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INTRAMOLECULAR ANIONIC CYCLIZATIONS OF o-CINNAMYLOXY- AND o-PHENYLPROPARGYLOXYBENZYLIDENEAMINES

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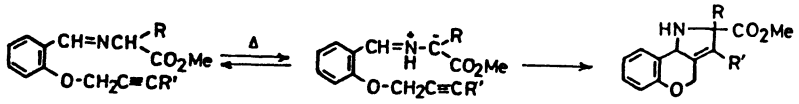
The intramolecular anionic cyclization of o-cinnamyloxybenzylideneamines proceeded via an allyl anion and/or an azaallyl anion to give a mixture of 2,3-dihydrobenzofurans and/or a perhydropyrro[3,2-c]benzopyrane. In a similar reaction o-phenylpropargyloxybenzylideneamines gave 2,3-dihydrobenzofurans and/or a benzoxepine derivative exclusively via a propargyl anion. It was revealed that the relative yields of the products were dependent on the nature of amines in imines.

We have recently reported that imines 1 of glycine esters bearing an alkynyl function undergo an intramolecular cycloaddition via their 1,3-dipolar tautomers, azomethine ylides, to the triple bond.[1)]

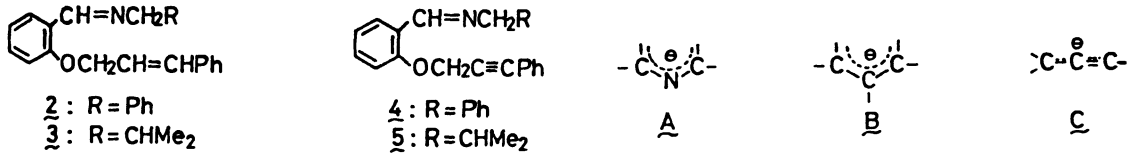


1 (R, R'=H, Ph)

It was, however, disclosed that unactivated imines, which have not an electron-withdrawing group such as methoxycarbonyl one in 1, remain virtually inactive against the intramolecular thermal cycloaddition.

As reviewed,[2)] 1,3-anionic cycloadditions of 2-azaallyl-, allyl-, and propargyllithium compounds are useful tool for the synthesis of five-membered cyclic compounds. It is particularly characteristic that 2-azaallyllithium compounds react with various multiple bonds, yielding five-membered heterocycles. Thus, even without an electron-withdrawing group, intramolecular 1,3-anionic cycloadditions of imines may develop a versatile route to fused heterocycles. However, little attention has so far been paid to the intramolecular cycloadditions.

We have investigated the reaction of unactivated imines, o-cinnamyloxybenzylideneamines 2, 3, and o-phenylpropargyloxybenzylideneamines 4, 5, with butyllithium (BuLi).[3)] This reaction seemed attractive, for imines 2 — 5 can generate not only 2-azaallyl anions A, but also an allyl anion B or a propargyl anion C (Scheme 1).



2: R=Ph
3: R=CHMe$_2$

4: R=Ph
5: R=CHMe$_2$

A B C

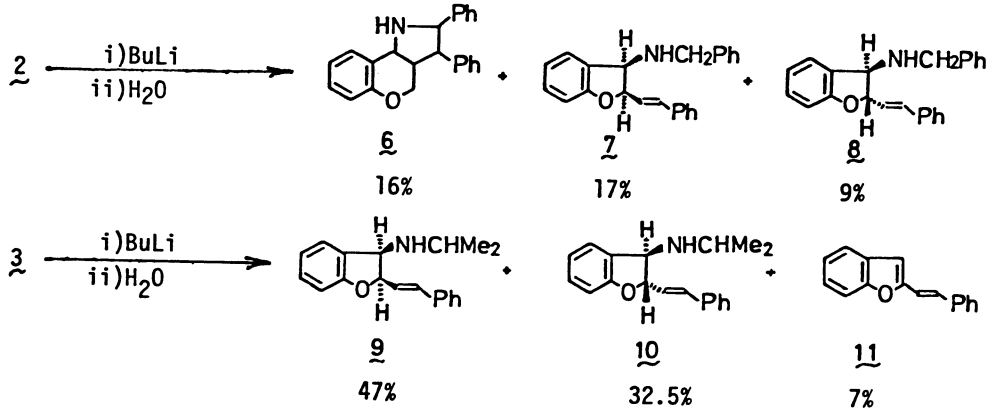
Scheme 1

A general procedure is illustrated as follows. A 15% hexane solution of BuLi (6.6 ml, ca 11 mmol) was diluted with THF (50 ml). The BuLi solution was added, drop by drop, to a solution of imine 2 (3.27 g, 10 mmol) in THF (100 ml) at - 70°C with stirring under nitrogen. The resultant solution was allowed to warm to room temperature during 1 h, and then stirred at the same temperature for 2 h. The reaction mixture was concentrated in vacuo at room temperature, and the residue was treated with water

(200 ml), and extracted with ether. The dried and evaporated extract was chromatographed on silica gel using benzene and chloroform as eluents to give three products 6, 7, and 8, together with intractable materials.

On the basis of spectral evidence,[4] structures 6, 7, and 8 were assigned as 2,3-diphenylperhydropyrro[3,2-c]benzopyrane and cis- and trans-3-benzylamino-2-styryl-2,3-dihydrobenzofuran, respectively. Although the stereochemistry of 6 will be described later, the configurational elucidation of 7 and 8 was based on the values of coupling constants, $J_{2,3}$, in the NMR spectra.[5]

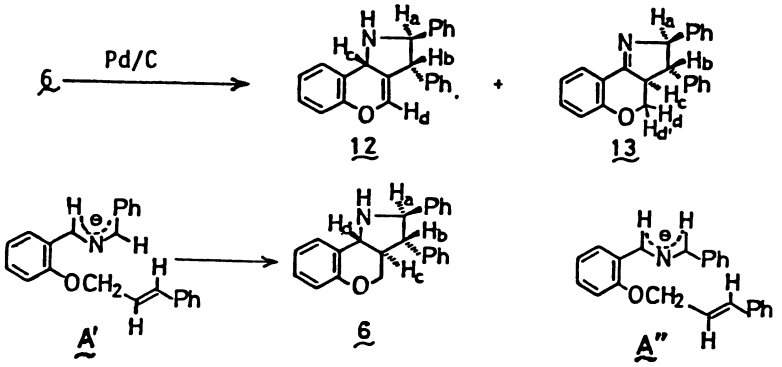
It is evident that 6 is formed via an azaallyl anion, whereas 7 and 8 are led via the allyl anion.



Scheme 2

In a similar reaction of imine 3, there were obtained cis- 9 and trans-2,3-dihydrobenzofuran 10, and 2-styrylbenzofuran 11, which proves that the reaction exclusively proceeds via an allyl anion. Structural elucidation of 9 — 11 was accomplished on the basis of spectral data.[6] The treatment of cis isomer 9 with BuLi in THF produced 11 in 56% yield, whereas trans isomer 10 remained unchanged under similar conditions. It is thus evident that 11 was formed via a deamination of cis isomer 9 under the reactions. It has also been found that in a similar reaction as mentioned above cis isomer 7 gave 11 in 68% yield, whereas trans isomer 8 remained unchanged. This deamination process is rather analogous to that previously reported on the formation of 2-arylbenzofurans in the reaction of o-benzyloxybenzylideneanilines with a base.[7]

The stereochemistry of 6 is hereinafter described. When a solution of 6 in xylene was refluxed with Pd-charcoal (5% Pd) for 3.5 h, two dehydrogenated compounds, 12 and 13, were isolated in 8 and 7% yields respectively, besides unchanged 6 (54%). Structural elucidation of 12 and 13 was based on spectral data.[8] In the NMR spectra, there was observed a long-range coupling of 2.5 Hz between H_b

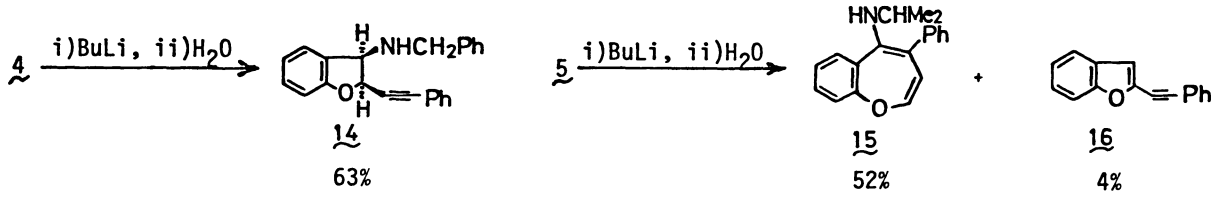


Scheme 3

and H_c in 12 or H_a and H_c in 13, which implies that H_b and H_c in 12 or H_a and H_c in 13 are cis.

Since it is known that 1,3-anionic cycloadditions proceed via a concerted fashion and the configuration in alkene part is retained in cycloadducts,[2] it may be reasonable to assume that H_b and H_c in 13 as well as those in 6 are trans.[9] It is thus possible to conclude that 1,3-anionic cycloadduct 6 has the H_a, H_b-trans, H_b, H_c-trans, and H_c,H_d-trans configurations, and Z,E-azaallyl anion (A'), initially generated from imine 2, undergoes the intramolecular 1,3-anionic cycloaddition before it has been rearranged to more stable E,E-azaallyl anion (A") (Scheme 3).

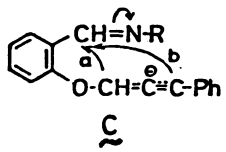
Next, anionic cyclizations of imines 4 and 5 were investigated under similar conditions. Imine 4 afforded cis-3-benzylamino-2-phenylethynyl-2,3-dihydrobenzofuran 14, whereas imine 5 gave 5-isopropylamino-4-phenylbenzo[f]oxepine 15 as the major product, together with a small amount of deaminated 2-phenylethynylbenzofuran 16 (Scheme 4). Structural elucidation of 14 — 16 was accomplished on the basis of spectral properties.[10] The NMR spectrum of 15 exhibited two doublets at δ 6.06 and 6.15 (each J=4.0 Hz), and the electronic spectrum is similar to those reported for benzo[f]oxepine and its



Scheme 4

5-acetoxy-4-phenyl derivative.[11]

It is evident that the reaction proceeds via an exclusive formation of a propargyl anion (C), and the cyclization of C via path a or b gives 2,3-dihydrobenzofuran or benzoxepine derivative, respectively.



C

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REFERENCES AND NOTES

1) O. Tsuge, K. Ueno, and K. Oe, Chem. Lett., 1979, 1407.

2) T. Kauffmann, Angew. Chem., 86, 715 (1974).

3) Imines 2 — 5 (yellow oil) were prepared by the reaction of o-cinnamyloxy- and o-phenylpropargyloxybenzaldehyde with the corresponding amines respectively. 2: IR (neat) 1630 cm^{-1} (C=N); NMR ($CDCl_3$) δ 4.70 (2H, d, J=5.0 Hz), 4.80 (2H, s), 6.10-7.06 (2H, m, =CH), 7.16-7.50, 7.95-8.12 (14H, m), 8.89 (1H, s, CH=N); MS m/e 327 (M^+). 3: IR (neat) 1630 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.24 (6H, d, J=6.0 Hz), 3.54 (1H, q, J=6.0 Hz), 4.67 (2H, m), 6.10-7.15 (2H, m, =CH), 7.20-8.05 (9H, m), 8.77 (1H, s, CH=N). 4: IR (neat) 2240 (C≡C), 1630 cm^{-1} (C=N); NMR ($CDCl_3$) δ 4.80, 4.95 (each 2H, m), 7.0-7.40 (9H, m), 8.86 (1H, s, CH=N); MS m/e 325 (M^+). 5: IR (neat) 2250 (C≡C), 1635 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.25 (6H, d, J=6.0 Hz), 3.58 (1H, q, J=6.0 Hz), 5.00 (2H, s), 6.96-8.10 (9H, m), 8.83 (1H, s, CH=N). All new compounds in this paper gave satisfactory elemental analyses.

4) 6: mp 124-125°C; IR (KBr) 3320 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (1H, broad, NH), 2.60-3.00 (2H, m, ≥CH), 3.80-4.67 (4H, m, CH_2 + ≥CH), 6.75-7.42 (14H, m); MS m/e 327 (M^+). 7: colorless viscous oil; IR (neat) 3300 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (1H, s, NH), 3.82 (2H, s), 4.38 (1H, d, ≥CH, J=7.5 Hz), 5.13 (1H, dd, ≥CH, J=7.5, 7.0 Hz), 6.57-7.50 (16H, m, =CH + ArH); MS m/e 327 (M^+). 8: colorless

viscous oil; IR (neat) 3300 cm^{-1}; NMR ($CDCl_3$) δ 1.73 (1H, broad, NH), 3.96 (2H, s), 4.38 (1H, d, ≥CH, J=4.0 Hz), 5.02 (1H, dd, ≥CH, J=7.0, 4.0 Hz), 6.25 (1H, dd, =CH, J=16.0, 7.0 Hz), 6.50-7.80 (15H, m, =CH + ArH); MS m/e 327 (M^+).

5) An inspection of the Dreiding models indicates that the dihedral angles between 2-H and 3-H in 7 and 8 are 10-15° and 130-135°, respectively. The calculated values of coupling constants, $J_{2,3}$, from the Karplus equation (M. Karplus, J. Am. Chem. Soc., 85, 2870 (1963)) are 8.0-7.6 and 3.4-4.7 Hz when the dihedral angles are 10-15° and 130-135°, respectively. The observed values, $J_{2,3}$, being 7.5 Hz for 7 and 4.0 Hz for 8 are compatible with the above respective calculated values. It has also been reported that the coupling constants, $J_{2,3}$, in cis-disubstituted 2,3-dihydrobenzofurans are larger than those in trans ones.[12]

6) 9: colorless viscous oil; IR (neat) 3300 cm^{-1}; NMR ($CDCl_3$) δ 0.97, 1.07 (each 3H, d, J=6.5 Hz), 1.29 (1H, s, NH), 2.94 (1H, q, J=6.5 Hz), 4.44 (1H, d, ≥CH, J=7.5 Hz), 5.11 (1H, dd, ≥CH, J=7.5, 7.0 Hz), 6.41 (1H, dd, =CH, J=16.0, 7.0 Hz), 6.80 (1H, d, =CH, J=16.0 Hz), 6.70-7.50 (9H, m); MS m/e 281 (M^+). 10: mp 55-56°C; IR (KBr) 3300 cm^{-1}; NMR ($CDCl_3$) δ 1.11 (6H, d, J=6.5 Hz), 1.40 (1H, s, NH), 3.15 (1H, q, J=6.5 Hz), 4.29 (1H, ≥CH, J=4.5 Hz), 5.00 (1H, dd, ≥CH, J=7.0, 4.5 Hz), 6.20 (1H, dd, =CH, J=16.0, 7.0 Hz), 6.75 (1H, d, =CH, J=16.0 Hz), 6.70-7.45 (9H, m); MS m/e 281 (M^+). 11: mp 122-123°C; NMR ($CDCl_3$) δ 6.62-7.60 (m); MS m/e 220 (M^+).

7) W. Sahm, E. Schinzed, and P. Jürges, Liebigs Ann. Chem., 1974, 35. However, they did not isolate intermediary 2,3-dihydrobenzofurans like 7 — 10.

8) 12: mp 175-176°C; IR (KBr) 3200-2000 cm^{-1}; NMR ($CDCl_3$) δ 3.84 (1H, ddd, H_b, J_{ab}=6.0, J_{bc}=2.5, J_{bd}=3.0 Hz), 5.20 (1H, d, H_c, J_{bc}=2.5 Hz), 5.31 (1H, d, H_a, J_{ab}=6.0 Hz), 5.91 (1H, d, H_d, J_{bd}=3.0 Hz), 6.90-7.44 (14H, m, NH + ArH), 7.84 (1H, m); MS m/e 325 (M^+). 13: mp 157-159°C; IR (KBr) 1620 cm^{-1} (C=N); NMR ($CDCl_3$) δ 3.00 (1H, dd, H_b, J_{bc}=J_{bd} (or $J_{bd'}$)=10.0 Hz), 3.60 (1H, dddd, H_c, J_{ac}=2.5, J_{bc}=10.0, J_{cd}, $J_{cd'}$=12.0, 6.0 Hz), 4.03 (1H, dd, H_d or $H_{d'}$, J_{cd} (or $J_{cd'}$)=12.0, $J_{dd'}$=10.4 Hz), 4.57 (1H, dd, $H_{d'}$ or H_d, $J_{cd'}$ (or J_{cd})=6.0, $J_{dd'}$=10.4 Hz), 5.10 (1H, dd, H_a, J_{ab}=10.0, J_{ac}=2.5 Hz), 6.70-7.46 (13H, m), 8.00-8.12 (1H, m); MS m/e 325 (M^+).

9) Although the configuration of the styryl group in 2 or 3 is not clear from the NMR spectral data, all the styryl groups in 7 — 10 have trans configuration.

10) 14: mp 58-60°C; IR (KBr) 2220, 3300 cm^{-1}; NMR ($CDCl_3$) δ 2.06 (1H, s, NH), 3.94 (2H, s), 4.55, 5.55 (each 1H, d, J=8.0 Hz), 6.75-7.50 (14H, m); MS m/e 325 (M^+). 15: mp 72-73°C; IR (CCl_4) 3520 cm^{-1}; ^1H NMR (CD_3CN) δ 1.16 (6H, d, J=7.0 Hz), 4.40 (1H, q, J=7.0 Hz), 6.06, 6.15 (each 1H, =CH, J=4.0 Hz), 6.60 (1H, s, NH), 6.86-7.60 (9H, m); ^{13}C NMR ($CDCl_3$) δ 23.2 (q), 49.4 (d), 109.8, 111.4, 115.2, 119.8, 126.9, 127.6, 128.4, 130.3, 132.7, 134.7, 137.3, 154.9; UV λ_{max} (EtOH) 287 nm (ε 3660); MS m/e 277 (M^+). 16: mp 88-90°C; NMR ($CDCl_3$) δ 6.7-7.8 (m); MS m/e 218 (M^+).

11) H. Hofmann and H.-J. Haberstroh, Liebigs Ann. Chem., 1973, 2032.

12) D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, J. Org. Chem., 31, 2192 (1966).

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