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Oxazoles as Dienophiles in Diels-Alder Reactions

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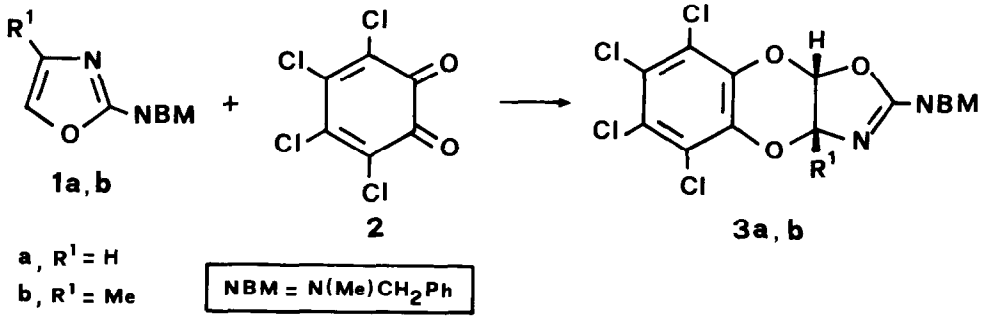
Abstract: 2-(N-Benzyl-N-methylamino)-oxazoles undergo (4+2)-cycloadditions across the C_4-C_5 bond by electron deficient dienes.

Oxazoles are well known to function as azadienes in Diels-Alder reactions with olefinic and acetylenic dienophiles to give primary cycloadducts which by loss of appropriate fragments evolve to pyridine and furan derivatives.[1] Some intramolecular versions of this behaviour in natural product synthesis have also been reported.[2] We describe here the hitherto unreported participation of the oxazole ring as 2 π-electron partner using the C_4-C_5 bond in (4+2)-cycloaddition reactions. In the course of our study towards efficient methodology for the functionalization of the oxazole ring,[3] we observed that on treating 2-(N-benzyl-N-methylamino)--oxazole (**1a**)[3a] and its 4-methyl derivative **1b**[3a] with an excess (2.5 mol. equiv.) of o-chloroanil **2** in benzene (r.t., 1 hr) afforded the benzo- and oxazolo-annulated 1,4-dioxin **3a** (87%)[4] and **3b** (71%)[4] respectively. The action of **2** as an efficient heterodiene partner towards 4-oxazolin-2-ones was previously reported.[5] In our case, the electron releasing N,N-dialkylamino group at C_2 of the oxazole ring appeared to exert a relevant effect on the dienophilic activity of this heterocycle[6] as indicated by the failure of 4-methyl-oxazole to react with **2** even under

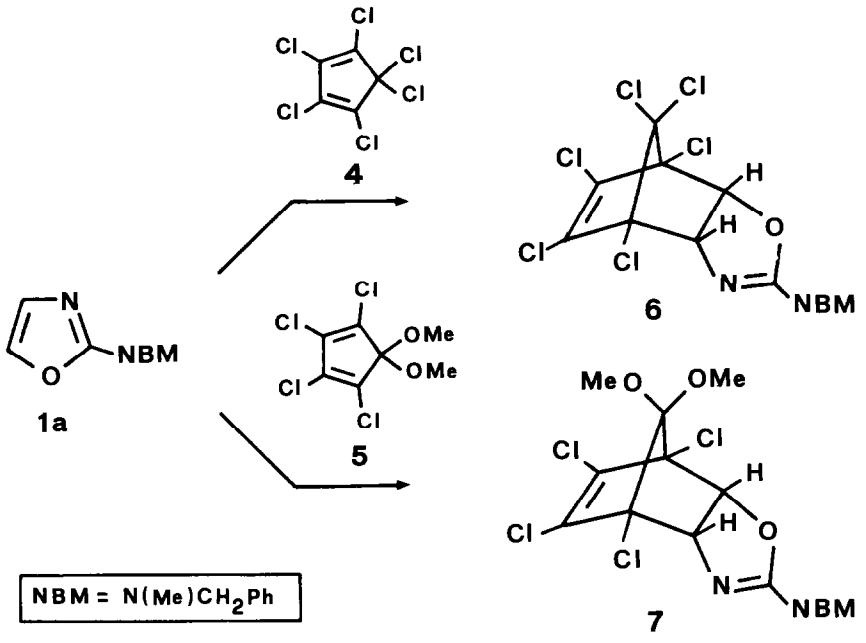


1a,b **2** **3a,b**

a, R^1 = H
b, R^1 = Me

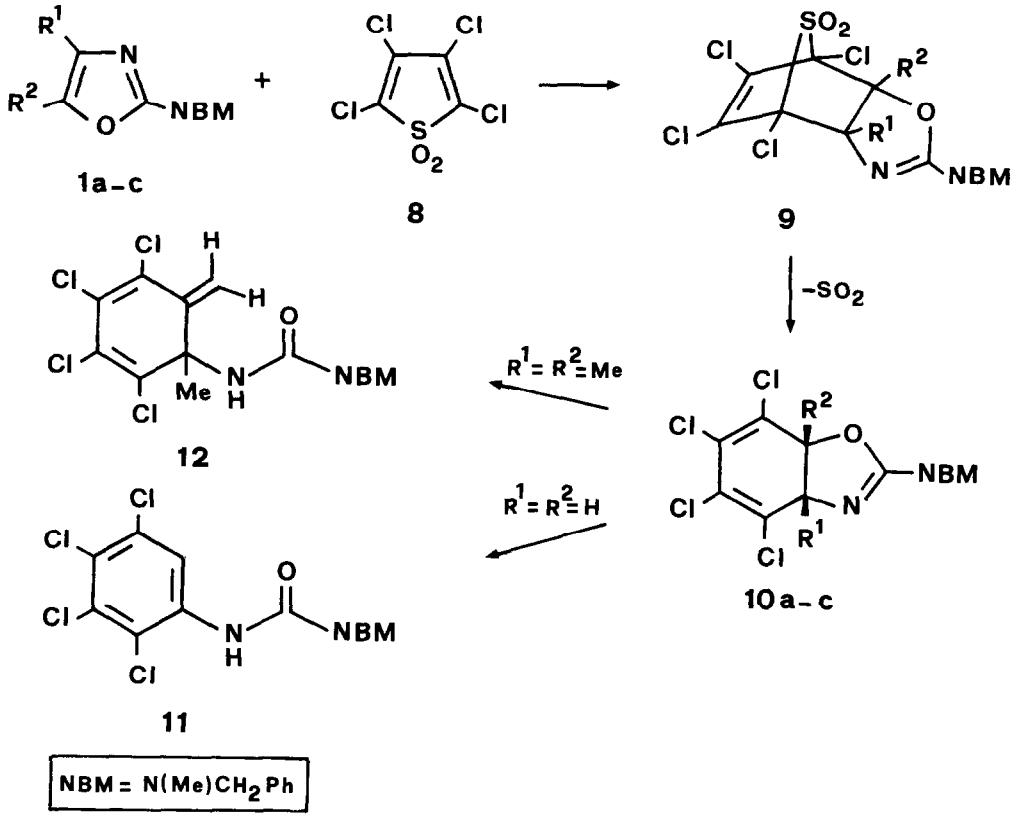
NBM = N(Me)CH_2Ph

more forcing conditions (benzene, 80°C, 3 days). This result is consistent with the higher electron density at the C_4-C_5 bond of the oxazole ring in **1a** with respect to the parent compound[3a]. Successful reactions of N,N-dialkylamino-oxazole **1a** were obtained with the highly reactive dienes hexachlorocyclopentadiene[7] (**4**) and 1,1-dimethoxy-tetrachlorocyclopentadiene[8] (**5**) to give under mild conditions (benzene, 50°C, 7 days) the corresponding (4+2)-cycloadducts **6**[9] and **7**[10] in very good yields. The stereochemistry of **6** (endo-adduct) was assigned by analogy to the reported cycloadducts of the diene **4** to oxazolin-[5] and imidazolin-2-ones[11] whereas the structure of **7** was established by X-ray crystallography[12]. The N,N-dialkylamino-4-methyl-oxazole **1b** failed to react with both dienes **4** and **5** even under more forcing conditions (refluxing toluene, 4-6 days). On the other hand both **1a** (benzene, r.t., 7 days) and **1b** (benzene, 50°C, 6



days), as well as the 4,5-dimethyl derivative **1c** (benzene, 50°C, 1 day), proved to cycloadd to the very highly reactive electron-deficient diene tetrachlorothiophene S,S-dioxide[13] (**8**). Although the isolated products varied in each case, all can be formulated to arise from the initial (4+2)-cycloaddition of **8** to **1** to give the annulated oxazoline **9** which by loss of sulphur dioxide rapidly transforms into the reduced benzo-oxazole **10**. This was the final product in the case of **10b**[14] (R^1 = Me, R^2 = H) whereas **10a**[15] and **10c**[16] (R^1 = R^2 = H or Me) rearranged into the substituted ureas **11**[17] and **12**[18] by oxazoline ring fission *via* formal 1,2-elimination reactions. Mechanistically, the above cycloadditions to N,N-dialkylamino-oxazoles **1a-c** can be viewed as

Diels-Alder reactions with an inverse electron demand.[7] The scope of the dienophilic reactivity of oxazoles appears worth of further investigation. The synthetic utility of the resulting cycloadducts may be foreseen in that they can be further elaborated by unmasking the 2-oxazoline system into various functional groups.[19]



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4) All new compounds gave satisfactory analyses and spectroscopic data (IR, NMR and MS): selected NMR data are given. **3a**: mp 181-182°C; NMR (C_6D_6) δ 5.47 (d,1, J = 5.4 Hz), 5.85 (d,1, J = 5.4 Hz). **3b**: mp 119-120°C; NMR ($CDCl_3$) δ 1.91 (s,3), 6.06 (s,1).

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6) This appears to be a relevant factor also in the thiazole series since the 2-dimethylamino-1,3-thiazole, unlike the parent term, cycloadds by the C_4-C_5 bond to **2** (C_6H_6, 80°C, 1 hr) to give the corresponding 1,4-dioxin (16%): mp 162-164°C; NMR ($CDCl_3$) δ 5.02 (d,1, J = 7 Hz), 5.30 (d,1, J = 7 Hz).

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9) **6**:(86%); mp 119-120°C; NMR ($CDCl_3$) δ 5.02 (d,1, J = 7 Hz), 5.30 (d,1, J = 7 Hz).

10) **7**: (85%); mp 108-109°C; NMR ($CDCl_3$) δ 4.71 (d,1, J = 7 Hz), 5.01 (d, 1, J = 7 Hz).

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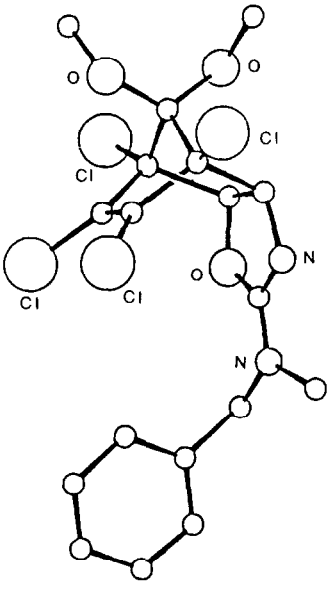
12) Crystal data of **7**: $C_{18}H_{18}N_2O_3Cl_4$, Formula weight 452.16. Monoclinic a = 9.692(5), b = 24.204(4), c = 8.664(5) Å, β = 85.55(5)°, Space group $P2_1/n$. V = 2026.3(1.6) Å^3, Z = 4, D_c = 1.48 g cm^{-3}, μ(Cu K_α) = 56.17 cm^{-1}, F(000) = 928. A total of 4226 reflections were collected at room temperature in the range $3° \leqslant \theta \leqslant 70°$ on a Siemens A.E.D. using Ni-filtered Cu-K_α radiation (λ = 1.54178 Å). 3438 symmetry dependent reflections with $I > 3\sigma(I)$ were retained as observed. The structure was solved by Direct Methods and refined by full matrix least-squares calculations with anisotropic temperature factors up to a final R = 0.070 for 3180 unique observed reflections. A view in minimum overlap projection of the molecule without H atoms (only non C-atoms are labelled) is shown hereabout.



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14) **10b** remained unaltered after heating at 50°C for several days: (64%); oil; NMR ($CDCl_3$) δ 1.57 (s, 3), 4.84 (s, 1).

15) A mixture of **10a** and **11** (6:1) was obtained from **1a** and **8** after 2 days at room temperature. Compound **10a** was partially purified by flash chromatography (silica, cyclohexane:diethyl ether 1:1). It rearranged to **11** (4 days) at room temperature. **10a**: (47%); mp 109-111°C; NMR ($CDCl_3$) δ 4.92 (d, 1, J = 11 Hz), 5.35 (d, 1, J = 11 Hz).

16) Compound **10c**, obtained after 1h at 50°C, was purified by flash chromatography (silica, cyclohexane-diethyl ether 1:1). It rearranged to **12** at 50°C (24 h). **10c**: (70%); oil; NMR ($CDCl_3$) δ 1.46 (s, 3), 1.59 (s, 3).

17) **11**: (96%); mp 100-101°C; NMR ($CDCl_3$) δ 6.96 (br, 1, NH), 8.44 (s, 1, ArH).

18) **12**: (95%); mp 170-171°C (dec.); NMR ($CDCl_3$) δ 1.37 (s, 3, Me), 4.96 (br,1, NH), 5.42 (s,1, =CH), 5.77 (s, 1, s, =CH).

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