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Authors

Zhu, Jie S
Son, Jung-Ho
Teuthorn, Andrew P
et al.

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Diverting Reactive Intermediates Toward Unusual Chemistry – Unexpected Anthranil Products from Davis–Beirut Reaction

Jie S. Zhu[≠], **Jung-Ho Son**[≠], **Andrew P. Teuthorn**[≠], **Makhluf J. Haddadin**[&], **Mark J. Kurth**[≠], and **Dean J. Tantillo**[≠]

[≠]Department of Chemistry, University of California Davis, 1 Shields Ave., Davis, CA 95616, USA

[&]Department of Chemistry, American University of Beirut, Beirut, Lebanon

Abstract

The discovery of a new variation on the Davis–Beirut reaction is described in which an atypical heterocyclic framework (the anthranil or benzo[c]isoxazole framework) is formed as the result of diversion of a key reactive intermediate away from its usual reactivity – a potentially general approach to reaction design and development. Experimental and computational support for the proposed mechanism and origins of altered reactivity are described.

Graphical Abstract

Introduction

The discovery of new synthetic methodology is catalyzed in numerous ways; for example, by challenges presented in complex natural product synthesis,[1] by needs associated with drug discovery,[2] by serendipitous observation,[3] and by rational development based on already existing technology.[4,5] As an example of the latter, the synthesis of key intermediates from named reactions using modern chemistry is a cornerstone of methodology development; consider the Buchwald modification[4] of the Fischer indole synthesis[6] where the key intermediate is made through *N*-aryl bond formation via Pd-catalyzed cross-coupling instead of via the traditional condensation of hydrazine with a ketone or aldehyde equivalent. However, far fewer methodology advancements exploit alternative chemistries of highly reactive intermediates, even though such strategies occasionally have been implemented to great effect. For example, controlling the reactivity of the final intermediate of the Fischer indole synthesis by blocking aromatization allows the construction of various indoline natural products in the interrupted Fischer indole synthesis.[5]

Correspondence to: Mark J. Kurth; Dean J. Tantillo.

Supporting information. Computational details, reaction mechanisms, NMR spectra, and X-ray crystallography data (PDF).

Altering the course of a highly reliable reaction to access atypical structural motifs requires careful consideration of the reaction mechanism, with the caveat that a reasonable mechanistic model must exist. Through the aid of increasingly powerful computational methods, even highly complex reaction mechanisms can be demystified.[7] To this end, we report the discovery of a pericyclic cascade[8] route to anthranils (also known as benzo[c]isoxazoles), which was developed by exploiting alternative reactivity of Davis–Beirut reaction intermediates.

Originally, reactions of diethyl 1-amino-2′-nitrobenzylphosphonates with aq. NaOH in MeOH reported by Boduszek[9a] and *o*-nitrosobenzaldehyde with benzylamine reported by Chen[9b] were claimed to deliver anthranils, but our reinvestigation of those studies established that indazolones were produced instead.[10] Thus was born the Davis–Beirut reaction, which provides a robust method for constructing 2*H*-indazoles from 2-nitrobenzylamines.[10] It is proposed that the Davis-Beirut reaction involves initial tautomerization of 2-nitrobenzylamine **1a** by hydroxide to generate *aci*-nitro intermediate **1b** (Scheme 1). This intermediate is thought to undergo a rapid internal reduction-oxidation to form nitrosophenylmethanimine **1c**. Nucleophilic addition to this imine intermediate by alcohol solvent would generate hemiaminal ether **1d**, which would subsequently form a five-membered ring via an N–N bond forming heterocyclization. The resulting ring can then be aromatized to deliver a 2*H*-indazole, which can be easily transformed to an indazolone.[11]

The putative mechanistic intermediates involved in the Davis–Beirut process share many structural similarities with intermediates proposed for the photodeprotection of the *o*-nitrobenzyl moiety – an established pH-sensitive photolabile protecting group for a variety of heteroatoms (Scheme 1).[12] Exposure of **2a** to light causes its tautomerization to *aci*-nitro species **2b**, which then cyclizes to give intermediate **2c**. Subsequent decomposition of this transient heterocycle gives hemiacetal **2d** and alcohol release proceeds by collapse of **2d** to *o*-nitrosobenzaldehyde.[13]

As reported here, exploiting alternative reactivity of Davis–Beirut reaction intermediates led to our discovery of a cascade[8] route to anthranils. Molecules with this core framework have pharmaceutical value[14] and this heterocycle has been previously synthesized via a variety of methods.[15–19] Recently, the transformation of anthranils to other heterocycles have found use in complex molecule synthesis.[20] The utility of this heterocycle, coupled with our group's long-standing interest in heterocycle-to-heterocycle strategies,[21] prompted us to investigate this route to anthranils.

Results and Discussion

We aimed to exploit the structural similarities and different reactivities of key intermediates found in the Davis–Beirut and *o*-nitrobenzyl deprotection pathways for the discovery of new heterocyclic synthetic methods. With that objective in mind, we set out to demonstrate the base-mediated deprotection of a 2-nitrobenzyl compound featuring a nitrogen attached to the benzylic carbon—i.e., an interrupted Davis–Beirut process—and indole-containing substrate **3a** (Scheme 2) was selected. If realized, the based-mediated reaction of **3a** would proceed

via **3a.1** to form dihyrdoanthranil intermediate **3a.2**. Subsequent ring-opening of this heterocyclic intermediate would produce nitrosoalcohol **3a.3** and, ultimately, release indole.

Indeed, when **3a** was microwave heated in MeOH in the presence of KOH (5 equiv.), indole was released via the deprotection pathway (Scheme 2). *o*-Nitrobenzoic acid was also isolated, evidencing the formation of *o*-nitrosobenzaldehyde (→ *o*-nitrobenzoic acid by air oxidation) over the course of the reaction. Since the microwave cavity is dark, intermediate **3a.1** is not generated by phototautomerization; however, the sufficiently low pK_a of the benzylic hydrogens in **3a** allows base to facilitate transformation of the starting material to *aci*-nitro **3a.1.** Formation of deprotection products (indole and *o*-nitrobenzoic acid) confirmed that base can affect the transformation outlined in Scheme 2.

With this calibrating study in hand, the benzylic indole moiety was replaced with a benzylic C2 linked benzimidazole. This substrate, **4a** (Scheme 3), was selected for study because it was not expected to undergo the deprotection reaction since cargo release would involve C–C bond cleavage and generation of a relatively high energy benzimidazolylidene. Simultaneously, the benzimidazole nitrogen of **4a**, being nucleophilic, offered the potential of intercepting the *in situ* generated nitroso moiety in **4a.2** with an N–N bond forming reaction (with subsequent dehydration and tautomerization) to generate benzoimidazocinnolinone **5**.

When **4a** was heated in MeOH with KOH, no deprotection products were found and a major product with a m/z of 235 was isolated – the mass corresponding to the anticipated benzoimidazocinnolinone. Surprisingly, when we attempted to confirm the structure of this product by X-ray crystallography, it was found instead to be anthranil **6a**. Although this was a surprising result based on our earlier work, which established that anthranils are not formed under Davis–Beirut reaction conditions,[10] serendipity, as noted by Hoye,[3] can “still play a pivotal role” in science.

Through X-ray crystallography, a side-product of this base-mediated reaction of **4a** was found to be condensation-derived compound **7**. As detailed in Scheme 4, we speculate that nitroso intermediate **4a.2** undergoes base-mediated condensation with starting material **4a** to give phenylmethanimine **4a.3**. Subsequent air oxidation of this intermediate, directly or perhaps via **4a.4**, delivers **7**. Although this side-product can be isolated in up to 37% yield, its formation can be minimized using the optimized reaction conditions described below.

The reaction of benzylic heteroaromatics such as **4a** to form anthranils was systematically optimized by varying solvent, base, temperature (see Supporting Information). While generally, both polar-protic and polar-aprotic solvents were effective for the reaction, the optimal conditions were found to be microwave irradiation in 0.05 M DMF with 5 equiv. NaO^{t}Bu for 6 h at 125 °C. The temperature needed to be ≥ 45 °C and excess alkoxide was needed to achieve complete conversion. Addition of 4Å molecular sieves improved the yield of the reaction. Substrates with minimal ring substitution (**6a-d, 6f, 6i**) resulted in higher than average yields, while **6e**, **6g**, **6h** resulted in lower than average yields (Scheme 5).

In addition, a diverse series of 2-nitrobenzyl compounds (Scheme 6) were prepared and subsequently treated under base and microwave irradiation, but LCMS analysis of each crude reaction mixture established that none of these substrates provided the targeted anthranil product. In each case, either no reaction occurred or the reaction resulted in a complicated mixture of products owing to the rich chemistry of nitro- and nitrosobenzenes, especially for **8a** and **8b**. Carbonyl-containing **8d**–**8f** likely failed to undergo the hoped-for anthranil-forming reaction because enolate formation probably competes with *aci*-nitro formation. Despite structural similarities with **4a**, the failure of **8h** and **8i** to give anthranil products suggests that the *NH*-containing heterocyclic moiety plays a critical role in the **4** → **6** heterocyclization reaction.

In pursuit of a mechanistic scheme consistent with these experimental results, reactions of **4a** were examined using density functional theory calculations [SMD(DMF)-M06-2X/6-31+G(d,p);[22] see Supporting Information for details]. Both neutral (green and blue) and anionic (red) pathways were examined and our results are summarized in Figure 1. The key issue here was the fact that, experimentally, an anthranil, rather than fragmented or cinnoline products, is formed although all three families of products arise from initial cyclization. Cyclization for the neutral system is predicted to require a barrier of approximately 32 kca/mol (from the blue reactant to the green product; note that the barrier for green reactant to green product is comparable to those predicted previously for systems with alkyl or alkoxyl groups in place of the benzimidazole),[23] while cyclization for the anionic system is predicted to require a barrier of approximately 36 kcal/mol. Given the nature of the theoretical methods used, either pathway appears to be viable, although the neutral route is perhaps more likely. Note that the product of cyclization for the anionic system is the OH/N:$^-$ tautomer. Proton transfer occurs during optimization when starting from NH/O:$^-$ species with NH and O:$^-$ groups *syn*, while ring-opened structures are found starting from NH and O:$^-$ groups *anti*.

One may question whether the initial cyclization reaction for the anionic system (Figure 2, left, red) is a pericyclic or pseudopericyclic reaction.[24] Unfortunately, the geometry of the transition state structure (Figure 2, left) does not provide a definitive answer this question. The calculated nucleus independent chemical shift (NICS, a measure of aromaticity)[25] for the partially formed ring (approximately-10) is indicative of aromaticity and comparable to that for the 5-membered ring in anthranil,[26] consistent with a pericyclic reaction, but non-pericyclic cyclization reactions have also been shown to have such NICS values.[27]

After cyclization, ring opening from the anionic cyclized product is predicted to occur readily (barrier of approximately 10 kcal/mol), leading to an alkoxide ion (via concerted proton transfer/ring-opening) that could partition between fragmentation and cinnoline formation pathways. In contrast to systems where the benzimidazole is replaced by an OR group (i.e., alcohol deprotection),[13] fragmentation of the benzimidazole system seems unlikely. Direct fragmentation is associated with a predicted barrier of approximately 24 kcal/mol, while protonation/fragmentation is associated with a barrier of approximately 50 kcal/mol from the nitrosophenyl/benzimizaole-substituted alcohol. Formation of cinnoline is predicted to be much more likely, with no high-energy transition state structures involved.

At this point we were faced with the task of rationalizing why cinnolines are not observed. The first pathway to anthranil products—proton transfer immediately following initial cyclization, then hydroxide ion loss (not shown)—that we examined was predicted to involve a transition state structure (for hydroxide loss) that was much higher in energy than any transition state structures en route to these heterocycles. After exploring many alternative mechanisms (see Supporting Information for details), we arrived at the "to anthranil products" pathway in Figure 1 and shown in Figure 2: tautomerization after ring-opening (which could be stepwise or a concerted [1,5] sigmatropic shift) → concerted proton transfer/electrocyclization → hydroxide loss. The highest energy transition state structure in this cascade, after initial cyclization and ring-opening, is predicted to be approximately 4 kcal/mol lower in energy than that for formation of cinnolines.

Thus, we arrive at a complex network of reactions, but one that is consistent with our experimental observations: predominant formation of anthranil rather than cinnolines or fragmentation products. Note that removing intermolecular hydrogen-bonds involving the benzimidazole NH (modeled by replacing the NH with NCH_3) leads to an increase in the relative energy of the transition state structure for ring closure en route to anthranil (by approximately 4 kcal/mol) and this is consistent with the lack of anthranil formation observed with an *N*-alkylated reactant (**8i**). Several alternative mechanistic pathways were examined, but none were found to be more favorable than those described above (see Supporting Information for details).

Conclusion

In summary, we described a pericyclic cascade route to anthranils. This work provides an example of reaction development via diversion of an expected reactive intermediate toward previously unexpected chemistry—here an intermediate proposed to play a key role in both the Davis–Beirut reaction and the photodeprotection of the *o*-nitrobenzyl protecting group was exploited. With sufficient mechanistic understanding, this scenario could be implemented as a strategy for designing new routes to valuable products with useful functions and, in so doing, create new opportunities for discovery.

Experimental Section

General procedures

All chemicals were purchased from standard commercial suppliers and used without further purification. Anhydrous solvents were dispensed from a solvent purification system utilizing two dry neutral alumina or prepared using dry molecular sieves. Analytical TLC was performed using pre-coated plates (silica gel 60 F_{254}) and visualized with UV light or I_2 chamber. Flash chromatography in glass columns was performed using 60 Å 230–400 mesh silica gel (Fisher). ^{1}H NMR spectra and proton decoupled ^{13}C NMR spectra were obtained on a 400 MHz Bruker, 600 MHz Varian, or 800 MHz Bruker NMR spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (*J*) are given in Hz. For HRMS analysis, samples were analyzed by flow-injection analysis into a Thermo Fisher Scientific LTQ Orbitrap (San Jose,

CA) operated in the centroided mode. Samples were injected into a mixture of 50% MeOH/H_2O and 0.1% formic acid at a flow of 0.2 mL/min. Source parameters were 5.5 kV spray voltage, capillary temperature of 275 °C, and sheath gas setting of 20. Spectral data were acquired at a resolution setting of 100,000 fwhm with the lockmass feature, which typically results in a mass accuracy.

Ethyl 2-nitrobenzeneacetimidate hydrochloride (S1)—A stoppered three-neck round bottom flask was charged with a stir bar, 2-(2-nitrophenyl)acetonitrile (2.66 g, 20 mmol), and toluene (20 mL). Ethanol (1.76 mL) was added to the flask stirred at room temperature for 3 minutes. HCl gas (generated by addition of HCl to H_2SO_4) was then vigorously bubbled through the reaction mixture for 20 minutes. This solution was stirred at room temperature overnight, poured into 350 mL of Et_2O, and placed in the freezer for 3 h. The solids were collected by vacuum filtration and washed 2 times with Et_2O (20 mL) to afford the product as a white solid (3.73 g, 93.3%) and used directly in the next step.

Ethyl 2-(4,5-dimethoxy-2-nitrophenyl)acetimidate hydrochloride (S2)—A stoppered three-neck round bottom flask was charged with a stir bar, 2-(4,5-dimethoxy-2-nitrophenyl)acetonitrile (2.00 g, 9.0 mmol), and toluene (20 mL). Ethanol (6 mL) was added to the flask stirred at room temperature for 3 minutes. HCl gas (generated by addition of H_2SO_4 to HCl) was then vigorously bubbled through the reaction mixture for 20 minutes. This solution was stirred at room temperature overnight, poured into 350 mL of Et_2O, and placed in the freezer for 3 h. The solids were collected by vacuum filtration and washed 2 times with Et_2O (20 mL) to afford the product as a white solid (2.00 g, 72.9%) and used directly in the next step.

***1*-Benzyl-2-(2-nitrobenzyl)-1*H*-benzo[d]imidazole (8i)—**A 20 mL Biotage microwave vial was charged with a stir bar, **S1** (0.500 g, 2.05 mmol), and methanol (10 mL). N^1-benzylbenzene-1,2-diamine (0.452 g, 2.28 mmol) was added to the flask and the reaction vial was sealed. The mixture was heated in the microwave at 60 °C for 6 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using a mixture of ethyl acetate/hexanes to afford the product as a tan solid (0.456 g, 64.8%); mp 128–130 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 8.1, 1H), 7.82 – 7.71 (m, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.26 (m, 7H), 7.05 (dd, *J* = 7.0, 2.5 Hz, 2H), 5.40 (s, 2H), 4.58 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.9, 148.6, 142.6, 135.7, 135.6, 133.6, 132.3, 131.5, 129.0, 128.2, 127.9, 126.3, 125.3, 122.8, 122.2, 119.8, 109.6, 47.2, 31.7. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{18}N_3O_2$: 344.1394; Found: 344.1389.

2-(2-Nitrobenzyl)-1H-benzo[d]imidazole (4a)—A 50 mL round bottom flask was charged with a stir bar, **S1** (1.30 g, 5.33 mmol), and methanol (30 mL). 1,2-Phenylenediamine (0.640 g, 5.92 mmol) was added to the flask and the reaction mixture was heated on the oil bath at 60 °C for 6 h. After cooling to room temperature, the solids were collected by vacuum filtration and washed with cold methanol to afford the product as a tan solid (1.25 g, 92.7%); mp 241–243°C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.2, 1H), 7.69 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.60 (td, *J* = 7.6, 1.4 Hz, 1H), 7.56 (broad, 1H), 7.44

(td, J = 7.9, 7.5, 1.5 Hz, 1H), 7.25 – 7.22 (m, 2H), 6.72 (d, J = 1.4 Hz, 1H), 4.54 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.2, 148.8, 133.7, 133.1, 131.9, 128.4, 124.8, 121.3, 118.4, 110.9, 32.5. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}N_3O_2$: 254.0924; Found: 254.0913.

7-Methyl-2-(2-nitrobenzyl)-1H-benzo[d]imidazole (4b)—A 20 mL Biotage microwave vial was charged with a stir bar, **S1** (0.600 g, 2.46 mmol), and methanol (15 mL). 3-Methylbenzene-1,2-diamine (0.333 g, 2.73 mmol) was added to the flask and the reaction vial was sealed. The mixture was heated in the microwave at 60 °C for 6 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using a mixture of ethyl acetate/hexanes to afford the product as a white solid (0.456 g, 62.4%); mp 201–203°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.3 Hz, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 4.55 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.3, 134.1, 133.3, 132.4, 128.8, 125.2, 32.8, 17.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3O_2$: 268.1086; Found: 268.1070.

5,6-Difluoro-2-(2-nitrobenzyl)-1H-benzo[d]imidazole (4c)—A 20 mL Biotage microwave vial was charged with a stir bar, **S1** (0.500 g, 2.05 mmol), and methanol (15 mL). 4,5-Difluorobenzene-1,2-diamine (0.328 g, 2.28 mmol) was added to the flask and the reaction vial was sealed. The mixture was heated in the microwave at 60 °C for 6 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using a mixture of ethyl acetate/hexanes to afford the product as a brown solid (0.151 g, 25.5%); mp 178–180°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.07 (dd, J = 8.1, 1.3 Hz, 1H), 7.73 (td, J = 7.6, 1.4 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.51 (dd, J = 10.9, 7.5 Hz, 2H), 4.54 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.4, 148.7, 147.6, 145.2, 133.8, 133.2, 131.6, 128.5, 124.9, 32.5. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{14}H_{10}F_2N_3O_2$: 290.0741; Found: 290.0736.

2-(2-Nitrobenzyl)-1H-naphtho[2,3-d]imidazole (4d)—A 20 mL Biotage microwave vial was charged with a stir bar, **S1** (0.492 g, 2.02 mmol), and methanol (15 mL). Naphthalene-2,3-diamine (0.354 g, 2.24 mmol) was added to the flask and the reaction vial was sealed. The mixture was heated in the microwave at 60 °C for 6 h. The solvent was removed under reduced pressure, the solids were collected by vacuum filtration and washed with cold dichloromethane to afford the product as a light brown solid (0.472 g, 69.4%); mp 190–192°C. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.04 (dd, J = 8.3, 1.3 Hz, 1H), 8.02 – 7.91 (m, 4H), 7.73 (dd, J = 7.8, 1.5 Hz, 1H), 7.62 (td, J = 7.5, 1.3 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.42 (dd, J = 6.4, 3.2 Hz, 2H), 4.61 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.5, 149.3, 134.3, 133.8, 131.8, 130.1, 129.1, 128.2, 125.4, 123.8, 33.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}N_3O_2$: 304.1086; Found: 304.1075.

6-Bromo-2-(2-nitrobenzyl)-1H-benzo[d]imidazole (4e)—A 50 mL round bottom flask was charged with a stir bar, **S1** (0.260 g, 1.07 mmol), and methanol (30 mL). 4-Bromobenzene-1,2-diamine (0.200 g, 1.08 mmol) was added to the flask and the reaction mixture was refluxed on the oil bath for 6 h. The solvent was removed under reduced

pressure and the crude product was purified by flash column chromatography using a mixture of ethyl acetate/hexanes to afford the product as a brown oil (0.090 g, 25.0%). ^{1}H NMR (800 MHz, Acetone-d_6) δ 8.09 (dd, J = 8.2, 1.3 Hz, 1H), 7.73 (td, J = 7.6, 1.4 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.64 (ddd, J = 7.7, 1.5, 0.6 Hz, 1H), 7.60 (ddd, J = 8.2, 7.4, 1.5 Hz, 1H), 7.44 (dd, J = 8.5, 0.6 Hz, 1H), 7.29 (dd, J = 8.5, 1.9 Hz, 1H), 4.65 (s, 2H).. ^{13}C NMR (201 MHz, Acetone-d_6) δ 153.5, 149.3, 131.8, 128.5, 124.9, 124.6, 114.0, 32.7. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{14}H_{11}BrN_3O_2$: 332.0035; Found: 332.0046.

6-Methoxy-2-(2-nitrobenzyl)-1H-benzo[d]imidazole (4f)—A 50 mL round bottom flask was charged with a stir bar, **S1** (0.491 g, 2.01 mmol), and methanol (30 mL). 4-Methoxybenzene-1,2-diamine (0.275 g, 1.99 mmol) was added to the flask and the reaction mixture was refluxed on the oil bath for 4 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using a mixture of ethyl acetate/hexanes to afford the product as a light brown solid (0.290 g, 51.0%); mp decomp. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (dd, J = 8.2, 1.3 Hz, 1H), 7.61 (dd, J = 7.8, 1.4 Hz, 1H), 7.55 (td, J = 7.5, 1.3 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.00 (s, 1H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 4.50 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 156.4, 151.1, 148.6, 134.0, 133.1, 131.9, 128.4, 125.1, 112.0, 55.8, 33.1. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{15}H_{14}N_3O_3$: 284.1035; Found: 284.1038.

5,6-Dimethyl-2-(2-nitrobenzyl)-1H-benzo[d]imidazole (4g)—A 50 mL round bottom flask was charged with a stir bar, **S1** (0.490 g, 2.00 mmol), and methanol (30 mL). 4-Bromobenzene-1,2-diamine (0.270 g, 1.98 mmol) was added to the flask and the reaction mixture was refluxed on the oil bath for 6 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using a mixture of ethyl acetate/hexanes to afford the product as a light brown solid (0.230 g, 41.0%); mp 272–274°C. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.05 (dd, J = 8.1, 1.4 Hz, 1H), 7.69 (td, J = 7.5, 1.4 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.25 (s, 2H), 4.59 (s, 2H), 2.31 (s, 6H). ^{13}C NMR (201 MHz, Acetone-d_6) δ 150.8, 150.8, 149.3, 133.4, 132.8, 132.4, 132.3, 130.1, 128.2, 124.7, 32.5, 19.4. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{16}H_{16}N_3O_2$: 282.1243; Found: 282.1254.

2-(4,5-Dimethoxy-2-nitrobenzyl)-1H-benzo[d]imidazole (4h)—A 20 mL Biotage microwave vial was charged with a stir bar, **S2** (0.304 g, 1.00 mmol), and methanol (10 mL). 1,2-Phenylenediamine (0.119 g, 1.10 mmol) was added to the flask and the reaction vial was sealed. The mixture was heated on the oil bath at 80 °C for 6 h. The solvent vessel was placed in the freezer overnight and the solids were collected by vacuum filtration to afford the product as an orange crystal (0.202 g, 64.4%); mp 224–226°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 7.71 (s, 1H), 7.47 – 7.38 (m, 2H), 7.27 (s, 1H), 7.10 (dd, J = 6.0, 3.2 Hz, 2H), 4.56 (s, 2H), 3.90 (s, 6H), 3.89 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.5, 153.2, 148.0, 141.2, 127.3, 115.9, 108.8, 56.7, 56.5, 33.7. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{16}H_{16}N_3O_4$: 314.1141; Found: 314.1130.

5-(2-Nitrobenzyl)-1H-tetrazole (4i)—A 20 mL Biotage microwave vial was charged with a stir bar, 2-(2-nitrophenyl)acetonitrile (0.324 g, 2.00 mmol), NH_4Cl (0.214 g, 4.00

mmol) and DMF (10 mL). Sodium azide (0.390 g, 6.00 mmol) was added to the flask and the reaction vial was sealed. The mixture was heated on the oil bath at 150 °C for 12 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using a mixture of ethyl acetate/hexanes to afford the product as a light orange solid (0.0937 g, 22.8%); mp 142–144°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (dd, J = 8.4, 1.3 Hz, 1H), 7.77 (td, J = 7.6, 1.3 Hz, 1H), 7.67 – 7.57 (m, 2H), 4.61 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 148.9, 134.6, 133.7, 130.8, 129.6, 125.6, 27.9. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_8H_8N_5O_2$: 206.0678; Found: 206.0667.

General Procedure for Synthesis of Anthranil

A 2–5 mL Biotage microwave vial was charged with a stir rod, 2-(2-nitrobenzyl)-1H-benzo[d]imidazole derivative (0.2 mmol), 4Å molecular sieves (0.2 g), and sodium *tert*-butoxide (1 mmol, 5 equiv.), and DMF (4 mL; 0.05 M). The mixture was heated under microwave irradiation at 125 °C for 6 hours. The reaction was cooled room temperature and 1 M HCl (100 mL) was added and the solution was extracted 3 times with ethyl acetate (50 mL). The organic layers were combined and removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography using mixtures of ethyl acetate/hexanes.

General remarks: The use of 1 M HCl significantly simplifies the purification process by removing the unwanted dimer and its decomposition products.

3-(1H-benzo[d]imidazol-2-yl)benzo[c]isoxazole (6a)—Synthesized according to the general procedure and isolated as an orange solid (0.0255 g, 54.3%); mp 246–248°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.78 (s, 1H), 8.28 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 9.0 Hz, 2H), 7.63 (broad, 1H), 7.54 (dd, J = 9.0, 6.3 Hz, 1H), 7.39 – 7.26 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.6, 156.3, 144.4, 141.2, 132.7, 126.7, 124.9, 123.4, 121.8, 120.4, 116.5, 115.2, 112.7. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{14}H_{10}N_3O$: 236.0824; Found: 236.0811.

3-(7-Methyl-1H-benzo[d]imidazol-2-yl)benzo[c]isoxazole (6b)—Synthesized according to the general procedure and isolated as a light yellow solid (0.0260 g, 52.2%); mp 240–242°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.75 – 13.66 (m, 1H), 8.33 – 8.26 (m, 1H), 7.74 – 7.77 (m, 1H), 7.68 – 7.61 (m, 1H), 7.55 – 7.49(m, 1H), 7.46 – 7.40 (m, 1H), 7.33 – 7.18 (m, 2H), 7.15 – 7.07 (m, 1H), 2.68 – 2.58 (d, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.6, 156.5, 144.2, 143.9, 141.2, 140.4, 134.6, 134.5, 132.6, 130.0, 126.5, 126.5, 125.2, 124.8, 123.4, 123.3, 122.9, 122.0, 121.9, 117.7, 116.5, 116.3, 115.1, 110.0, 17.5, 16.9. HRMS (ESI-Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{15}H_{12}N_3O$: 250.0980; Found: 250.0975.

3-(5,6-Difluoro-1H-benzo[d]imidazol-2-yl)benzo[c]isoxazole (6c)—Synthesized according to the general procedure and isolated as a brown solid (0.0262 g, 48.3%); mp decomp. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.05 (s, 1H), 8.21 (dt, J = 8.9, 1.0 Hz, 1H), 7.89 (broad, 1H), 7.75 (d, J = 9.1, 1H), 7.63 (broad, 1H), 7.53 (ddd, J = 9.1, 6.4, 1.0 Hz, 1H), 7.29 (dd, J = 8.9, 6.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.3, 157.1, 155.2,

142.5, 132.2, 126.4, 121.0, 116.0, 114.8, 59.7, 20.7, 14.1. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_8F_2N_3O$: 272.0635; Found: 272.0625.

3-(1H-naphtho[2,3-d]imidazol-2-yl)benzo[c]isoxazole (6d)—Synthesized according to the general procedure and isolated as a yellow solid (0.0283 g, 49.6%); mp 230–232°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.80 (s, 1H), 8.41 (s, 1H), 8.39 – 8.32 (m, 1H), 8.18 – 8.01 (m, 3H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.62 – 7.53 (m, 1H), 7.40 – 7.48 (m, 2H), 7.37 (dd, *J* = 8.8, 6.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.2, 155.5, 144.5, 144.0, 134.7, 132.3, 131.1, 130.2, 128.3, 127.5, 126.8, 124.5, 123.6, 121.3, 116.8, 116.7, 115.0, 107.6. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{12}N_3O$: 286.0980; Found: 286.0970.

3-(6-Bromo-1H-benzo[d]imidazol-2-yl)benzo[c]isoxazole (6e)—Synthesized according to the general procedure and isolated as a yellow powder (0.0181 g, 28.9%); mp 245–247°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.28 – 8.21 (m, 1H), 8.00 (broad, 1H), 7.83 – 7.72 (m, 2H), 7.59 – 7.51 (m, 1H), 7.48 (s, 1H), 7.36 – 7.28 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.6, 155.8, 132.7, 127.6, 126.9, 126.4, 122.6, 122.1, 121.6, 116.7, 115.3, 114.4, 79.6. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_9BrN_3O$: 313.9929; Found: 313.9917.

3-(6-Methoxy-1H-benzo[d]imidazol-2-yl)benzo[c]isoxazole (6f)—Synthesized according to the general procedure and isolated as a dark yellow solid (0.0254 g, 47.9%); mp decomp. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.69 – 13.58 (m, 1H), 8.29 – 8.21 (m, 1H), 7.77 – 7.69 (m, 2H), 7.56 – 7.47 (m, 1H), 7.31 – 7.23 (m, 1H), 7.07 – 6.90 (m, 2H), 3.86 – 3.82 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.9, 157.5, 156.4, 145.3, 140.3, 139.0, 135.8, 132.6, 126.3, 121.9, 121.0, 115.9, 115.0, 113.9, 113.0, 101.8, 94.7, 56.0. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{12}N_3O_2$: 266.0930; Found: 266.0915.

3-(5,6-Dimethyl-1*H*-benzo[d]imidazol-2-yl)benzo[c]isoxazole (6g)—Synthesized according to the general procedure and isolated as a yellow powder (0.0160 g, 30.4%); mp 268–270°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.81 (s, 1H), 8.42 (s, 1H), 8.36 (d, *J* = 8.8 Hz, 1H), 8.16 – 8.03 (m, 3H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.58 (dd, *J* = 9.1, 6.3 Hz, 1H), 7.43 (d, *J* = 6.0 Hz, 2H), 7.37 (dd, *J* = 8.8, 6.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.5, 156.6, 140.3, 132.6, 126.3, 121.9, 116.1, 115.1, 20.6. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{14}N_3O$: 264.1137; Found: 264.1122.

3-(1H-benzo[d]imidazol-2-yl)-5,6-dimethoxybenzo[c]isoxazole (6h)—Synthesized according to the general procedure and isolated as a yellow powder (0.0191 g, 32.4%); mp decomp. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.56 (s, 1H), 7.71 (broad, 2H), 7.34 (s, 1H), 7.32 (broad, 2H), 7.04 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 155.9, 155.8, 153.0, 151.5, 141.7, 112.8, 95.7, 91.7, 79.6, 56.6, 56.4. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{14}N_3O_3$: 296.1035; Found: 296.1030.

3-(1H-tetrazol-5-yl)benzo[c]isoxazole (6i)—Synthesized according to the general procedure and isolated as a yellow solid (0.0232 g, 62.0%); mp 142–144°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.42 (ddd, *J* = 9.1, 6.3, 1.1 Hz, 1H), 7.11 (dd, *J* = 8.8, 6.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ

157.0, 153.2, 132.0, 124.2, 122.8, 114.6, 114.5. HRMS (ESI-Orbitrap) *m/z*: $[M - H]^-$ Calcd for $C_8H_4N_5O$: 186.0421; Found: 186.0423.

(E)-(2-(((1H-benzo[d]imidazol-2-yl)(2-nitrophenyl)methylene)amino)phenyl)(1H-benzo[d]imidazol-2-yl)methanone (7)—A 2–5 mL Biotage microwave vial was charged with a stir rod, **4a** (0.0506 g, 0.2 mmol), and potassium hydroxide (0.056 g, 1 mmol), and methanol (4 mL) and water (0.4 mL). The mixture was heated under microwave irradiation at 60 °C for 6 hours. The reaction was cooled room temperature and water (100 mL) was added and the solution was extracted 3 times with ethyl acetate (50 mL). The organic layers were combined and removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography using mixtures of ethyl acetate/hexanes to afford the product as a yellow solid (0.0182 g, 18.7%); mp decomp. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.77 (broad, 2H), 8.29 (d, J = 1.1 Hz, 1H), 8.26 (d, J = 1.1 Hz, 1H), 7.98 (td, J = 7.5, 1.1 Hz, 2H), 7.92 – 7.84 (m, 4H), 7.70 (broad, 1H), 7.68 (broad, 1H), 7.62 (broad, 1H), 7.60 (broad, 1H), 7.41 (broad, 2H), 7.29 (broad, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 184.8, 147.7, 147.4, 142.9, 134.8, 134.6, 133.7, 132.1, 129.9, 126.2, 124.2, 123.4, 121.3, 113.0. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{19}N_6O_3$: 487.1519; Found: 487.1490.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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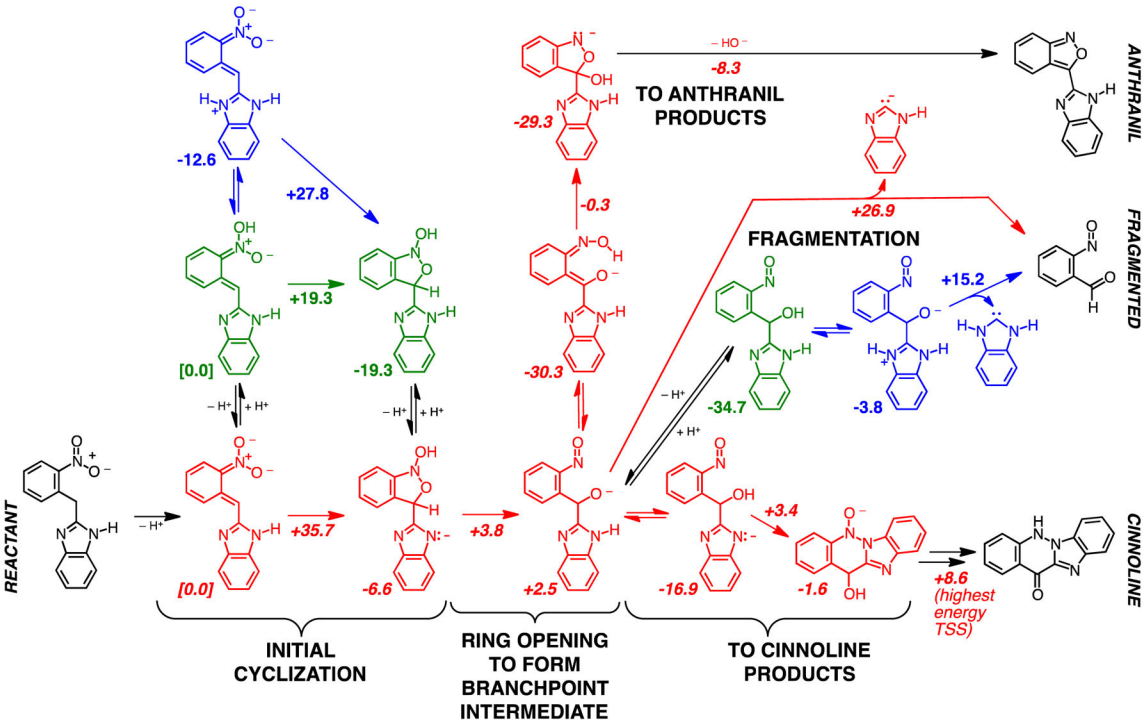


Figure 1.

Reaction network examined at the SMD(DMF)-M06-2X/6-31+G(d,p) level of theory. Energies of transition state structures are shown on arrows. Black structures represent reactants and products (not calculated). Blue and green energies can be compared to each other; red energies cannot be compared to these, since the red structures have one less proton than do the green and blue structures. See Supporting Information for additional details and results on other possible pathways.

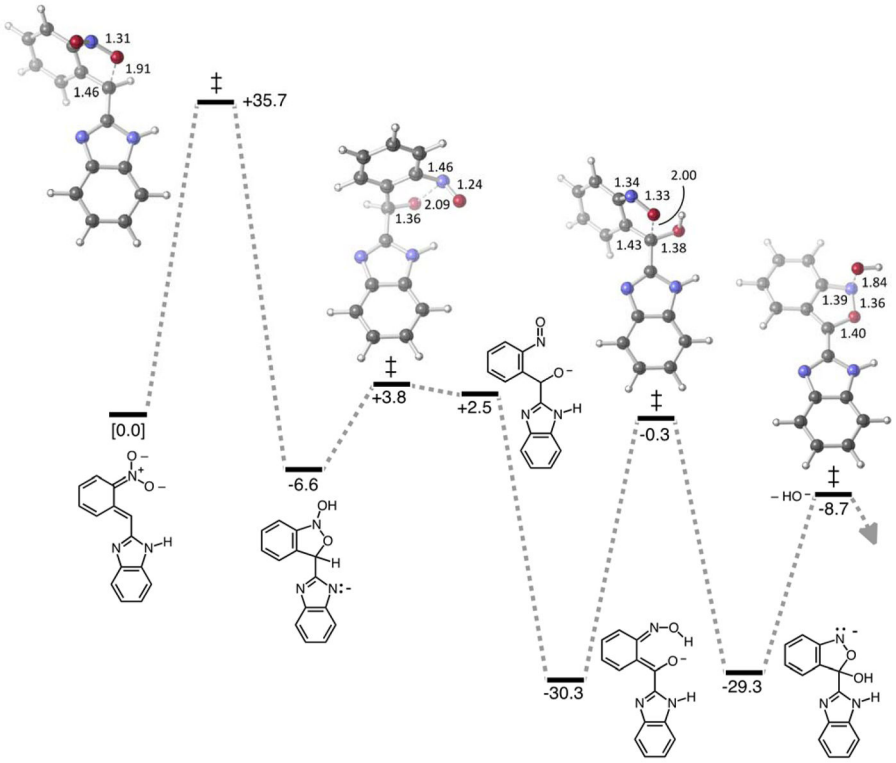
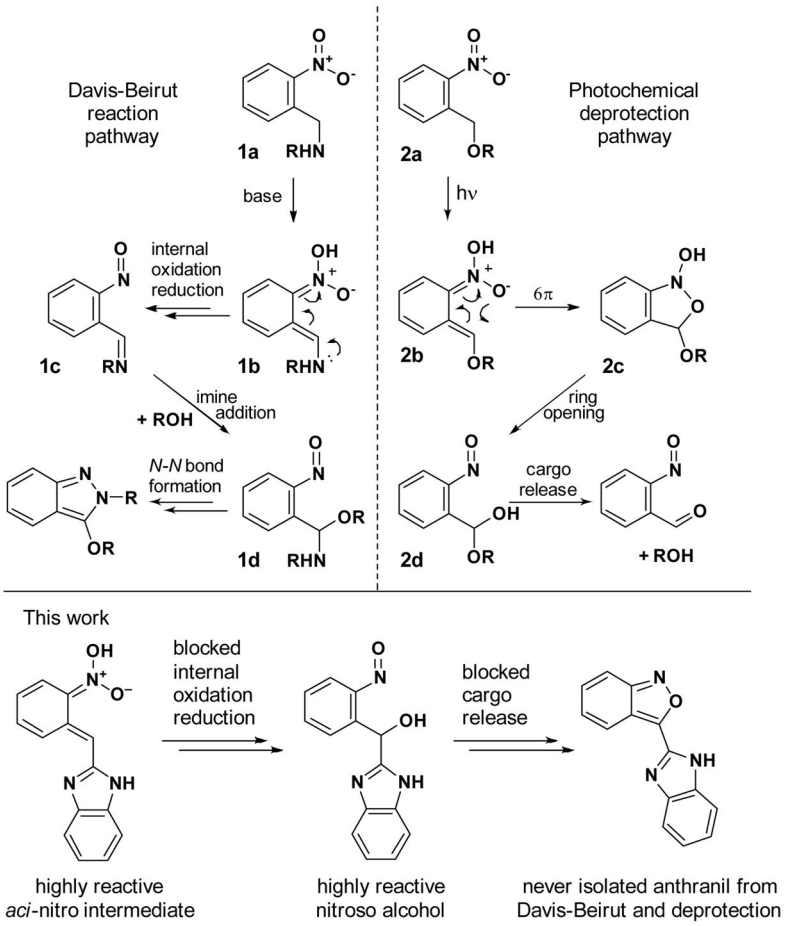


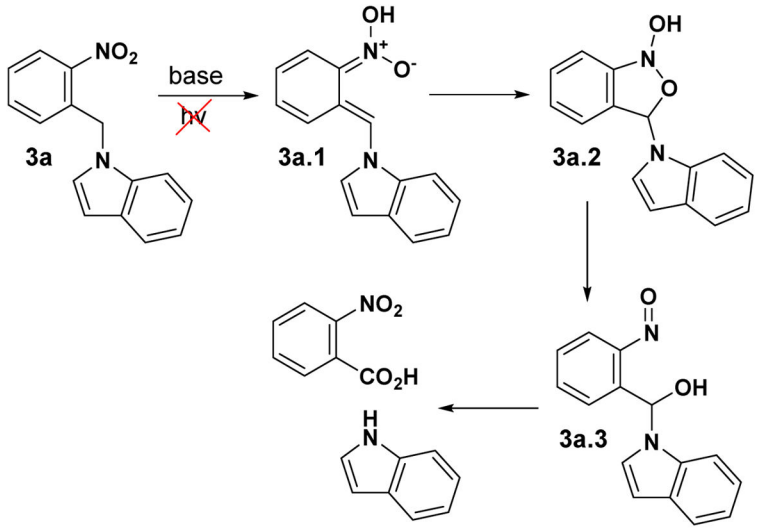
Figure 2.

Reaction coordinate diagram for the preferred pathway to anthranils. Relative energies (kcal/mol) from the SMD(DMF)-M06-2X/6-31+G(d,p) level of theory are shown, as are selected distances (Å) for transition state structures.



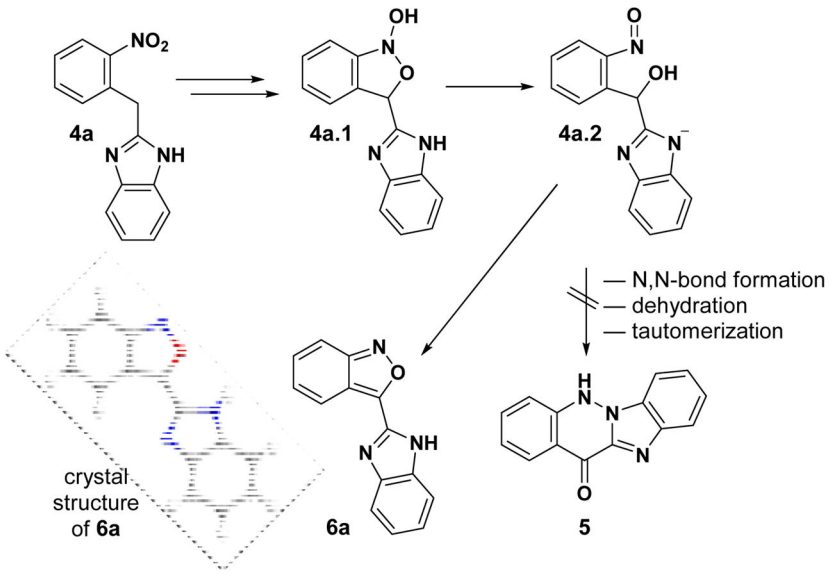
Scheme 1.

Davis–Beirut reaction mechanism and photochemistry of *o*-nitrobenzyl compounds.



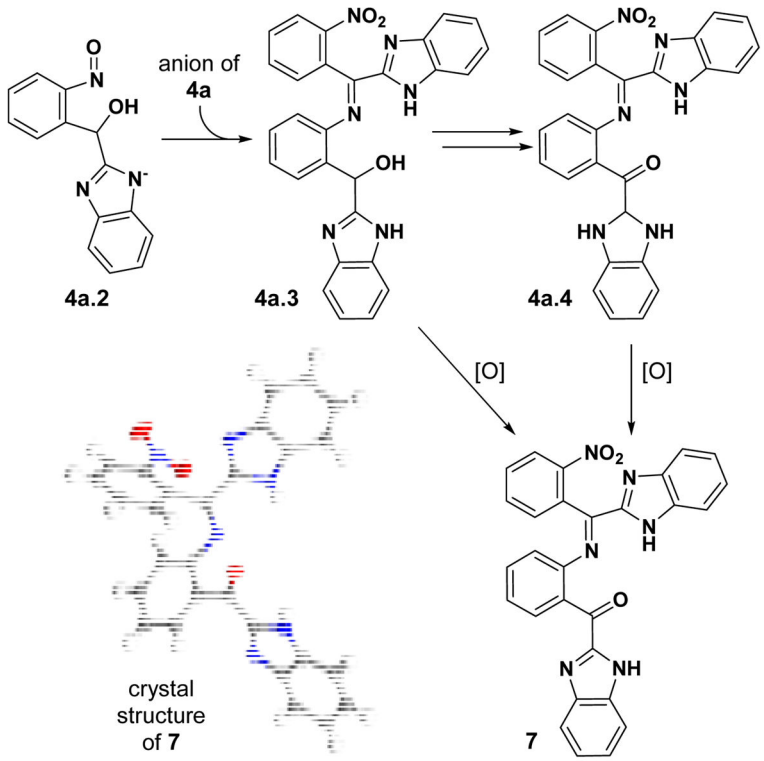
Scheme 2.

Exploring the reactivity of **3a.1**.

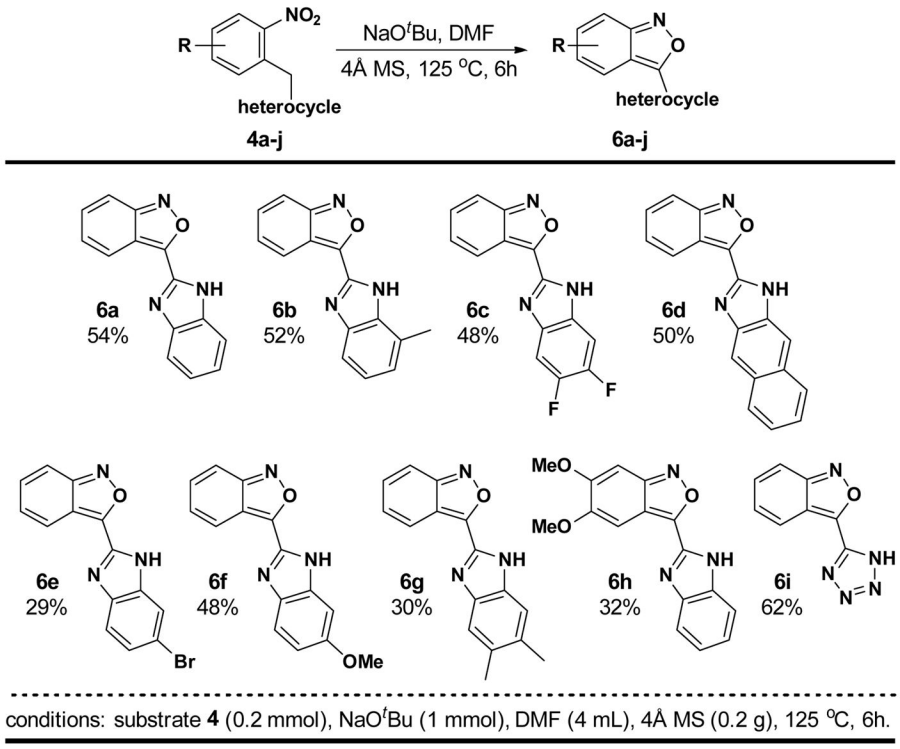


Scheme 3.

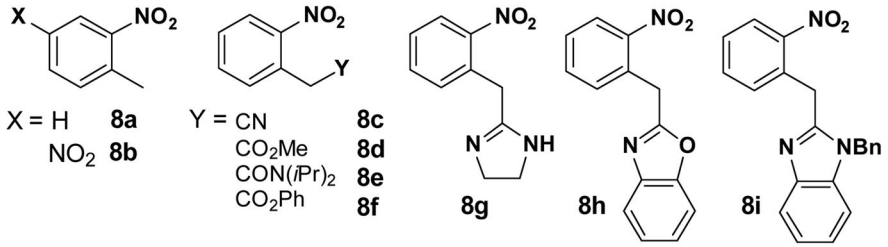
Exploring the reactivity of **4a**.



Scheme 4.
Side-product identification and mechanism of its formation.



Scheme 5.
Base mediated formation of anthranils; isolated yields.



Scheme 6.

Substrates which failed to give an anthranil.