1,3-Dipolar Cycloadditions to 2-Phenyl-1-azaspiro[2.2]pent-1-ene[1)]

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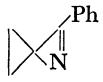
Benzonitrilium-*p*-nitrobenzylide undergoes 1,3-dipolar cycloaddition to highly strained 2-phenyl-1-azaspiro-[2.2]pent-1-ene, yielding the cycloadduct which is thermally converted to the dihydrobenzo[*f*]quinazoline and pyrimidine. In the reaction with α,*N*-diarylnitrone, the spiroazapentene gives 1-(benzylideneamino)-1-(*N*-phenylbenzamido)cyclopropane arising from the initial cycloadduct.

It seemed of interest to investigate the cycloadditions of highly strained 2-phenyl-1-azaspiro[2.2]pent-1-ene (**1**)[2)] having an 1-azirine moiety, because it is known that 1-azirines are useful reagents for the synthesis of a large number of heterocyclic systems.[3)] However, no studies on the cycloadditions to **1** have so far been



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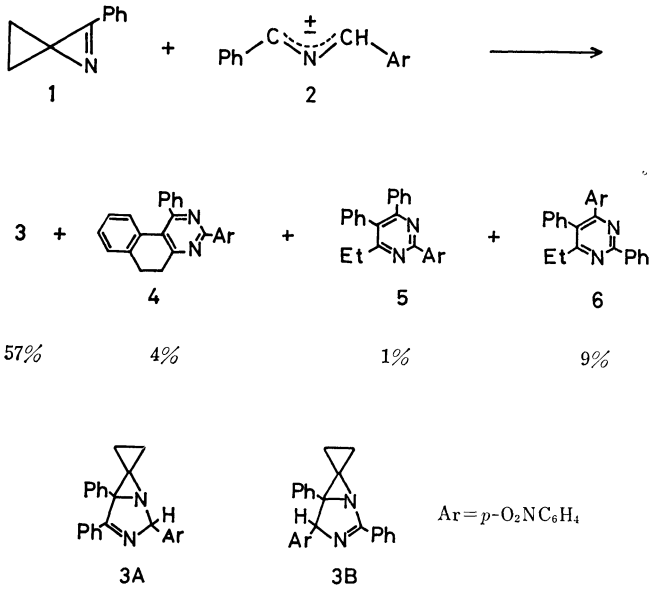
reported. We now wish to report on the reactions of **1** with benzonitrilium-*p*-nitrobenzylide (**2**) and α,*N*-diarylnitrones (**8**).

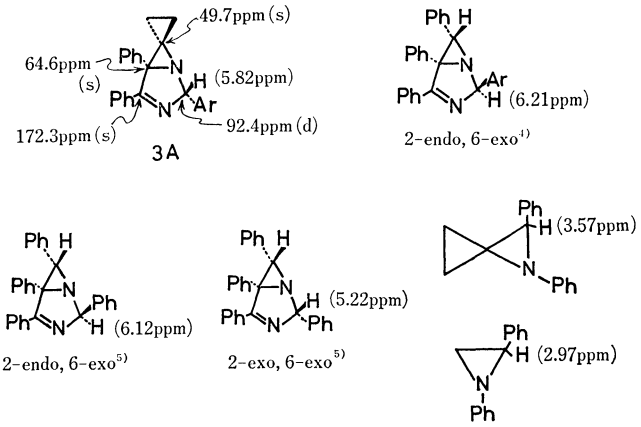
*Reaction with Benzonitrilium-*p*-nitrobenzylide.* Schmid and his co-workers[4)] reported that benzonitrilium-*p*-nitrobenzylide (**2**) undergoes 1,3-dipolar cycloaddition to 2-phenyl- and 2,3-diphenyl-1-azirines, yielding the bicyclic adducts. However, 3,3-dimethyl-2-phenyl-1-azirine does not react with **2**. Although **1** is a 3,3-disubstituted 2-phenyl-1-azirine, **1** might react with **2** due to its highly strained structure.

When **1** was allowed to react with 1 equivalent of **2** generated *in situ* from *N*-*p*-nitrobenzylbenzimidoyl chloride and triethylamine in benzene under nitrogen at room temperature, the 1:1 cycloadduct **3** was obtained as the major product, along with by-products **4**, **5**, and **6** (Scheme 1). Structural elucidation of these products, **3**—**6**, was accomplished on the basis of their spectral data and chemical correlations.



Scheme 1.

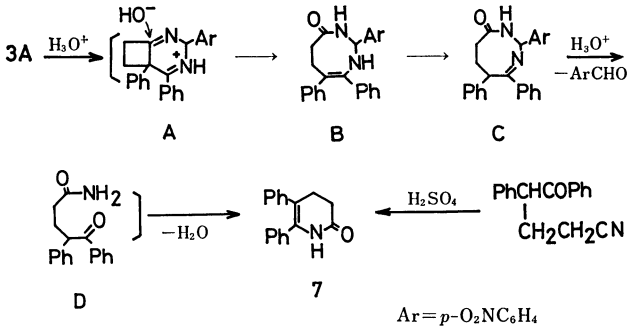
Although ^{1}H- and ^{13}C-NMR spectra of **3** (see Scheme 2 and Experimental Section) do not permit a clear assignment as to which structures, 2′-(*p*-nitrophenyl)-4′,5′-diphenylspiro[cyclopropane-1,6′-[1,3]diazabicyclo-[3.1.0]hex-3′-ene] (**3A**) or 4′-(*p*-nitrophenyl)-2′,5′-diphenylspiro[cyclopropane-1,6′-[1,3]diazabicyclo[3.1.0]-hex-2′-ene] (**3B**), would be more reasonable for **3**, **3** was assigned to be **3A** on the basis of results of chemical conversions which will be described below.



Scheme 2.

The stereochemistry of **3A** is hereinafter described. As illustrated in Scheme 2, the value of chemical shift of benzylic methine proton in **3A** is situated between those of *endo*- and *exo*-benzylic methine protons in other reported 1,3-diazabicyclo[3.1.0]hex-3-enes. On the other hand, the benzylic methine proton of 1,2-diphenyl-1-azaspiro[2.2]pentane[6)] appears at a lower field than that of 1,2-diphenylaziridine,[7)] because of anisotropy effect of cyclopropyl ring of the azaspiropentane. From a consideration of anisotropy effect of cyclopropyl ring in **3A**, it seems most reasonable to conclude that **3A** is the 2-*exo* structure.

Hydrolysis of **3** with 10% hydrochloric acid afforded 3,4-dihydro-5,6-diphenyl-2-pyridone (**7**) and *p*-nitrobenzaldehyde in 26 and 20% yields respectively. The structure of **7** was confirmed by the identification with an authentic sample prepared by a modification of the reported method.[8)] This result strongly supports that **3** is **3A** but not **3B**.[9)] The pathway for the formation of **7** from **3A** is illustrated in Scheme 3. The compound **3A** undergoes hydrolysis with concurrent ring expansions to form **C** through **A** and then **B**. This is followed by further hydrolysis of the cyclic amidine **C** to yield the benzaldehyde and amide **D**, and subsequent cyclization of **D** with dehydration leads to the formation of **7**.

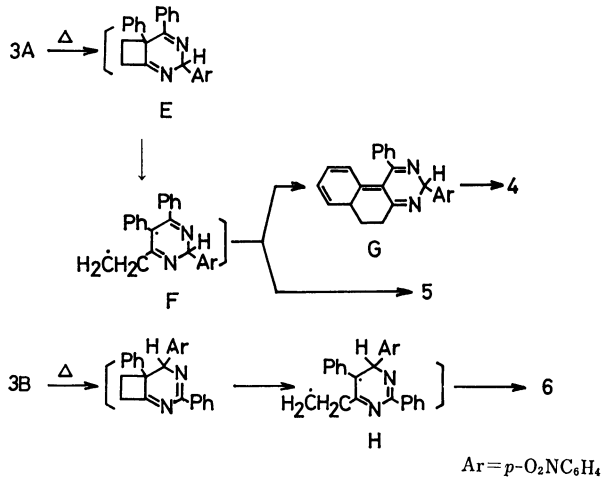


Scheme 3.

Contrary to the formation of pyridazine compound from the bicyclic adduct of **2** to 2,3-diphenyl-1-azirine,[4] thermolysis of **3A** in boiling xylene afforded 5,6-dihydro-3-*p*-nitrophenyl-1-phenylbenzo[*f*]quinazoline (**4**) and 6-ethyl-2-*p*-nitrophenyl-4,5-diphenylpyrimidine (**5**) in 64 and 8% yields respectively. It is thus evident that the products **4** and **5** of the reaction are derived from **3A**.

The product **6** which is an isomer of **5** was deduced to be 6-ethyl-4-*p*-nitrophenyl-2,5-diphenylpyrimidine.

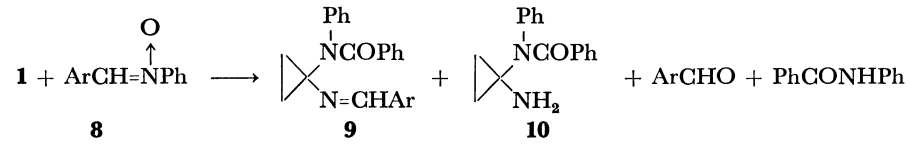
The pathways for the formation of **4**, **5**, and **6** are illustrated in Scheme 4. The initial adduct **3A** is subjected to ring expansion to form **E**. This is followed by homolytic rupture of the cyclobutane ring of **E** to yield biradical **F**, which can lead to **4** through **G** and to **5**. The formation of **6** can be also interpreted as arising from the initial reversed cycloadduct **3B** through biradical **H**. It is thought that **3B** whose structure is a cyclic amidine could not be isolated owing to its lability.



Scheme 4.

Reaction with α,N-Diarylnitrones. Although nitrones undergo 1,3-dipolar cycloaddition to C=N bonds of heterocumulenes such as isocyanates, isothiocyanates, and carbodiimides,[10] no studies on the cycloaddition of nitrones to simple C=N bonds have been reported. As mentioned above, the C=N bond of **1** exhibited high reactivity toward **2**. Thus our attention was directed to the reaction of **1** with α,*N*-diarylnitrones (**8**).

After **1** was allowed to react with 1 equivalent of α,*N*-diphenylnitrone (**8a**) in boiling benzene, the reaction mixture was chromatographed on silica gel to give 1-amino-1-(*N*-phenylbenzamido)cyclopropane (**10**), benzaldehyde, and benzanilide. A similar reaction of **1** with α-(*p*-nitrophenyl)-*N*-phenylnitrone (**8b**) afforded 1 : 1 adduct, 1-(*p*-nitrobenzylideneamino)-1-(*N*-phenylbenzamido)cyclopropane (**9b**), *p*-nitrobenzaldehyde, and benzanilide (Scheme 5). Structural elucidation of **9b** and **10** was accomplished on the basis of spectral data as well as of chemical conversions. Hydrolysis of **9b** gave **10** and *p*-nitrobenzaldehyde, while **10** reacted with the benzaldehyde to give **9b**.



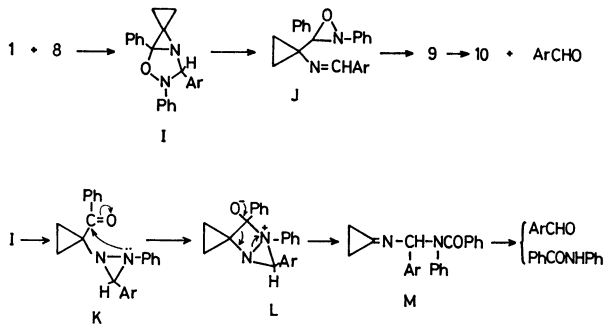
a : Ar=Ph	—	51%	14%	39%
b : Ar=*p*-$O_2NC_6H_4$	16%	—	33%	23%

9b ⇌ **10** + ArCHO

Scheme 5.

The pathways for the formation of products are assumed as depicted in Scheme 6. The nitrone **8** undergoes 1,3-dipolar cycloaddition to **1**, yielding labile cycloadduct **I**. The formation of **9** can be understood as proceeding through the oxaziridine **J** which is arising from **I**, since it is known that *C*,*N*-diaryloxaziridines are readily isomerized into the amides.[11]

As described above, hydrolysis of **9b** afforded **10** and the benzaldehyde, but not benzanilide. This fact suggests that benzanilide obtained from the reaction is derived from hydrolysis of a compound other than **9**. Although mechanistic considerations are still speculative, a possible pathway is also shown in Scheme 6. The rearrangement of **I** to the diaziridine **K**,



Scheme 6.

followed by a nucleophilic attack of the nitrogen atom on the carbonyl carbon atom yields the tricyclic betaine **L**. This is followed by ring cleavage to give **M**, which on hydrolysis gives the benzaldehyde and benzanilide. The process (**K**→**L**→**M**) is similar to that proposed for the formation of *N,N*-dibenzoylaniline from the photooxygenation of 1,2-diphenyl-2-(phenylimino)-1-ethanone.[12,13]

Experimental

All melting points are uncorrected. IR, NMR, and mass spectra were obtained on a JASCO IRA-1 spectrometer, Hitachi R-40, JEOL SX-100 spectrometers, and a Hitachi RMS-4 spectrometer, respectively.

Materials. Azaspiropentene **1**,[2] *N-p*-nitrobenzylbenzimidoyl chloride,[14] and α,*N*-diarylnitrones **8a**,[15] **8b**[16] were prepared by the reported methods respectively.

*Reaction of Azaspiropentene **1** with Benzonitrilium-p-nitrobenzylide (**2**).* To a vigorously stirred solution of **1** (0.44 g, 3 mmol) and *N-p*-nitrobenzylbenzimidoyl chloride (0.85 g, 3 mmol) in benzene (30 ml) was dropwise added a solution of NEt_3 (1.75 g, 17.3 mmol) in benzene (10 ml) at 0 °C over a period of 1 h under nitrogen. The reaction mixture was stirred at room temperature for 24 h, and then filtered to remove formed triethylammonium chloride. The filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (Wako gel C-300) using benzene as the eluent.

The first fraction gave crystals which were recrystallized from benzene to give 53 mg (4%) of 5,6-dihydro-3-*p*-nitrophenyl-1-phenylbenzo[*f*]quinazoline (**4**), mp 225—226 °C, as yellow needles. ^{1}H-NMR ($CDCl_3$) δ 3.09 (s, 4H), 6.8—7.8 (m, 9H), 8.28 8.73 (each d, 2H, *J*=9 Hz). ^{1}H-NMR (C_6D_6) δ 2.4—3.0 (m, 4H), 6.6—7.4 (m, 7H), 7.6—7.8 (m, 2H), 8.08, 8.67 (each d, 2H, *J*=9 Hz). ^{13}C-NMR ($CDCl_3$) δ 28.3 (t), 32.0 (t), 123.5, 125.1, 126.1, 127.9, 128.4, 128.6, 128.9, 129.5, 129.6, 130.5, 138.3, 138.9, 143.3, 149.0, 159.2, 162.1, 169.3. MS *m/e* 379 (M^+, base peak). Found: C, 76.05; H, 4.43; N, 10.92%. Calcd for $C_{24}H_{17}N_3O_2$: C, 75.97; H, 4.52; N, 11.08%.

The second fraction afforded crystals which were recrystallized from hexane to give 108 mg (9%) of 6-ethyl-4-*p*-nitrophenyl-2,5-diphenylpyrimidine (**6**), mp 134—135 °C, as colorless needles. ^{1}H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7 Hz), 2.75 (q, 2H, *J*=7 Hz), 6.9—7.7 (m, 10H), 8.03 (d, 2H, *J*=9 Hz), 8.45—8.80 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ 12.7, 28.9, 122.8, 128.0, 128.5, 128.8, 129.9, 130.8, 135.7, 137.5, 145.0, 147.5, 161.1, 162.8, 171.0. MS *m/e* 381 (M^+), 380 (base peak). Found: C, 75.50; H, 4.85; N, 10.89%. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02%.

The third fraction gave 12.3 mg (1%) of 6-ethyl-2-*p*-nitrophenyl-4,5-diphenylpyrimidine (**5**), mp 194—195 °C, as colorless needles (from EtOH). ^{1}H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.6 Hz), 2.76 (q, 2H, *J*=7.6 Hz), 6.6—7.5 (m, 10H), 8.27, 8.77 (each d, 2H, *J*=9 Hz). ^{13}C-NMR ($CDCl_3$) δ 12.7, 28.9, 123.5, 127.8, 128.5, 128.8, 129.0, 129.8, 130.0, 130.9, 136.2, 138.2, 143.9, 149.1, 160.4, 163.8, 170.8. MS *m/e* 381 (M^+), 380 (base peak). Found: C, 75.42; H, 5.05; N, 11.13%. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02%.

The fourth fraction gave crystals which were recrystallized from ether to give 2′-(*p*-nitrophenyl)-4′,5′-diphenylspiro-[cyclopropane-],6′-[1,3]diazabicyclo[3.1.0]hex-3′-ene] (**3A**), mp 167—169 °C, as colorless prisms. IR (KBr) 1602 (C=N), 1575, 1339 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.8—1.2 (m, 2H), 1.4—2.1 (m, 2H), 5.82 (s, 1H), 7.2—7.5 (m, 8H), 7.5—7.9 (m, 4H), 8.22 (d, 2H, *J*=9 Hz). ^{13}C-NMR ($CDCl_3$) δ 0.6 (t), 9.4 (t), 49.7 (s), 64.6 (s), 92.4 (d), 123.7, 128.0, 128.4, 128.5, 129.0, 131.1, 131.9, 135.1, 147.5, 148.0, 172.3. MS *m/e* 381 (M^+). Found: C, 75.60; H, 4.98; N, 11.08%. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02%.

*Hydrolysis of 1 : 1 Adduct **3A**.* A suspension of **3A** (110 mg) in 10% HCl (10 ml) was stirred at room temperature for 30 h. Filtration gave crystals which were recrystallized from EtOH to give 18.2 mg (26%) of 3,4-dihydro-5,6-diphenyl-2-pyridone (**7**), mp 220—221 °C, as colorless needles. This compound was identical with an authentic sample prepared by the method described below.

The filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel using benzene as the eluent, giving 9 mg (20%) of *p*-nitrobenzaldehyde.

*3,4-Dihydro-5,6-diphenyl-2-pyridone (**7**).* A solution of deoxybenzoin (3.0 g) in THF (50 ml) was treated with NaH (0.8 g, 50% suspension in oil) at 60—70 °C for 1 h, and then a solution of 3-chloropropionitrile (1.4 g) in THF (10 ml) was added to the resultant solution at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and refluxed for 2 h, and then poured into water to give solid (1.9 g). After a solution of the solid (1.9 g) in concd H_2SO_4 (50 ml) was stirred at room temperature for 12 h, the solution was poured into water to give crystals which were recrystallized from EtOH to afford 1.95 g (51%) of **7**, mp 220—221 °C (lit,[8] mp 218—219 °C). Found: C, 81.79; H, 5.83; N, 5.72%. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62%.

*Thermolysis of 1 : 1 Adduct **3A**.* A solution of **3A** (100 mg) in xylene (4 ml) was refluxed for 15 h. The solvent was evaporated *in vacuo* to leave the residue which was chromatographed on silica gel using benzene as the eluent to give 64 mg (64%) of **4** and 8 mg (6%) of **5**.

*Reaction of Azaspiropentene **1** with α,N-Diarylnitrones (**8**).* A solution of **1** (326 mg, 2.28 mmol) and α,*N*-diphenylnitrone (**8a**) (450 mg, 2.28 mmol) in benzene (10 ml) was refluxed for 3 h under nitrogen. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on silica gel using $CHCl_3$ as the eluent. From the first and second fractions, 40 mg (14%) of benzaldehyde and 78 mg (39%) of benzanilide were obtained respectively. The third fraction gave 215 mg (51%) of 1-amino-1-(*N*-phenylbenzamido)cyclopropane (**10**) as colorless oil. IR (neat) 3400, 3320 (NH), 1650 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ 0.5—1.4 (m, 4H), 2.27 (broad, 2H), 6.8—7.5 (m, 10H). MS *m/e* 252 (M^+), 147 (M^+—PhCO, base peak), 105.

A similar reaction of **1** (400 mg, 2.81 mmol) and α-(*p*-nitrophenyl)-*N*-phenylnitrone (**8b**) (680 mg, 2.81 mmol) in benzene (10 ml) for 5 h afforded 140 mg (33%) of *p*-nitrobenzaldehyde, 184 mg (23%) of benzanilide, and 170 mg (16%) of 1-(*p*-nitrobenzylideneamino)-1-(*N*-phenylbenzamido)cyclopropane (**9b**), mp 185—186 °C, as colorless prisms (from EtOH). IR (KBr) 1662 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ 1.20—1.83 (m, 4H), 6.8—7.5 (m, 10H), 7.90, 8.25 (each d, 2H, *J*=9 Hz), 8.51 (s, 1H, N=C**H**). ^{13}C-NMR ($CDCl_3$) δ 21.3, 62.6, 123.7, 126.5, 127.9, 128.6, 128.8, 129.0, 130.1, 135.9, 141.5, 142.9, 151.9, 170.7. MS *m/e* 385 (M^+). Found: C, 71.72; H, 4.93; N, 10.84%. Calcd for $C_{23}H_{19}N_3O_2$: C, 71.67; H, 4.97; N, 10.90%.

The reaction of **10** with 1 equivalent of *p*-nitrobenzaldehyde in boiling EtOH for 3 h afford **9b** in 36% yield.

*Hydrolysis of 1 : 1 Adduct **9b**.* A suspension of **9b** (47 mg) in EtOH (6 ml) was stirred with concd HCl (2 drops) at room temperature. After 1 h the suspension turned to a clear solution. After the solution was concentrated *in vacuo*, water was added to the residue and then the mixture was extracted with ether. The extract was concentrated

to give 7 mg (38%) of *p*-nitrobenzaldehyde. The aqueous layer was made basic with NaOH aq solution, and then extracted with ether. The extract was evaporated *in vacuo* to leave 30 mg (100%) of **10**.

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