Tetrahedron Letters 53 (2012) 6475–6478

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Acid and base catalyzed Davis–Beirut reaction: experimental and theoretical mechanistic studies and synthesis of novel 3-amino-2*H*-indazoles

Belem Avila [a], Mohammad H. El-Dakdouki [b], Musa Z. Nazer [c], Jason G. Harrison [a], Dean J. Tantillo [a], Makhluf J. Haddadin [b], Mark J. Kurth [a,*]

[a] Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616, United States
[b] Department of Chemistry, American University of Beirut, Bliss Street, Lebanon
[c] Department of Chemistry, University of Jordan, Queen Alia Boulevard, Amman, Jordan

ARTICLE INFO

Article history:
Received 21 August 2012
Revised 5 September 2012
Accepted 6 September 2012
Available online 15 September 2012

Keywords:
Davis–Beirut reaction
2*H*-Indazole
o-Nitrosobenzaldehyde
Mechanism
Catalysis

ABSTRACT

The Davis–Beirut reaction, which provides an efficient synthesis of 2*H*-indazoles and, subsequently, indazolones, is shown to proceed rapidly from *o*-nitrosobenzaldehyde and primary amines under both acid and base catalysis. Experimental and theoretical evidence in support of a reaction mechanism is provided in which *o*-nitrosobenzylidine imine is a pivotal intermediate in this *N*,*N*-bond forming heterocyclization reaction. The Davis–Beirut reaction is also shown to effectively synthesize a number of novel 3-amino-2*H*-indazole derivatives.

Indazoles and indazolones are privileged heterocycles with many biological applications, which have prompted the development of numerous methods for the construction of these heterocyclic systems.[1] While the chemistries to and of 1*H*-indazoles are well developed,[2] 2*H*-indazoles are considerably less well studied.[3] In recent years, we have reported the syntheses of a number of pyrazolo-based heterocycles (**1**), 2*H*-indazoles (**2**), and, subsequently, 1*H*-indazolones (**3a/b**) that were obtained via the Davis–Beirut reaction (Fig. 1).[4] We previously suggested that *o*-nitrosobenzylidine was an important intermediate in this chemistry. As a part of our ongoing interest in the development of the Davis–Beirut reaction, we report here both acid and base-catalyzed examples that provide mechanistic insight into the reactions shown in Scheme 1. Computational studies are also reported, which provided for a detailed understanding of this intriguing reaction.

We have previously shown that 3-alkoxy-2*H*-indazoles (**6**) and 5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazines (**2**) can be obtained from either 2-nitrobenzaldehyde (**4**) or 1-(bromomethyl)-2-nitrobenzene (**5**) by Davis–Beirut reactions mediated by KOH and water in alcoholic solvent (Scheme 1).[4b,4c] As depicted in Scheme 2, we propose that *o*-nitrobenzylamine **7** delivers hemiaminal nitroso intermediate **8** under basic conditions and subsequent loss of water renders *o*-nitrosobenzylidine imine **9**. This *o*-nitrosobenzylidine imine is an important intermediate that engages two possible pathways to the 2*H*-indazole product. Path (a) proceeds by stepwise *N*,*N*-cyclization (**9** → **10**), alkoxyaminal formation (**10** → **11**), and 1,4-elimination of water (**11** → **12** → **2**). The path (b) variant has *N*,*N*-cyclization and alkoxyaminal formation occurring in a concerted manner (**9** → **11**) followed by 1,4-elimination of water. Given this framework, it was envisioned that *o*-nitrosobenzaldehyde (**13a**) and 2-aminobenzyl alcohol (**14**) could serve as precursors to intermediate **9** and, by a Davis–Beirut reaction, lead to 2*H*-indazole **2**.

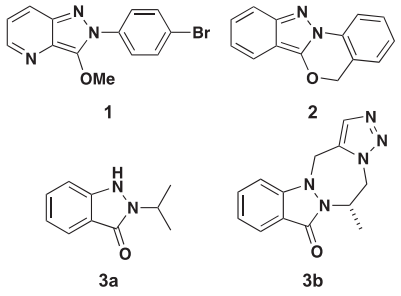
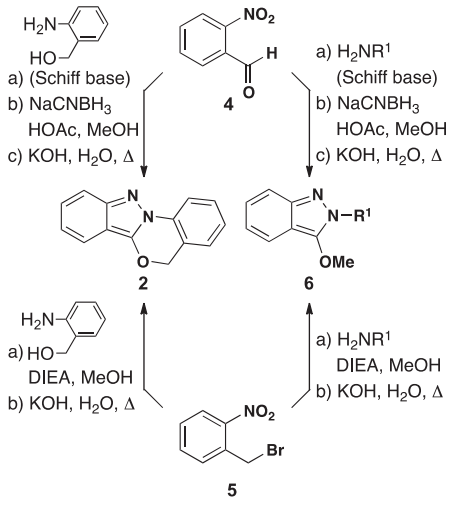


Figure 1. 2*H*-Indazole and indazolone examples.

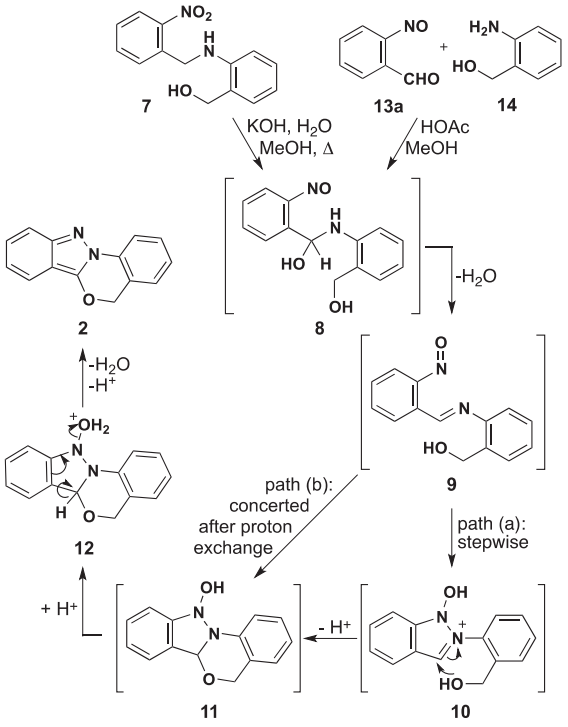
Experimental studies to probe this possibility started with the photolysis of *o*-nitrobenzyl alcohol (**15**) to give *o*-nitrosobenzaldehyde (**13a**) in 48% yield (Scheme 3;[5a] isolation and handling of **13a**

* Corresponding author.
E-mail address: mjkurth@ucdavis.edu (M.J. Kurth).

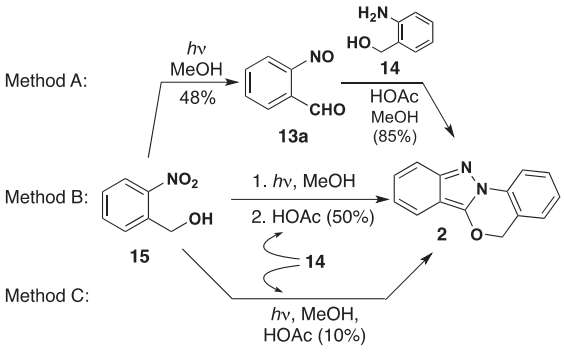
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.09.026



Scheme 1. The Davis–Beirut reaction.



Scheme 2. Proposed mechanism for the formation of 2*H*-indazole **2** by the Davis–Beirut reaction.



Scheme 3. Acid-catalyzed Davis–Beirut reactions to **2**.[6]

requires attention as it decomposes readily—especially upon heating in solution or exposure to light). We also investigated the hydrolysis of *o*-nitrobenzyl tosylates and mesylates as routes to **13a**,[5b] but the yields were poor and variable in our hands. Subjecting **13a** and 2-aminobenzyl alcohol (**14**) to typical Davis–Beirut heterocyclization conditions (aqueous KOH in MeOH) failed to deliver indazolobenzoxazine **2** at room temperature; indeed, the starting materials were found to be still present (with stoichiometry-based evidence of *o*-nitrosobenzaldehyde decomposition). In contrast, catalytic acetic acid in MeOH at room temperature led to the rapid formation (~1 min.) of **2** in 85% yield (Scheme 3; Method A). This transformation constitutes the first example of an acid-catalyzed Davis–Beirut reaction.

With these acid catalysis conditions in hand, we next tested a one-pot sequential protocol where step one was photolysis of a methanolic solution of **15** (14 h) followed by an addition of **14** in catalytic acetic acid (step two). This method, which avoids the isolation of **13a**, delivered **2**, but in 50% yield (Scheme 3, Method B). ^{1}H NMR analysis of the crude reaction mixture established that starting material **15** remained (incomplete photolysis; prolonged photolysis reduced the amount of **15**, but did not improve the yield of **2** due to the instability of **13a**). Method B circumvents the isolation of the rather unstable *o*-nitrosobenzaldehyde and, additionally, proceeds in a slightly higher overall yield than the two independent steps of Method A. Finally, these results with **13a** + **14** lend credence to the formation of hemiaminal nitroso intermediate **8** and its conversion to o-nitrosobenzylidine imine **9** in the Davis–Beirut reaction.

We next investigated a one-pot–one-step photolysis/Davis–Beirut reaction (Method C, Scheme 3). For this method, a methanolic solution of **14** and **15** plus catalytic acetic acid was photolyzed (14 h), giving **2** but in only 10% yield. While low yielding, it is interesting to note that this one-pot–one-step reaction (**14** + **15** → **2**) is a clean process, giving only product and recovered starting materials.

In order to gain further insight into the reaction mechanism, density functional theory calculations[7] were performed on the intermediates of the proposed reaction mechanism as shown in Figure 2. The results of these calculations indicate that all proposed intermediates are thermodynamically viable under the experimental conditions. Further, formation of final product **2** is extremely exergonic (nearly 60 kcal/mol lower in energy than the individual reactants).[8] Also of interest was the nature of the key transition

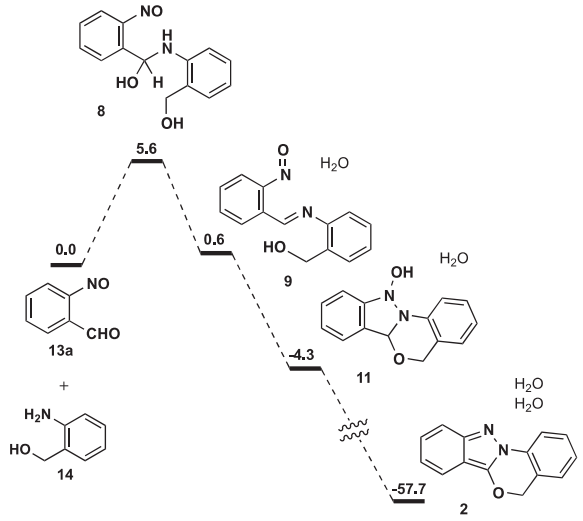


Figure 2. Overall reaction energetics (free energies in kcal/mol), calculated at the M06-2X/6-31+G(d,p) level in implicit solvent (CPCM, methanol).

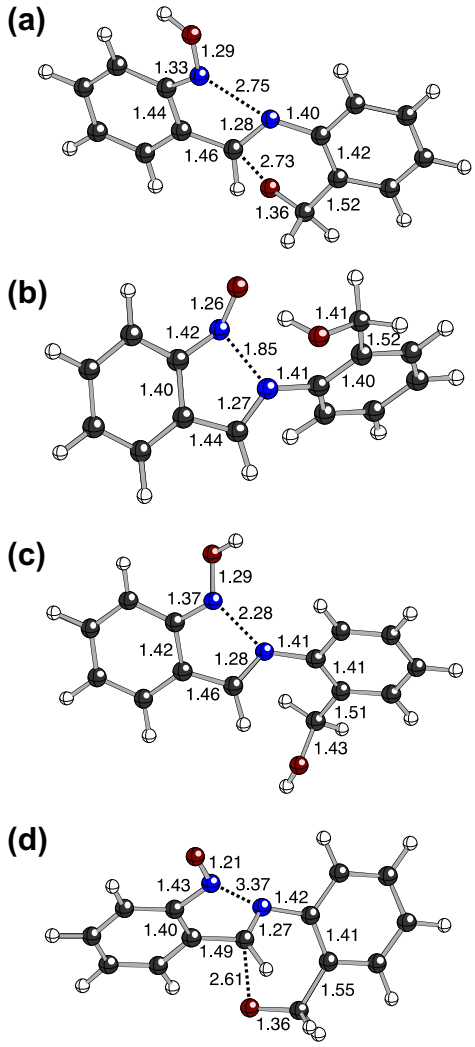
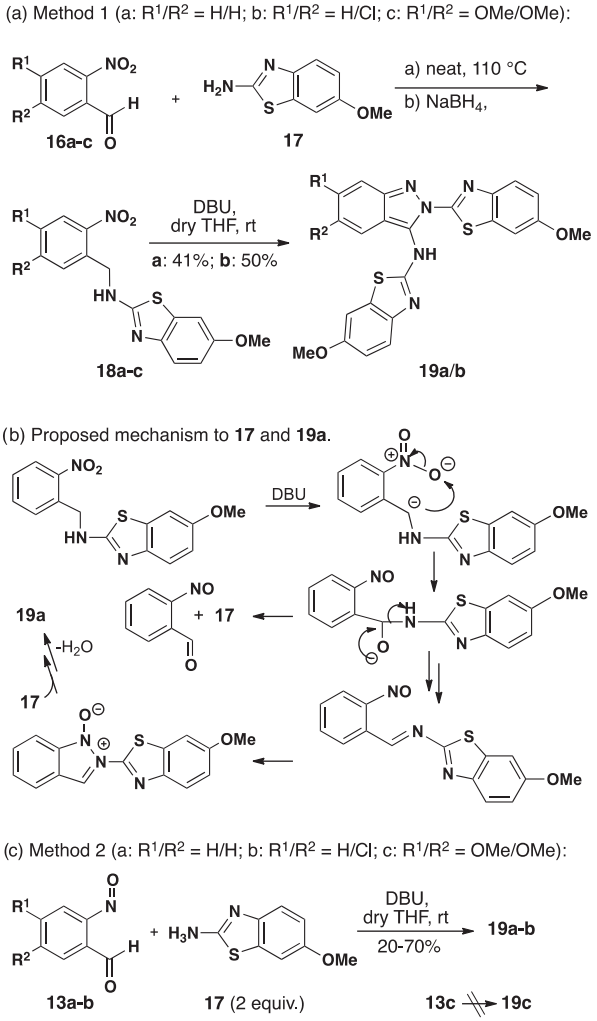


Figure 3. Key transition state structures for cyclization processes (M06-2X/6-31+G(d,p) in implicit solvent (CPCM, methanol)). Key distances are shown in Angstroms. (a) Concerted, neutral. (b) Stepwise, neutral. (c) Stepwise, protonated. (d) Concerted, deprotonated.



Scheme 4. Base-catalyzed Davis–Beirut reactions.[11]

state(s) involved in the conversion of **9** to **11**. Our calculations suggest that a concerted attack [see Scheme 2, path (b) after proton exchange] is possible,[9] with the alkoxide oxygen attacking the carbon of the imine, whose nitrogen lone-pair attacks the nitrogen of the protonated nitroso group. The transition state structure for this reaction (Fig. 3a)[10] is predicted to be associated with a barrier of only 3.7 kcal/mol. A stepwise process is also possible, but this has a higher barrier (the transition state structure for the first step, associated with a predicted barrier of 16.8 kcal/mol, is shown in Fig. 3b). Promoting the reaction by protonation or deprotonation was also examined. The former is predicted to lead to a stepwise process with a barrier of 9.6 kcal/mol (the transition state structure for the first step is shown in Fig. 3c). The latter leads to another concerted process (transition state structure shown in Fig. 3d; note that this process is less synchronous than that shown in Fig. 3a[9]), also with a low predicted barrier, 6.5 kcal/mol. Overall, concerted double cyclization is predicted to predominate under neutral or basic conditions, while a stepwise process is predicted for acidic conditions.

Encouraged by these initial studies, we carried out the Davis–Beirut reactions outlined in Scheme 4. Treatment of *o*-nitrobenzaldehydes **16a–c** with 6-methoxybenzo[*d*]thiazol-2-amine (**17**) followed by reduction of the resulting imines with $NaBH_4$ gave *o*-nitrobenzylamines **18a–c** (Scheme 4a; Method 1) in yields ranging from 86–93%. These *o*-nitrobenzylamines **18a–b** were then reacted with DBU in THF under anhydrous conditions at room temperature to affect Davis–Beirut heterocyclizations to 2-amino-2*H*-indazoles **19a** and **19b** in yields of 41% and 50%, respectively. The presence of the 6-methoxy-2-aminobenzothiazole moieties at the 3-position of 2H-indazoles **19a/b** was, initially, surprising. However, mechanistic considerations lead us to speculate that 6-methoxy-2-aminobenzothiazole (**17**) is generated during the reaction of *o*-nitrobenzylamines **18a/b** with DBU. In Scheme 4b, we offer an explanation for how **17** is formed. In support of this mechanism, it was found that an addition of excess **17** to the Method 1 reaction of **18a/b** (DBU/THF) increased the yields of **19a** and **19b** to 60–75%.

Finally, we extended the photolysis method for the preparation of *o*-nitrosobenzaldehyde (**13a**) to the preparation of *o*-nitrosobenzaldehyde analogs **13b/c**. Treating compounds **13a/b** with two equivalents of 6-methoxybenzothiazol-2-amine **(17)** under basic conditions delivered **19a/b** in yields of 41% and 50%, respectively (Scheme 4c; Method 2). It is interesting to note that **19c** could not be isolated from either procedure (Scheme 4a/c)—presumably because the *o*-nitrosobenzylidine intermediate (analog of **9**) was not formed under the reaction conditions.

In summary, the acid- and base-catalyzed Davis–Beirut reactions to 2*H*-indazoles were studied experimentally and

theoretically (DFT calculations) and several unique 2-amino-2*H*-indazoles were synthesized. All evidence supports the reaction proceeding through an *o*-nitrosobenzylidine imine intermediate, which can undergo a concerted *N*,*N*-bond forming heterocyclization reaction. Indeed, the mechanistic insights reported here may provide the basis for developing other substrates for the Davis–Beirut reaction.

Acknowledgments

Financial support was provided by the National Science Foundation (CHE-0910870) and the National Institutes of Health (GM089153). We also acknowledge the National Science Foundation's Partnership for Advanced Computational Infrastructure (Pittsburgh Supercomputer Center). J.G.H. thanks the United States Department of Education for a GAANN Fellowship and B.A. thanks the Bristol–Myers Squibb Graduate Chemist Fellowship and Alfred P. Sloan Minority Ph.D. Program for fellowship support.

Supplementary data

Supplementary data (additional computational details) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.026.

References and notes

1. (a) Haddadin, M. J.; Conrad, W. B.; Kurth, M. J. *Mini-Rev. Med. Chem.* **2012**, 12, 1293.; (b) Cankarova, N.; Hlavac, J.; Krchnak, V. *Org. Prep. Proc. Int.* **2010**, *42*, 433–465; (c) Schmidt, A. B.; Snovydovych, B. *Eur. J. Org. Chem.* **2008**, 4073–4095; (d) Huang, L. J.; Shih, M. L.; Chen, H. S.; Pan, S. L.; Teng, C. M.; Lee, F. Y.; Kuo, S. C. *Bioorg. Med. Chem.* **2006**, *14*, 528–536; (e) De Angelis, M.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2005**, *48*, 1132–1144.
2. Jung, N.; Brase, S. *Sci. Synth.* **2010**, *41*, 613.
3. (a) Stadlbauer, W.; Camp, N. In *Science of Synthesis Houben–Weyl Methods of Molecular Transformations*; Bellus, D., Ley, S. V., Noyori, R., Regitz, M., Schaumann, E., Shinkai, E., Thomas, E. J., Trost, B. M., Reider, P. J., Eds.; Thieme: Stutggart, 2002; Vol. 12, p 227; (b) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234–2237.
4. (a) Kurth, M. J.; Olmstead, M. M.; Haddadin, M. J. *J. Org. Chem.* **2005**, *70*, 1060–1062; (b) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687–2689; (c) Mills, A. D.; Maloney, P.; Hassanein, E.; Haddadin, M. J.; Kurth, M. J. *J. Comb. Chem.* **2007**, *9*, 171–177; (d) Butler, J. D.; Solano, D. M.; Robins, L. I.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2008**, *73*, 234–240; (e) Solano, D. M.; Butler, J. D.; Haddadin, M. J.; Kurth, M. J. *Org. Syn.* **2010**, *87*, 339–349; (f) Avila, B.; Solano, D. M.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2011**, *13*, 1060–1063; (g) Oakdale, J. S.; Solano, D. M.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2009**, *11*, 2760–2763; (h) Donald, M. B.; Conrad, W. E.; Oakdale, J. S.; Butler, J. D.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2010**, *12*, 2524–2527; (i) Conrad, W. E.; Fukazawa, R.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2011**, *13*, 2141–3138; (j) Conrad, W. E.; Rodriguez, K. X.; Nguyen, H. H.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2012**, *14*, 3870–3873.
5. (a) Bamberger, E. *Chem. Ber.* **1918**, *51*, 606–612; (b) Chen, L.-J.; Burka, L. T. *Tetrahedron Lett.* **1998**, *39*, 5351–5354.
6. (a) *Method A.* *o*-Nitrobenzyl alcohol (2.61 mmol) was dissolved in MeOH (400 mL) and was placed under a 500 W halogen lamp for 14 h. The solution was concentrated by rotary evaporation at a temperature below 30 °C, and purified by flash chromatography (100% DCM) to afford o-nitrosobenzaldehyde **13** as a white solid (168 mg, 48% yield). Spectral data is in accord with literature values.[9] 5*H*-benzo[4,5][1,3]oxazino[3,2-*b*]indazole (**2**). To a solution of **13** (0.44 mmol) and **14** (0.44 mmol) in MeOH (4.4 mL) in a round-bottom flask equipped with a stir bar was added acetic acid (26 μL). The reaction mixture was allowed to stir until TLC indicated the disappearance of *o*-nitrosobenzaldehyde. The reaction was complete after 1 min., after which saturated bicarbonate was added and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by flash chromatography yielding **2**, a white solid (85 mg, 85% yield). Spectral data is in accord with literature values.[3d,e] (b) *Method B.* Synthesis of 5*H*-benzo[4,5][1,3]oxazino[3,2-*b*]indazole (**3**). *o*-Nitrobenzyl alcohol (0.74 mmol) was dissolved in MeOH (100 mL) in a glass beaker and was placed under a 500 W halogen lamp for 14 h. After photolysis, the solution was placed in round-bottom flask equipped with a stir bar, after which, **14** (0.74 mmol) and acetic acid (24 μL) was added to the solution. The reaction mixture was allowed to stir until TLC indicated the disappearance of *o*-nitrosobenzaldehyde. The resulting mixture was then diluted with saturated bicarbonate was added and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by flash chromatography yielding **3**, a white solid (82 mg, 50% yield). Spectral data is in accord with literature values.[3d,e] (c) *Method C.* Synthesis of 5*H*-Benzo[4,5][1,3]oxazino[3,2-*b*]indazole (**3**). To a solution of *o*-nitrobenzyl alcohol (0.74 mmol) and **14** in MeOH (100 mL) in a glass beaker was added acetic acid (24 μL) and was placed under a 500 W halogen lamp for 14 h. The resulting mixture was then diluted with saturated bicarbonate was added and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by flash chromatography yielding **3**, a white solid (16 mg, 10% yield). Spectral data is in accord with literature values.[3d,e]
7. All calculations were performed using GAUSSIAN09. Structures were fully optimized at the M06-2X/6-31+G(d,p) level with an implicit solvent continuum model (CPCM) in methanol. Full references and coordinates can be found in the Supplementary data.
8. As the reaction proceeds, there are several equivalents of water lost. To compensate for this in the calculations, the energy of isolated water molecules were calculated and their energy added to those of the various intermediates as indicated; this allows all structures to be compared on the same energy scale.
9. See Supplementary data for intrinsic reaction coordinate and brief discussion. Leading references on concerted but highly asynchronous reactions: (a) Tantillo, D. J. *J. Phys. Org. Chem.* **2008**, *21*, 561–570; (b) Williams, A. *Concerted Organic and Bio-Organic Mechanisms*; CRC Press: USA, 2000; (c) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209–219.
10. See Supplementary data for further discussion.
11. *(a) Preparation of **18a–c**.* Equimolar amounts of *o*-nitrobenzaldehyde derivatives **16a** [**or b or c**] and 2-amino-6-methoxybenzothiazole (**17**) were mixed thoroughly and heated at 110 °C. The Schiff base, initially a viscous red liquid, solidified upon cooling and was dissolved in the minimal volume of methanol for reduction with $NaBH_3$ at room temperature. The pure (TLC) *o*-nitobenzylamine derivatives **18a** [**b or c**] precipitated as yellow a solid, which was collected and washed with cold methanol. The structures of **18a–c** were supported by IR, ^{1}H NMR, ^{13}C NMR and MS. (b) *Preparation of **19a/b**.* (i) *Method 1*. From **18a/b**. Equimolar amounts of *o*-nitrobenzylamine derivative **18a** [or **b**] and 2-amino-6-mehoxybenzothiazole (**17**) were dissolved in dry THF in a round bottom flask wrapped with aluminum foil. Five drops of DBU were added the reaction mixture was stirred for 4 h at room temperature. The solution was concentrated by rotary evaporation and purified by column chromatography using 9:1 DCM:*n*-hexane as eluent. The green fluorescing fraction was collected and the solvent was evaporated under vacuum at 35 °C to yield **19a** [or **b**] as a yellow solid in 41% yield [50% for **19b**]. (ii) *Method 2*. From *o*-nitrosobenzaldehyde **13a/b**. One equivalent of *o*-nitrosobenzaldehyde derivative **13a** [or **b**] and two equivalents of 2-amino-6-methoxybenzothiazole were dissolved in dry THF in a round bottom flask wrapped with aluminum foil. Five drops of DBU were added to the reaction mixture, which was then stirred for 3 h at room temperature (reaction monitored by TLC). When all of the *o*-nitrosobenzaldehyde had been consumed, THF was evaporated at room temperature. The resulting dark brown mixture was purified by column chromatography using 9:1 DCM:*n*-hexane as eluent. The green fluorescing fraction was collected by evaporation of the solvent using a rotary evaporator set at 35 °C. The yellow solid was collected and placed in a vacuum oven over night. The structures of **19a/b** prepared by *Methods 1 and 2* were verified by IR, ^{1}H NMR, ^{13}C NMR and MS.