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Authors

Zhu, Jie S
Duong, Matthew R
Teuthorn, Andrew P
et al.

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

Jie S. Zhu[†], **Matthew R. Duong**[†], **Andrew P. Teuthorn**[†], **Julia Y. Lu**[†], **Jung-Ho Son**[†], **Makhluf J. Haddadin**[‡], and **Mark J. Kurth**[*,†]
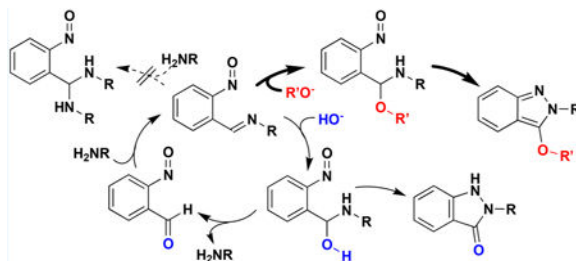
[†]Department of Chemistry, University of California Davis, 1 Shields Avenue, Davis, California 95616, United States

[‡]Department of Chemistry, American University of Beirut, Beirut 1107 2020, Lebanon

Abstract

Reaction options, alkoxide vs hydroxide vs amine addition to the key intermediate (*o*-nitrosoimine) generated in the Davis–Beirut reaction of an *o*-nitrobenzyl-amine 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.

Graphical Abstract

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*-nitrobenzyl-amine **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**.

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 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*-butyl] (Table 1, entry 1).

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 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 bisindazole-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, disappointing. However, the mechanistic insights gained with these substrates were exploited to design double Davis–Beirut substrate **21** [prepared by reductive amination of *o*-nitro- benzaldehyde 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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

## REFERENCES

(1). (a) Mu Q-C; Lv J-Y; Chen M-Y; Bai X-F; Chen J; Xia C-G; Xu L-W RSC Adv. 2017, 7, 37208.(b) Park SW; Choi H; Lee J.-h.; Lee Y-J; Ku J-M; Lee SY; Nam T.-g. Arch. Pharmacal Res. 2016, 39, 302.(c) Diccianni JB; Hu C; Diao T Angew. Chem., Int. Ed. 2016, 55, 7534.(d) Lin W; Hu M-H; Feng X; Cao C-P; Huang Z-B; Shi D-Q Tetrahedron 2013, 69, 6721.(e) Evans LE; Cheeseman MD; Jones K Org. Lett. 2012, 14, 3546. [PubMed: 22734502] (f) Wegner HA Angew. Chem., Int. Ed. 2012, 51, 4787.(g) Pangerl M; Hughes CC; Trauner D Tetrahedron 2010, 66, 6626.

(2). Haddadin MJ; Conrad WE; Kurth MJ Mini-Rev. Med. Chem. 2012, 12, 1293. [PubMed: 23092440]

(3). Donald MB; Conrad WE; Oakdale JS; Butler JD; Haddadin MJ; Kurth MJ Org. Lett. 2010, 12, 2524. [PubMed: 20438102]

(4). (a) Qian Y; Bolin D; Conde-Knape K; Gillespie P; Hayden S; Huang K-S; Olivier AR; Sato T; Xiang Q; Yun W; Zhang X Bioorg. Med. Chem. Lett. 2013, 23, 2936. [PubMed: 23582275] (b) Vega MC; Rolón M; Montero-Torres A; Fonseca-Berzal C; Escario JA; Gómez-Barrio A; Gálvez J; Marrero-Ponce Y; Arán VJ Eur. J. Med. Chem. 2012, 58, 214. [PubMed: 23124218] (c) Cappelli A; Nannicini C; Gallelli A; Giuliani G; Valenti S; Mohr G. l. P.; Anzini M; Mennuni L; Ferrari F; Caselli G J. Med. Chem. 2008, 51, 2137. [PubMed: 18318468]

(5). For a recent application of the Davis–Beirut reaction, see: El-Dakdouki MH; Hussein A-S; Abdallah H; Shatila R; Mouneimne Y Tetrahedron 2017, 73, 5769.

(6). Avila B; El-Dakdouki MH; Nazer MZ; Harrison JG; Tantillo DJ; Haddadin MJ; Kurth MJ Tetrahedron Lett. 2012, 53, 6475. [PubMed: 23139435]

(7). Zhu JS; Son J-H; Teuthorn AP; Haddadin MJ; Kurth MJ; Tantillo DJ J. Org. Chem. 2017, 82, 10875. [PubMed: 28922917]

(8). Klan P; Solomek T; Bochet CG; Blanc A. l.; Givens R; Rubina M; Popik V; Kostikov A; Wirz J Chem. Rev. 2013, 113, 119. [PubMed: 23256727]

(9). (a) Il'ichev YV; Schwörer MA; Wirz JJ Am. Chem. Soc. 2004, 126, 4581.(b) Corrie JE; Barth A; Munasinghe VRN; Trentham DR; Hutter MC J. Am. Chem. Soc. 2003, 125, 8546. [PubMed: 12848562]

(10). (a) Conrad WE; Fukazawa R; Haddadin MJ; Kurth MJ Org. Lett. 2011, 13, 3138. [PubMed: 21612219] (b) Oakdale JS; Solano DM; Fettinger JC; Haddadin MJ; Kurth MJ Org. Lett. 2009, 11, 2760. [PubMed: 19505119] (c) Mills AD; Nazer MZ; Haddadin MJ; Kurth MJ J. Org. Chem. 2006, 71, 2687. [PubMed: 16555821]

(11). Phan TB; Breugst M; Mayr H Angew. Chem.y Int. Ed. 2006, 45, 3869.

(12). Chen Y-F; Chen J; Lin L-J; Chuang GJ J. Org. Chem. 2017, 82, 11626. [PubMed: 28980464]

(13). For a current bis-indazole ligand study, see: Gamonal A; Brunet E; Juanes O; Rodriguez-Ubis JC J. Photochem. Photobiol., A 2017, 342, 53.

14. () Virta P; Leppänen M; Lönnberg H J. Org. Chem. 2004, 69, 2008.
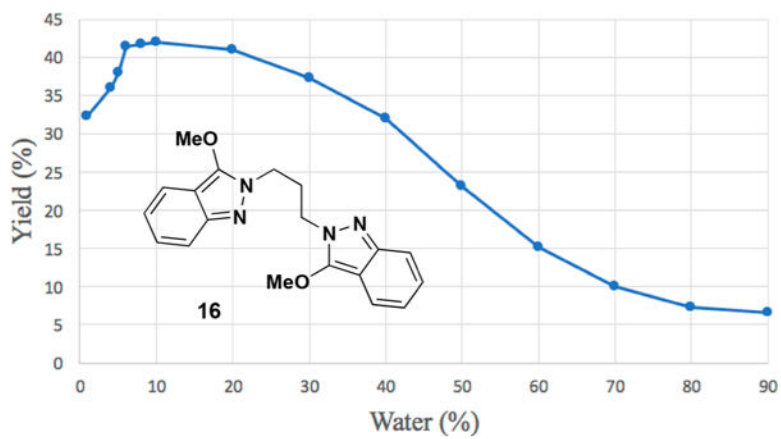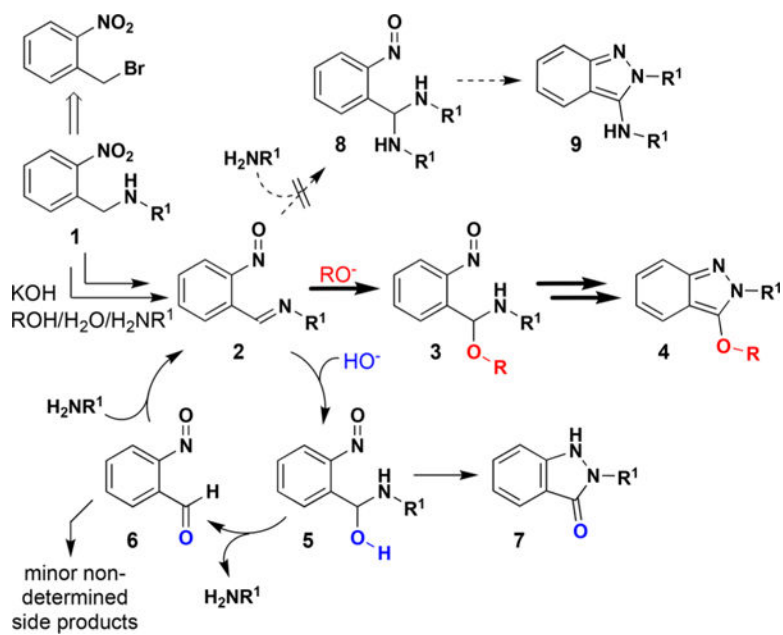
Figure 1.
Yield consequence of added water in double Davis–Beirut reaction 15 → 16.
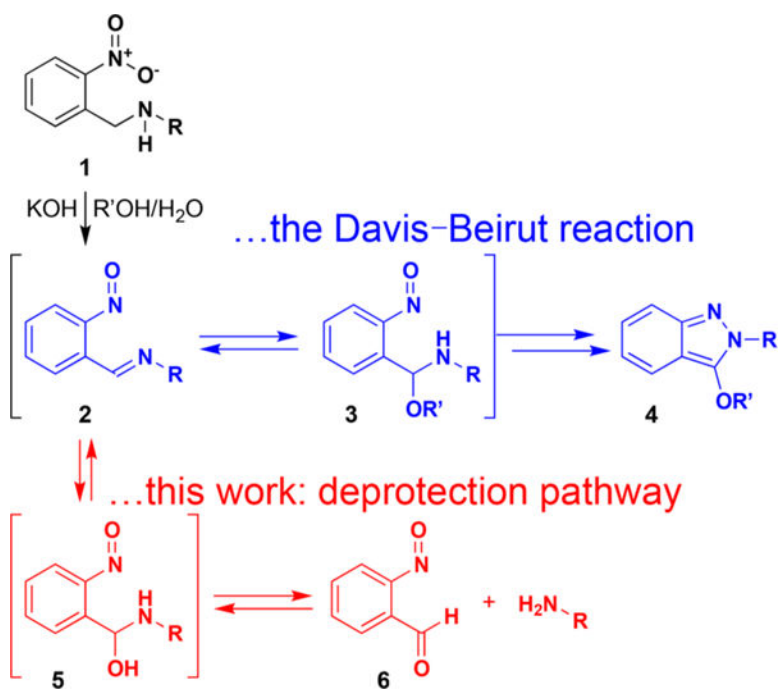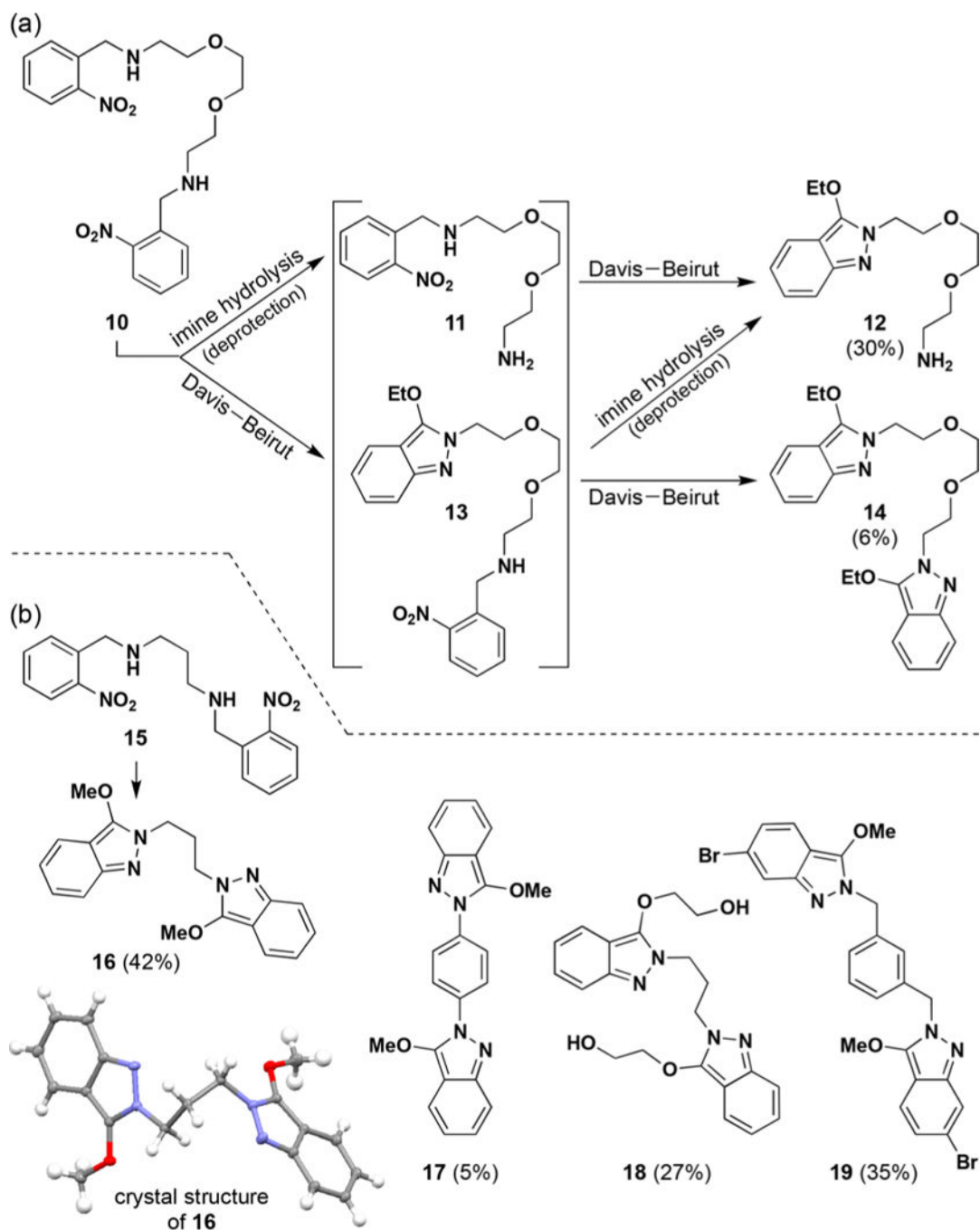
Scheme 1.
Davis–Beirut and Deprotection Reactions of *o*- Nitrosoimine 2

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

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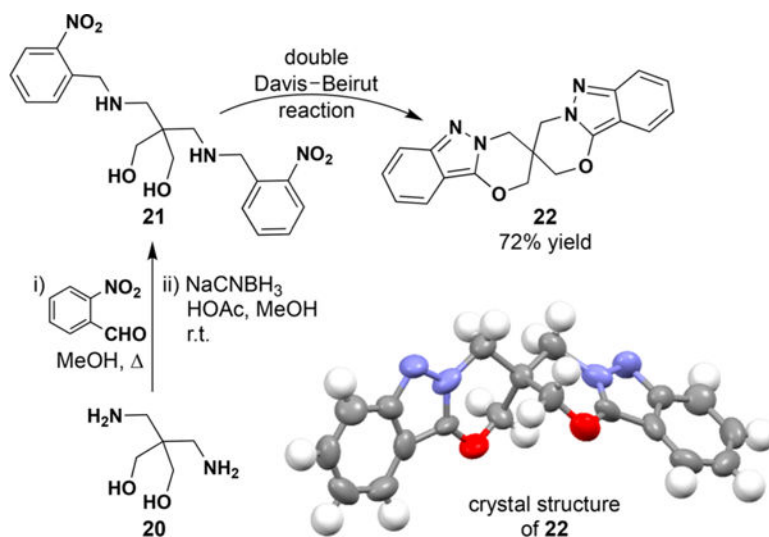
Scheme 4.
Substrate 21, Which Provides Two Internal Nucleophiles, Results in a High-Yielding Double Davis–Beirut Transformation

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.