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INVESTIGATION OF THE BROMINATION OF TETRAHYDROBENZIMIDAZOLES†

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Abstract – During an investigation of the bromination of tetrahydrobenzimidazoles, an interesting dimerization reaction was observed. This dimerization pathway can be attenuated by conducting the reaction in the presence of silica gel.

INTRODUCTION

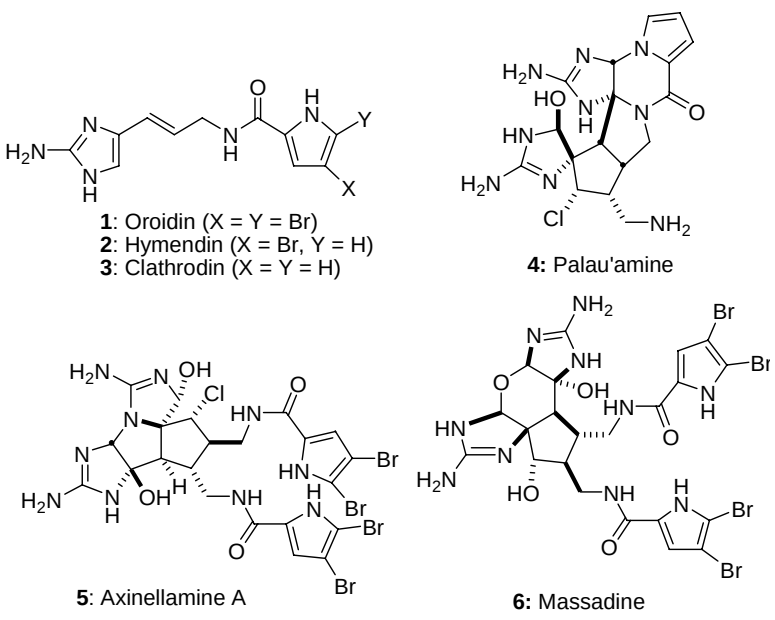
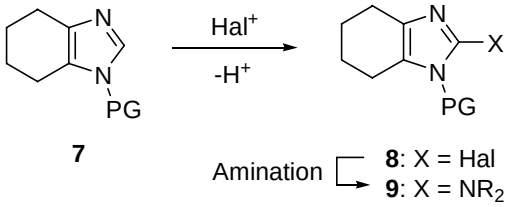


Figure 1: Oroidin and some derived natural products

Our lab has been interested for some time in the development of concise methods for the elaboration of simple imidazole derivatives for application in total synthesis efforts towards the oroidin family of pyrrole-imidazole natural products (e.g., **1**-**6**, Figure 1).[1,2] One of the key structural features of these alkaloids is the presence of a 2-aminoimidazole moiety; therefore, we required efficient methods for the incorporation of this functional group.[3] Our approaches towards many of the more complex oroidin natural products featured tetrahydrobenzimidazole (THB) derivatives as key intermediates;[1,4] thus, we began to investigate methods for accomplishing this transformation on THB's. Among many possibilities, we considered the intermediacy of 2-halo-THB's (**8**), and subsequent nucleophilic amination either directly or via

† Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday

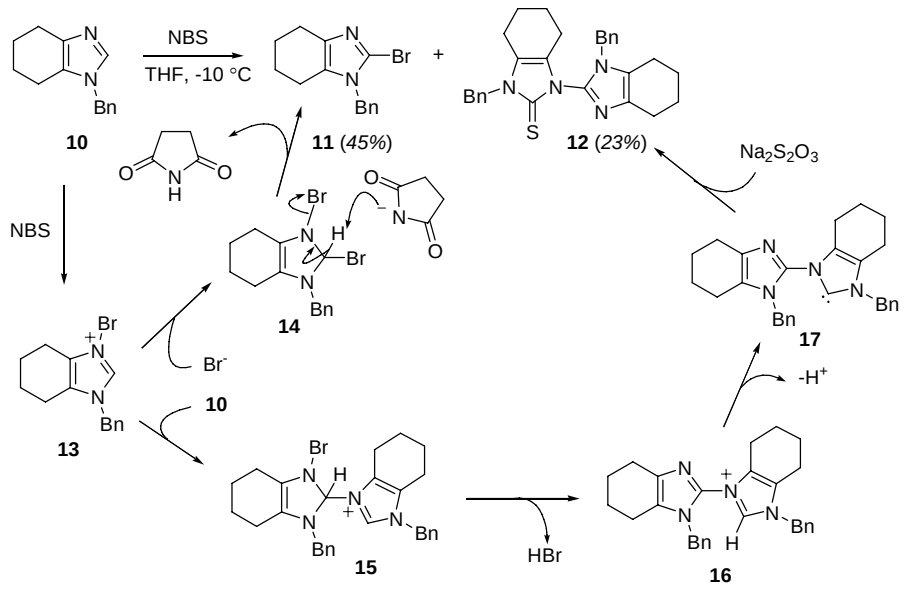
Pd-catalyzed pathways (**7**→**8**→**9**, Scheme 1).[3] Successful reports of the latter approach with benzimidazoles have appeared in the literature.[5,6] However, a search of the literature indicated that neither the parent 2-haloTHB's nor the N-alkylated 2-haloTHB's were known;[3] therefore before investigating the feasibility of the amination reaction, we had to develop a method to access 2-haloTHB derivatives.[7]



Scheme 1

RESULTS AND DISCUSSION

Since in practice we anticipated that halogenation would have to be performed on an N-protected intermediate, we initially investigated reactions of *N*-benzyl THB (**10**) as a model substrate.[4] As a preliminary experiment, NBS was added to an acetonitrile solution of **10** at -10 to -15 °C and then allowed to warm to room temperature. On completion of the reaction and work-up (thiosulfate wash to remove residual bromine), the 2-bromoTHB (**11**) was obtained in ~30% yield. We briefly screened a few solvents to see whether the yield could be improved, and while to a limited extent an increase was realized, the improvement was to a modest 56% in CCl_4. However, we were concerned about the material balance in this process, particularly since essentially all of **10** was consumed. Examination of the ^{1}H NMR spectrum of the crude product indicated that in addition to a small amount of unreacted **10**, **11**, and succinimide, there were other species in the reaction mixture; therefore, we attempted to isolate these products. Thus, in addition to the expected 2-BrTHB (**11**),[8] we obtained one other compound after purification by column chromatography. Analysis by ^{1}H NMR spectroscopy quickly indicated that this byproduct was dimeric in nature, and that it possessed an element of asymmetry as the protons due to the benzylic methylenes were non-equivalent (AB quartet and a pair of doublets).[9] Furthermore, in the ^{13}C NMR spectrum, ten signals were observed for simple aliphatic carbons instead of the five that were expected, again indicating the lack of symmetry. Further analysis of this byproduct by HRMS was very informative, clearly supporting the dimeric nature of the product, but it also provided a surprise – the product contained sulfur. The presence of sulfur was confirmed through an elemental analysis, which provided results in complete agreement with those obtained by MS. Fortunately, this byproduct was highly crystalline and a suitable crystal was obtained for analysis by X-Ray crystallography, the results of which are depicted in Figure 2.[10] As can be clearly seen, the byproduct is dimeric in nature, with a bond between N3 and C2', and it possesses a thiocarbonyl moiety.[11]



Scheme 2

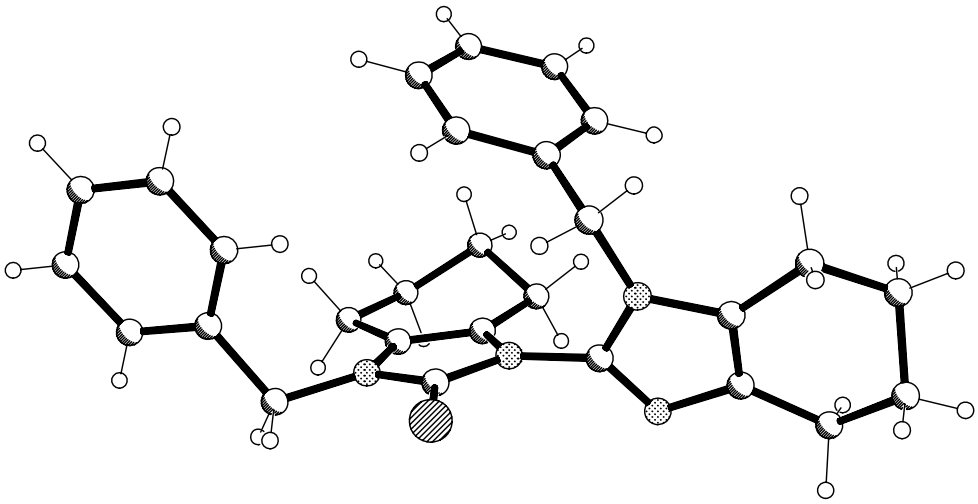


Figure 2: X-Ray structure of dimeric byproduct (**12**)

The only source of sulfur to which this reaction was exposed was in the work-up where $Na_2S_2O_3$ was employed, and so presumably the sulfur is incorporated at this point. A possible mechanism for the formation of this dimer is depicted in Scheme 2. We propose that bromination occurs at N3 leading to formation of the N-bromoiminium ion (**13**), which undergoes nucleophilic addition with bromide and elimination of HBr to afford **11** or nucleophilic substitution with a second molecule of THB (also at N3) to give **15**. Elimination of HBr forms the imidazolium salt (**16**), which undergoes deprotonation, generating the carbene (**17**), and subsequent reaction with thiosulfate leads to the formation of the thiocarbonyl moiety. We attempted to isolate the intermediate carbene (**17**) by concentration of the crude reaction mixture, avoiding exposure to water or thiosulfate, and purification of the mixture by

chromatography. Unfortunately, we were unable to obtain the carbene through this approach, however, examination of the ^{1}H NMR spectrum of the crude reaction mixture indicated the presence of a dimeric species (non-equivalent signals for the benzylic protons), which was spectroscopically distinguishable from **12**.

We have investigated several approaches to minimizing this dimerization process (concentration, temperature, addition order, etc.), however the utilization of the silica gel-supported process reported by Smith and co-workers provided the greatest improvement.[12] Utilizing these conditions (CH_2Cl_2, 5 min), the brominated THB was obtained in higher yield 65-67%. The work-up was also simplified, requiring washing of the silica gel, and then washing of the filtrate with aqueous base to remove residual succinimide. Presumably, **10** is adsorbed onto the surface of the silica gel which physically separates the substrate molecules, thereby attenuating the dimerization pathway, although not completely eliminating the formation of **12**. Unfortunately, although we now had a reasonable route to 2-BrTHB's, we were unable to convert this material into 2-amino substituted congeners.

In summary, in the course of investigating the halogenation of THB derivatives we have observed an unusual dimerization pathway leading to the isolation of **12**, which has been characterized by X-Ray crystallography. This dimerization can be prevented by conducting the reaction in the presence of silica gel, providing a convenient method for introducing a halogen in the 2-position of THB's.

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REFERENCES (AND NOTES)

1. Y. He, H. Du, R. Sivappa, and C. J. Lovely, *Synlett,* 2006, 965.
2. H. Hoffmann and T. Lindel, *Synthesis,* 2003, 1753.
3. I. Kawasaki, Y. Taguchi, M. Yamashita, and S. Ohta, *Heterocycles,* 1996, **43**, 1375.
4. C. J. Lovely, H. Du, Y. He, and H. V. R. Dias, *Org. Lett.,* 2004, **6**, 735.
5. M. W. Hooper, M. Utsunomiya, and J. F. Hartwig, *J. Org. Chem.,* 2003, **68**, 2861.
6. Y. Hong, C. H. Senanayake, T. Xiang, C. P. Vandenbossche, G. J. Tanoury, R. P. Bakale, and S. A. Wald, *Tetrahedron Lett.,* 1998, **39**, 3121.
7. J. F. O'Connell, J. Parquette, W. E. Yelle, W. Wang, and H. Rapoport, *Synthesis,* 1988, 767.
8. **1-Benzyl-2-bromo-4,5,6,7-tetrahydro-1*H*-benzimidazole (11)**: A colorless solid. mp 138–139

°C. ^{1}H NMR: δ = 7.35–7.26 (m, 3H), 7.06 (app. d, *J* = 6.9 Hz, 2H), 5.02 (s, 2H), 2.56 (m, 2H), 2.36-2.33 (m, 2H), 1.76-1.73 (m, 4H); ^{13}C NMR: δ = 138.2, 136.0, 128.9, 128.8, 127.9, 126.6, 117.6, 48.5, 24.3, 23.1, 22.8, 21.3; IR (KBr, cm^{-1}): 3026, 2947, 2847, 1602, 1494, 1422, 1215, 782, 718. EI-MS (*m/z*): 292.1 (M^++2, 49%), 290.1 (M^+, 52%), 91.0 (100%), 64.9 (15%). Anal. Calcd for $C_{14}H_{15}N_2Br$: C, 57.75; H, 5.19; N, 9.62. Found: C, 57.97; H, 5.33; N, 9.44.

9. **3-Benzyl-1-(1-benzyl-4,5,6,7-tetrahydro-1*H*-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-2(3*H*)-thione (12)**: A colorless solid. mp 221-222 ºC. ^{1}H NMR: δ = 7.34-7.24 (m, 5H), 7.18-7.11 (m, 3H), 6.92 (app. d, *J* = 6.9 Hz, 2H), 5.31 (d, *J* = 16.0 Hz, 1H), 5.33-24 (m, 2H), 4.92 (d, *J* = 16.0 Hz, 1H), 2.69-2.50 (m, 4H), 2.29-2.20 (m, 1H), 2.18-2.06 (m, 2H) 1.90-1.80 (m, 4H), 1.58-1.40 (m, 3H) 1.26-1.16 (m, 2H); ^{13}C NMR: δ = 163.6, 136.6, 136.2, 135.3, 134.2, 128.7, 128.6, 127.8, 127.7, 127.6, 127.4, 126.6, 126.0, 124.4, 48.4, 47.7, 24.2, 23.3, 22.9, 22.0, 21.8, 21.2, 20.7, 20.2; FT-IR (KBr, cm^{-1}): 3434, 3030, 2940, 2850, 1707, 1675, 1593, 1520, 1475, 1418, 1346, 1259, 1239, 1076; HR-ESIMS (*m/z*): calcd. for MH^+ $C_{28}H_{31}N_4S$ 455.2264, found 455.2262. Anal. Calcd for $C_{28}H_{30}N_4S$: C, 73.97; H, 6.65; N, 12.32; S, 7.05. Found: C, 74.09; H, 6.76; N, 12.18; S, 7.24.

10. X-Ray data for compound (**12**): Formula: $C_{28}H_{30}N_4S$, FW: 454.62, System: Monoclinic, Space group: $P2_1/n$; Temp. 298 K, a = 11.4643(15) Å, b = 9.916(2) Å, c = 21.911(3) Å, β = 94.328(17)°, V = 2483.7(7) $Å^3$, Z = 4, R_1 (all data) = 6.31%, wR_2 (all data) = 13.35%, GOF = 1.016.

11. E. S. Hand and W. W. Paudler, *J. Org. Chem.*, 1980, **45**, 19.

12. A. G. Mistry, K. Smith, and M. R. Bye, *Tetrahedron Lett.*, 1986, **27**, 1051.