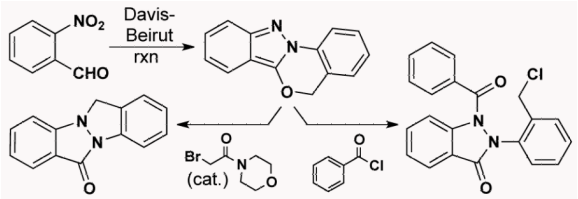
Published in final edited form as:
Org Lett. 2011 June 17; 13(12): 3138–3141. doi:10.1021/ol2010424.

The Davis-Beirut Reaction: *N*[1],*N*[2]-Disubstituted-1 *H*-Indazolones via 1,6-Electrophilic Addition to 3-Alkoxy-2*H*-Indazoles

Wayne E. Conrad[†], **Ryo Fukazawa**[†], **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

Abstract



A variety of electrophiles (anhydrides, acid chlorides, carbonochloridates, sulfonyl chlorides, and alkyl bromides) react with 3-methoxy-2*H*-indazole (1a), benzoxazin[3,2-b]indazole (1d), and oxazolino[3,2-b]indazole (1e) – substrates available by the Davis-Beirut reaction – to yield a diverse set of *N*[1],*N*[2]-disubstituted-1*H*-indazolones. With certain electrophiles, an AERORC (Addition of the Electrophile, Ring Opening, and Ring Closure) process on indazole 1d results in indazoloindazolone formation. An intriguing aspect of these *N*[1],*N*[2]-disubstituted-1*H*-indazolones is that they are poised for diversification through, for example, azide-alkyne cycloaddition chemistry reported here.

The indazole and indazolone ring systems are privileged heterocycles[1] known to exhibit analgesic, antitumor, anticancer, antiangiogenic, antiviral, and antiinflammatory activities. Of the two isomers, 2*H*-indazoles are less explored than 1*H*-indazoles.[2] In previous reports,[3] our laboratory has demonstrated the utility of the Davis-Beirut reaction – an effective *N*,*N*-bond forming heterocyclization reaction – to deliver 3-alkoxy-*2H*-indazoles, benzoxazin[3,2-b]-indazole, oxazolino[3,2-b]indazole, and a variety of other indazolo-fused hetero-cycles from 2-nitrobenzaldehyde or 1-(bromomethyl)-2-nitrobenzene.

We showed more recently that 3-alkoxy-2*H*-indazoles can be converted into *N*[2]-substituted-1*H*-indazolones by treatment with various nucleophiles.[4] For example, reaction of indazole **1a** with sodium ethanethiolate under microwave conditions (155 °C, 10 min) delivers, by demethylation, indazolone **2** in 62% yield (Scheme 1). This led to an investigation of the scope of nucleophilic ring-opening of indazoles **1b-d** and established that a variety of nucleophiles can be employed to produce a diverse set of *N*[2]-substituted-1*H*-indazolones.

[*]Corresponding authors. haddadin@UAB.edu.lb; mjkurth@ucdavis.edu.
[†]University of California.
[§]American University of Beirut.

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.

With these results as a backdrop, we speculated that 3-alkoxy-2*H*-indazoles, available by the Davis-Beirut reaction, might also react with an electrophile to give a positively charged N^1 which would, in turn, drive a counter anion to attack giving net 1,6-electrophilic addition across the 2H-indazole. In fact, treating indazole **1a** with refluxing HOAc affords indazolone **2** (Scheme 2), while heating with sodium acetate in DMF for the same period of time (118 °C, 17 h) gives no reaction.

Building on this simple but encouraging result, we launched an investigation of the effectiveness of 1,6-electrophilic addition to indazole **1a** using the diverse set of electrophiles shown in Scheme 3 (**E1**-**E9**). This study revealed that indazole **1a** reacts with each of these various electrophiles to produce a diverse set of N^1,N^2-disubstituted-1*H*-indazolones. Reaction optimization established that thermal heating, although requiring a longer reaction time than microwave irradiation, results in higher yields. Additionally, for all electrophiles except **E1** and **E2** where reactions were performed in HOAc and Ac_2O (respectively), solvent optimization showed that CH_3CN led to higher yields than either DMF or DMSO.

We next investigated the 1,6-electrophilic addition reactivity of oxazolino[3,2-*b*]indazole **1e**. As presented in Scheme 4, indazole **1e** reacts with all nine electrophiles (**E1**-**E9**) to produce a diverse set of N^1,N^2-disubstituted-1*H*-indazolones in excellent yield. It was also noted that electrophilic addition to **1e** was generally much faster and higher yielding than addition to indazole **1a** – most likely due to relief of strain in the 5-membered oxazolino ring.

An interesting turn of events occurred when we investigated the electrophilic addition to indazole **1d**. While treatment of **1d** with benzoyl chloride in acetronitrile at 60 °C delivered the anticipated indazolone **20** in 99% yield, treating it with 2-bromo-1-morpholinoethanone in acetonitrile at 82 °C gave indazolo[2,1-a]indazol-6(12*H*)-one **22** as the sole product (Scheme 5). LCMS monitoring of the reaction indicated that the originally anticipated indazolone **21** was indeed formed as a transient intermediate, but, under the conditions of the reaction, it quickly converted to indazoloindazolone **22**. Based on the fact that **22** is not formed when N^1 of the indazole is acylated (**1d** → **20**), we speculate that indazoloindazolone formation occurs via an AERORC (Addition of the Electrophile, Ring Opening, and Ring Closure)[6] process that we speculate transposes through the intermediacy of indazoloindazolium **21′**. Indeed, this AERORC process (**1d** → **22**) is competitive in rate with the alkylation/ring-opening reaction (**1d** → **21**) and the only way to obtain appreciable amounts of **21** (28%) is to stop the reaction early (~57% conversion of **1d**). It was also found that treating **1d** with catalytic (10 mol%) 2-bromo-1-morpholinoethanone delivers **22** in high yield (82 °C, 7 d, 79% yield; μw, 150 °C, 5 h, 92 % yield).

An intriguing aspect of many of the indazolones presented in Schemes 3 and 4 is that they are poised for further diverstification through, for example, azide-alkyne cycloaddition chemistry.[7] Capitalizing on this opportunity, we next set out to synthesize a small library of twenty triazolyl-indazolones (**23**-**32** and **33**-**42**) as a part of our commitment to the NIH Molecular Libraries Small Molecule Repository for high-throughput biological screening. As illustrated in Scheme 6, indazolone **7** (entry 6, Scheme 3), containing a propynyl moiety, was used for part one of this click diversification study. *In situ* generated azides – prepared from amines **A1**-**A10** by treatment with 1*H*-imidazole-1-sulfonyl azide[8] and $CuSO_4$ – were employed in these copper(I)-catalyzed cycloadditions to give indazolones **23**-**32** in high yields.

For part two of this click diversification study, we decided to prepare a collection of ten triazolyl-indazolones based on indazole **19** (entry 9, Scheme 4). We envisioned a one-pot reaction[9] for this process wherein indazolone **19** was heated first with sodium azide,

followed by the addition of copper (I) and the alkyne. To test the reliability of the first step (R-Br → R-N_3), indazolone **19** was treated with sodium azide at 60 °C in DMF and the corresponding primary azide was cleanly obtained in 3 hours reaction time. We next sought to trap the azide with an alkyne in a one-pot, two-step reaction to give the corresponding triazole product. The results of ten such reactions are summarized in Scheme 7 and show that a variety of alkynes react to give 1,4-triazoles in good to excellent yields.

In summary, we have demonstrated that electrophilic addition to 3-methoxy-2*H*-indazole (**1a**), benzoxazin[3,2-b]indazole (**1d**), and oxazolino[3,2-b]indazole (**1e**) substrates can lead to novel N^1,N^2-disubstituted-1*H*-indazolones that are difficult to access by other methods. A rare example of a heterolytic AERORC reaction has been demonstrated with the rearrangement of benzoxazin-[2,3-b]indazole **1d** to indazolonoindazole **22** via the intermediacy of indazolone **21**. Finally, further diversification of two N^1,N^2-disubstituted-1*H*-indazolone products through azide-alkyne cycloaddition chemistry was demonstrated yielding a small library of novel triazoles.

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. WEC acknowledges the United States Department of Education for a GAANN Fellowship.

References

(1). (a) Schmidt A, Beutler A, Snovydovych B. Eur. J. Org. Chem. 2008:4073.(b) Fletcher SR, McIver E, Lewis S, Burkamp F, Leech C, Mason G, Boyce S, Morrison D, Richards G, Sutton K, Jones AB. Biorg. Med. Chem. Lett. 2006; 16:2872.(c) Kawanishi N, Sugimoto T, Shibata J, Nakamura K, Masutani K, Ikuta M, Hirai H. Biorg, Med. Chem. Lett. 2006; 16:5122.(d) 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.(e) Cerecetto H, Gerpe A, Gonzalez M, Aran VJ, Ochoa de Ocariz C. Mini-Rev, Med. Chem. 2005; 5:869. [PubMed: 16250831]

(2). (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 JL, San Feliciano A. Org. Lett. 2007; 9:525. [PubMed: 17249803] (c) Stadlbauer W. Science of Synthesis. 2002; 12:227.(d) Elguero, I. Comprehensive Heterocyclic Chemistry. Katritzky, AR.; Rees, CW.; Scriven, EFV., editors. Vol. 3. Pergamon; Oxford: 1996. p. 1-75.

(3). (a) Avila B, Solano DM, Haddadin MJ, Kurth MJ. Org. Lett. 2011; 13:1060. [PubMed: 21294577] (b) Solano DM, Butler JD, Haddadin MJ, Kurth M,J. Org. Synth. 2010; 87:339.(c) Butler JD, Solano DM, Robins LI, Haddadin MJ, Kurth MJ. J. Org. Chem. 2008; 73:234. [PubMed: 18052193] (d) Mills AD, Maloney P, Hassanein E, Haddadin MJ, Kurth M,J. J. Comb. Chem. 2007; 9:171. [PubMed: 17206845] (e) Mills AD, Nazer MZ, Haddadin MJ, Kurth MJ. J. Org. Chem. 2006; 71:2687. [PubMed: 16555821] (f) Kurth MJ, Olmstead MM, Haddadin MJ. J. Org. Chem. 2005; 70:1060. [PubMed: 15675871]

(4). (a) Oakdale JS, Solano DM, Fettinger JC, Haddadin MJ, Kurth MJ. Org. Lett. 2009; 11:2760. [PubMed: 19505119] (b) Donald MB, Conrad WE, Oakdale JS, Butler JD, Haddadin MJ, Kurth MJ. Org. Lett. 2010; 12:2524. [PubMed: 20438102]

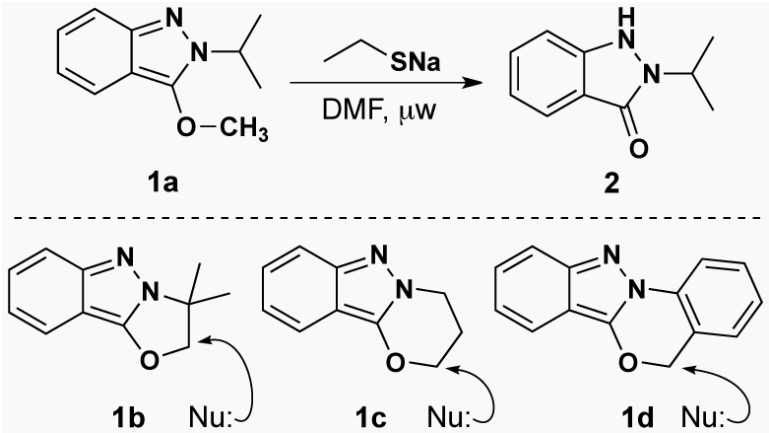
(5). Liu Y, Cui Z, Liu B, Cai B, Li Y, Wang Q. J. Agric. Food Chem. 2010; 58:2685. [PubMed: 20000686]

(6). (a) While the ANRORC[6b-6d] process is well documented, this is a rare example of a heterocyclic AERORC process. (b) Van der Plas HC. Acc. Chem. Res. 1978; 11:462. (c) Van der Plas HC. Adv. Heterocycl. Chem. 1999; 74:1. (d) See reference 8.

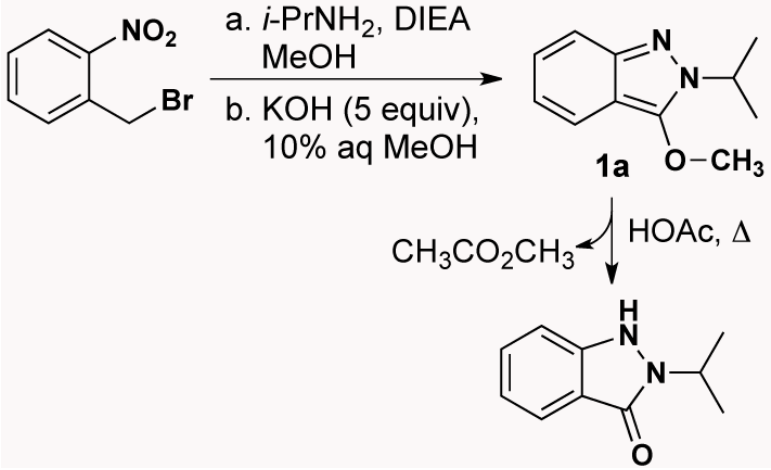
(7). (a) Rostovtsev VV, Green LG, Fokin VV, Sharpless BK. Angew. Chem., Int. Ed. 2002; 41:2596. (b) Tornoe CW, Christensen C, Meldal M. J. Org. Chem. 2002; 67:3057. [PubMed: 11975567] For Reveiews of Click Chemistry, see: (c) Meldal M, Tornøe W. Chem. Rev. 2008; 108:2952. [PubMed: 18698735] (d) Hein JE, Fokin VV. Chem. Soc. Rev. 2010; 39:1302. [PubMed: 20309487]

(8). Goddard-Borger ED, Stick RV. Org. Lett. 2007; 9:3797. [PubMed: 17713918]

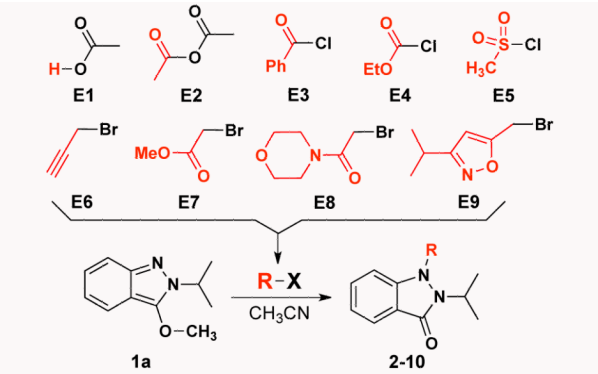
(9). Feldman AK, Colasson B, Fokin VV. Org. Lett. 2004; 6:3897. [PubMed: 15496058]



Scheme 1.
Nucleophilic ring-opening of 3-alkoxy-*2H*-indazoles



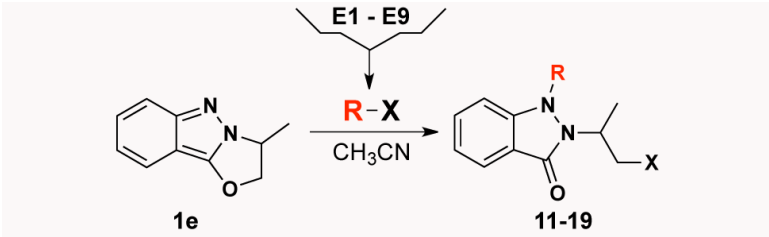
Scheme 2.
Davis-Beirut recation → **1a** → **2**



entry	electrophile	indazolone	yield (%)
1	**E1**	**2**	86[a]
2	**E2**	**3**	83[b]
3	**E3**	**4**	94
4	**E4**	**5**	95
5	**E5**	**6**	70
6	**E6**	**7**	83
7	**E7**	**8**	95
8	**E8**	**9**	84
9	**E9**[5]	**10**	91

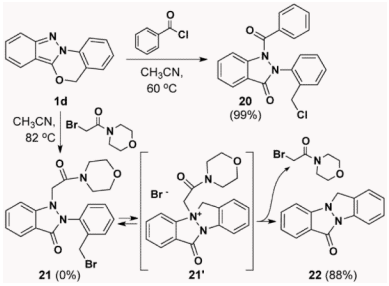
[a]Performed at reflux in HOAc. [b]Performed at reflux in Ac_2O.

Scheme 3.
1,6-Electrophilic addition to 3-methoxy-2*H*-indazole **1a**

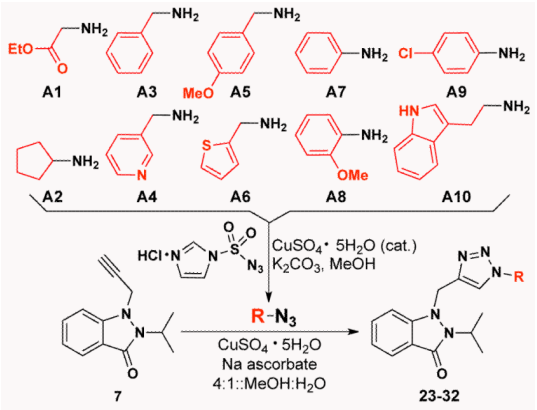


entry	electrophile	indazolone	yield (%)
1	**E1**	**11**	94
2	**E2**	**12**	99
3	**E3**	**13**	90
4	**E4**	**14**	97
5	**E5**	**15**	94
6	**E6**	**16**	98
7	**E7**	**17**	91
8	**E8**	**18**	86
9	**E9**[5]	**19**	95

Scheme 4.
1,6-Electrophilic addition to oxazolino[3,2-b]-indazole **1e**

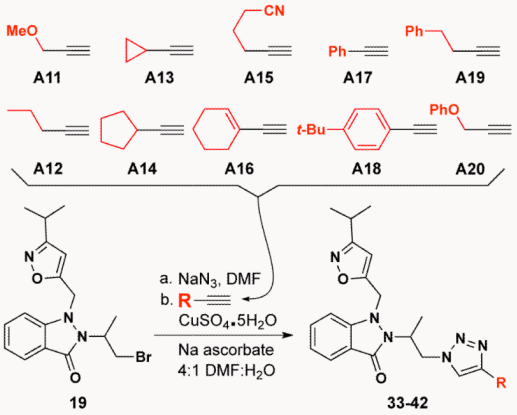


Scheme 5.
1,6-Electrophilic addition (→ **20**) vs. AERORC (→ **22**)



entry	amine	indazolone	yield (%)
1	**A1**	**23**	80
2	**A2**	**24**	99
3	**A3**	**25**	96
4	**A4**	**26**	99
5	**A5**	**27**	99
6	**A6**	**28**	92
7	**A7**	**29**	98
8	**A8**	**30**	73
9	**A9**	**31**	81
10	**A10**	**32**	88

Scheme 6.
CuAAC reactions on indazolone **7**



entry	alkyne	indazolone	yield (%)
1	**A11**	**33**	90
2	**A12**	**34**	95
3	**A13**	**35**	99
4	**A14**	**36**	82
5	**A15**	**37**	99
6	**A16**	**38**	82
7	**A17**	**39**	95
8	**A18**	**40**	99
9	**A19**	**41**	97
10	**A20**	**42**	78

Schcme 7.
CuAAC reactions on indazolone **19**