INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS OF BENZYLIDENE-α-CYANO-BENZYLAMINES BEARING NON-ACTIVATED ALKYNYL AND ALKENYL FUNCTIONS

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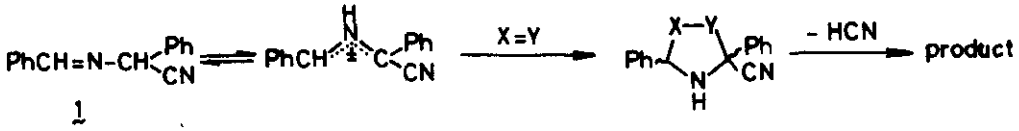
Abstract —— Benzylidene-α-cyanobenzylamine systems undergo an intramolecular cycloaddition via their 1,3-dipolar tautomers, azomethine ylides, to non-activated alkynyl and alkenyl functions, and give mainly dehydrocyanated fused heterocycles.

Recently, we have reported[1] that in a similar manner as imines of glycine esters[2] benzylidene-α-cyanobenzylamine 1 undergoes 1,3-dipolar cycloaddition via its 1,3-dipolar tautomer, an azomethine ylide, to an activated alkyne and alkene. In most cases, however, the products derived from initially formed [3 + 2] cycloadducts with the elimination of hydrogen cyanide were obtained. Thus, the imine 1 not only reacts as an azomethine ylide but also can be formally regarded as a synthetic equivalent of nitrile ylide.



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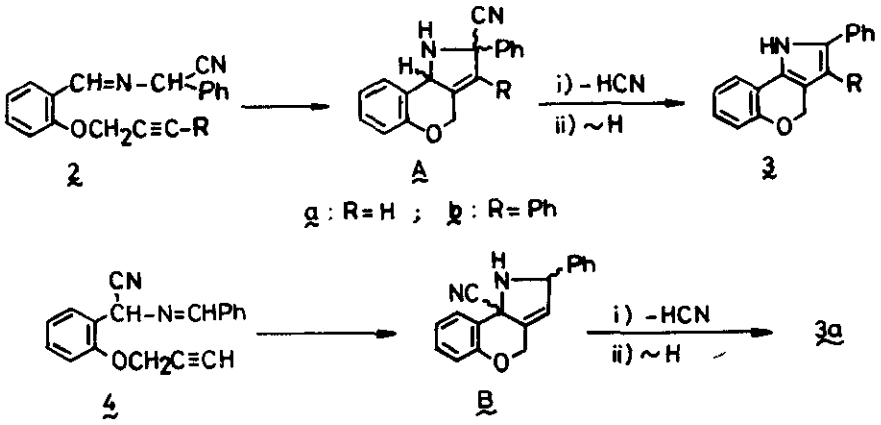
X=Y: activated alkyne or alkene

Although the intermolecular cycloaddition of the imine 1 did not occur to non-activated alkenes, it is known that 1,3-dipolar substrates containing a non-activated dipolarophile undergo intramolecular cycloadditions leading to fused or bridged ring heterocycles[3,4]. To extend the versatility of a benzylidene-α-cyanobenzylamine system as a 1,3-dipole, we planned to investigate intramolecular cycloadditions of the system to non-activated alkynyl and alkenyl functions.

A solution of o-propargyloxybenzylidene-α-cyanobenzylamines, 2a and 2b[5], in xylene was refluxed for 5 h, and then the reaction mixture was purified by chromatography

(SiO_2, $CHCl_3$) to give the corresponding 1,4-dihydro[1]benzopyrano[4,3-b]pyrroles, 3a and 3b, in 65 and 61% yields, respectively[6]. Similarly, an isomeric imine of 2a, benzylidene-o-propargyloxy-α-cyanobenzylamine 4, afforded 3a in 55% yield (Scheme 1). Structural elucidation of the products, 3a and 3b, was accomplished on the basis of spectral data[7].

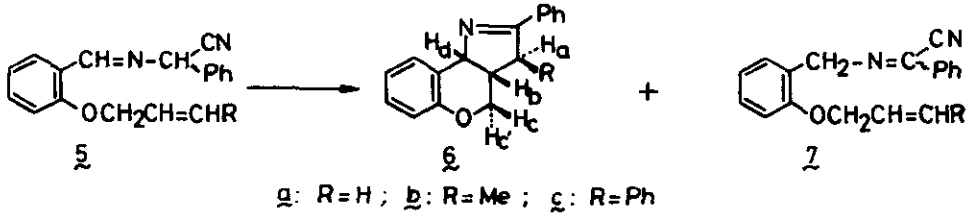


Scheme 1

It is evident that 3a and 3b are derived from initially formed cycloadducts such as A or B with the elimination of hydrogen cyanide, followed by a hydrogen shift. The reaction mode is closely similar to that of the intermolecular cycloaddition of the imine 1 to dimethyl acetylenedicarboxylate[1].

Next, intramolecular cycloadditions of the systems to alkenyl functions were investigated under similar conditions. However, the reactivity toward alkenyl groups was found to be lower than that toward alkynyl ones.

When o-allyloxybenzylidene-α-cyanobenzylamine 5a was heated in xylene under reflux for 3h, three products, 6a and isomeric imines, 7a and 7a'[8], were obtained in 26, 12 and 4% yields, respectively. On the basis of spectral data[9], the main product 6a was identified as 2-phenyl-3,3a,4,9b-tetrahydro[1]benzopyrano[4,3-b]pyrrole



Scheme 2

whose structure corresponded to the dehydrocyanated compound of an initial cycloadduct. The cis-fused ring system of 6a was based on the value of coupling constant (J=7.0 Hz) of the ring junction protons[10] (Table I).

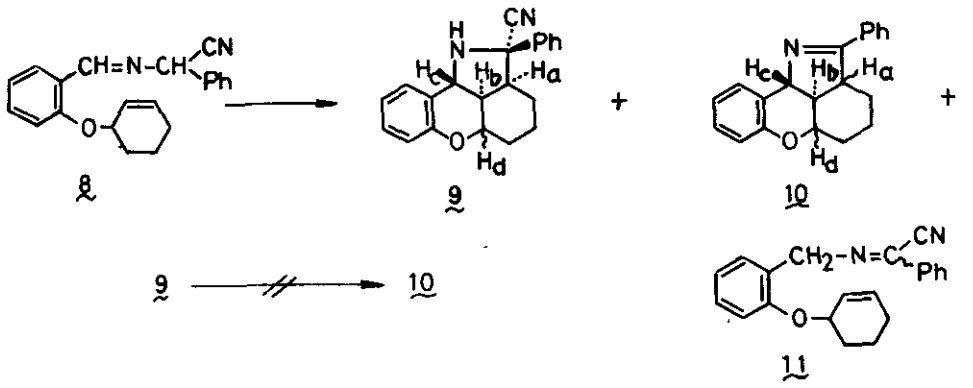
Under similar conditions, o-crotyloxybenzylidene- 5b and o-cinnamyloxybenzylidene-α-cyanobenzylamine 5c afforded the corresponding tetrahydrobenzopyranopyrroles, 6b and 6c[11], in 28 and 44% yields respectively, accompanied by an isomeric imine 7b (15%)[12] in the case of 5b. The stereochemistry of 6b and 6c (both Ha, Hb-trans and Hb, Hd-cis configurations) was again deduced on the ground of ^{1}H NMR spectral data (Table I).

Table I. ^{1}H NMR Spectral Data of Tetrahydro[1]benzopyrano[4,3-b]pyrroles 6 (in $CDCl_3$)

	Chemical shift, δ						
	H_a	R	H_b	H_c	$H_{c'}$	H_d	ArH
6a	2.88 (ddd)	R=H 3.28 (ddd)	2.99 (m)	3.51 (dd)	4.14 (dd)	5.14 (broad d)	6.86-7.88 (m)
6b	3.11 (qdd)	R=CH_3 1.28 (d)	2.55 (dddd)	3.40 (dd)	4.12 (dd)	5.08 (broad d)	6.77-7.80 (m)
6c	4.25 (dd)	R=Ph	2.88 (dddd)	3.64 (dd)	4.30 (dd)	5.28 (dd)	6.80-7.80 (m)

	Coupling constant, Hz								
	J_{aR}	J_{ab}	J_{Rb}	J_{bc}	$J_{bc'}$	J_{bd}	J_{ad}	J_{Rd}	$J_{cc'}$
6a	17.0	2.9	8.1	10.8	4.9	7.0	1.1	2.7	10.8
6b	6.0	2.0	—	10.5	5.0	7.0	1.3	—	10.0
6c	—	3.0	—	11.0	5.0	7.0	1.5	—	11.0

On heating in xylene under reflux for 4.5 h, o-(3-cyclohexenyloxy)benzylidene-α-cyanobenzylamine 8 afforded an initial cycloadduct 9 and a dehydrocyanated cycloadduct 10 in 25 and 6% yields respectively, accompanied by an isomeric imine 11 (19%)[13] (Scheme 3). The stereochemistry of 9 and 10 could not be fully solved because of their complex NMR patterns. On the basis of the following evidences, however, it can be concluded that the main product 9 is 1H-2-cyano-2-phenyl-2,2a,-2b,3,4,5,5a,10b-octahydro[1]benzopyrano[4,3,2-bc]isoindole which has Ha, Hb-cis, Hb, Hc-trans, and Ha, CN-cis configurations, and the minor one 10 is 2aH-2-phenyl-2b,3,4,5a,10b-hexahydro[1]benzopyrano[4,3,2-bc]isoindole in which Hb and Hc are



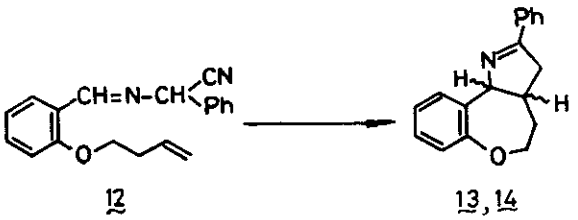
Scheme 3

trans.

Both the coupling constants between Hb and Hc in 9 and 10 are 12.0 Hz, indicating that Hb and Hc are trans. It is also reasonable to deduce that Ha and Hb originated from the cyclohexenyl moiety of 8 in 9 are cis, because it is known that cycloadditions of the imine 1[1], as well as inter-[2] and intramolecular cycloadditions[14] of imines of glycine esters, proceed via a concerted and stereospecific manner. In a previous paper[1], we have postulated that dehydrocyanation of initial cycloadducts of 1 to alkenes does not occur between neighboring NH and cyano groups but instead takes place between neighboring methylene- or methine-hydrogen and cyano group via an anti-elimination process. The cycloadduct 9 was unchanged even on heating in xylene under reflux for a long time; this implies that Ha and cyano group in 9 are cis.

The formations of 6 from 5, and of 9 and 10 from 8 can be reasonably interpreted by considering preferable geometry for transition states leading to initial cycloadducts[15].

When o-(1-butenyloxy)benzylidene-α-cyanobenzylamine 12 was heated in o-dichlorobenzene under reflux for 4.5 h, two stereoisomeric dehydrocyanated cycloadducts, 13 (mp 160-161 °C) and 14 (mp 99-101 °C), were isolated in 10 and 7% yields, re-



Scheme 4

spectively (Scheme 4). However, the stereochemistry is not clear and under investigation. The forced conditions and low yields in this reactions are presumably due to an entropically unfavored closure of a seven-membered ring.

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2. R. Grigg and J. Kemp, J. Chem. Soc., Chem. Commun., 1977, 125; ibid., 1978, 109; M. Joucla and J. Hamelin, Tetrahedron Lett., 1978, 2885; R. Grigg and J. Kemp, ibid., 1980, 2461.
3. A. Padwa, Angew. Chem., 1976, 88, 131.
4. W. Oppolzer, ibid., 1977, 89, 10.
5. The imines, 2, 5, 8 and 12 were prepared by the reaction of the corresponding o-substituted benzaldehyde with 2-phenylglycinonitrile, and the imine 4 was obtained from the reaction of o-propargyloxy-α-cyanobenzylamine with benzaldehyde; the yields were almost quantitative, and the structures were confirmed by the analytical and spectral data.
6. All new compounds gave satisfactory elemental analyses. In all thermal cycloaddition reactions, the corresponding benzaldehyde arising from hydrolysis of the starting imine was isolated on purification by chromatography. Thus the yields of products were based on the consumed starting imine.
7. 3a: colorless prisms; mp 134-136 °C; IR (KBr) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.37 (2H, s, CH_2), 6.33 (1H, d, =CH, J=3.0 Hz, changed into a singlet when treated with D_2O), 6.85-7.80 (9H, m, ArH), 8.50 (1H, broad, NH, exchanged with D_2O); MS m/e 247 (M^+).

   3b: colorless prisms; mp 126-128 °C; IR (KBr) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.31 (2H, s, CH_2), 6.75-7.40 (14H, m, ArH), 8.30 (1H, m, NH); MS m/e 323 (M^+).
8. The stereochemistry of 7a (11%) and 7a' (4%) was uncertain. 7a: pale yellow prisms; mp 48-49 °C; IR (KBr) 2420, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.56 (2H, m, CH_2), 5.17 (2H, s, CH_2), 5.20-5.50 (2H, m, $=CH_2$), 5.84-6.26 (1H, m, =CH), 6.80-8.10 (9H, m, ArH); MS m/e 276 (M^+). 7a': oil; IR (neat) 2410, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52 (2H, m, CH_2), 5.15 (2H, s, CH_2), 5.20-5.50 (2H, m, $=CH_2$), 5.82-6.23 (1H, m, =CH), 6.78-8.10 (9H, m, ArH); MS m/e 276 (M^+).
9. 6a: pale yellow prisms; mp 118-119 °C; IR (KBr) 1610 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 35.31 (d, 3a-C), 38.56 (t, 3-C), 66.52 (t, 4-C), 69.16 (d, 9b-C), 117.00,

121.46 (each d), 123.46 (s), 127.66, 128.04, 128.37, 130.66, 131.19 (each d), 134.17 (s), 155.54 (s, 5a-C), 171.27 (s, 2-C); MS m/e 249 (M^+).

10. W. Oppolzer, Tetrahedron Lett., 1970, 3091.

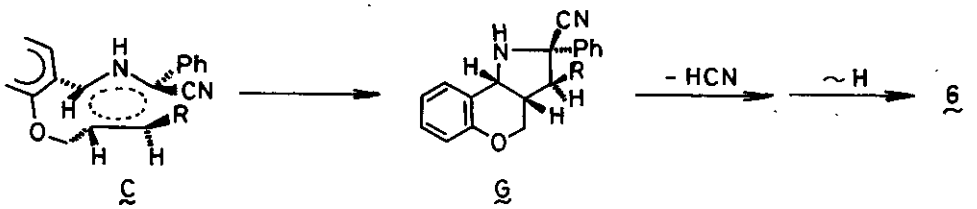
11. 6b: yellow viscous oil; MS m/e 263 (M^+). 6c: colorless prisms; mp 120-122 °C; MS m/e 325 (M^+).

12. 7b: yellow viscous oil; IR (neat) 2210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (3H, d, CH_3, J=4.0 Hz), 4.55 (2H, m, CH_2), 5.15 (2H, s, CH_2), 5.70 (2H, m, =CH), 6.80-8.05 (9H, m, ArH); MS m/e 290 (M^+).

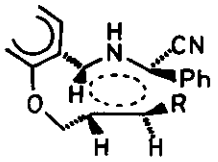
13. 9: colorless prisms; mp 160-162 °C; IR (KBr) 3330, 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-2.60 (8H, m, $3CH_2$ + Ha, Hb), 2.90 (1H, broad, NH, exchanged with D_2O), 4.32-4.55 (1H, m, Hd), 4.50 (1H, d, Hc, J=12.0 Hz), 6.77-7.65 (9H, m, ArH); MS m/e 319 (M^+). 10: colorless needles; mp 134-135 °C; ^1H NMR ($CDCl_3$) δ 0.82-2.40 (7H, m, $3CH_2$ + CH), 3.48, 4.68 (each 1H, m, CH), 4.86 (1H, d, Hc, J=12.0 Hz), 6.79-7.97 (9H, m, ArH); MS m/e 289 (M^+). 11: yellow oil; IR (neat) 2250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26-2.23 (6H, m, CH_2), 4.83 (1H, m, CH), 5.14 (2H, s, CH_2), 5.85 (2H, m, =CH), 6.80-8.05 (9H, m, ArH); MS m/e 316 (M^+).

14. O. Tsuge, K. Ueno, and K. Oe, Chem. Lett., 1979, 1407; R. Grigg, M. Jordan, and J. F. Malone, Tetrahedron Lett., 1979, 3877; O. Tsuge, K. Ueno, and I. Ueda, Heterocycles, 1981, 16, 1503.

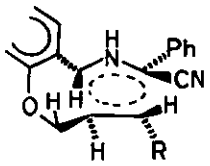
15. Among the transition states, C-F, leading to cycloadducts from 5, C and D have more preferable geometry than E and F in which there are a significant steric interaction between the azomethine hydrogen and methylene. Although D has a favored geometry in the 1,3-dipole moiety, there is a steric interaction between the phenyl group in the 1,3-dipole and the substituent (R). Thus, the most favorable one C yields G, which gives stable 6 via an anti-elimination of hydrogen cyanide, followed by a hydrogen shift. Similarly, among four transition states leading to cycloadducts from 8, the most favored state H gives the stable 9 in which the cyano group and hydrogen atom are cis, and the dehydrocyanated product 9 is formed from less favored one I.



C G



D



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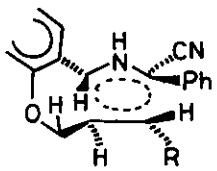

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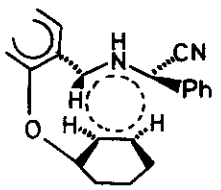
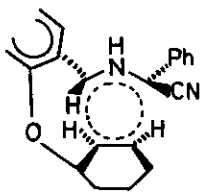


H → 9 ;



I → -HCN → ~H → 10

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