DIELS-ALDER TYPE REACTIONS OF 2-PHENYL-1-AZASPIRO[2.2]PENT-1-ENE

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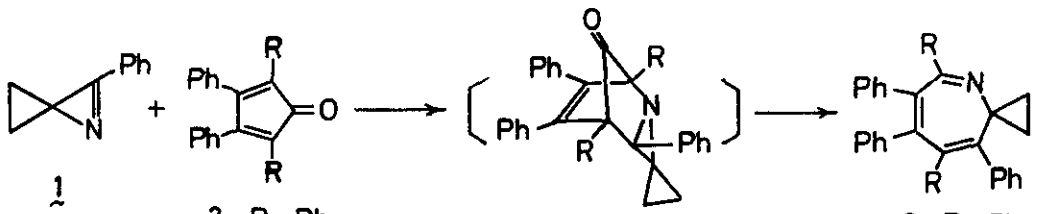
Abstract —— Highly strained 2-phenyl-1-azaspiro[2.2]pent-1-ene reacted with cyclopentadienones to give the corresponding 2H-azepine-2-spiro-cyclopropanes directly, with loss of carbon monoxide. However, the reaction of the azaspiropentene with 1,3-diphenylisobenzofuran afforded the exo-Diels-Alder adduct. The azaspiropentene reacted with thiobenzoyl isocyanates to give 3-aryl-5-oxo-2,4,6-thiadiazabicyclo[5.2.0]nona-3,6-dienes arising from the rearrangement of initial [4 + 2] cycloadducts.

In contrast to a trisubstituted 1-azirine such as 3,3-dimethyl-2-phenyl-1-azirine[1], 2-phenyl-1-azaspiro[2.2]pent-1-ene 1[2], whose structure is a trisubstituted 1-azirine, exhibited high reactivity toward 1,3-dipoles[3,4]. The high reactivity of 1 may be attributable to its highly strained structure. We have now found that 1 was also reactive for Diels-Alder reactions. In this paper we wish to report on the cycloaddition reactions of 1 with cyclopentadienones, 1,3-diphenylisobenzofuran, and thiobenzoyl isocyanates.

Reaction of 1 with Cyclopentadienones. It is known that the reaction of monosubsituted and 2,3-disubstituted 1-azirines with cyclopentadienones proceeds via initial formation of Diels-Alder adducts, followed by loss of carbon monoxide to give primarily 2H-azepines which in many cases rearranged to the more stable 3H-azepines[5]. However, 3,3-dimethyl-2-phenyl-1-azirine did not react with tetracyclone even on being refluxed in xylene for 13 days[5a]. We report here the first example for the cycloaddition of a trisubstituted 1-azirine to cyclopentadienones.

When a solution of 1 in toluene was refluxed for a long time with an equimolar amount of tetracyclone 2 under nitrogen, a 2H-azepine, pentaphenyl-2H-azepine-2-spiro-cyclopropane 3, was obtained in a low yield. However, the same reaction in higher boiling solvents such as xylene and o-dichlorobenzene gave 3 in good yields respectively. Similarly, 1 reacted with 2,5-dimethyl-3,4-diphenylcyclopentadienone 4 in refluxing xylene to give the corresponding 2H-azepine derivative 5 (Scheme 1).



in toluene, reflux, 48 h	3	23.5%
in xylene, reflux, 48 h	3	76%
in o-dichlorobenzene, reflux, 15 h	3	86%
in xylene, reflux, 48 h	5	76%

Scheme 1

Structural elucidation of 3 and 5 was accomplished on the basis of spectral data[6]. The ^1H and ^{13}C NMR spectra indicated the presence of cyclopropyl ring, and mass spectrum exhibited the major fragment ion [M^+ - RCN] besides molecular ion [M^+].

3: mp 188-189°; colorless prisms; ^1H NMR ($CDCl_3$) δ 0.90-1.40 (4H, m), 6.50-7.58 (25H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.1 (each $\underline{C}H_2$), 47.1 (quat. $\underline{C}$), 171.5 ($\underline{C}$=N); $UV\lambda_{max}^{EtOH}$ nm (log ε) 236 (4.23), 280 (3.92); MS m/e (rel. intensity %) 499 (M^+, 100), 396 (M^+ - PhCN, 90), 321 (M^+ - Ph-C≡C-Ph, 92).

5: mp 172-173°; colorless prisms; ^1H NMR ($CDCl_3$) δ 0.60-1.45 (4H, m), 1.61, 2.07 (each 3H, s), 6.97-7.45 (15H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.2 (each $\underline{C}H_2$), 19.0, 27.8 (each $\underline{C}H_3$), 46.1 (quat. $\underline{C}$), 169.6 ($\underline{C}$=N); $UV\lambda_{max}^{EtOH}$ nm (log ε) 225 (4.17), 256 (3.95), 307 (3.29); MS m/e (rel. intensity %) 375 (M^+, 100), 360 (M^+ - Me, 35), 334 (M^+ - MeCN, 26).

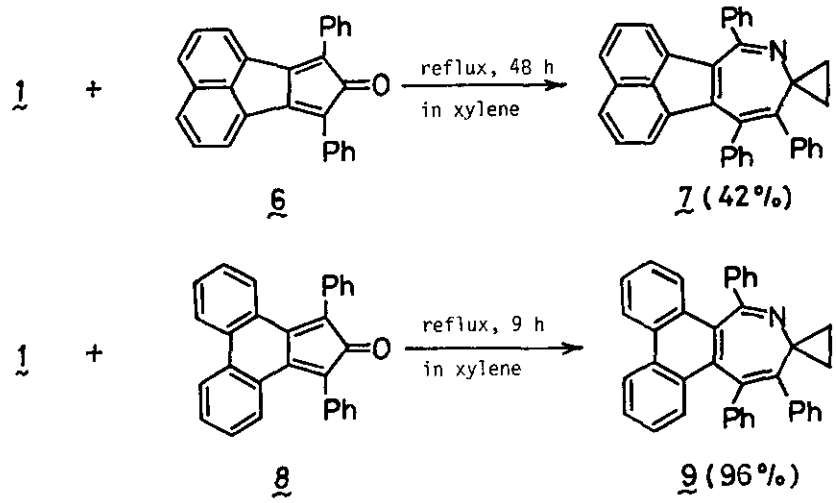
It is thus clear that in analogy with the reactions of 1-azirines with cyclopentadienones[5], 1 adds to cyclopentadienones 2 and 4 to yield Diels-Alder adducts. This is followed by the elimination of carbon monoxide to give 2H-azepines 3 and 5 which are stabilized by the conjugation with spirocyclopropyl ring.

Azaspiropentene 1 reacted with diphenylacecyclone 6 and diphenylphencyclone 8 in refluxing xylene to give the corresponding 2H-azepines 7 and 9 (Scheme 2). The spectral data for 7 and 9 are in agreement with the assigned structures, respectively.

7: mp 235-236°; orange prisms; ^1H NMR ($CDCl_3$) δ 0.50-0.82, 1.05-1.50 (each 2H, m), 6.60-7.80 (21H, m); ^{13}C NMR ($CDCl_3$) δ 14.3, 16.4 (each $\underline{C}H_2$), 47.9 (quat. $\underline{C}$), 168.5 ($\underline{C}$=N); $UV\lambda_{max}^{EtOH}$ nm (log ε) 237 (4.30), 273 (3.85), 320 (3.74), 336 (3.78); MS m/e (rel. intensity %) 471 (M^+, 100), 394 (M^+ - Ph, 58), 368 (M^+ - PhCN, 15).

9: mp > 300°; colorless prisms; ^1H NMR ($CDCl_3$) δ 0.20-0.68, 0.90-1.45 (each 2H, m), 6.80-8.75 (23H, m); ^{13}C NMR ($CDCl_3$) δ 12.7, 14.8 (each $\underline{C}H_2$), 48.4 (quat. $\underline{C}$), 170.6 ($\underline{C}$=N); $UV\lambda_{max}^{EtOH}$ nm (log ε) 227

(4.94), 251 (4.63), 265 (4.68), 280 (4.54); MS m/e (rel. intensity %) 497 (M^+, 100), 420 (M^+ - Ph, 23), 394 (M^+ - PhCN, 11).



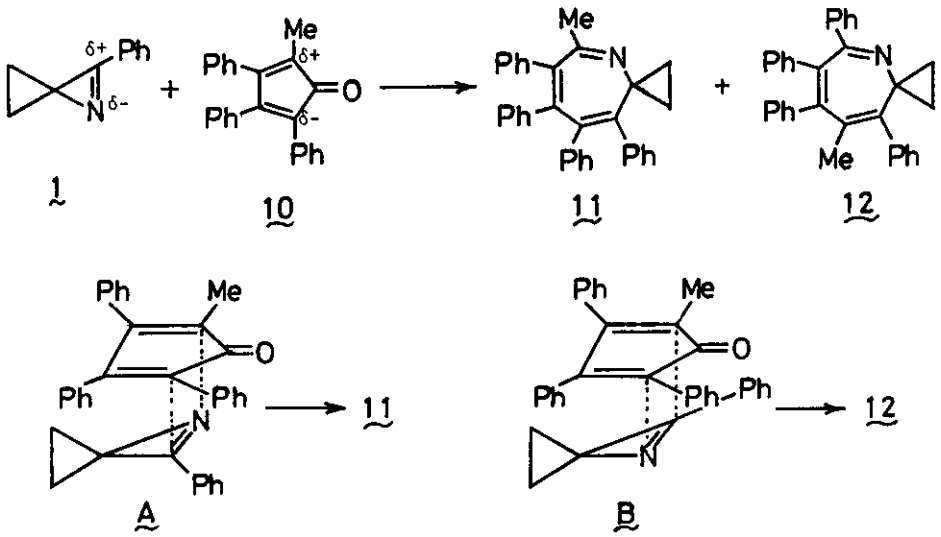
Scheme 2

The regiochemistry of the cycloaddition reaction of 1 was next examined, using unsymmetrical cyclopentadienone 10. Azaspiropentene 1 reacted with 10 in refluxing xylene for 26 h to give 7-methyl-2H-azepine 11 and 4-methyl-2H-azepine 12 in 62 and 37% yields, respectively. Structural elucidation of 11 and 12 was accomplished on the basis of spectral data.

11: mp 108-111°; colorless prisms; ^{1}H NMR ($CDCl_3$) δ 0.70-1.35 (4H, m), 2.07 (3H, s), 6.50-7.30 (20H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.4 (each $\underline{C}H_2$), 24.9 ($\underline{C}H_3$), 46.6 (quat. $\underline{C}$), 170.4 ($\underline{C}$=N); $UV\lambda_{max}^{EtOH}$ nm (log ε) 255 (3.85), 310 (3.24); MS m/e (rel. intensity %) 437 (M^+, 100), 422 (M^+ - Me, 24), 396 (M^+ - MeCN, 91), 360 (M^+ - Ph, 30).

12: mp 169-171°; colorless prisms; ^{1}H NMR ($CDCl_3$) δ 0.65-1.40 (4H, m), 1.77 (3H, s), 6.97-7.70 (20H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.1 (each $\underline{C}H_2$), 19.2 ($\underline{C}H_3$), 46.8 (quat. $\underline{C}$), 171.0 ($\underline{C}$=N); $UV\lambda_{max}^{EtOH}$ nm (log ε) 220 (4.35), 262 (4.03), 320 (3.20); MS m/e (rel. intensity %) 437 (M^+, 100), 422 (M^+ - Me, 18), 360 (M^+ - Ph, 13), 334 (M^+ - PhCN, 40).

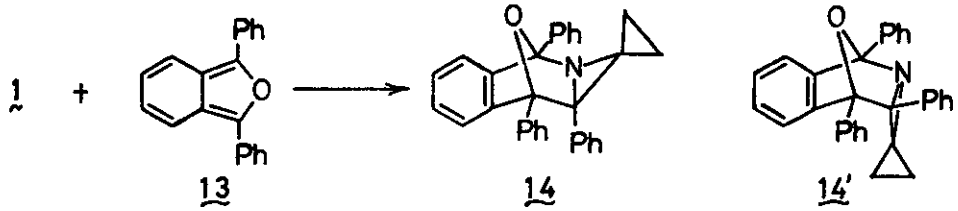
It is noteworthy that 7-methyl-2H-azepine 11 was formed in much larger amount than 4-methyl-2H-azepine 12 from the reaction of 1 with 10, since it has been reported that 2-phenyl-3-methyl(or phenyl)-1-azirine reacted with 10 to afford the 5-methyl-3H-azepine (arising from the 4-methyl-2H-azepine) as the major product accompanied by the 2-methyl-3H-azepine (arising from the 7-methyl-2H-azepine), whereas a reversal of the product ratios occurred when 2-aryl-1-azirines having no 3-substituents were used[5c]. Hassner and Anderson[5c] assumed that the relative amounts of two 3H-azepine isomers depended on the electronic nature of the azirine C=N bond and the steric factors involved in the addition. If the Hassner's hypothesis is appicable to our case, in the reaction of



Scheme 3

1 with 10 it appears that the electronically favorable transition state A overcomes the sterically favorable one B (Scheme 3).

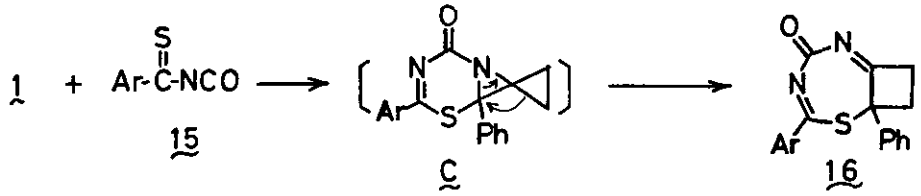
Reaction of 1 with 1,3-Diphenylisobenzofuran. Monosubstituted and 2,3-disubstituted 1-azirines reacted with 1,3-diphenylisobenzofuran 13 to give the corresponding exo-Diels-Alder adducts[7,8]. However, no reaction of trisubsituted 1-azirines with 13 has so far been reported. When 1 was treated with 13 in refluxing xylene for 7 h, an 1:1 adduct was obtained in 76% yield. On the basis of the spectral evidence and inspection of the Dreiding models, the adduct was assigned as exo-Diels-Alder adduct 14 but not endo-adduct 14'. The ^{1}H NMR and ^{13}C NMR spectra showed the presence of cyclopropyl ring and four quaternary carbon atoms. Inspection of the Dreiding models indicates



that there is a significant interaction between the cyclopropyl ring and benzene ring in 14' but not in 14. It was thus proved that in analogy with monosubstituted and 2,3-disubstituted 1-azirines 1 undergoes the cycloaddition reaction with 13.

14: mp 178-179°C; colorless prisms; ^{1}H NMR ($CDCl_3$) δ 0.50-1.55 (4H, m), 6.70-8.00 (19H, m); ^{13}C NMR ($CDCl_3$) δ 3.7, 5.5 (each $\underline{C}H_2$), 49.9, 58.9, 90.1, 101.4 (each quat. C); MS m/e (rel. intensity %) 413 (M^+, 26), 359 ($M^+ - C_3H_4N$, 99), 336 ($M^+ - Ph$, 77), 270 (13$^+$, 100), 143 (1$^+$, 9).

Reaction of 1 with Thiobenzoyl Isocyanates. Thiobenzoyl isocyanates react with a variety of C=N bonds by a 1,4-cycloaddition process[9]. 2-Phenyl-1-azirine and 2-phenyl-3-phenyl(or methyl)-1-azirine reacted with thiobenzoyl isocyanate at room temperature to give the corresponding bicyclic [4 + 2] cycloadducts, which at higher temperature were transformed into the thiadiazepinones[10]. Thus, we have investigated the reaction of 1 with p-substituted thiobenzoyl isocyanates 15. Azaspiropentene 1 did not react with thiobenzoyl isocyanate 15a[11], generated in situ from 2-phenylthiazoline-4,5-dione in xylene, at room temperature. When 1 was treated with 15a in xylene at 120° for 1 h, however, 1:1 adduct 16a was obtained in 52% yield. Similarly, 1 reacted with p-methylthiobenzoyl 15b, p-methoxythiobenzoyl 15c, and p-chlorothiobenzoyl isocyanate 15d to give the corresponding 1:1 adducts 16b, 16c, and 16d in 66, 65, and 70% yields, respectively.



a: Ar=Ph; b: Ar=p-MeC_6H_4; c: Ar=p-$MeOC_6H_4$; d: Ar=P-ClC_6H_4

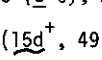
On the basis of spectral data, the 1:1 adducts were assigned as the corresponding 3-aryl-5-oxo-2,4,6-thiadiazabicyclo[5.2.0]nona-3,6-dienes arising from the rearrangement of initial [4 + 2] cycloadducts C.

16a: mp 142-143°; colorless prisms; IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.38-2.80, 3.18-3.80 (each 2H, m), 7.16-7.60 (8H, m), 7.70-7.95 (2H, m); ^{13}C NMR ($CDCl_3$) δ 32.9, 33.1 (each CH_2), 63.4 (quat. C), 161.7, 166.7 (each C=N), 170.6 (C=O); MS m/e (rel. intensity %) 306 (M^+, 11), 175 (M^+ - Ph-(azirine)=O, 18), 163 (15a$^+$, 12), 143 (M^+ - 15a, 9), 142 (16), 121 ($PhCS^+$, 100), 103 ($PhCN^+$, 63).

16b: mp 178-180°; colorless prisms; IR (KBr) 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 2.36 (3H, s), 2.45-2.80, 3.20-3.82 (each 2H, m), 7.10-7.60 (7H, m), 7.70-7.90 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.3 (CH_3), 32.9, 33.1 (each CH_2), 63.3 (quat. C), 161.8, 166.6 (each C=N), 170.7 (C=O); MS m/e (rel. intensity %) 320 (M^+, 15), 177 (15b$^+$, 4), 175 (M^+ - Ar-(azirine)=O, 25), 143 (M^+ - 15b, 10), 142 (20), 135 ($ArCS^+$, 23), 121 ($PhCS^+$, 100), 117 ($ArCN^+$, 33).

16c: mp 163-164°; colorless prisms; IR (KBr) 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.40-2.78, 3.40-3.72 (each 2H, m), 3.81 (3H, s), 6.75-7.05 (2H, m), 7.10-7.60 (5H, m), 7.80-8.0 (2H, m); ^{13}C NMR ($CDCl_3$) δ 32.8, 33.0 (each CH_2), 55.5 (OCH_3), 63.3 (quat. C), 163.6, 165.8 (each C=N), 170.6 (C=O); MS m/e (rel. intensity %) 336 (M^+, 31), 203 (M^+ - ArCN, 21), 175 (M^+ - Ar-(azirine)=O, 28), 151 ($ArCS^+$, 31), 143 (M^+ - 15c, 10), 142 (17), 133 ($ArCN^+$, 100), 121 ($PhCS^+$, 61).

16d: mp 164-165°C; colorless prisms; IR (KBr) 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.45-2.80, 3.25-3.75 (each 2H, m), 7.15-7.60 (7H, m), 7.75-7.95 (2H, m); ^{13}C NMR ($CDCl_3$) δ 33.0, 33.2 (each CH_2),

63.5 (*quat.* C), 161.5, 165.2 (each C=N), 170.6 (C=O); MS m/e (rel. intensity %) 342 (M^+, 24), 340 (M^+, 59), 305 (M^+ - Cl), 199 (15d$^+$, 18), 197 (15d$^+$, 49), 175 (M^+ - Ar-  , 23), 157 ($ArCS^+$, 12), 155 ($ArCS^+$, 30), 143 (M^+ - 15d, 14), 142 (26), 139 ($ArCN^+$, 22), 137 ($ArCN^+$, 63), 121 ($PhCS^+$, 100).

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Received, 8th August, 1981