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

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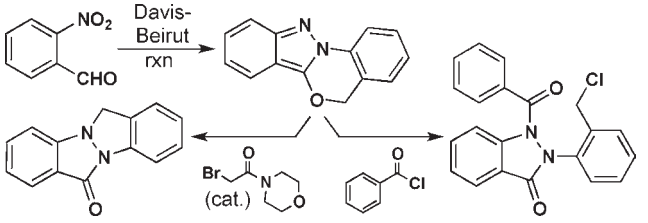
ABSTRACT



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 anti-inflammatory 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-2*H*-indazoles, benzoxazin[3,2-*b*]-indazole, oxazolino[3,2-*b*]indazole, and a variety of other indazolo-fused heterocycles 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

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(1) (a) Schmidt, A.; Beutler, A.; Snovydovych, B. *Eur. J. Org. Chem.* **2008**, 4073. (b) Fletcher, S. R.; McIver, E.; Lewis, S.; Burkamp, F.; Leech, C.; Mason, G.; Boyce, S.; Morrison, D.; Richards, G.; Sutton, K.; Jones, A. B. *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, V. J.; Ochoa de Ocariz, C. *Mini-Rev. Med. Chem.* **2005**, *5*, 869.

(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, J. L.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525. (c) Stadlbauer, W. *Sci. Synth.* **2002**, *12*, 227. (d) Elguero, I. *Comprehensive Heterocyclic Chemistry*, Vol. 3; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; pp 1–75.

(3) (a) Avila, B.; Solano, D. M.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2011**, *13*, 1060. (b) Solano, D. M.; Butler, J. D.; Haddadin, M. J.; Kurth, M, J. *Org. Synth.* **2010**, *87*, 339. (c) Butler, J. D.; Solano, D. M.; Robins, L. I.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2008**, *73*, 234. (d) Mills, A. D.; Maloney, P.; Hassanein, E.; Haddadin, M. J.; Kurth, M, J. *J. Comb. Chem.* **2007**, *9*, 171. (e) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687. (f) Kurth, M. J.; Olmstead, M. M.; Haddadin, M. J. *J. Org. Chem.* **2005**, *70*, 1060.

(4) (a) Oakdale, J. S.; Solano, D. M.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2009**, *11*, 2760. (b) Donald, M. B.; Conrad, W. E.; Oakdale, J. S.; Butler, J. D.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2010**, *12*, 2524.

(5) Liu, Y.; Cui, Z.; Liu, B.; Cai, B.; Li, Y.; Wang, Q. *J. Agric. Food Chem.* **2010**, *58*, 2685.

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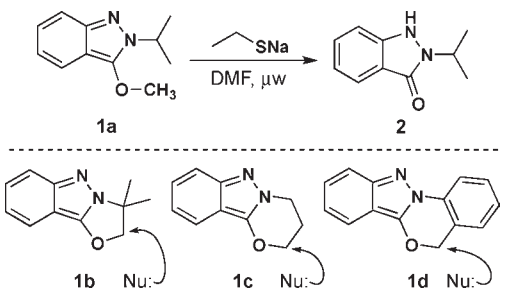
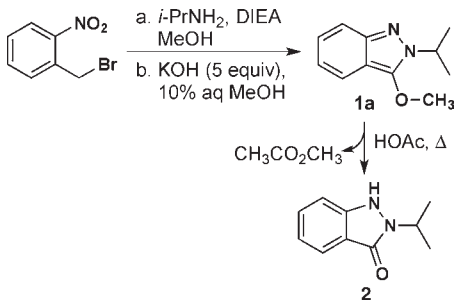
investigation of the scope of nucleophilic ring opening of indazoles **1b**–**d** and established that a variety of nucleophiles can be employed to produce a diverse set of N^2-substituted-1*H*-indazolones.

Scheme 1. Nucleophilic Ring Opening of 3-Alkoxy-2*H*-indazoles



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 counteranion to attack giving net 1,6-electrophilic addition across the 2*H*-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.

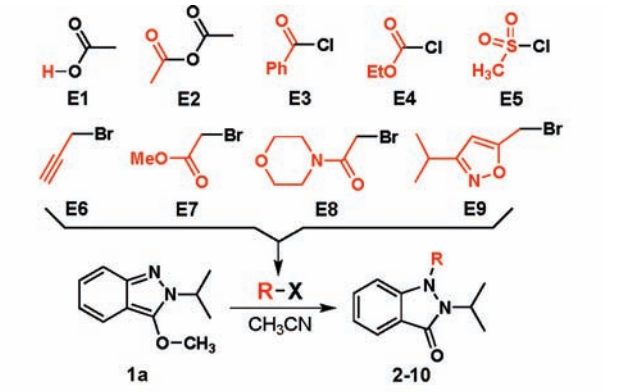
Scheme 2. Davis–Beirut Reaction → **1a** → **2**



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 3. 1,6-Electrophilic Addition to 3-Methoxy-2*H*-indazole **1a**



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

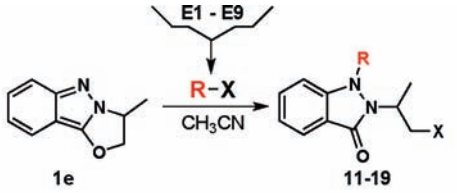
[a]Performed at reflux in HOAc. [b]Performed at reflux in Ac_2O.

Scheme 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 five-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 acetonitrile 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

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

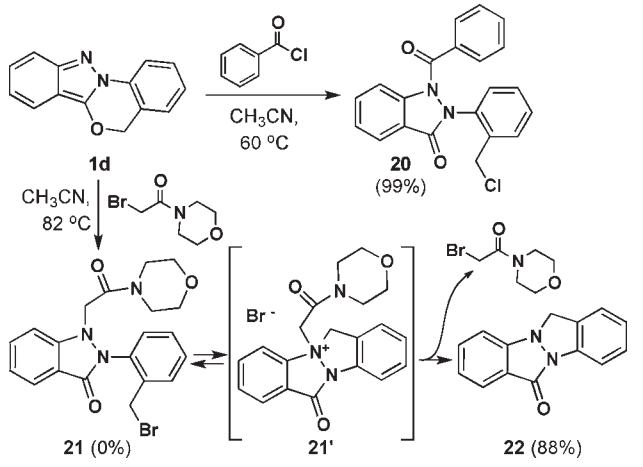
Scheme 4. 1,6-Electrophilic Addition to Oxazolino[3,2-*b*]-indazole **1e**



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

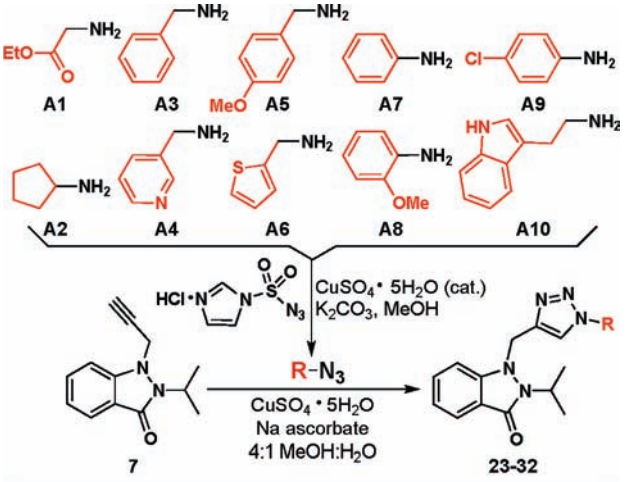
indazoloindazolium **21′**. Indeed, this AERORC process (**1d** → **22**) is competitive in rate with the alkylation/ring opening reaction (**1d** → **21**) and the only way to obtain appreciable amounts of **21** (28%) is to stop the reaction early (~57% conversion of **1d**). It was also found that 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).

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



(7) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, B. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. For reveiews of click chemistry, see:(c) Meldal, M.; Tornøe, W. *Chem. Rev.* **2008**, *108*, 2952. (d) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302.

Scheme 6. CuAAC Reactions on Indazolone **7**



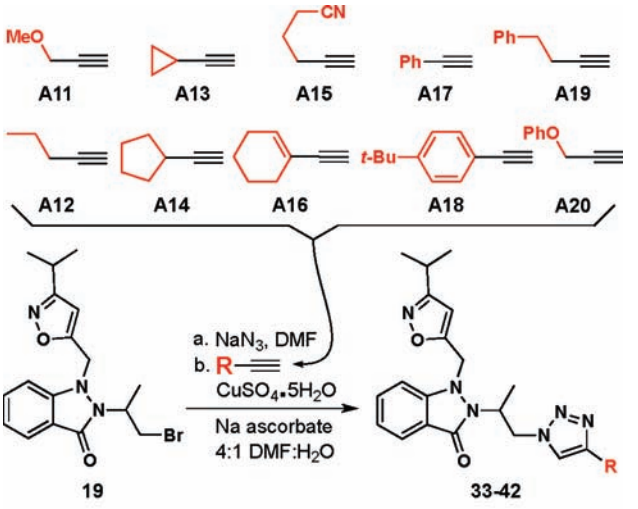
entry	amine	indazolone	yield (%)
1	**A1**	**23**	80
2	**A2**	**24**	99
3	**A3**	**25**	96
4	**A4**	**26**	99
5	**A5**	**27**	99
6	**A6**	**28**	92
7	**A7**	**29**	98
8	**A8**	**30**	73
9	**A9**	**31**	81
10	**A10**	**32**	88

An intriguing aspect of many of the indazolones presented in Schemes 3 and 4 is that they are poised for further diversification through, for example, azide–alkyne cycloaddition chemistry.[7] Capitalizing on this opportunity, we next set out to synthesize a small library of 20 triazolyl-indazolones (**23**–**32**, Scheme 6; and **33**–**42**, Scheme 7) 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 10 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

(8) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.
(9) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897.

Scheme 7. CuAAC Reactions on Indazolone **19**



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

with sodium azide at 60 °C in DMF and the corresponding primary azide was cleanly obtained within a 3 h 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 10 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.

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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.