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Davis−Beirut Reaction: Alkoxide versus Hydroxide Addition to the Key *o*-Nitrosoimine Intermediate

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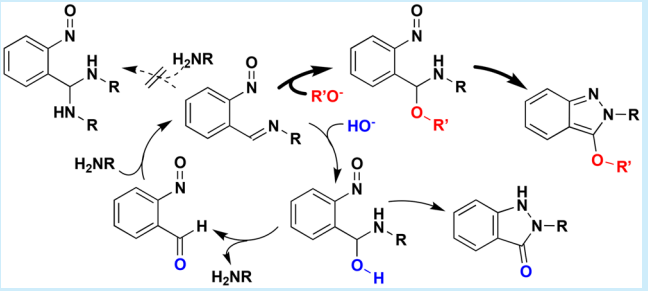
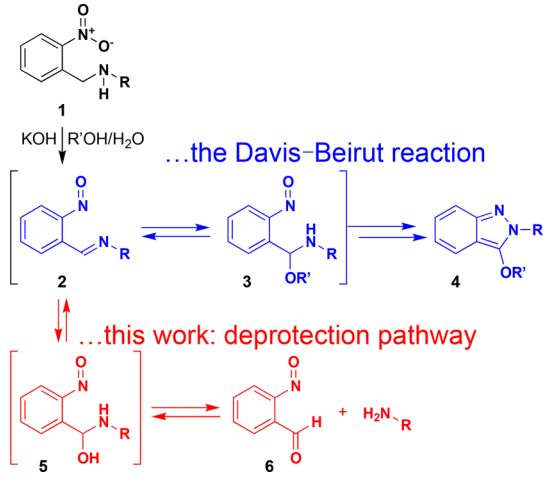
Supporting Information

ABSTRACT: Reaction options, alkoxide vs hydroxide vs amine addition to the key intermediate (*o*-nitrosoimine) generated in the Davis−Beirut reaction of an *o*-nitrobenzylamine substrate, are reported to explain the nucleophilic addition selectivity of this one-pot indazole-forming process. The hydroxide addition/deprotection pathway as well as the fate of the resulting *o*-nitrosobenzaldehyde were both uncovered with several *o*-nitrobenzylamine substrates, and design elements required for an efficient double Davis−Beirut reaction, inspired by new mechanistic insights, were defined.



A number of versatile protocols have been developed for N−N bond formation, with beneficial applications to a variety of intriguing heterocyclic targets.[1] One of these targets, indazoles, exhibit a wide range of biological activities[2] and reactivities, for example, readily undergoing rearrangement in the presence of electrophiles to indazolones,[3] which also have considerable potential as biologically relevant targets.[4] The versatile Davis−Beirut reaction[5] provides a robust method for the construction of indazoles[2] and has been extensively studied experimentally and computationally.[6] The proposed Davis−Beirut mechanism (Scheme 1) involves generation of transient *o*-nitrosoimine intermediate **2** by treatment of *o*-nitrobenzylamine **1** with hydroxide. The imine moiety in **2** is susceptible to attack by alkoxide, which then triggers an N−N-bond forming reaction that results in formation of indazole product **4**.

Scheme 1. Davis−Beirut and Deprotection Reactions of *o*-Nitrosoimine 2



One unanswered mechanistic question in this **1** → indazole **4** process is why does alkoxide outcompete hydroxide in addition to the key *o*-nitrosoimine intermediate? The origin of this "alkoxide over hydroxide" selectivity is ambiguous since addition of water (and hydroxide) to imines, i.e., the first step in imine hydrolysis, represents a fundamental reaction in organic chemistry. Our recent work on exploiting alternative chemistries of Davis−Beirut reaction intermediates[7] caused us to consider other possible reactions of transient *o*-nitrosoimine **2**. In one hypothesized side reaction, **2** reacts with hydroxide (or water) to form hemiaminal **5**, which can subsequently collapse to *o*-nitrosobenzaldehyde **6** (Scheme 1). Indeed, this previously overlooked **2** → **6** reversible process provides a mechanistic model, which underscores the question of alkoxide vs hydroxide chemoselectivity in the Davis−Beirut reaction. Herein, we unveil these mechanistic details through intermediate trapping strategies and insights gained from "double" Davis−Beirut reactions.

The *o*-nitrobenzyl group is a well-known photolabile protecting group for heteroatoms[8] where each deprotection event generates a molecule of *o*-nitrosobenzaldehyde.[9] If a **2** → **5** → **6** process is indeed occurring during the Davis−Beirut reaction, the resulting *o*-nitrosobenzaldehyde could be trapped by reacting with the primary amine liberated during the formation of **6** to regenerate **2**. Therefore, it can be anticipated that less nucleophilic amines, like aniline, released in **2** → **6** would not successfully compete in an "added amine" experiment, for example, where added *n*-butylamine could

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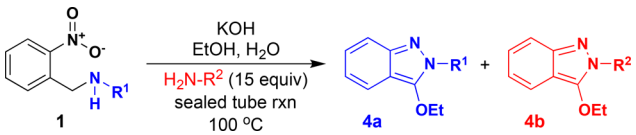
trap released *o*-nitrosobenzaldehyde. Indeed, when *N*-(2-nitrobenzyl)aniline was reacted under standard Davis–Beirut reaction conditions but with 15 equiv of added *n*-butylamine, ^{1}H NMR of the crude reaction mixture showed the presence of both *N*-phenylindazole, via the normal uninterrupted Davis–Beirut reaction, and *N*-butylindazole, via the *o*-nitrosobenzaldehyde pathway and subsequent **6** → **2**$^{R=n\text{-butyl}}$ (Table 1, entry 1).

Table 1. Amine Exchange in the "Added Amine" Davis–Beirut Reactions[a]



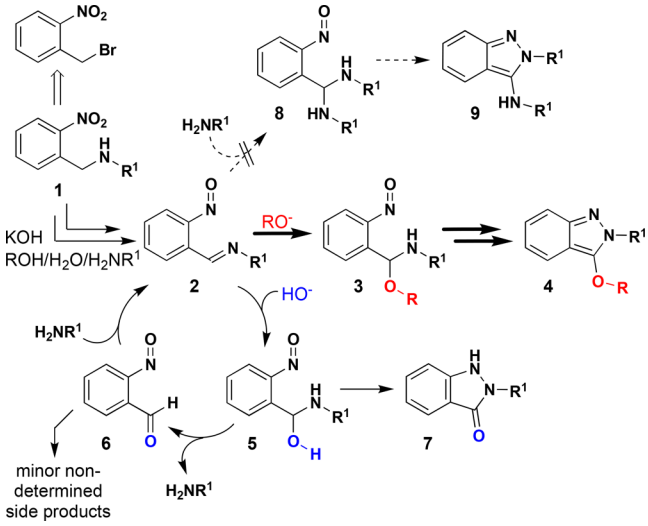
entry	R^1	R^2	H_2O (%)	4a : 4b[b]
1	Ph	nBu	20	91:9
2	Ph	nBu	0	4a only
3	iPr	nBu	20	80:20
4	nBu	Ph	20	4a only
5	nBu	iPr	20	4a only

[a]See the SI for the crude ^{1}H NMR data for Table 1, entries 1–3. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

When water was excluded from the added amine reaction, the *o*-nitrosoimine intermediate was not expected to hydrolyze to a significant extent and, indeed, only the *N*-phenylindazole was observed (entry 2). Moreover, there is a relatively demanding steric environment at the imine carbon of *o*-nitrosoimine intermediate **2** as evidenced by failure of the Davis–Beirut reaction when bulky alcohols like isopropanol are employed.[10] As a result, we anticipated trapping of the liberated *o*-nitrosobenzaldehyde with the less hindered of the two competing alkyl amines in this added amine experiment. Indeed, when *N*-(2-nitrobenzyl)isopropylamine was subjected to the Davis–Beirut reaction with 15 equiv of added *n*-butylamine, both *N*-isopropyl- and *N*-butylindazoles were observed (entry 3). Finally, when *N*-(2-nitrobenzyl)butan-1-amine was employed as the starting material, neither added excess aniline nor isopropylamine were competitive, and only *N*-butylindazole was detected (entries 4 and 5).

The starting *o*-nitrobenzylamines (**1**) are readily prepared by amine *N*-alkylation with *o*-nitrobenzyl bromide (Scheme 2). Upon treatment with KOH in ROH/H_2O (simple alcohols like MeOH and EtOH work best), an internal oxidation (benzylic amine → benzylic imine) reduction (nitro → nitroso) reaction takes place to deliver *N*-alkyl-1-(2-nitrosophenyl)methanimine **2**. In the added amine experiment, this key intermediate confronts three potential nucleophiles: (i) alkoxide (→ 1-(2-nitrosophenyl)methanamine **3**); (ii) hydroxide (→ (2-nitrosophenyl)methanol **5**); and (iii) added amine (→ 1-(2-nitrosophenyl)methanediamine **8**). Since a 1°-amine is an order of magnitude less nucleophilic than a simple alkoxide (like methoxide or ethoxide)[11] and since no trace of **9** (or its tautomers) is detected in the crude reaction mixture, we concluded that **2** → **8** is a nonviable pathway when the reaction is run in methanol or ethanol.[6] Alkoxide addition **2** → **3** is the preferred pathway, delivering indazole **4** in generally excellent yield (for example, when R^1 = isopropyl, indazole **4** is obtained in 87% overall yield from *o*-nitrobenzyl bromide). Competing hydroxide addition to intermediate **2** is a viable, but minor, pathway that leads to (2-nitrosophenyl)methanol **5**, which can

Scheme 2. Reaction Options Confronted by Transient *o*-Nitrosoimine 2



undergo N–N-bond formation to indazolone **7** (trace amounts detected by LCMS) or loss of amine to *o*-nitrosobenzaldehye (**6**; i.e., deprotection). The implications of the data in Table 1 are that liberated *o*-nitrosobenzaldehyde (**6** in Scheme 2) can condense with the added amine (H_2NR^1) to regenerate *N*-alkyl-1-(2-nitrosophenyl)methanimine **2** or lead to the formation of minor undetermined side products.[12]

With these results as backdrop, we next set out to isolate the amine released when water or hydroxide adds to intermediate **2** (Scheme 1). However, when typical Davis–Beirut substrates undergo deprotection (i.e., **1** → **6**; Scheme 1), isolating the resulting relatively low molecular weight amine is complicated by the reaction workup sequence. A "double" Davis–Beirut substrate (**10** in Scheme 3a) was developed to mitigate this issue since deprotection product **12** would be highly compatible with the employed experimental procedures and analytical methods, such as TLC and LCMS. When substrate **10** was subjected to standard Davis–Beirut reaction conditions, indazolylamine **12**, the cumulative consequence of one Davis–Beirut reaction (**10** → **13** or **11** → **12**) and one deprotection reaction (**10** → **11** or **13** → **12**), was isolated in appreciable quantities (30% yield), indicating that deprotection can indeed be a competing process. Bis-indazole[13] **14**, the cumulative consequence of two Davis–Beirut reactions (**10** → **13** → **14**), was a minor product (6% yield) in this reaction. These **10** → **12** + **14** results were mirrored in several other double Davis–Beirut reactions (→ bis-indazoles **16**–**19**; Scheme 3b), although in quite variable yields.

As a further probe of transfomation dynamics in the bis-indazole-forming process, N^1,N^2-bis(2-nitrobenzyl)ethane-1,2-diamine (**15**), the substrate leading to bis-indazole **16**, was subjected to Davis–Beirut conditions where various amounts of water were employed (Figure 1). The presence of at least ~5% water in methanol is clearly advantageous,[11] but the upper limit of beneficial effects seemed to be at about 15–20% added water as a downward trend in yield was observed with each incremental increase past ~20% added water.

Although the double Davis–Beirut reactions delineated in Scheme 3 served the purpose of illuminating a much more complete mechanistic model for this indazole-forming reaction, the low bis-indazole product yields were, nonetheless,

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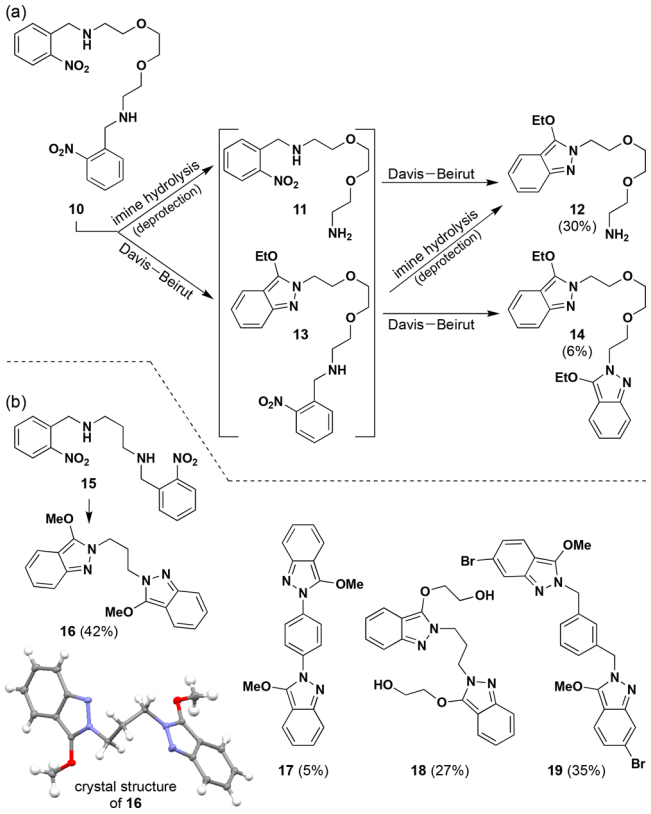
Scheme 3. Double Davis–Beirut Reactions: (a) Contending Pathways and (b) Bis-indazole Examples[a]



[a]The generally improved double Davis–Beirut product yields for **16**–**19** vs **14** perhaps reflect the increased nucleophilicity of MeOH vs EtOH.[11]

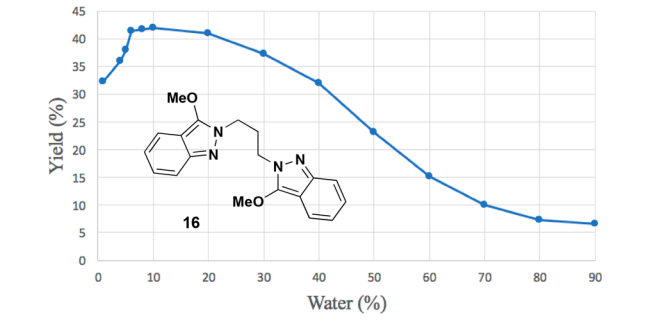
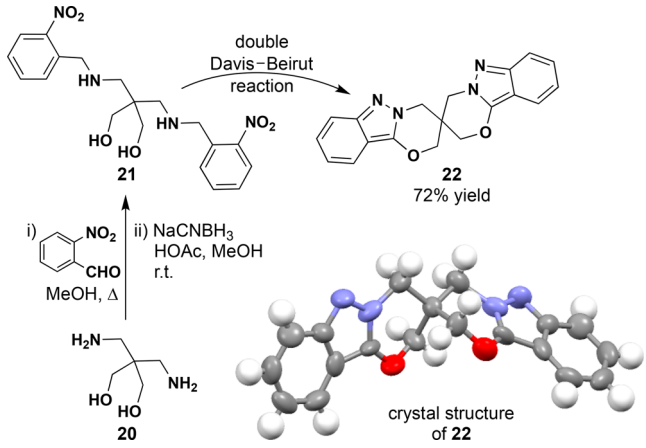


Figure 1. Yield consequence of added water in double Davis–Beirut reaction **15** → **16**.

disappointing. However, the mechanistic insights gained with these substrates were exploited to design double Davis–Beirut substrate **21** [prepared by reductive amination of *o*-nitrobenzaldehyde with 2,2-bis(aminomethyl)propane-1,3-diol (**20**);[14] Scheme 4], which was expected to perform optimally in bis-indazole formation. Specifically, since diaminodiol **21** contains an internal nucleophile for each Davis–Beirut transformation in **21** → **22**, this substrate effectively overwhelmed intermolecular with intramolecular nucleophilic additions to the two short-lived *o*-nitrosoimine intermediates, and indeed, **21** was converted to spiro-fused bis-indazole **22** in an impressive 72% yield, which translates to 85% yield per Davis–Beirut reaction.

Scheme 4. Substrate 21, Which Provides Two Internal Nucleophiles, Results in a High-Yielding Double Davis–Beirut Transformation



In conclusion, the work reported here decrypts the issues involved in alkoxide vs hydroxide selectivity in the Davis–Beirut reaction. The hydroxide addition/deprotection pathway and the role of *o*-nitrosobenzaldehyde were both delineated with several *o*-nitrobenzylamine substrates, and design elements required for an efficient double Davis–Beirut reaction, inspired by new mechanistic insights, were defined.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00036.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1813045–1813046 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 emailing 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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Notes

The authors declare no competing financial interest.

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■ DEDICATION

We dedicate this work in memory of Dorothy J. Schoening, a wonderful and gracious mentor.

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