ORGANIC LETTERS

2010
Vol. 12, No. 11
2524−2527

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

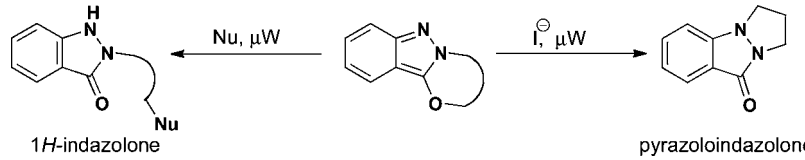
Michael B. Donald,[†] Wayne E. Conrad,[†] James S. Oakdale,[†] Jeffrey D. Butler,[†] Makhluf J. Haddadin,[*,‡] and Mark J. Kurth[*,†]

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

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

Received March 31, 2010

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 antifertility 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-nitrobenzylamino)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).

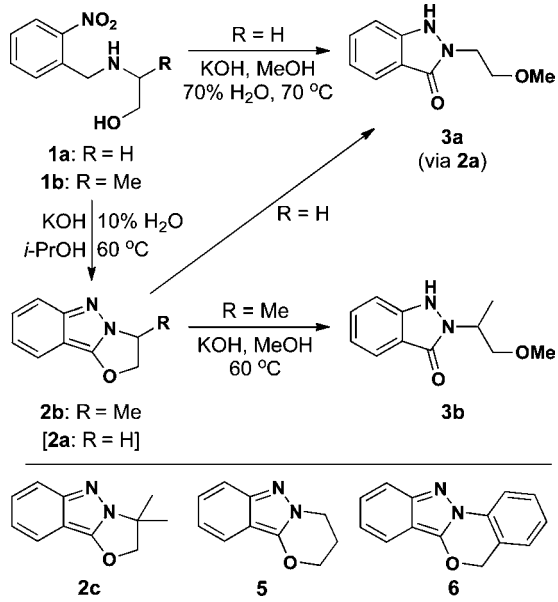
Herein, we report a study of indazole-based nucleophilic ring-opening reactions on substrates **2c**, **5**, and **6**. Indazole

[†] University of California.
[‡] American University of Beirut.

(1) Fletcher, S. R.; Mclver, 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.
(2) Wang, H.; Han, H.; Von Hoff, D. D. *Cancer Res.* **2006**, *66*, 9722.
(3) Kawanishi, N.; Sugimoto, T.; Shibata, J.; Nakamura, K.; Masutani, K.; Ikuta, M.; Hirai, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5122.
(4) Abouzid, K. A. M.; El-Abhar, H. S. *Arch. Pharmacal Res.* **2003**, *26*, 1.
(5) (a) Silvestrini, B.; Cheng, C. Y. US Patent Appl. 99-304042, 1999. (b) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; de Ocariz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869.
(6) (a) Halland, N.; Nazaré, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6879. (b) Viña, D.; del Olmo, E.; Lopez-Pérez, J. L.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525. (c) Stadlbauer, W.; Camp, N. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Bellus, D., Ley, S. V., Noyori, R., Regitz, M., Schaumann, E., Shinkai, E., Thomas, E. J., Trost, B. M., Reider, P. J., Eds.; Thieme: Stuggart, 2002; Vol. 12, p 227.
(7) (a) Dou, G.; Shi, D. *J. Comb. Chem.* **2009**, *11*, 1073. (b) Tanimori, S.; Ozaki, Y.; Iesaki, Y.; Kirihata, M. *Synlett* **2008**, *19*, 1973.
(8) Oakdale, J. S.; Solano, D. M.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2009**, *11*, 2760.

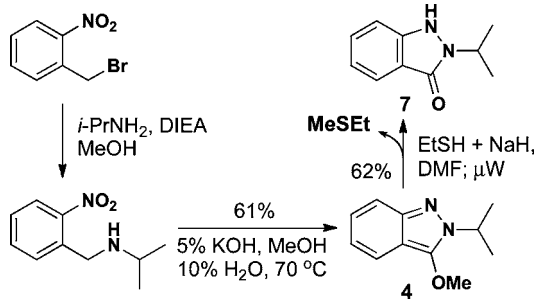
10.1021/ol100751n
Published on Web 05/03/2010

Scheme 1. Nucleophilic Opening of Oxazolo[3,2-*b*]indazoles



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).

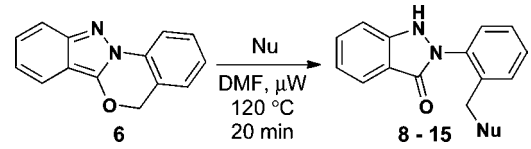
Scheme 2. Dealkylative Indazole → Indazolone Conversion



Treating indazole **4** with sodium ethanethiolate under microwave conditions (155 °C, 10 min) delivered the anticipated dealkylated indazolone **7** in 62% unoptimized yield and 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,

Table 1. Nucleophilic Ring-Opening of Indazole **6**



entry	nucleophile	indazolone	yield (%)
1	CH_3CH_2SNa	**8**	77
2	C_6H_5SNa	**9**	99
3	$HO(CH_2)_2SNa$	**10**	74
4	$CH_3(CH_2)_7ONa$	**11**	52
5	c-C_5H_9ONa	**12**	35
6	$iPrNH_2$	**13**	NR[b]
7[a]	$C_6H_5NH_2$	**14**	58
8	KI	**15**	see Scheme 5

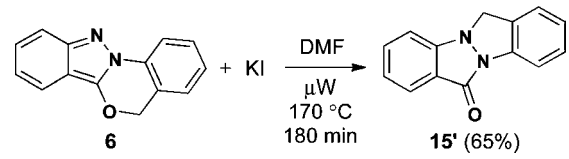
[a] 140 °C for 30 min. [b] NR = no reaction.

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 indazolobenzoxazine **6**. Thiolate, alkoxy, and primary 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 toward 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

Scheme 3. Potassium Iodide Mediated ANRORC Reaction of **6**



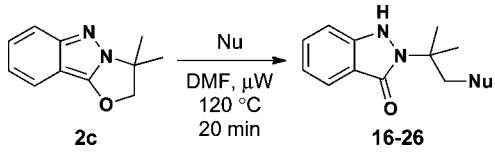
benzoxazine heterocycle as anticipated to presumably give potassium 2-(2-(iodomethyl)phenyl)-3-oxo-2,3-dihydroindazol-1-ide which, by a subsequent intramolecular *N*-alkylation, cyclizes to indazolo[2,1-*a*]indazol-6(12*H*)-one (**15′**). This **6** → **15′** conversion proceeds by an ANRORC (addition of the nucleophile, ring-opening, and ring closure) reaction.[11]

With these ecouraging 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

(9) A detailed description of the preparation of indazole **6** has been submitted to *Organic Syntheses*.

(10) Caution: Although no safety issues arose with the combination of NaH/DMF in this work, large batches have resulted in uncontrollable exotherms. See: (a) Urben, P. G., Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Elsevier: San Francisco, 2007; Vol. 1, p 1672. (b) Buckley, J.; Webb, R. L.; Laird, T.; Ward, R. J. *Chem. Eng. News* **1982**, *60*, 5. (c) De Wall, G. *Chem. Eng. News* **1982**, *60*, 5–43.

Table 2. Nucleophilic Ring-Opening of Indazole **2c**



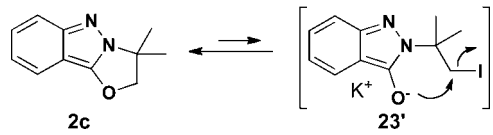
entry	nucleophile	indazolone	yield (%)	yield w/KI (%)
1	CH_3CH_2SNa	**16**	85	
2	C_6H_5SNa	**17**	99	
3	$HO(CH_2)_2SNa$	**18**	95	
4	KCN	**19**	38	58
5	$CH_3(CH_2)_7ONa$	**20**	88	
6	c-C_5H_9ONa	**21**	80	
7[a]	*i*$PrNH_2$	**22**	59	61
8	KI	**23**	see Scheme 4	
9	O=C=NK	**24**	NR[b]	44
10	NaN_3	**25**	NR	48
11	H_3CMgBr	**26**	NR	

[a] 170 °C for 120 min. [b] NR = no reaction.

nucleophilic attack and, in most cases, delivered the ring-opened product in higher yield compared to **6**.

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 four-membered ring, we postulate that **23′** instead cyclizes back to **2c** via an *O*-alkylation reaction (Scheme 4).

Scheme 4. Potassium Iodide Reaction with Indazole **2c**



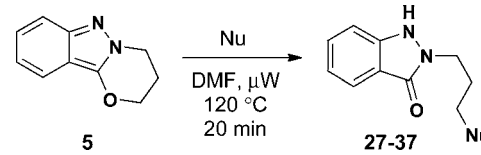
Based on the assumption that **2c** and **23′** are in equilibrium in the presence of KI under thermal conditions, we speculated that **2c** could be effectively opened with less reactive nucleophiles via the intermediacy of **23′**. To test this, stochiometric KI was added to the reaction mixture to 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 method[12] 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

(11) (a) Van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 1. (b) Van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462.

(12) (a) Cronan, J. M.; Lee, A.; Liang, J.; Clardy, J.; Cardellina, J. H., II. *J. Nat. Prod.* **2010**, *73*, 346–351. (b) Finkelstein, H. *Chem. Ber.* **1910**, *43*, 1528–1532.

Table 3. Nucleophilic Ring-Opening of Indazole **5**

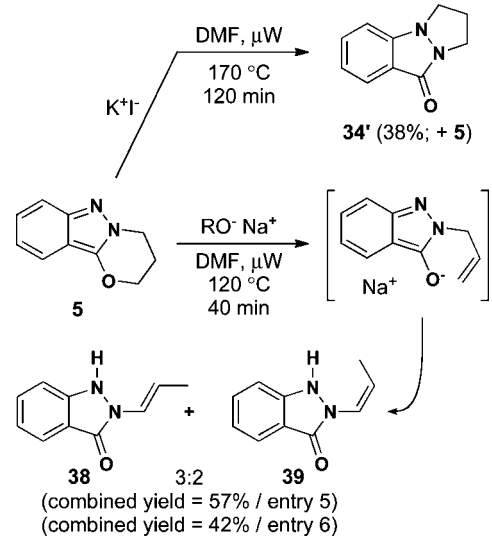


entry	nucleophile	indazolone	yield (%)
1	CH_3CH_2SNa	**27**	53
2	C_6H_5SNa	**28**	67
3	$HO(CH_2)_2SNa$	**29**	47
4	KCN	**30**	NR[b]
5	$CH_3(CH_2)_7ONa$	**31**	see Scheme 5
6	c-C_5H_9ONa	**32**	see Scheme 5
7[a]	*i*$PrNH_2$	**33**	38%
8	KI	**34**	see Scheme 5
9	O=C=NK	**35**	NR
10	NaN_3	**36**	NR
11	H_3CMgBr	**37**	NR

[a] 170 °C for 120 min. [b] NR = no reaction.

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′**; Scheme 5)

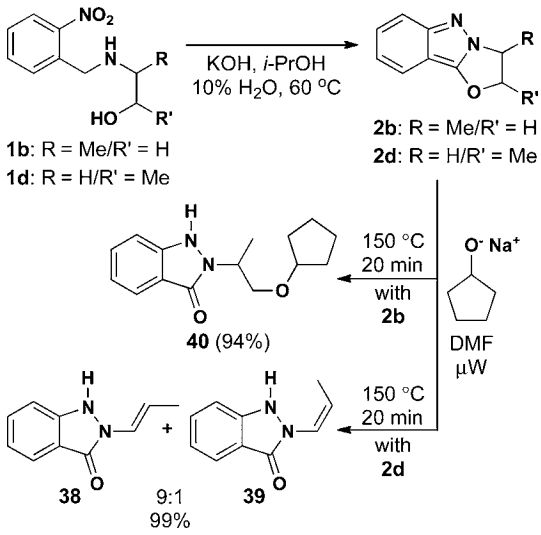
Scheme 5. ANRORC and Elimination Reactions with Indazole **5**



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 transformation, alkoxides, even primary alkoxides, react with

Scheme 6. Alkoxide-Mediated Chemistry of Indazoles **2b** and **2d**



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 amide[13] delivers an (*E*)-**38**/(*Z*)-**39** mixture in 57% combined yield (3:2 nonthermodynamic 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.

Acknowledgment. We thank the National Science Foundation (CHE-0910870) and the National Institutes of Health (GM089153) for generous financial support.

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

OL100751N

(13) Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257–5261.