VIP Cycloaddition

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# Facile Dearomatization of Nitrobenzene Derivatives and Other Nitroarenes with *N*-Benzyl Azomethine Ylide

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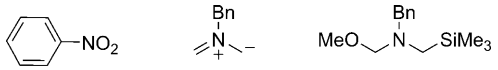
*In memory of Heinz-Günter Viehe*

In recent decades, aromatic compounds derived from the primary petrochemicals found in crude oils have provided a major source of substrates for polymers, paints, cosmetics, agrochemicals, and pharmaceuticals which surround us in everyday life. Therefore, one of the crucial transformations of oil organochemicals en route to more sophisticated molecules is the dearomatization process. The metal-based reductions, transition-metal interactions, oxidative processes on oxygenated arenes, chemical or microbial oxidation, and nucleophilic additions exemplify the importance of the dearomatization process.[1]

One of the most popular ways to irreversibly transform a carbon–carbon double bond into a saturated one relies on cycloaddition processes.[2] However, metal-free benzene rings have long eluded this type of reactivity under practical conditions because of their inherent stability.[3,4] Herein we report that nitrobenzene derivatives undergo a facile dearomatizing [3+2] cycloaddition when reacted with *N*-benzyl azomethine ylide.

Nitrobenzene (**1**) was chosen as the electron-poor 2π component based on the documented strong electron-withdrawing power of the nitro substituent (Scheme 1).[5] On



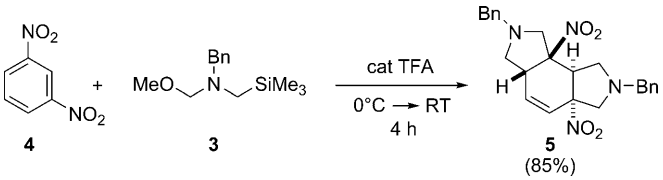

1 2 3

***Scheme 1.*** Structures of **1**, **2**, and **3**. Bn = benzyl.

the assumption that a stable nitrobenzene requires a very reactive electron-rich 4π partner, the nonstabilized azomethine ylide **2** was considered. The high-energy HOMO of this species, and thus the smaller frontier molecular orbital gap, as well as the lack of stabilizing substituent(s) indeed generate a powerful reactant.[6] In addition, the symmetry of an *N*-alkyl azomethine ylide suppresses the possible formation of regioisomeric pyrrolidines.

Among the various methods described for generating azomethine ylides, the metal-free procedure involving the treatment of silylated hemiaminal **3** with catalytic trifluoroacetic acid (TFA) was chosen because of its mild preparation conditions.[7] Treating a mixture of nitrobenzene (**1**) and *N*-benzylamine **3** (9 equiv)[8] at room temperature with TFA, however, resulted only in the production of dimeric and oligomeric amines, and recovered nitrobenzene. This result confirms the high stability of the substrate, which is often used as a high-boiling solvent.

*meta*-Dinitrobenzene (**4**) was next chosen as a more electron-deficient substrate. This time, a complete and smooth transformation occurred within four hours and a single product was formed. NMR and mass spectrometry analyses on the purified compound (85% yield) indicated the structure to be the biscycloadduct **5** (Scheme 2).[9] NOESY




4 3 5 (85%)

***Scheme 2.*** Representative dearomatization of a nitrobenzene derivative with dipole precursor **3**.

spectra clearly showed the *cis*-fused stereochemistry of the new heterocycles and the *trans* relationship between the pyrrolidine rings in the tricyclic product.[10] *para*-Dinitrobenzene (**6**) reacted also at room temperature to furnish the analogous bis(pyrrolidine) compound **7** (Table 1, entry 2).

Similarly, methyl *meta*-nitrobenzoate (**8**) underwent a complete and smooth transformation, and two products were formed (ca. 1:1 mixture). Separation and purification led to the isolation of both compounds in a 62% combined yield. NMR spectroscopy and mass spectrometry analyses indicated the compounds to be the biscycloadducts **9** and **10** (entry 3). HMQC and HMBC experiments carried out on both products revealed the regioisomeric nature of the structural difference, the relative stereochemistry of the stereocenters being again ascertained with the help of NOESY spectra.

The use of nitrobenzene derivatives featuring only inductive electron-withdrawing substituents is illustrated by the reaction of 5-chloro-3-trifluoromethylnitrobenzene (**11**;

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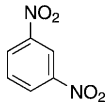
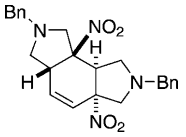
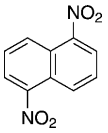
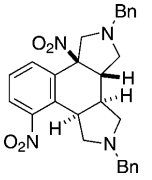
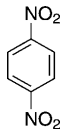
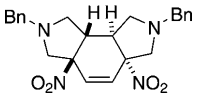
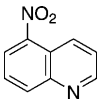
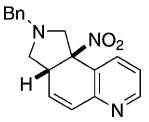
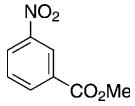
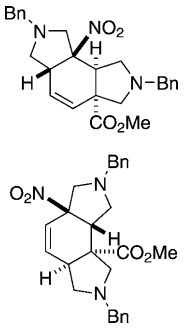
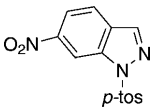
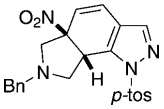
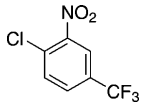
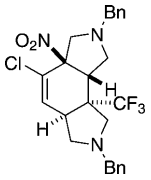
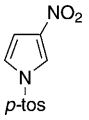
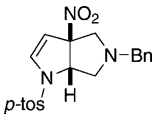
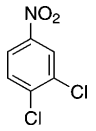
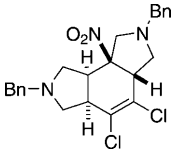
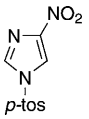
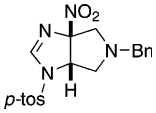
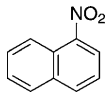
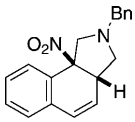
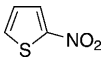
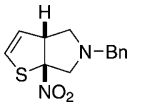
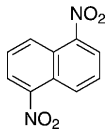
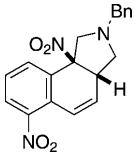
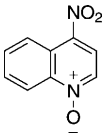
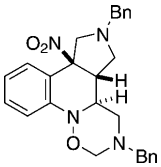
***Table 1:*** Dearomatization reactions of nitroarenes with **3**.[a]

| Entry | Substrate | **3** [equiv] | *t* [h] | Product | Yield [%][b] | Entry | Substrate | **3** [equiv] | *t* [h] | Product | Yield [%][b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 |  | **4** 9 | 4 |  | **5** 85 | 8 |  | **17** 6 | 26 |  | **19** 57 |
| 2 |  | **6** 6 | 4 |  | **7** 69 | 9 |  | **20** 2 | 0.5 |  | **21** 80 |
| 3 |  | **8** 9 | 24 |  | **9** **10** 62 | 10 |  | **22** 6 | 0.5 |  | **23** 64 |
| 4 |  | **11** 9 | 3.5 |  | **12** 77 | 11 |  | **24** 3 | 21 |  | **25** 95 |
| 5 |  | **13** 9 | 23 |  | **14** 81 | 12 |  | **26** 2 | 2 |  | **27** 62 |
| 6 |  | **15** 3 | 8 |  | **16** 89 | 13 |  | **28** 4[c] | 22 |  | **29** 94 |
| 7 |  | **17** 2 | 5.5 |  | **18** 66 | 14 |  | **30** 5[c] | 23 |  | **31** 85 |

[a] Unless otherwise stated, 7.5% mol of TFA (relative to **3**) was used to generate **2**. [b] Yields of isolated products. [c] 10% mol of TFA were used to generate **2**.

entry 4). The *trans*-bisadduct **12** was formed as a single regioisomer. Here again, simple chromatography allowed the isolation of the product in pure form.[11] An interesting case was found with 3,4-dichloronitrobenzene (**13**) which only delivered the bisadduct **14** as the *trans* isomer. The three possible chlorinated carbon–carbon double bonds were all found to be unreactive, thereby raising the question of how the sequence of events unfolds during the reaction. The inductive electron-withdrawing effect of the chlorine atom at C3 presumably induces the C1–C2 double bond to be more reactive than the C1–C6 bond. Steric hindrance from the two chlorine atoms then forces the second reaction to occur on the unsubstituted bond of the intermediate cycloadduct.

Entries 6–8 in Table 1 show the results obtained for nitronaphtalene derivatives. The reportedly more reactive (relative to nitrobenzene) 1-nitronaphtalene (**15**) regioselectively reacted with **2** to cleanly furnish the expected monoadduct **16** (entry 6).[12] The presence of an additional nitro group on the second ring (C5) increased the reactivity, thus inducing a faster reaction (entry 7). This time, monocycload-

duct **18** was mainly formed, but traces of a bisadduct were observed by $^1$H NMR spectroscopic analysis of the crude sample (96% conversion). When longer reaction times and more equivalents of the ylide precursor **3** were used, the same adduct **19** was the major product isolated (entry 8).[13] $^1$H NMR analysis unambiguously showed that the two pericyclic processes had occurred on the same ring, allowing the second one to remain aromatic.[14]

5-Nitroquinoline (**20**) reacted completely in 30 minutes: only the nitrated, all-carbon cycle underwent a cycloaddition and tricyclic product **21** was isolated in high yield (entry 9). 6-Nitro-1-*p*-tosylbenzopyrazole (**22**) behaved similarly (entry 10).

Extending the above reactivity to five-membered heteroaromatic cycles constituted our next task. The putative cycloadducts represent a class of heteroatom-containing [3,3,0] bicyclic compounds, which are much sought after by pharmaceutical, agrochemical, and cosmetic companies. In addition, derivatives may also find applications as ligands of various receptors. We found that the *N*-tosyl pyrrole **24** and imidazole **26**, as well as thiophene **28**, readily produced the desired cycloadducts in useful yields (entries 11–13).[15]

Finally, 4-nitroquinolinium oxide (**30**) was chosen as substrate with the aim of carrying out an X-ray diffraction study. Subjecting the substrate to the same conditions yielded the single product **31** (85%) that could be crystallized (entry 14). Diffraction analysis showed an adduct resulting from a [3+2] cycloaddition at the C3–C4 double bond and the reaction of a second equivalent of the azomethine ylide **2** with the nitrone unit.[16] The product **31** clearly has a *trans* relationship between the two newly formed rings (Figure 1).[17]

Central to the fact that benzene derivatives undergo [3+2] cycloaddition at room temperature is the involved mechanism of the first cyclization. All the above substrates bear one or two nitro group(s). The possible role of the acidic conditions required to generate the ylide **2** has to be taken into account. However, nitroaromatic compounds have been reported to be generally inert to strongly acidic conditions.[18] The measured p$K_a$ values of protonated nitrobenzene (−11.3) indicates that nitrobenzene itself has weak basic properties.[19] It thus seems reasonable to assume that there is no reaction between the nitrobenzene derivatives and TFA.

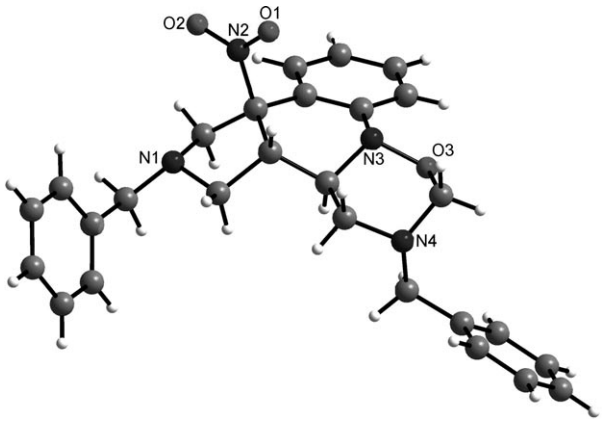
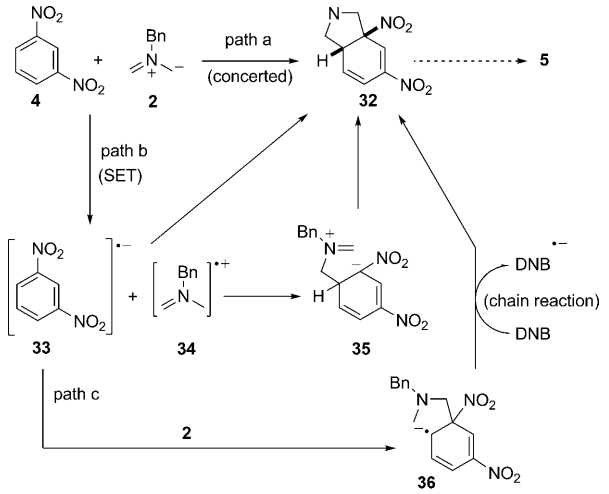



***Figure 1.*** Space-filling graphic of the cycloadduct **31**.

The most widely invoked mechanism for 1,3-dipolar processes is the concerted one, albeit alternate stepwise diradical or ionic pathways have been described in a few cases. The fact that all fused rings arising from the cyclization above have a *cis* relative stereochemistry is in line with a concerted process (Scheme 3, path a).




***Scheme 3.*** Possible mechanistic pathways for the dearomatization of nitroarenes using **3**, example shown with 1,3-dinitrobenzene (DNB).

However, the literature is replete with nitro compounds undergoing a one-electron reduction, giving rise to radical anions.[18–20] An analogous oxidation process has long been observed with various electron-rich substrates. Hence a single-electron transfer (SET) might also be envisioned as the first step in the reaction of a nitrobenzene derivative (e.g., **4**) with **2**, the resultant radical-anion **33** and radical-cation **34** then undergoing either a stepwise or a concerted cyclization process (Scheme 3, path b). Alternatives are represented by chain reactions involving, for instance the addition of the radical-anion **33** to dipole **2**, then a reductive step involving another equivalent of **4**, with concomitant production of the cycloadduct (Scheme 3, path c).[20–22]

The results described herein represent the first practical cases of uncomplexed benzene derivatives acting as 2π components in an intermolecular pericyclic process. Expectedly, carbacycles and heterocycles featuring a less pronounced aromatic character display similar reactivity. The products listed in Table 1 are advantageously functionalized and constitute scaffolds prone to a number of potentially interesting derivatizations. The unprecedented loss of aromaticity of nitrobenzenes and other nitroarenes generated by the 4π-electron-component **2** raises questions regarding the mechanism of this transformation. Efforts to address this issue and extend this reactivity to other 2π-electron and 4π-electron systems are under way.

## Experimental Section

Representative procedure for the cycloaddition between 1,3-dinitrobenzene (**4**) and hemiaminal **3**: A solution of TFA in $CH_2Cl_2$ (1.6 mL; 0.18 M) was added dropwise to a solution of hemiaminal **3** (426 mg,

1.8 mmol) and 1,3-dinitrobenzene (**4**; 34 mg, 0.2 mmol) in dry $CH_2Cl_2$ (0.8 mL), which was kept under an inert atmosphere at 0 °C. The resultant mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with a saturated solution of $NaHCO_3$, and the mixture was extracted with EtOAc (3 times). The combined extracts were washed with brine and dried over $Na_2SO_4$. The residue was purified by flash chromatography on silica gel (EtOAc/cyclohexane = 1:7) to yield **5** (74 mg, 85 %) as a light yellow oil. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ = 7.23–7.09 (m, 10 H), 5.96 (ddd, $J$ = 1.0, 2.2, 10.1, 1 H), 5.85 (dd, $J$ = 3.0, 10.1, 1 H), 4.11 (ddd ≈ td, $J$ ≈ 8.4, 8.4, 1.0 Hz, 1 H), 3.82–3.77 (m, 1 H), 3.67–3.50 (m, 6 H), 3.40 (dd ≈ t, $J$ ≈ 9.6, 9.0 Hz, 1 H), 2.91 (dd ≈ t, $J$ ≈ 8.4, 8.4 Hz, 1 H), 2.77 (d, $J$ = 10.7, 1 H), 2.82–2.73 (m, 1 H), 2.34 (dd ≈ t, $J$ ≈ 8.4, 8.4, 1 H), 2.39–2.32 ppm (m, 1 H). $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 137.06, 132.65, 128.50 (4 C), 128.39 (4 C), 128.18, 127.51, 127.26, 121.98, 95.69, 91.24, 66.59, 60.58, 58.92, 58.65, 57.34, 55.61, 42.95, 37.00 ppm. IR (NaCl): $\tilde{\nu}$ = 2810, 1543, 1347, 1131, 738 cm$^{-1}$. MS (ESI, *iso*-butane) *m*/*z* (%) 435 (100) $[M+H]^+$, 388 (30) Elemental Analysis cald for $C_{24}H_{26}N_4O_4$: C, 66.34; H, 6.03; N, 12.89 found C, 66.39, H, 6.18; N, 12.76.

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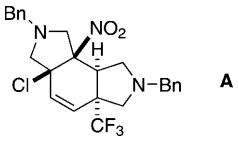
[8] The azomethine ylide **2** undergoes several competitive dimerization and oligomerization reactions which effectively decrease the amount of usable **2**. The excess **3** reported in this paper parallels in some ways the stability of the substrate.

[9] The number of equivalents used in this reaction is what is required for the reaction to reach completion. Only the tricyclic adduct was isolated and no trace of a bicyclic adduct was ever observed during or after the transformation, presumably because of the much higher reactivity of the intermediate nitrodiene. Notably, no tetracycle was ever formed in this reaction.

[10] See the Supporting Information.

[11] No trace of the alternate putative cycloadduct **A** was formed, probably a result of steric reasons.




**A**

[12] Z. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta, P. v. R. Schleyer, *Chem. Rev.* **2005**, *105*, 3842–3888.

[13] Only traces of the adduct **18** were observed in the $^1$H NMR spectrum of the crude reaction mixture.

[14] Both the inductive and mesomeric effects were strong enough to generate complete chemoselectivity in favor of the unsubstituted carbon–carbon double bond.

[15] Gribble has recently reported the reaction of nitroindoles with an analogous azomethine ylide: S. Roy, T. L. S. Kishbaugh, J. P. Jasinski, G. W. Gribble, *Tetrahedron Lett.* **2007**, *48*, 1313–1316.

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[17] CCDC 793306 (**31**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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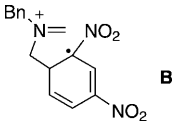
[20] N. Kornblum, *Aldrichimica Acta* **1990**, *23*, 71 – 78, and references cited therein. A mechanism of the $SRN_1$ type involving the loss of nitrite ion and its readdition after cyclization can also be considered.

[21] Another possibility is represented by the reaction of the radical-cation **34**[21] with **4** to deliver the new radical-cation **B** which, upon subsequent interaction with **2**, would generate product **32** en route to the cycloadduct **5**, and another equivalent of **34**.




**B**

[22] Radical-cation **34** could also be produced from ylide **2** and traces of oxygen. However, the fact that the reactions were carried out under inert atmosphere renders this possibility unlikely.