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CYCLOADDITIONS OF N-BENZYLIDENEAMINOACETONITRILE AS A SYNTHETIC EQUIVALENT OF METHANENITRILE BENZYLIDE

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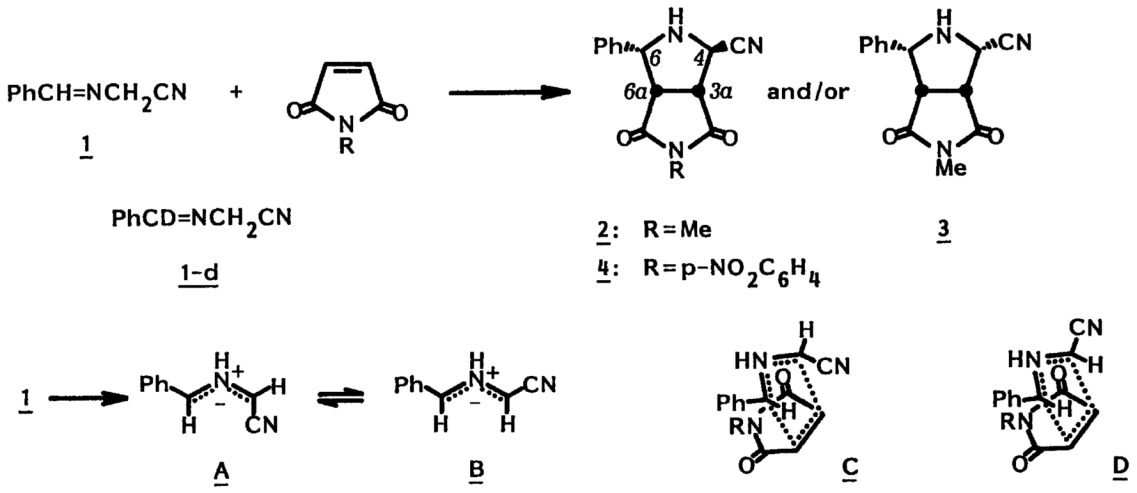
N-Benzylideneaminoacetonitrile is a synthetic equivalent of methanenitrile benzylide via a cycloaddition and elimination sequence. Its reactions with olefinic dipolarophiles provide stereochemically defined 1- or 2-pyrrolines.

Efficiency of an N-protonated azomethine ylide with a leaving group in heterocyclic synthesis has been recently reported.[1] Although an N-protonated azomethine ylide is a tautomeric isomer of imine, such tautomerism is in general energetically disfavored. Only when an α-hydrogen in the N-alkyl substituent of imine is highly acidic, the N-protonated azomethine ylide structure becomes important. α-Imino esters are the only investigated example.[2]

As iminoacetonitriles bear an equally acidic α-hydrogen, they would serve as N-protonated azomethine ylides of cyano-stabilized type. Through their cycloadditions and the subsequent elimination of hydrogen cyanide,[3] these imines could be synthetic equivalents of methanenitrile methylides which are otherwise hardly accessible.[4]

The present communication describes the stereoselective cycloadditions of N-

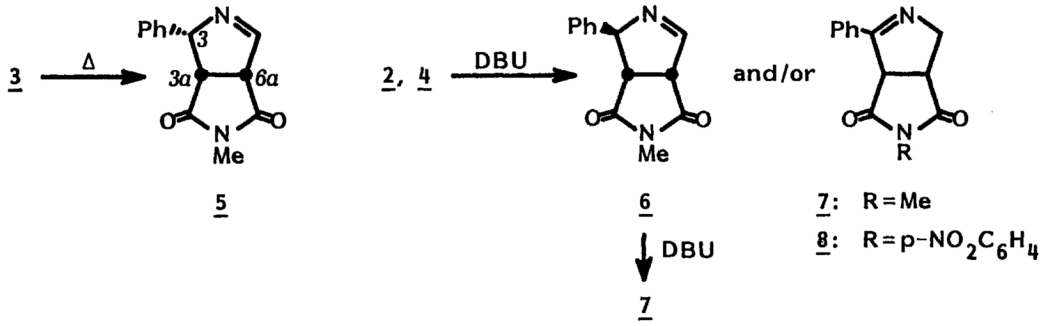


Scheme 1.

benzylideneaminoacetonitrile 1 to olefinic dipolarophiles leading to stereochemically defined 1- or 2-pyrrolines after the elimination of hydrogen cyanide.

Heating an equimolar mixture of 1 and N-methylmaleimide under reflux in toluene gave a quantitative yield of cycloadduct 2 as a single isomer (Scheme 1 and Table 1). On the other hand, the same reaction under reflux in a rather polar solvent (MeCN) or in the presence of a catalytic amount of acetic acid at room temperature produced another cycloadduct 3 along with 2 as listed in Table 1. The stereostructures of 2 and 3 were determined as 3a,4-trans-6,6a-cis and 3a,4-cis-6,6a-cis cycloadducts, respectively, on the basis of the ^{1}H-NMR spectra in which the signal assignment was based on the corresponding cycloadducts obtained from the reaction of a monodeuterio derivative 1-d of the imine 1.[5)]

The selective formation of 2 has resulted from the exclusive participation of the anti ylide A in an endo fashion C, while the endo approach D of the syn ylide B has coincided under a polar environment forming the stereoisomeric cycloadduct 3. A similar reaction, however, with N-(p-nitrophenyl)maleimide gave the stereoselective cycloadduct 4 regardless of the reaction conditions.



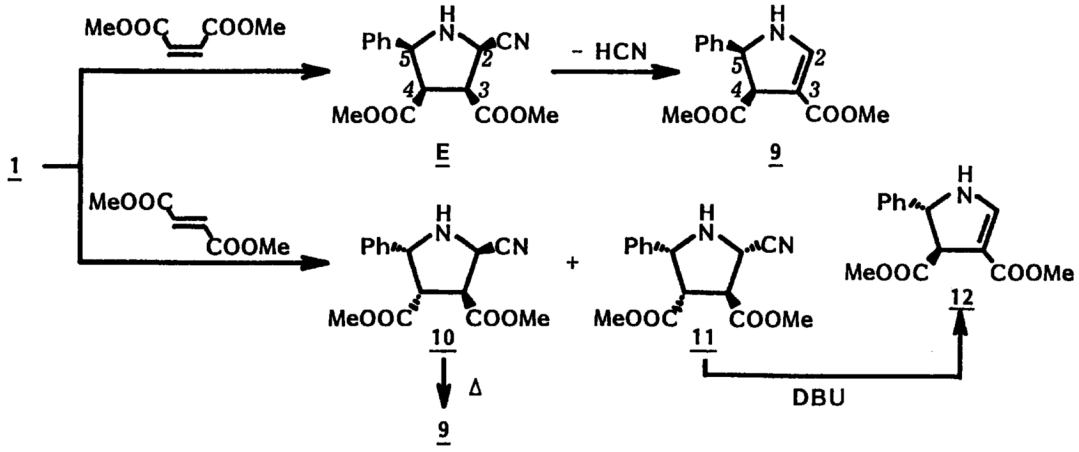
Scheme 2.

Table 1. Cycloadditions of 1 to Olefinic Dipolarophiles

Olefin[a)]	Reaction conditions[b)]				Product	Yield/%[c)]	Isomer ratio[d)]
	Solvent	Catalyst	Temp	Time/h			
MMI	toluene	-	reflux	6.5	2	100	
	MeCN	-	reflux	62	2+3	100	2:3 = 3:1
	MeCN	5 mol%	rt	24	2+3	100	2:3 = 1:1
NPMI	toluene	-	reflux	16	4	100	
	MeCN	10 mol%	rt	30	4	100	
DMM	toluene	-	reflux	27	9	66	
DMF	toluene	-	reflux	24	10+11	86	10:11 = 1:1.9
	MeCN	5 mol%	rt	38	10+11	72	10:11 = 2.2:1
MA	neat	-	reflux	12	13-16	100	13+14:15+16 = 3:2

a) MMI: N-methylmaleimide; NPMI: N-(p-nitrophenyl)maleimide; DMM: dimethyl maleate; DMF: dimethyl fumarate; MA: methyl acrylate. b) Acetic acid was used as a catalyst. c) Isolated yields. d) Determined by ^{1}H-NMR spectroscopy.

On heating 3 in xylene, the elimination of hydrogen cyanide occurred with the retention of stereochemistry giving a fused 1-pyrroline 5, whereas 2 was recovered unchanged under the same conditions (Scheme 2 and Table 2). In the presence of a catalytic amount of DBU, 2 underwent the elimination affording the stereochemically inverted 1-pyrroline 6 and the double bond-migrated isomer 7, the former being converted into the latter in a quantitative yield by the prolonged heating in the presence of DBU.



Scheme 3.

The reaction of 1 with dimethyl maleate produced a single isomer of 2-pyrroline 9 which was presumably derived via the stereoselective cycloadduct E (Scheme 3). On the other hand, the reaction with dimethyl fumarate gave a mixture of two isomeric cycloadducts 10 and 11, the isomer ratio depending upon the reaction conditions (Table 1). Only 10 succeeded in the thermal elimination into 9 with the retention of stereochemistry. The DBU-catalyzed elimination of 11 led to only the inverted 2-pyrroline 12 as a stereoisomer of 9.

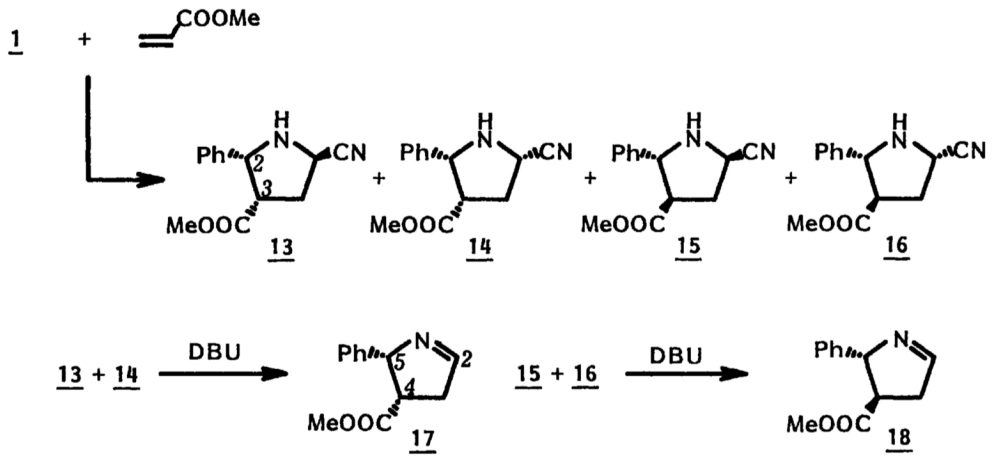
Although all the above cycloadditions showed high stereoselectivity between the phenyl and one of the two electron-withdrawing substituents, all of four possible stereoisomers 13-16 of the regioselective cycloadduct were obtained in the re-

Table 2. Elimination of Hydrogen Cyanide from the Cycloadducts

Cycloadduct	Reaction conditions[a]				Product (yield/%)[b]			
	Solvent	Catalyst	Temp	Time/h				
3	xylene	-	reflux	19	5 (60)			3 (40)
2	xylene	DBU	reflux	7		6 (19)	7 (68)	
4	xylene	DBU	reflux	7			8 (83)	
10	xylene	-	reflux	9	9 (42)			10 (58)
11	toluene	DBU	reflux	12.5		12 (100)		
13+14	toluene	DBU	reflux	17	17 (82)			
15+16	toluene	DBU	reflux	18	18 (81)			

a) Catalytic amount of DBU was used. b) Isolated yields.

action of 1 with methyl acrylate (Scheme 4). The separated mixtures of stereoisomers, the 2,3-cis 13+14 and 2,3-trans isomers 15+16, were effectively converted in a stereospecific manner into the cis 17 and trans 1-pyrroline 18, respectively, by heating with DBU (Table 2). Both the pyrrolines 17 and 18 could be further dehydrogenated with DDQ into the same compound, methyl 2-phenylpyrrole-3-carboxylate.



Scheme 4.

References

1) O. Tsuge, S. Kanemasa, T. Yamada, and K. Matsuda, Heterocycles, 23, in press; O. Tsuge, S. Kanemasa, and K. Matsuda, Chem. Lett., 1985, 1411.

2) R. Grigg and J. Kemp, J. Chem. Soc., Chem. Commun., 1977, 125 and 1978, 109; O. Tsuge, K. Ueno, and K. Oe, Chem. Lett., 1979, 1407; R. Grigg, Bull. Soc. Chim. Belg., 93, 593 (1984) and references cited therein.

3) O. Tsuge and K. Ueno, Heterocycles, 19, 1411 (1982) and 20, 2133 (1983).

4) Although 2-unsubstituted 1-azirines are known, their photolysis aiming at the generation of methanenitrile methylides has not been reported so far.

4) All new compounds reported herein were fully characterized on the basis of spectral data as well as elemental analyses. Two examples are as follows:

2: colorless prisms (benzene-hexane); mp 152-153 °C; IR (KBr) 3300, 2220, and 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.40 (1H, br. s, NH), 2.85 (3H, s, NMe), 3.45 (1H, t, $J_{6a-3a}=J_{6a-6}=8.0$ Hz, 6a-H), 3.54 (1H, d, $J_{3a-6a}=8.0$ Hz, 3a-H), 4.66 (1H, s, 4-H), 4.78 (1H, d, $J_{6-6a}=8.0$ Hz, 6-H), and 7.18-7.38 ppm (5H, m, ArH); ^{13}C-NMR ($CDCl_3$) δ=25.14 (q, NMe), 47.66, 49.51, 49.85, 63.26 (each d), 118.66 (s, CN), 126.99, 128.45, 128.55, 136.00, 174.01 (s, CON), and 175.24 ppm (s, CON).

3: colorless prisms (acetone-hexane); mp 199-200 °C; IR (KBr) 3300, 2250, and 1690 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ=2.50 (1H, br. s, NH), 2.72 (3H, s, NMe), 3.42 (1H, t, $J_{6a-3a}=J_{6a-6}=7.5$ Hz, 6a-H), 3.56 (1H, t, $J_{3a-4}=J_{3a-6a}=7.5$ Hz, 3a-H), 4.22 (1H, d, $J_{4-3a}=7.5$ Hz, 4-H), 4.32 (1H, d, $J_{6-6a}=7.5$ Hz, 6-H), and 7.16-7.32 ppm (5H, m, ArH); ^{13}C-NMR (DMSO-d_6) δ=24.46 (q, NMe), 46.59, 47.85, 48.58, 62.19 (each d), 117.44 (s, CN), 127.09, 127.62, 137.62, 174.40 (s, CON), and 174.99 ppm (s, CON).

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