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Journal

Journal of the American Chemical Society, 141(15)

ISSN

0002-7863

Authors

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Publication Date

2019-04-17

DOI

10.1021/jacs.8b13481

Peer reviewed

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Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2020 April 17.

Published in final edited form as:

J Am Chem Soc. 2019 April 17; 141(15): 6247–6253. doi:10.1021/jacs.8b13481.

Accessing Multiple Classes of 2*H*-Indazoles: Mechanistic Implications for the Cadogan and Davis-Beirut Reactions

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Abstract

The Cadogan cyclization is a robust but harsh method for the synthesis of 2*H*-indazoles, a valuable class of nitrogen heterocycles. Although nitrene generation by exhaustive deoxygenation is widely accepted as the operating mechanism in the reductive cyclization of nitroaromatics, non-nitrene pathways have only been theorized previously. Here, 2*H*-indazole *N*-oxides were synthesized through an interrupted Cadogan/Davis-Beirut reaction and are presented as direct evidence of competent oxygenated intermediates; mechanistic implications for both reactions are discussed. Isolation and characterization of these *N*-oxides enabled a formal Cadogan cyclization at room temperature for 2*H*-indazole synthesis.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13481.

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra, crystallographic information, and details of quantum chemical calculations (PDF)

X-ray crystallographic data (CIF)

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The authors declare no competing financial interest.

CCDC 1883187, 1883188, and 1883189 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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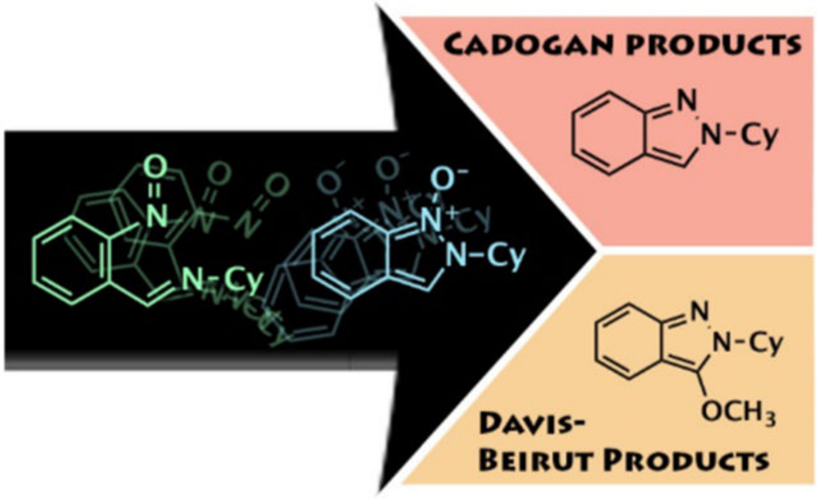

INTRODUCTION

The synthesis of nitrogen heterocycles is of paramount importance due to their high value in pharmaceutical applications. In particular, 2*H*-indazoles and their derivatives have highly desirable therapeutic properties,[1] for example, modulation of PARP,[2] VEGF,[3] GK,[4] and CRAF.[5]

The Cadogan reaction is a classical reductive cyclization method for synthesizing 2*H*-indazoles from nitroaromatic compounds.[6] The reaction is generally carried out at high temperatures, i.e., refluxing in excess trialkyl phosphites or trialkyl phosphines (typically at >150 °C). Recent advances made by Genung and co-workers allow the Cadogan reaction to proceed under milder, although not mild, conditions (80 °C).[7] The Cadogan cyclization using a catalytic amount of phosphorus based on a P^{III}/P^{V} redox cycling strategy has also been recently reported by Radosevich[8] and Nazaré.[9] This reductive heterocyclization is widely accepted to proceed via a nitrene intermediate derived by exhaustive deoxygenation of the nitro group (Scheme 1; **1a** → **2** → **3** → **4**). This mechanistic model is supported by the fact that aromatic azides can also be used to generate the targeted 2*H*-indazoles.[10]

On the other hand, studies of the related Sundberg reductive cyclization for indole synthesis have shown that N—O bond-containing indole byproducts can be isolated, an observation that seems incompatible with a nitrene mechanism.[6b] The Sundberg system has since been theoretically studied, and a five-center 6π electrocyclization was found to be a viable alternative pathway.[11] Taken together, these results imply that more than one mechanistic pathway may be operational in the reductive cyclization of nitroaromatics. Analogous N—O bond-containing byproducts have not been observed in the Cadogan cyclization, and a non-nitrene pathway has yet to be established.[11] This is perhaps due to the challenges associated with stopping the Cadogan reaction at the 2*H*-indazole *N*-oxide stage, because *N*-oxide-containing heterocycles are known to undergo rapid deoxygenation by phosphorus reagents at just 60—70 °C.[12] In contrast, hydroxy indoles are resistant to deoxygenation by triethyl phosphite even at >160 °C.[6b] Therefore, we have explored the chemistry of *o*-nitrosoimine **2**

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(Scheme 1) under non-deoxygenating conditions, with the complementary goals of developing synthetically useful reactions and increasing the understanding of the Cadogan and related reactions.

Our group previously reported the synthesis and applications of *in situ* generated *o*-nitrosobenzaldehyde in connection with the Davis—Beirut synthesis of 3-alkoxy 2*H*-indazoles[1] and indazolones.[13] Throughout these studies, nitrogen nucleophiles were found to react with the nitroso group, leading us to suggest that the imine of **2** can be recruited to react intramolecularly with its nitroso moiety to generate 2*H*-indazole *N*-oxide (Scheme 1; **2** → **5** ↔ **6**). Indeed, many well-known reactions are thought to rely on an imine being nucleophilic at nitrogen, such as the Staudinger reaction for *β*-lactam synthesis,[14] the Paal–Knorr pyrrole synthesis,[15] the Shaw four-component reaction for *γ*-lactam synthesis,[16] and the Castagnoli-Cushman reaction for δ-lactam synthesis[17] (note: nucleophilic attack by imine intermediates has not been fully demonstrated in all cases).

Biological activities of *N*-oxygenated derivatives of privileged heterocycles have been repeatedly demonstrated,[18] as shown by librium,[19] minoxidil,[20] tirapazamine,[21] and the widespread application of carbadox/olaquindox/cyadox.[22] The relative scarcity of 2*H*-indazole *N*-oxides perhaps accounts for their lack of representation among clinical candidates, although the antiprotozoal activity of 2*H*-indazole *N*-oxides has been reported.[23] Known methods for their construction involve the use of cyanide salts,[23] isocyanides,[24] 1,7-electrocyclizations,[25] 1,3-dipolar cycloadditions,[26] and rearrangements of sulfonyl amides.[27] Here, the development of a new and convenient method for 2*H*-indazole *N*-oxide synthesis is disclosed, with an eye toward empowering future studies on their medicinal potential.

RESULTS AND DISCUSSION

For the proposed intramolecular cyclization between the nitroso and the imine groups of **2** to occur, several reaction manifolds must be shut down. First, the formation of **2** must not involve external reduction of the nitro group due to the possibility of over-reduction.[28] Second, the solvent for the reaction must not be a primary alcohol due to the possibility of hemiaminal ether formation, which ultimately would lead to the corresponding 3-alkoxy-2*H*-indazole.[1] To address these issues, the following strategies were applied. First, a straightforward base-mediated conversion[29] of **9** → **2** (Table 1) was used rather than external reduction. Second, the reaction solvent employed was ^{i}PrOH because it is not effective[13] at converting **2** to the corresponding hemiaminal ether or subsequent 3-isopropoxy 2*H*-indazole. [29] In addition, base-mediated *N*-oxide deoxygenation[30] or indazolone formation could compete with the desired cyclization.[13] While base-mediated deoxygenation of the target *N*-oxides was circumvented by lowering the reaction temperature, indazolone formation is known to occur under ambient photochemical conditions.[31] Nonetheless, despite the relative uncertainty regarding whether indazolone formation would outcompete *N*-oxide formation, the outlined conditions were selected as a launch point for this investigation.

The reaction between *o*-nitrobenzyl bromide **9** and *n*-butylamine was performed in ^{i}PrOH, water, and KOH at room temperature to generate **2** *in situ*. LCMS analysis of the crude

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reaction mixture after 24 h revealed a mixture of products, including indazolone (Table 1). However, also in this mixture was a compound containing the targeted mass for 2*H*-indazole *N*-oxide **10**, and the mass spectrum of this compound featured a fragment consistent with N—O bond cleavage (see Table 1, mass spectrum at top right). This compound was isolated and the ^{13}C NMR data were in good agreement with *N*-oxide product **10**; these initial conditions gave **10** in only 15% yield (Table 1; entry 1). Next, a variety of non-alcohol solvents were screened (entries 2–7), and *N*-alkylation dominated in all solvents explored except DMSO (entry 7), which instead gave the *N*-oxide in 22% yield. The amount of water present was critical for the success of the reaction: water exclusion gave a complex mixture (entry 8), while increasing the amount of water to 1 mL resulted in a yield increase to 54% (entry 9). Further increasing the amount of water to 1.5 mL lowered the yield of **10** to 47% (entry 10). The reaction was also sensitive to the equivalents of base used. For example, using 40 equiv of KOH reduced the yield of **10** to 42% (entry 12), while using 10 equiv of KOH resulted in a 78% yield (entry 13). Further decreasing the amount of base to 5 or 2 equiv gave *N*-oxide in 58% yield (entries 14 and 15). As expected, increasing the reaction temperature above 40 °C led to a complex mixture of products, which did not contain the desired *N*-oxide (entries 16–19). Finally, *n*-butylamine equivalents were varied, and the reaction was found to be sensitive to this parameter. Decreasing the amine to 1 equiv resulted in a lower yield (entry 20), but 2 equiv gave similar results to 5 equiv (entries 13 and 21). Increasing to 10 equiv of amine gave the *N*-oxide in 91% yield (entry 22).

The scope of the reaction was explored using both 2 and 10 equiv of amine (Table 2). Consistent with the optimization studies described above, yields generally increased when 10, rather than 2, equiv of amine was used (**16**, **21**, and **22** are the exceptions). Yields of ~90% could be achieved in some cases; for example, compound **11** was synthesized in 92% yield at small scale and a comparable 89% yield at gram scale. Much of the trifluoromethyl-containing *N*-oxide **22** was deoxygenated even at room temperature. Using benzylamine as the starting material did not deliver **23** under basic conditions due to side-reactions leading to 3-phenylquinazoline formation,[13] but when KOH was excluded and the reaction was carried out under photochemical conditions,[31] **23** was obtained in 29% yield. Unfortunately, use of an aryl rather than alkyl amine is incompatible with these reaction conditions; for example, *N*-aryl 2*H*-indazole *N*-oxide **24** was not produced under either basic or photochemical conditions.

When the amine or *o*-nitrobenzyl bromide component of the reaction is either precious or of limited availability, 2*H*-indazole *N*-oxides may alternatively be synthesized using secondary *o*-nitrobenzyl amines (Table 3) by reductive amination of *o*-nitrobenzaldehyde using just **1** equiv of amine. Indeed, **10** was synthesized from the preformed benzylic amine in a yield (72%) comparable to that for the reaction using *o*-nitrobenzyl bromide (74%, Table 2, where 2 equiv of amine was used). Compound **25** could not be synthesized from the amine and benzyl bromide due to *N*-alkylation regioselectivity issues, but reductive amination of *o*-nitrobenzaldehyde followed by treatment with base gives **25** in 66% yield. Disappointingly, the starting material for **26** was difficult to dissolve in the DMSO/water mixture, and consequently, the yield of **26** was only 33%. This was not an issue with **27**, which was

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isolated in 62% yield. Attempts to synthesize *N*-aryl products (e.g., **28** and **24**) again were not successful; for example, in targeting **24**, *p*-anisidine was recovered instead in 14% yield.

The isolation of *p*-anisidine from the attempted synthesis of **24** suggests that water/hydroxide-promoted cleavage (akin to deprotection)[29] of the nitroso imine may be operational under the reaction conditions reported here, consistent with *N*-oxide **5**/**6** being in equilibrium with **2**, its ring-opened form (Scheme 1). This type of ring-opening/ring-closing process is well documented in the literature for *N*-oxide heterocycles.[32] While X-ray crystal structures for compounds **11**, **12**, and **16** (Figure 1) were consistent with the proposed 2*H*-indazole *N*-oxide, it was not possible to rule out that perhaps the ring-closed form is favored only in the solid state. Therefore, we turned to solution NMR and compared experimental ^{13}C NMR values for our compounds to reported literature values of related compounds [25] and found them to be in good agreement. In addition, we sought an additional layer of reassurance using quantum chemically computed NMR chemical shifts.[33] Thus, the ^{1}H and ^{13}C chemical shifts for **11** and its ring-opened form were calculated using the gauge-including atomic orbital (GIAO) method.[34] The geometries of all conformers for each structure were optimized at the B3LYP/6-31+G(d,p) level.[35] NMR calculations were performed on the optimized structures at the mPW1PW91/6-311+G(2d,p) level,[36] using the SMD continuum model for chloroform.[37] A linear scaling approach was used.[33b,38] The calculated chemical shifts of **11** (Table 1 and 2 in the Supporting Information) were consistent with the experimentally observed shifts (mean absolute deviations of only 0.14 and 1.29 ppm for ^{1}H and ^{13}C chemical shifts, respectively). In contrast, computed shifts for the ring-opened form, which is predicted to be ~5 kcal/mol higher in energy than **11**, deviate greatly from the experimental shifts. Note that there exists a C—H…O interaction between the O and secondary amine carbon in the lowest energy conformer of **11**;[39] conformers without this interaction have significantly different chemical shifts.

The proposed ring-closing mechanism was also subjected to computational scrutiny (Figure 2) using a variety of methods: PCM(DMSO)-B3LYP/6-31+G(d,p),[35,40] PCM(DMSO)-B3LYP-D3(Bj)/6-31+G(d,p),[41] SMD(DMSo)-B3LYP-D3(Bj)/6-31+G(d,p), and PCM(DMSO)-M06-2X/6-31+G-(d,p).[42] These methods provide a consistent picture (standard corrections for changing from gas phase to solution were computed, but found not to change the results; see SI for details).

Conversion of **29** to **11** (Figure 2, top) is predicted to be kinetically feasible and exergonic, consistent with experiment. Conversion of **30** to **28** (Figure 2, bottom) is also predicted to be feasible, if slightly less exergonic, despite our inability to isolate **28**, perhaps a result of as-yet unidentified competing reactions.

In that heterocyclization is predicted to be facile for structures such as **29**, it is possible that this type of process also occurs in classic Cadogan reactions, rather than, or in addition to, nitrene formation. We carried out computations on nitrene formation as well, examining both singlet and triplet pathways (see SI for details) and have yet to find a nitrene formation pathway with a lower barrier than cyclization, although we cannot definitively rule out this process as contributing.

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On the basis of the results of our calculations, we propose an alternative route to formal Cadogan products in which a phosphine (here, PMe_3) is used to promote deoxygenation. For example, we predict that deoxygenation of **29**, which is in equilibration with **11**, has an activation barrier of less than 20 kcal/mol (relative to **29**), whether nitrogen or oxygen is attacked first, and is greater than 70 kcal/mol downhill in energy overall (Figure 3), consistent with expectations for a reaction making a new P≐O bond. Such a process (**1b** → **2** → **4** in Scheme 1) may well occur during Cadogan reactions. Oxygen transfer from N to P is well established in the literature for *N*-oxides (generally requiring temperatures in the 60–70 °C range),[12] but we propose here that 2*H*-indazole *N*-oxide deoxygenation would occur via a ring-opening then deoxygenation/ring-closure process.

Deoxygenation also can be carried out under reductive conditions (Table 4). Unsurprisingly, the reduction of these *N*-oxide-bearing heterocycles occurred rapidly, even at room temperature. Overall, the reported **1b** → **2** → **6** → **4** reaction sequence is formally a Cadogan cyclization carried out under phosphorus-free conditions at ambient temperature, the mildest conditions yet reported for this type of nitroaromatic reductive cyclization.

Finally, prior to the isolation and characterization of the *N*-oxide heterocycles reported here, **2** was the only common intermediate in the Cadogan and Davis–Beirut reactions (Scheme 1). However, it is possible that both reactions also share structure **5** ↔ **6**. Indeed, when *N*-oxide **10** was treated with typical Davis–Beirut conditions, 3-alkoxy-2*H*-indazoles were obtained in high yields (Table 4).

CONCLUSIONS

In summary, we report the design and optimization of a method for controlling highly reactive nitroso imines, using them to produce 2*H*-indazole *N*-oxides. This reaction provides access, under mild conditions, to a synthetically and biologically underutilized class of *N*-oxide heterocycles. The structures of these compounds were determined using X-ray crystallography and computational NMR. Moreover, isolation of these *N*-oxides under ambient conditions has significant implications for mechanistic models of both the Cadogan and Davis–Beirut reactions. For both transformations, *N*-oxides appear to be competent intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the National Institutes of Health (DK072517 and DK067003) and NSF XSEDE program (CHE030089 to D.J.T.). Funding for NMR spectrometers was provided by National Science Foundation (DBI722538 and CHE9808183) and NIH National Institute of Environmental Health Sciences ES00570713. J.S.Z. is supported by the UC Davis Tara K. Telford CF Fund, UC Davis Dissertation Year Fellowship, and R. Bryan Miller Graduate Fellowship. N.K. is supported by the UC Davis Provost's Undergraduate Fellowship. We dedicate this work in memory of Tara K. Telford, a young wife and mother of twins, who inspired everyone who knew her by living so graciously and resolutely with cystic fibrosis.

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REFERENCES

(1). Haddadin MJ; Conrad WE; Kurth MJ The Davis-Beirut Reaction: A Novel Entry into 2*H*-indazoles and Indazolones. Recent Biological Activity of Indazoles. Mini-Rev. Med. Chem. 2012, 12, 1293–1300. [PubMed: 23092440]

(2). Jones P; Altamura S; Boueres J; Ferrigno F; Fonsi M; Giomini C; Lamartina S; Monteagudo E; Ontoria JM; Orsale MV; Palumbi MC; Pesci S; Roscilli G; Scarpelli R; Schultz-Fademrecht C; Toniatti C; Rowley M Discovery of 2-{4-[(3S)-Piperidin-3-yl]phenyl}-2*H*-indazole-7-carboxamide (MK-4827): A Novel Oral Poly(ADP-ribose)polymerase (PARP) Inhibitor Efficacious in BRCA-1 and −2 Mutant Tumors. J. Med. Chem. 2009, 52, 7170–7185. [PubMed: 19873981]

(3). Harris PA; Boloor A; Cheung M; Kumar R; Crosby RM; Davis-Ward RG; Epperly AH; Hinkle KW; Hunter RN; Johnson JH; Knick VB; Laudeman CP; Luttrell DK; Mook RA; Nolte RT; Rudolph SK; Szewczyk JR; Truesdale AT; Veal JM; Wang L; Stafford JA Discovery of 5-[[4-[(2,3-Dimethyl-2*H*-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-benzenesulfonamide (Pazopanib), a Novel and Potent Vascular Endothelial Growth Factor Receptor Inhibitor. J. Med. Chem. 2008, 51, 4632–4640. [PubMed: 18620382]

(4). Pfefferkorn JA; Tu M; Filipski KJ; Guzman-Perez A; Bian J; Aspnes GE; Sammons MF; Song W; Li J-C; Jones CS; Patel L; Rasmusson T; Zeng D; Karki K; Hamilton M; Hank R; Atkinson K; Litchfield J; Aiello R; Baker L; Barucci N; Bourassa P; Bourbounais F; D'Aquila T; Derksen DR; MacDougall M; Robertson A The design and synthesis of indazole and pyrazolopyr-idine based glucokinase activators for the treatment of Type 2 diabetes mellitus. Bioorg. Med. Chem. Lett. 2012, 22, 7100–7105. [PubMed: 23089526]

(5). Aman W; Lee J; Kim M; Yang S; Jung H; Hah J-M Discovery of highly selective CRAF inhibitors, 3-carboxamido-2*H*-indazole-6-arylamide: In silico FBLD design, synthesis and evaluation. Bioorg. Med. Chem. Lett. 2016, 26, 1188–1192. [PubMed: 26810260]

(6) (a). Cadogan JIG; Cameron-Wood M; Mackie RK; Searle RJG 896. The reactivity of organophosphorus compounds. Part XIX. Reduction of nitro-compounds by triethyl phosphite: a convenient new route to carbazoles, indoles, indazoles, triazoles, and related compounds. J. Chem. Soc. 1965, 4831–4837.(b)Sund-berg RJ Deoxygenation of Nitro Groups by Trivalent Phosphorus. Indoles from o-Nitrostyrenes. J. Org. Chem. 1965, 30, 3604–3610.

(7). Genung NE; Wei L; Aspnes GE Regioselective Synthesis of 2H-Indazoles Using a Mild, One-Pot Condensation–Cadogan Reductive Cyclization. Org. Lett. 2014, 16, 3114–3117. [PubMed: 24848311]

(8). Nykaza TV; Harrison TS; Ghosh A; Putnik RA; Radosevich AT A Biphilic Phosphetane Catalyzes N–N Bond-Forming Cadogan Heterocyclization via P^{III}/P^{V}=O Redox Cycling. J. Am. Chem. Soc. 2017, 139, 6839–6842. [PubMed: 28489354]

(9). Schoene J; Bel Abed H; Schmieder P; Christmann M; Nazare M A General One-Pot Synthesis of 2*H*-Indazoles Using an Organophosphorus–Silane System. Chem. - Eur. J. 2018, 24, 9090–9100. [PubMed: 29644761]

(10). Chung CK; Bulger PG; Kosjek B; Belyk KM; Rivera N; Scott ME; Humphrey GR; Limanto J; Bachert DC; Emerson KM Process Development of C–N Cross-Coupling and Enantioselective Biocatalytic Reactions for the Asymmetric Synthesis of Niraparib. Org. Process Res. Dev. 2014, 18, 215–227.

(11). Davies IW; Guner VA; Houk KN Theoretical Evidence for Oxygenated Intermediates in the Reductive Cyclization of Nitrobenzenes. Org. Lett. 2004, 6, 743–746. [PubMed: 14986964]

(12) (a). Aguirre G; Boiani L; Boiani M; Cerecetto H; Maio RD; Gonzalez M; Porcal W; Denicola A; Piro OE; Castellano E ; Sant'Anna CMR; Barreiro EJ New potent 5-substituted benzofuroxans as inhibitors of Trypanosoma cruzi growth: Quantitative structure–activity relationship studies. Bioorg. Med. Chem. 2005, 13, 6336–6346. [PubMed: 16202608] (b)Ruggeri SG; Bill DR; Bourassa DE; Castaldi MJ; Houck TL; Ripin DHB; Wei L; Weston N Safety vs Efficiency in the Development of a High-Energy Compound. Org. Process Res. Dev. 2003, 7, 1043–1047.(c)Sheng J; He R; Xue J; Wu C; Qiao J; Chen C Cu-Catalyzed π-Core Evolution of Benzoxadiazoles with Diaryliodonium Salts for Regioselective Synthesis of Phenazine Scaffolds. Org. Lett. 2018, 20, 4458–4461. [PubMed: 30040430] (d)Wang L; Zhang Y-Y; Wang L; Liu F.-y.; Cao L-L; Yang J;

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Author Manuscript

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Qiao C; Ye Y Benzofurazan derivatives as antifungal agents against phytopathogenic fungi. Eur. J. Med. Chem. 2014, 80, 535–542. [PubMed: 24813881]

(13). Zhu JS; Kraemer N; Shatskikh ME; Li CJ; Son J-H; Haddadin MJ; Tantillo DJ; Kurth MJ N–N Bond Formation between Primary Amines and Nitrosos: Direct Synthesis of 2-Substituted Indazolones with Mechanistic Insights. Org. Lett. 2018, 20, 4736–4739. [PubMed: 30067041]

(14). Jiao L; Liang Y; Xu J Origin of the Relative Stereoselectivity of the *β*-Lactam Formation in the Staudinger Reaction. J. Am. Chem. Soc. 2006, 128, 6060–6069. [PubMed: 16669675]

(15). Amarnath V; Anthony DC; Amarnath K; Valentine WM; Wetterau LA; Graham DG Intermediates in the Paal-Knorr synthesis of pyrroles. J. Org. Chem. 1991, 56, 6924–6931.

(16). Wei J; Shaw JT Diastereoselective Synthesis of *γ*-Lactams by a One-Pot, Four-Component Reaction. Org. Lett. 2007, 9, 4077–4080. [PubMed: 17760458]

(17). Chizhova M; Khoroshilova O; Dar'in D; Krasavin M Unusually Reactive Cyclic Anhydride Expands the Scope of the Castagnoli–Cushman Reaction. J. Org. Chem. 2018, 83, 12722–12733. [PubMed: 30226770]

(18). Mfuh AM; Larionov OV Heterocyclic *N*-Oxides - An Emerging Class of Therapeutic Agents. Curr. Med. Chem. 2015, 22, 2819–2857. [PubMed: 26087764]

(19). Randall LO; Schallek W; Heise GA; Keith EF; Bagdon RE the Psychosedative Properties of Methaminodiazepoxide. J. Pharmacol. Exp. Ther. 1960, 129, 163–171. [PubMed: 14436141]

(20). Olsen EA; Weiner MS; Delong ER; Pinnell SR Topical minoxidil in early male pattern baldness. J. Am. Acad. Dermatol. 1985, 13, 185–192. [PubMed: 3900155]

(21). von Pawel J; von Roemeling R; Gatzemeier U; Boyer M; Elisson LO; Clark P; Talbot D; Rey A; Butler TW; Hirsh V; Olver I; Bergman B; Ayoub J; Richardson G; Dunlop D; Arcenas A; Vescio R; Viallet J; Treat J Tirapazamine Plus Cisplatin Versus Cisplatin in Advanced Non–Small-Cell Lung Cancer: A Report of the International CATAPULT I Study Group. J. Clin. Oncol. 2000, 18, 1351–1359. [PubMed: 10715308]

(22). Miao X-S; Bishay F; Chen M; Metcalfe CD Occurrence of Antimicrobials in the Final Effluents of Wastewater Treatment Plants in Canada. Environ. Sci. Technol 2004, 38, 3533–3541. [PubMed: 15296302]

(23). Gerpe A; Aguirre G; Boiani L; Cerecetto H; González M; Olea-Azar C; Rigol C; Maya JD; Morello A; Piro OE; Arán VJ; Azqueta A; de Ceráin AL; Monge A; Rojas MA; Yaluff G Indazole *N*-oxide derivatives as antiprotozoal agents: Synthesis, biological evaluation and mechanism of action studies. Bioorg. Med. Chem. 2006, 14, 3467–3480. [PubMed: 16483783]

(24). Cioc RC; Preschel HD; van der Heijden G; Ruijter E; Orru RVA Trityl Isocyanide as a Mechanistic Probe in Multicomponent Chemistry: Walking the Line between Ugi- and Strecker-type Reactions. Chem. - Eur. J. 2016, 22, 7837–7842. [PubMed: 27112103]

(25). Nyerges M; Virányi A; Zhang W; Groundwater PW; Blaskó G; Tőke L Synthesis of indazole-*N*-oxides via the 1,7-electrocyclization of azomethine ylides. Tetrahedron 2004, 60, 9937–9944.

(26). Nyerges M; Somfai B; Tóth J; Tőke L; Dancsó A; Blaskó G A Novel One-Pot, Three-Component Access to Hexahydropyrrolo[2,1-a]isoquinolines by an Alkylation-Dehydroha-logenation-1,3-Dipolar Cycloaddition Sequence. Synthesis 2005, 2005, 2039–2045.

(27). Křupková S; Slough GA; Krchňák V Synthesis of Quinazolines from *N*-(2-Nitrophenylsulfonyl)iminodiacetate and α-(2-Nitrophenylsulfonyl)amino Ketones via 2*H*-Indazole 1-Oxides. J. Org. Chem. 2010, 75, 4562–4566. [PubMed: 20524619]

(28). Gui J; Pan C-M; Jin Y; Qin T; Lo JC; Lee BJ; Spergel SH; Mertzman ME; Pitts WJ; La Cruz TE Practical olefin hydroamination with nitroarenes. Science 2015, 348, 886–891. [PubMed: 25999503]

(29). Zhu JS; Duong MR; Teuthorn AP; Lu JY; Son J-H; Haddadin MJ; Kurth MJ Davis—Beirut Reaction: Alkoxide versus Hydroxide Addition to the Key *o*-Nitrosoimine Intermediate. Org. Lett. 2018, 20, 1308–1311. [PubMed: 29431446]

(30). Bjørsvik H-R; Gambarotti C; Jensen VR; González RR A Novel Efficient Deoxygenation Process for *N*-Heteroarene *N*-Oxides. J. Org. Chem. 2005, 70, 3218–3224. [PubMed: 15822984]

(31). Zhu JS; Kraemer N; Li CJ; Haddadin MJ; Kurth MJ Photochemical Preparation of 1,2-Dihydro-3*H*-indazol-3-ones in Aqueous Solvent at Room Temperature. J. Org. Chem. 2018, 83, 15493–15498. [PubMed: 30468072]

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(32). Issidorides CH; Haddadin MJ Benzofurazan oxide. II. Reactions with enolate anions. J. Org. Chem. 1966, 31, 4067–4068.

(33) (a). Krivdin LB Calculation of ^{15}N NMR chemical shifts: Recent advances and perspectives. Prog. Nucl Magn. Reson. Spectrosc. 2017, 102–103, 98–119.(b)Lodewyk MW; Siebert MR; Tantillo DJ Computational Prediction of ^{1}H and ^{13}C Chemical Shifts: A Useful Tool for Natural Product, Mechanistic, and Synthetic Organic Chemistry. Chem. Rev. 2012, 112, 1839–1862. [PubMed: 22091891] (c)Saielli G; Nicolaou KC; Ortiz A; Zhang H; Bagno A Addressing the Stereochemistry of Complex Organic Molecules by Density Functional Theory-NMR: Vannusal B in Retrospective. J. Am. Chem. Soc. 2011, 133, 6072–6077. [PubMed: 21438587] (d)Willoughby PH; Jansma MJ; Hoye TR A guide to small-molecule structure assignment through computation of (^{1}H and ^{13}C) NMR chemical shifts. Nat. Protoc. 2014, 9, 643. [PubMed: 24556787]

(34). Cheeseman JR; Trucks GW; Keith TA; Frisch MJ A comparison of models for calculating nuclear magnetic resonance shielding tensors. J. Chem. Phys. 1996, 104, 5497–5509.

(35) (a). Becke AD Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys. 1993, 98, 5648–5652.(b)Lee C; Yang W; Parr RG Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B: Condens. Matter Mater. Phys. 1988, 37, 785–789.(c)Miehlich B; Savin A; Stoll H; Preuss H Results obtained with the correlation energy density functionals of becke and Lee, Yang and Parr. Chem. Phys. Lett. 1989, 157, 200–206.

(36). Adamo C; Barone V Exchange functionals with improved long-range behavior and adiabatic connection methods without adjustable parameters: The mPW and mPW1PW models. J. Chem. Phys. 1998, 108, 664–675.

(37) (a). Frisch MJ; Trucks GW; Schlegel HB; Scuseria GE; Robb MA; Cheeseman JR; Scalmani G; Barone V; Petersson GA; Nakatsuji H; Li X; Caricato M; Marenich AV; Bloino J; Janesko BG; Gomperts R; Mennucci B; Hratchian HP; Ortiz JV; Izmaylov AF; Sonnenberg JL; Williams; Ding F; Lipparini F; Egidi F; Goings J; Peng B; Petrone A; Henderson T; Ranasinghe D; Zakrzewski VG; Gao J; Rega N; Zheng G; Liang W; Hada M; Ehara M; Toyota K; Fukuda R; Hasegawa J; Ishida M; Nakajima T; Honda Y; Kitao O; Nakai H; Vreven T; Throssell K; Montgomery JA Jr.; Peralta JE; Ogliaro F; Bearpark MJ; Heyd JJ; Brothers EN; Kudin KN; Staroverov VN; Keith TA; Kobayashi R; Normand J; Raghavachari K; Rendell AP; Burant JC; Iyengar SS; Tomasi J; Cossi M; Millam JM; Klene M; Adamo C; Cammi R; Ochterski JW; Martin RL; Morokuma K; Farkas O; Foresman JB; Fox DJ Gaussian 09; Gaussian Inc.: Wallingford, CT, 2016.(b)Marenich AV; Cramer CJ; Truhlar DG Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. J. Phys. Chem. B 2009, 113, 6378–6396. [PubMed: 19366259]

(38). Scaling factors were obtained from chesirenmr.info.

(39). Johnston RC; Cheong PH-Y C–H…O non-classical hydrogen bonding in the stereomechanics of organic transformations: theory and recognition. Org. Biomol Chem. 2013, 11, 5057–5064. [PubMed: 23824256]

(40). Cammi R; Mennucci B; Tomasi J In Computational Chemistry: Reviews of Current Trends; Leszczynski J, Ed.; World Scientific Publishing Co. Pte. Ltd.: Singapore, 2003; Vol. 8.

(41). Grimme S; Ehrlich S; Goerigk L J. Comput. Chem. 2011, 32, 1456. [PubMed: 21370243]

(42). Zhao Y; Truhlar DG Theor. Chem. Acc. 2008, 120, 215–41.

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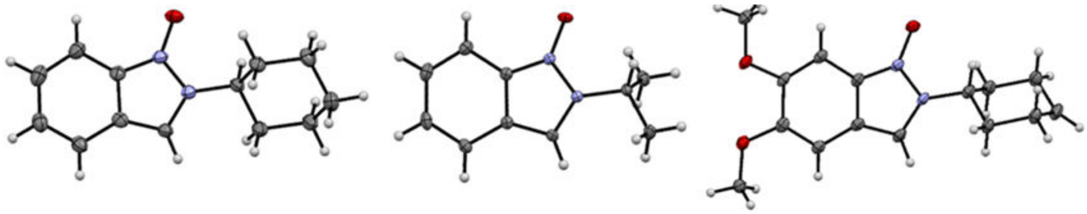

Figure 1.

Crystal structures of **11**, **12**, and **16**, respectively.

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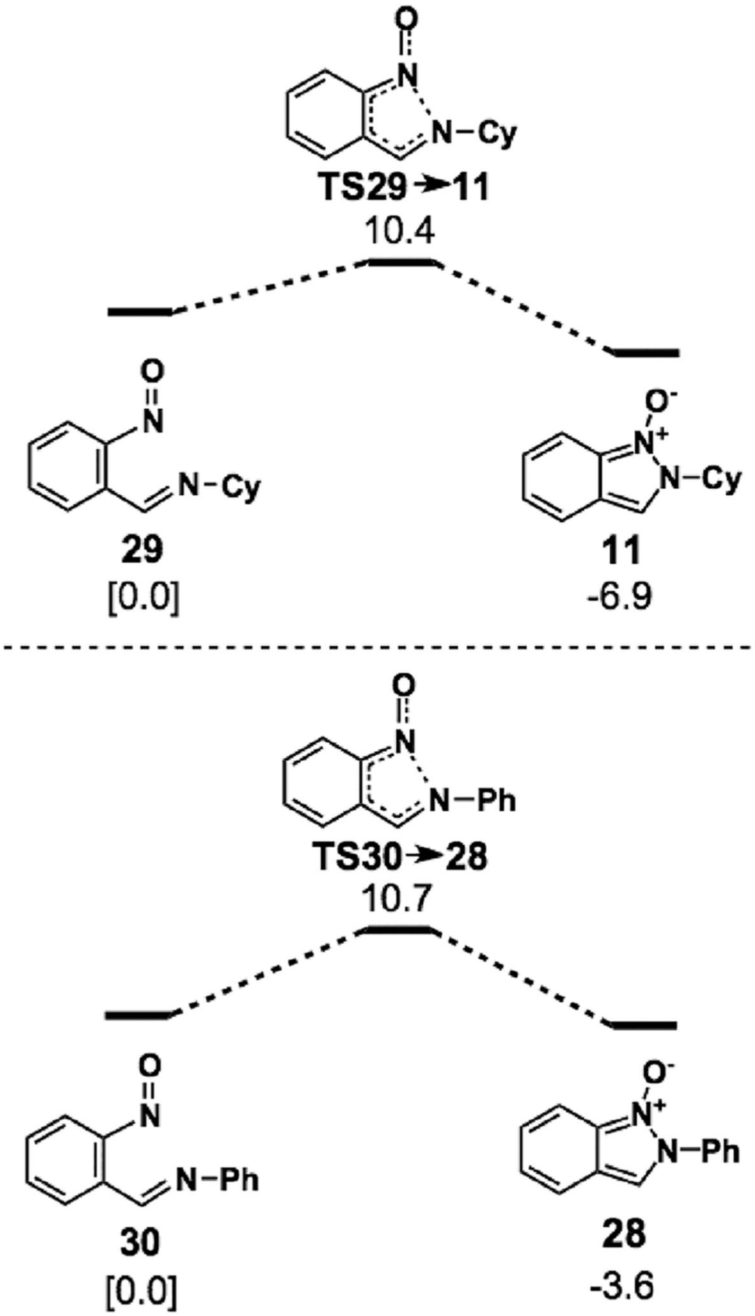

Figure 2.

Computed energetics (PCM(DMSO)-B3LYP-D3(Bj)/6-31+G(d,p), free energies, kcal/mol; see SI for results from other methods) for ring-closure reactions to form **11** and **28**.

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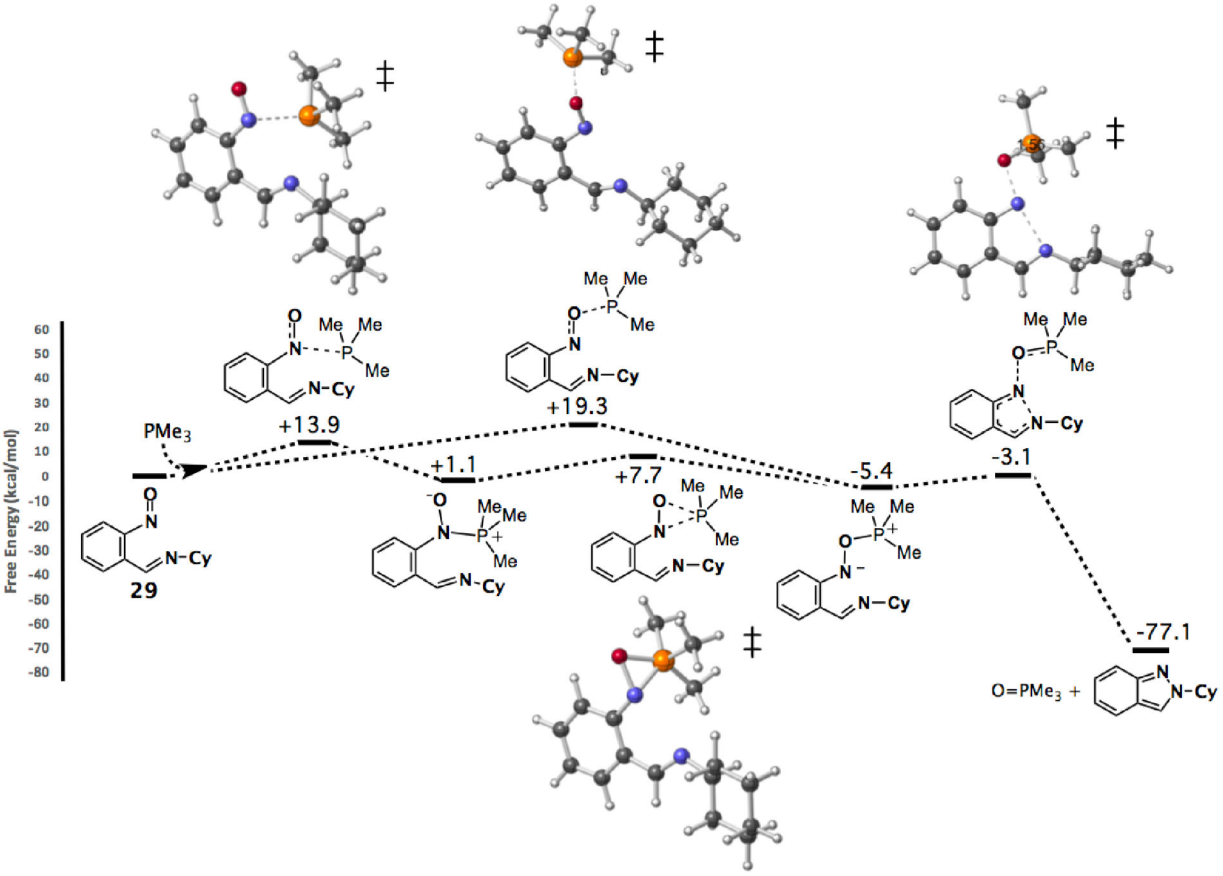

Figure 3.

Computed reaction pathways for the **29** → **32** conversion. Relative free energies (kcal/mol; PCM(DMSO)-B3LYP-D3(BJ)/6-31+G(d,p)) are shown; see SI for results from other levels of theory and data for other, higher energy, pathways.

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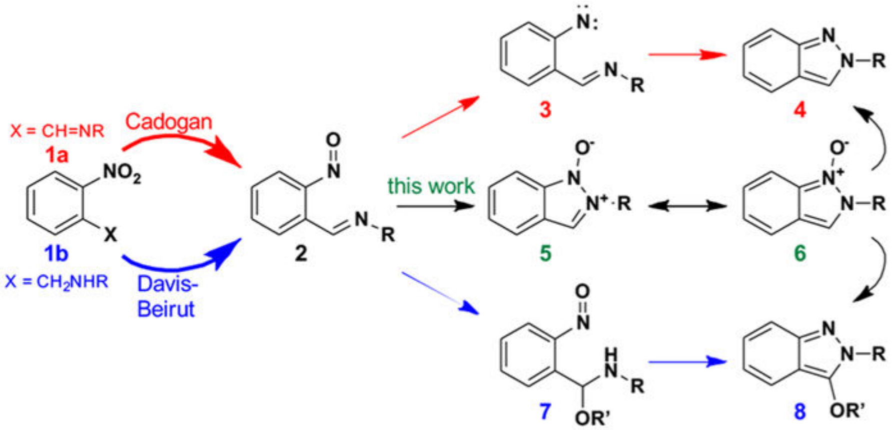

Scheme 1.

Previously Proposed Mechanism of the Cadogan and Davis–Beirut Reactions: Concept of This Work

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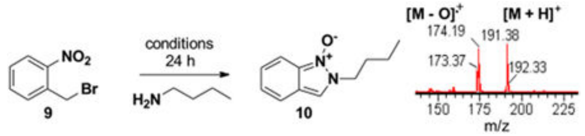
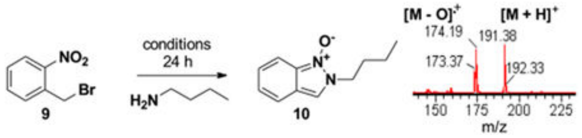
Table 1.

Reaction Optimization[a]



entry	base	amine	solvent	water	heat	yield
1	20 equiv KOH	5 equiv	6 mL ^{i}PrOH	0.5 mL	rt	15%
2	20 equiv KOH	5 equiv	6 mL 1,4-dioxane	0.5 mL	rt	N.D.[b]
3	20 equiv KOH	5 equiv	6 mL THF	0.5 mL	rt	N.D.[b]
4	20 equiv KOH	5 equiv	6 mL MeCN	0.5 mL	rt	N.D.[b]
5	20 equiv KOH	5 equiv	6 mL DCM	0.5 mL	rt	N.D.[b]
6	20 equiv KOH	5 equiv	6 mL $CHCl_3$	0.5 mL	rt	N.D.[b]
7	20 equiv KOH	5 equiv	6 mL DMSO	0.5 mL	rt	22%
8	20 equiv KOH	5 equiv	6.5 mL DMSO	0 mL	rt	N.D.[c]
9	20 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	rt	54%
10	20 equiv KOH	5 equiv	5 mL DMSO	1.5 mL	rt	47%
11	20 equiv NaO*t*-Bu	5 equiv	5.5 mL DMSO	1 mL	rt	35%
12	40 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	rt	42%
13	10 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	rt	78%
14	5 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	rt	58%
15	2 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	rt	58%
16	10 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	40 °C	55%
17	10 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	60 °C	N.D.[c]
18	10 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	80 °C	N.D.[c]
19	10 equiv KOH	5 equiv	5.5 mL DMSO	1 mL	100 °C	0%[d]
20	10 equiv KOH	1 equiv	5.5 mL DMSO	1 mL	rt	32%
21	10 equiv KOH	2 equiv	5.5 mL DMSO	1 mL	rt	74%



entry	base	amine	solvent	water	heat	yield
22	10 equiv KOH	10 equiv	5.5 mL DMSO	1 mL	rt	91%

[a] Reaction conducted on a 0.5 mmol scale. Isolated yields are reported.

[b] Major product is simple *N*-alkylation.

[c] Complex mixture.

[d] 16% deoxygenation product 2*H*-indazole was isolated.

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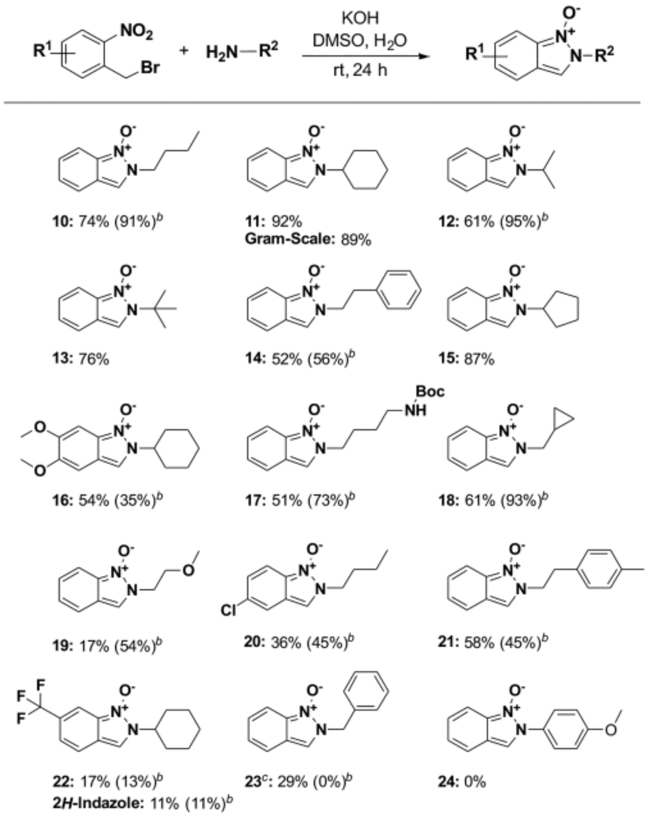
Table 2.

Base-Mediated 2*H*-Indazole *N*-Oxide Synthesis [a]



10: 74% (91%)^b

11: 92%
Gram-Scale: 89%

12: 61% (95%)^b

13: 76%

14: 52% (56%)^b

15: 87%

16: 54% (35%)^b

17: 51% (73%)^b

18: 61% (93%)^b

19: 17% (54%)^b

20: 36% (45%)^b

21: 58% (45%)^b

22: 17% (13%)^b
2*H*-Indazole: 11% (11%)^b

23^c: 29% (0%)^b

24: 0%

---

[a] Reaction conditions: *o*-nitrobenzyl bromide (0.5 mmol), amine (1 mmol), KOH (5 mmol), DMSO (5.5 mL), water (1 mL), room temperature, 24 h reaction time. Isolated yields are reported.

[b] Yield when 5 mmol of amine was used.

[c] Under photochemical conditions.

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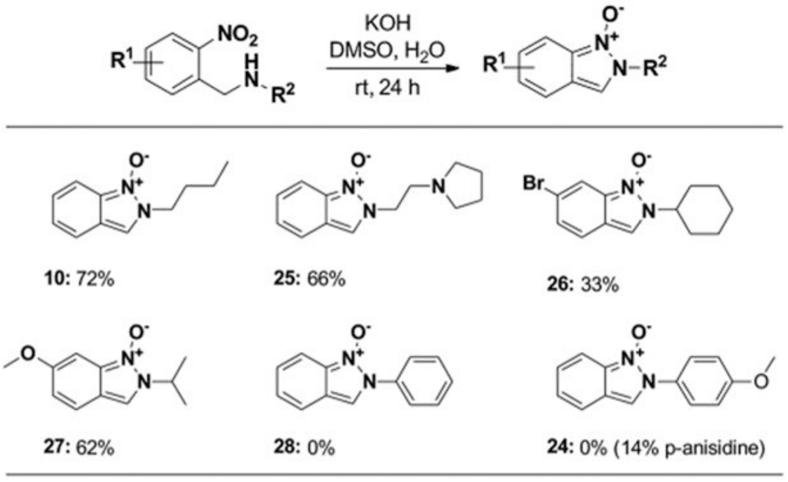
Table 3.

Base-Mediated 2*H*-Indazole *N*-Oxide Synthesis [a]



[a] Reaction conditions: *o*-nitrobenzyl amine (0.5 mmol), KOH (5 mmol), DMSO (5.5 mL), water (1 mL), room temperature, 24 h reaction time. Isolated yields are reported.

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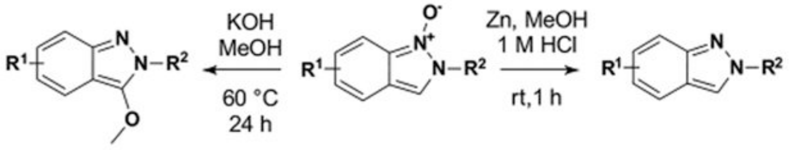
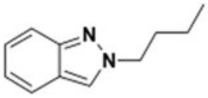
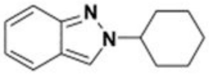
Table 4.

Derivatization of 2*H*-Indazole *N*-Oxides[a]

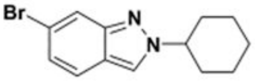




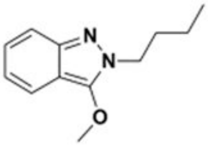
31: 94%



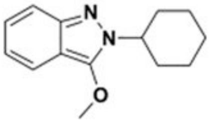
32: 93%



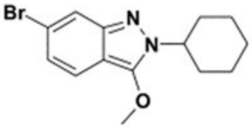
33: 98%



34: 90%



35: 80%



36: 92%

[a] Isolated yields are reported