THERMAL CYCLOADDITION REACTIONS OF 4,5-EPOXY-4-AZAHOMOADAMANTANES WITH ACETYLENIC 1,3-DIPOLAROPHILES. NOVEL FORMATION OF 4-AZAHOMOADAMANTANO[4,5-a]PYRROLE DERIVATIVES[1]

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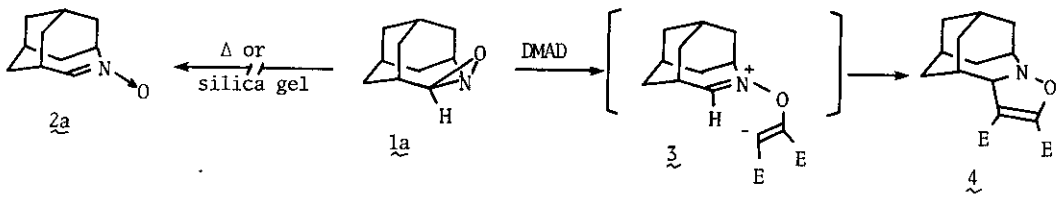
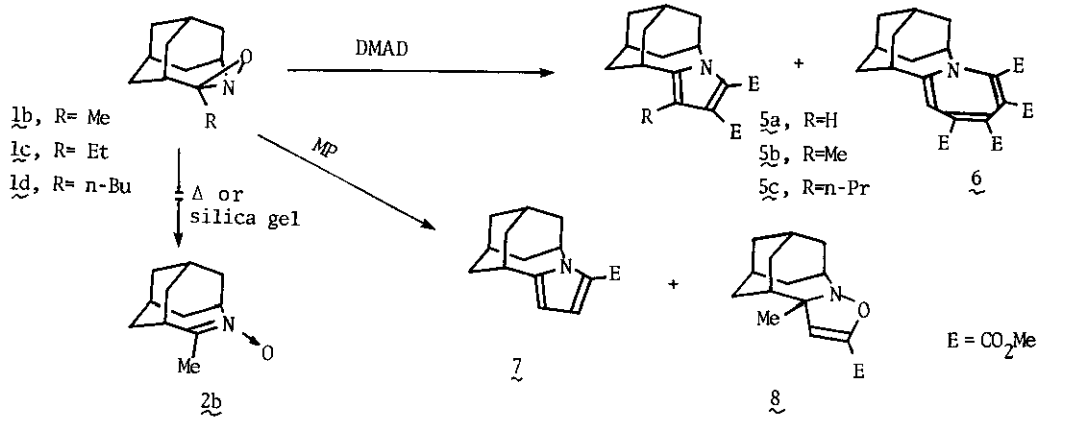
Abstract — Thermal cycloaddition reactions of 5-alkyl-4,5-epoxy-4-azahomoadamantanes 1b-d with dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate afforded 4-azahomoadamantano[4,5-a]pyrrole derivatives 5a-c and 7, while the reaction of the 5-unsubstituted epoxy-4-azahomoadamantane 1a with DMAD gave the oxazoline derivative 4 in a low yield.

We have reported recently a novel route to the 2-azaadamantyl system via photochemical ring contraction of 4,5-epoxy-4-azahomoadamantanes 1,[2] and also, synthesis of 4-azahomoadamantano[4,5-a]pyrroles by enamine cyclizations and 1,3-dipolar cycloadditions.[3] As an extension of these studies, we report here novel thermal cycloaddition behaviors of 1 with some acetylenic compounds. The thermal[4] or silica gel catalyzed isomerizations[5] of oxaziridines to the corresponding nitrones are well known. In an attempt to isomerize 1 to the corresponding nitrones, 1a and 1b were heated in dry benzene at 130 °C for 15 h. However, both 1a and 1b were recovered. Heating at 150 °C without solvent resulted only in decompositions, and no trace amount of nitrones 2a and 2b could be obtained. Treatment of 1a and 1b on a silica gel (Kiesel gel and Mallincrodt silicic acid) column for 2 days according to the procedure by Keana and Lee[5a] did not afford the desired nitrones 2a and 2b at all, only recovering the starting oxaziridines 1a and 1b. Therefore, we examined direct reactions of 1 with acetylenic dipolarophiles. A 1:2 molar mixture of 1a and DMAD in dry benzene was stirred at room temperature (20-28 °C) for 20 h to afford a complex mixture. Removal of the solvent and excess DMAD under reduced pressure and purification of the residue on a preparative TLC (Merck, Aluminium oxide 60 PF_{254}, Type E, ethyl acetate/hexane 1:3) gave an oily 1:1 adduct 4 (15%) as the major product (Scheme 1). The Δ^4-isoxazoline structure[6] was supported by C,H,N elemental analysis[7] and spectral data: Ir(neat) 2920, 2850, 1725, 1660, 1430, 1350, 1290, and 1200 cm^{-1}; ^1H nmr[8] δ 5.66 (s, 1H), 3.72 (s, 3H), 3.70 (br s, 1H), 3.68 (s, 3H), 2.77 (br s, 1H), 2.7-1.5 (m, 12H). The same reaction at 85 °C for 20 h afforded a more complex mixture and the yield of 4 could not be improved.



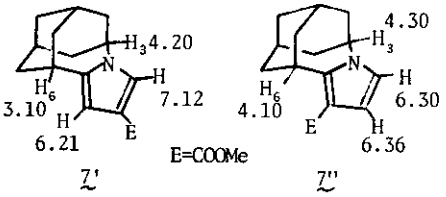
Scheme 1

The reaction of 1b with DMAD (1:2 molar ratio) proceeded slowly at room temperature in benzene. After 21 days, usual work up and PTLC as above gave 5a (36%), mp 73.0-74.5 °C, and an oily 1:2 adduct 6 (7%) (Scheme 2). The same reaction at 85 °C for 48 h gave a higher yield (67%) of 5a along with a trace of 6. The pyrrole structure of 5a was based on elemental analysis and spectral data: Ir(KBr) 2910, 2840, 1705, 1500, 1450, 1440, 1205 cm^{-1}; ^1H nmr δ 6.04 (s, 1H), 4.94 (br s, 3.79 (s, 3H), 3.71 (s, 3H), 3.07 (br s, 1H), 2.4-1.5 (m, 12H); uv λ_{max}(MeOH) 204 nm (ε 15,500), 243 (6,960), 282 (7,360). The minor product 6 was characterized as an azepine derivative:[9] Ir(neat) 2910, 2840, 1720, 1500, 1430, 1240, 1210 cm^{-1}; ^1H nmr δ 6.86 (s, 1H), 5.05 (br s, 1H), 3.77, 3.69, 3.61, 3.58 (each s, each 3H), 2.75 (br s, 1H), 2.3-1.6 (m, 12H); uv λ_{max}(MeOH) 202 nm (ε 15,600), 278 (4,380); ms m/z(%) 445 (M^+, 100), 387 (13), 386 (59), 385 (16), and 354 (28). The reactions of 1c and 1d with DMAD (1:2 molar ratio) at 80 °C for 80 h afforded the pyrrole derivatives 5b, mp 103-105 °C, and 5c (oil) in 83 and 78% yields, respectively. 5b: Ir(KBr) 2910, 2840, 1700, 1495, 1435, 1250, 1210, 1150, 1080 cm^{-1}; ^1H nmr δ 5.05 (br s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.16 (br s, 1H), 2.00 (s, 3H), 2.3-1.4 (m, 12H); uv λ_{max}(MeOH) 202 nm (ε 11,000), 251 (5,930), 290 (9,030). 5c: Ir(neat) 2920, 2850, 1700, 1485, 1450, 1295, 1205, 750 cm^{-1}; ^1H nmr δ 5.18 (br s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.15 (br s, 1H), 2.6-1.1 (m, 16H), and 0.84 (t, J=6.5 Hz, 3H); uv λ_{max}(MeOH) 202 nm (ε 10,500), 250 (5,380) and 289 (9,060). On the other hand, the reaction of 1b with methyl propiolate (MP) in a 1:5 molar ratio did not proceed at room



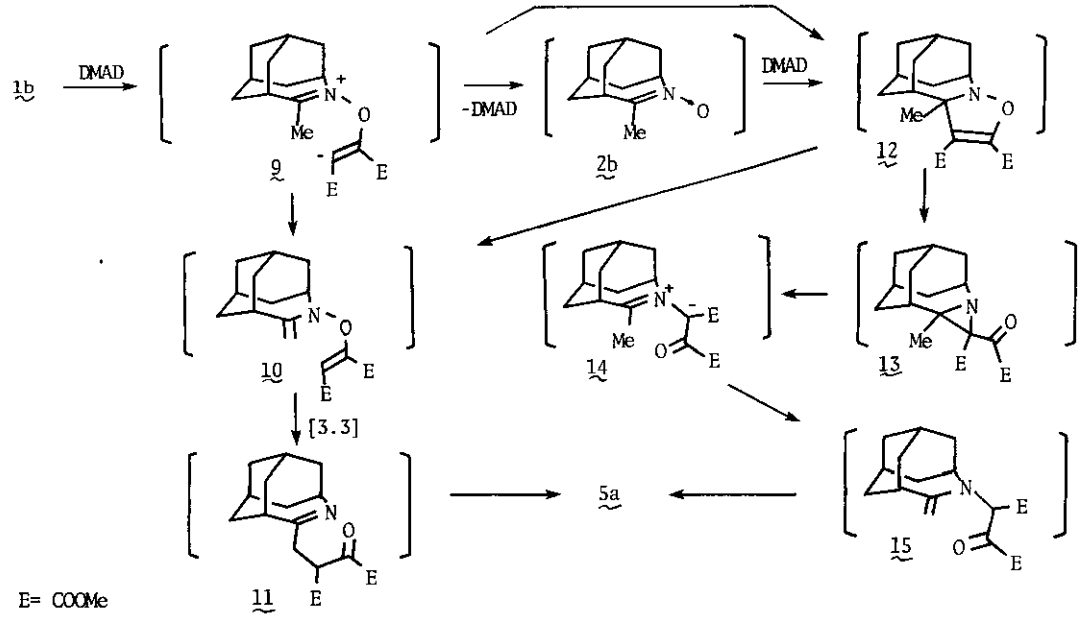
Scheme 2

temperature, but the reaction at 95 °C for 48 h gave also pyrrole 7 (16%), mp 51-54 °C, and isoxazoline 8 (27%), mp 114-117 °C.[10] The structures of 7 and 8 were compatible with spectral data. 7: Ir(KBr) 2920, 2840, 1695, 1485, 1435, 1295, 1205, 1125, 1090, 750 cm^{-1}; ^1H nmr(CCl_4) δ 6.79 (d, J=4 Hz, 1H), 5.83 (br s, 1H), 5.81 (d, J=4 Hz, 1H), 3.77 (s, 3H), 3.15 (br s, 1H), 2.3-1.2 (m, 12H); uv λ_{max}(MeOH) 205 nm (ε 3,530) and 216 (3,720). Previously prepared regioisomers 7' and 7'' had different chemical shifts.[3] 8: Ir(neat) 2920, 2850, 1710, 1660, 1590, 1230, 1180 cm^{-1}; ^1H nmr(CCl_4) δ 3.97 (s, 1H), 3.65 (br s, 1H), 3.52 (s, 3H), 2.16 (s, 3H), 2.3-1.5 (m, 13H); ms m/z(%) 263 (M^+, 21), 252 (17), 221 (100), 193 (20), 75 (35).



7' 7''

The observed novel cycloadditions of 1 with DMAD and could be explained in terms of a generation of the corresponding betaines such as 3 and 9 via the C-O bond cleavage of the oxaziridines with electrophilic acetylenes (Scheme 1 and 3). The pyrrole formation from Δ^4-isoxazolines had been reported previously,[11] and two reaction paths (a and b) had been suggested: (a) an initial enamine formation, a hetero-Cope rearrangement, and final cyclization, and (b) an initial acylaziridine formation followed by ring opening to a betaine, a proton shift, and cyclization. Both routes have been shown to occur depending on the substituents.[11c] In the present reactions of 1b-d with DMAD, we could not isolate the corresponding isoxazolines such as 12, and hence, we examined ^1H nmr spectral change using an equimolar mixture of 1b and DMAD in $CDCl_3$ at 25 °C. During 48 h, the initially observed signals at δ 3.84 (COOMe, H_5 of 1b), 2.36 (H_6 of 1b), and 1.47 (Me of 1b)[2]



Scheme 3

changed gradually to signals at δ 4.10 (H_3 of 9), 3.82, 3.67 (COOMe), 3.11 (H_6 of 9), and 2.45 ($MeC=N^+$), indicating initial formation of betaine 9.[12] Direct or indirect foramtion of enamine 10 from 9, followed by hetero-Cope rearrangement leads to 11 which can afford the pyrrole 5a by cyclodehydration. Alternatively, acylaziridine route via 12, 13, 14 and 15 can not be ruled out, even though 12 was not detectable by the ^1H nmr analysis. The relatively long-lived betaine 9 may react with another molecule of DMAD to afford 6 via yet unclarified path.[9] The formation of 7 from 1b and MP can only be explained by the hetero-Cope rearrangement route because the known isomeric pyrrole 7'[3] should be produced by the acylaziridine route.

To the best of our knowledge, direct formation of pyrroles and also isoxazolines from oxaziridines and acetylenic dipolarophiles seem to be unprecedented, though intramolecular and intermolecular cycloadditions of C-aryl oxaziridines with olefinic dipolarophiles,[13a] cycloadditions of fluorinated oxaziridines with fluoroolefins and ketones,[13b] and cycloadditions of oxaziridines with heterocumulenes[13c,d] have been recorded previously.

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