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The first application of an imidazole *o*-quinodimethane in Diels–Alder reactions leading to the synthesis of benzimidazoles

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Abstract—An efficient procedure for the generation of the imidazole-4,5-quinodimethane intermediate **4** from 2-bromo-4,5-bis(bromomethyl)imidazole derivative **3** in boiling toluene in the presence of 18-crown-6 is described. *o*-Quinodimethane **4** was captured for the first time by several symmetrically and unsymmetrically substituted dienophiles to afford the corresponding Diels–Alder benzimidazole adducts.

The heterocyclic analogs of *o*-quinodimethane (*o*-QDM) are of considerable interest both from a theoretical point of view and for their potential in organic synthesis[1] as useful dienes. Their use in annulations of aromatic systems has now acquired practical importance and has been exploited in efficient syntheses of a wide range of polycyclic natural products.[2] The most widely used routes to these heterocyclic *o*-QDMs involve flash vacuum pyrolysis,[3] thermal extrusion of sulfur dioxide from heteroaromatic fused 3-sulfolenes,[4] and 1,4-elimination of suitable precursors.[5]

Flash pyrolytic 1,4-elimination requires very harsh reaction conditions resulting in the formation of polymeric products, thus precluding trapping of the *o*-QDM intermediates except in the most stable cases. However, heterocyclic fused 3-sulfolenes have been shown to be useful precursors for generation and trapping[4] of heterocyclic *o*-QDMs, although sometimes fairly harsh reaction conditions are required and the reagents are heated to high temperatures, up to 200 °C. Similarly, several heterocyclic *o*-QDMs have been generated by 1,4-elimination in solution and are efficiently trapped by various dienophiles to afford[5] the corresponding adducts in good yields.

Although a substantial number of heterocyclic *o*-QDMs have been explored, very recently some new methods for their preparation involving MW irradiation,[6] allenylanilines,[7] and ene-bis(sulfinylallenes)[8] have appeared in the literature. Concerning the imidazole *o*-QDM, although the formation of the 1-methylimidazole *o*-QDM by flash pyrolysis has been reported,[9] all attempts at its trapping with dienophiles were unsuccessful. Moreover, imidazole based heterocyclic molecules play important roles in various biochemical processes.[10] The imidazolyl moiety is used as a building block in developing new drugs,[10b,11] and also has wide-ranging applications in organometallic catalysis,[12] in asymmetric catalysis[13] and in coordination chemistry.[14] There are several reports of the synthesis and functionalization of the imidazole moiety.[15] For all these reasons the synthesis and Diels–Alder reactions of an imidazole *o*-quinodimethane were undertaken.

Our synthetic approach is depicted in Scheme 1. To generate the required imidazole *o*-QDM we envisaged NBS bromination of 1-phenylmethylamino-4,5-dimethylimidazole **1**, followed by the formation of the imidazole *o*-QDM through 1,4-elimination, and trapping with various symmetrical and unsymmetrical dienophiles. However, NBS bromination either in the presence of light or in the presence of radical initiators [$(PhCOO)_2$ or AIBN] led preferentially to 1-(4-bromophenyl)-2-bromo-4,5-dimethylimidazole **2**. Thus, bromination was performed with 6.0 equiv of NBS under reflux in CCl_4 solution in the presence of a 200 W light bulb for 1 h, whereupon

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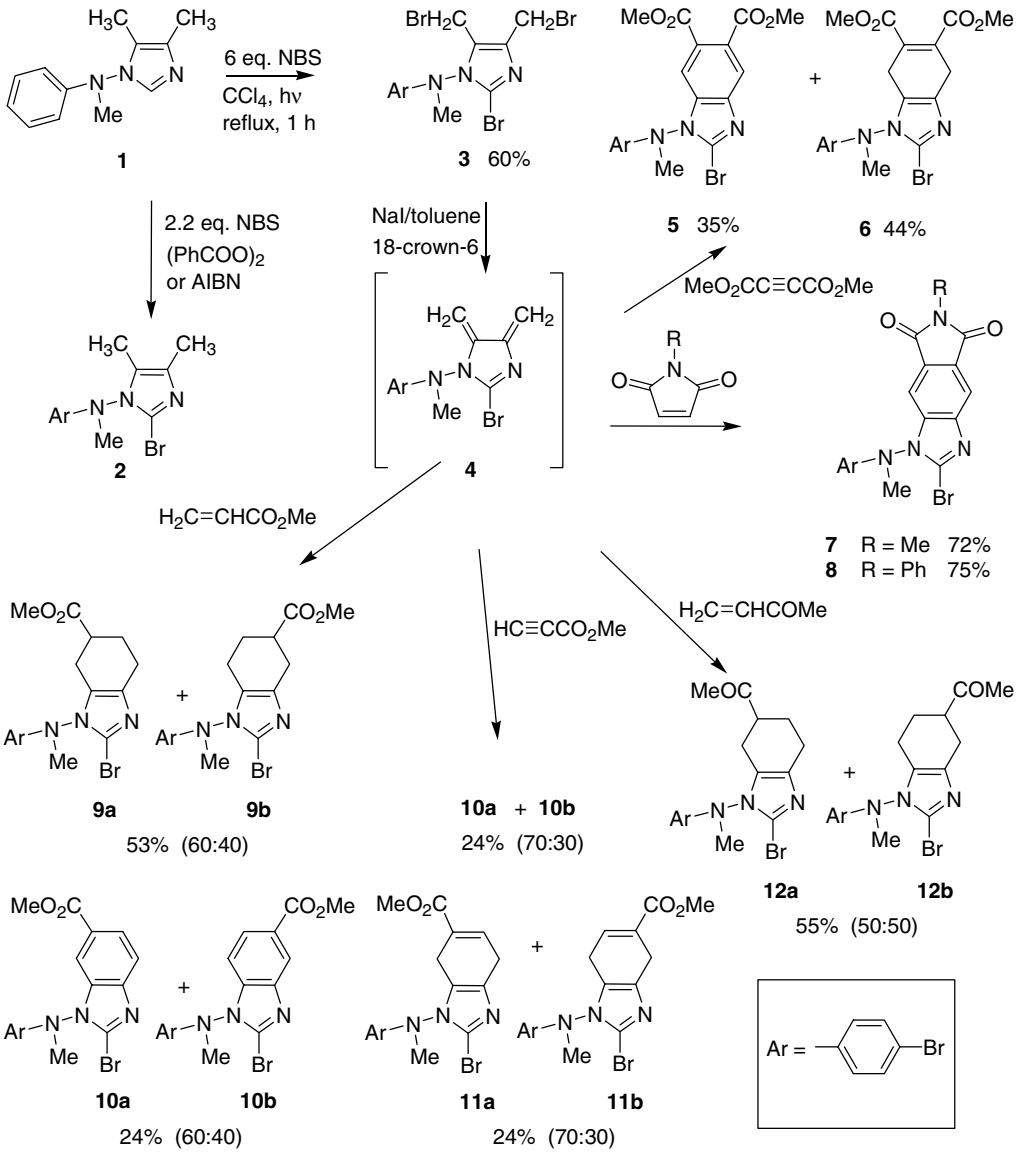

Scheme 1. Bromination of compound **1**, preparation and Diels–Alder trapping of *o*-QDM **4** with symmetrically and unsymmetrically substituted dienophiles.

the tetrabromo-derivative **3**, a suitable *o*-QDM precursor was formed, in 60% yield.

Due to the instability of **3** on silica gel, it was not purified but instead was treated directly with sodium iodide in boiling toluene in the presence of 18-crown-6 to afford imidazole *o*-QDM **4**, which was reacted in situ with dienophiles. From the reaction with dimethyl acetylenedicarboxylate, a mixture of the fully and the partially aromatized benzimidazole cycloadducts **5** and **6** in 35% and 44% yields, respectively, were obtained.[16] Using similar conditions, *o*-QDM **4** reacted with the symmetrical dienophiles *N*-methyl- and *N*-phenylmaleimide, whereupon the initially formed Diels–Alder cycloadducts were not isolated but, under the reaction conditions, underwent subsequent oxidation to give aromatized products **7** and **8**, in 72% and 75% yields, respectively[17] (Scheme 1). A note should be made to the change of solvent from DMF to toluene in the presence of 18-crown-6, since it was found to give much better yields.[5e]

To further extend the scope of this method the reactions of **4** with the asymmetrically substituted dienophiles methyl acrylate, methyl propiolate, and methyl vinyl ketone were studied. In all cases, inseparable mixtures of the two possible regioisomers **9a** and **9b** (ratio 60:40), **11a** and **11b** (70:30) and **12a** and **12b** (50:50) were isolated in 53%, 24%, and 55% yields, respectively. However, in the case of methyl acrylate and methyl propiolate, the regioisomeric fully aromatized compounds, **10a** and **10b**, (24% yield, 60:40 ratio and 24% yield, 70:30 ratio) were also formed.

In conclusion, an efficient route for the synthesis of imidazole *o*-quinodimethane **4** and its in situ trapping, for the first time, with dienophiles yielding benzimidazole derivatives has been described. Further applica-

tions and theoretical investigations on the observed regioselectivity are being studied.

References and notes

1. (a) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199–3246; (b) Collier, S. J.; Storr, R. C. *Prog. Heterocycl. Chem.* **1998**, *10*, 25–43.
2. (a) Nicolaou, K. C.; Gray, D. L. F. *J. Am. Chem. Soc.* **2004**, *126*, 607–612; (b) Oumzil, K.; Ibrahim-Ouali, M.; Santelli, M. *Steroids* **2006**, *71*, 886–901; (c) Barluenga, J.; Garcia-Garcia, P.; Fernandez-Rodriguez, M. A.; Aguilar, E.; Merino, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 5875–5878.
3. Potter, A. J.; Storr, R. C. *Tetrahedron Lett.* **1994**, *35*, 5293–5296.
4. (a) Chaloner, L. M.; Crew, A. P. A.; O' Neill, P. M.; Storr, R. C. *Tetrahedron* **1992**, *48*, 8101–8116; (b) Ko, C. W.; Chou, T. S. *J. Org. Chem.* **1998**, *63*, 4645–4653; (c) Liu, W. D.; Chi, C. C.; Pai, I. F.; Wu, A. T.; Chung, W. S. *J. Org. Chem.* **2002**, *67*, 9267–9275; (d) Govaerts, T. C.; Vogels, I. A.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2003**, *59*, 5481–5494.
5. (a) Port, M.; Lett, R. *Tetrahedron Lett.* **2006**, *47*, 4671–4675; (b) Mehrabani, F.; Pindur, U. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1406–1412; (c) Díaz-Ortiz, A.; De la Hoz, A.; Moreno, A.; Prieto, P.; Léon, R.; Herrero, M. A. *Synlett* **2002**, 2037–2038; (d) Valderrama, J. A.; González, M. F.; Pessoa-Mahana, D.; Tapia, R. A.; Fillion, H.; Pautet, F.; Rodriguez, J. A.; Theoduloz, C.; Schmeda-Hirschmann, G. *Bioorg. Med. Chem.* **2006**, *14*, 5003–5011; (e) Terzidis, M.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Tetrahedron Lett.* **2005**, *46*, 7239–7242.
6. Díaz-Ortiz, A.; Herrero, M. A.; De la Hoz, A.; Moreno, A.; Carrillo, J. R. *Synlett* **2006**, 579–582.
7. Kuroda, N.; Takahashi, Y.; Yoshinaga, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 1843–1845.
8. Kitagaki, S.; Katoh, K.; Ohdachi, K.; Takahashi, Y.; Shibata, D.; Mukai, C. *J. Org. Chem.* **2006**, *71*, 6908–6914.
9. Chauhan, P. M. S.; Crew, A. P. A.; Jenkins, G.; Storr, R. C.; Walker, S. M.; Yelland, M. *Tetrahedron Lett.* **1990**, *31*, 1487–1490.
10. (a) Barnard, E. A.; Stein, W. D. *Adv. Enzymol. Relat. Sub. Biochem.* **1958**, *20*, 51–110; (b) Boiani, M.; Gonzalez, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 409–424; (c) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196–229.
11. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.
12. Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309.
13. Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619–636.
14. Nieto, I.; Cervantes-Lee, F.; Smith, J. M. *Chem. Commun.* **2005**, 3811–3813.
15. (a) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187; (b) Khramov, D. M.; Bielawski, C. W. *Chem. Commun.* **2005**, 4958–4960; (c) Majo, V. J.; Perumal, P. T. *J. Org. Chem.* **1998**, *63*, 7136–7142; (d) Parenty, A. D. C.; Guthrie, K. M.; Song, Y.-F.; Smith, L. V.; Burgholder, E.; Cronin, L. *Chem. Commun.* **2006**, 1194–1196.
16. Selected data for compound **5**. Mp 175–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.51 (s, 3H, N–Me), 3.89 (s, 3H, 6-COOMe), 3.94 (s, 3H, 5-COOMe), 6.37–6.41 (m, 2H, C(2′, 6′)), 7.34–7.39 (m, 2H, C(3′, 5′)), 7.56 (d, *J* 0.75 Hz, 1H, C(7)), 8.13 (d, *J* 0.75 Hz, 1H, C(4)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.2 (N–Me), 52.77 (6-COOMe), 52.82 (5-COOMe), 110.8 (C-7), 112.7 (C-2), 114.1 (C-4′), 114.4 (C-2′, 6′), 121.7 (C-4), 128.0 (C-5), 128.5 (C-6), 132.6 (C-3′, 5′), 134.9 (C-7a), 142.4 (C-3a), 145.8 (C-1′), 167.65 (5-CO), 167.78 (6-CO). Anal. Calcd for $C_{18}H_{15}Br_2N_3O_4$ (497.138): C, 43.49; H, 3.04; N 8.45. Found: C, 43.79; H, 3.00; N 8.50. Diagnostic COLOC correlations are depicted in Figure 1.

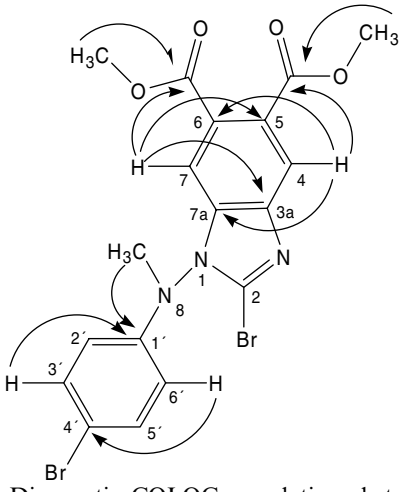

Figure 1. Diagnostic COLOC correlations between protons and carbons (via $^3J_{C-H}$) in compound **5**.

17. Selected data for compound **7**. Mp 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20 (s, 3H, CONMeCO), 3.53 (s, 3H, N–Me), 6.43 (d, *J* 8.5 Hz, 2H, C(2′, 6′)), 7.37 (d, *J* 8.5 Hz, 2H, C(3′, 5′)), 7.64 (s, 1H, C(7)), 8.18 (s, 1H, C(4)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2 (CONMeCO), 40.3 (N–Me), 105.7 (C-7), 113.8 (C-2), 114.4 (C-4′), 114.5 (C-2′, 6′) 116.4 (C-4), 127.9 (C-5), 128.2 (C-6), 132.7 (C-3′, 5′), 137.2 (C-7a), 145.0 (C-3a), 145.6 (C-1′), 167.9 (5-CO, 6-CO). Anal. Calcd for $C_{17}H_{12}Br_2N_4O_2$ (464.111): C, 43.99; H, 2.61; N 12.07. Found: C, 43.72; H, 2.80; N 12.31.