	67%
3	HO(CH ₂) ₂ SNa	29	47%
4	KCN	30	NR
5	CH ₃ (CH ₂) ₇ ONa	31	<i>see</i> Scheme 5
6	<i>n</i> -C ₅ H ₉ ONa	32	<i>see</i> Scheme 5
7*	<i>i</i> PrNH ₂	33	38%
8	KI	34	<i>see</i> Scheme 5
9	O=C=NK	35	NR
10	NaN ₃	36	NR
11	H ₃ CMgBr	37	NR

^{NR} No Reaction.

* 170 °C for 120 min.