CHEMISTRY LETTERS, pp. 519-522, 1983. © The Chemical Society of Japan 1983

DOUBLE CYCLOADDITION REACTION OF PYRIDINIUM N-METHYLIDES TO METHYLENECYCLOPROPENES LEADING TO CAGE COMPOUNDS

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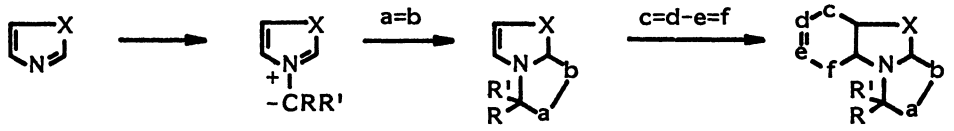
A new functionalization of pyridine has been demonstrated by the double cycloaddition reactions between pyridinium N-methylides and methylenecyclopropenes with unsaturated substituents at the 4-position forming a new type of cage compounds.

In recent years, a variety of heterocyclic compounds have been used as a synthetic tool for the construction of carbon flamework. A wide range of employment of heterocyclic compounds in organic synthesis would be depending upon how the heterocycles are suitably functionalized.

The double cycloaddition reactions between thiazolium N-methylides and methylenecyclopropenes with unsaturated substituents at the 4- position[1,2] provide us an idea that not only a thiazole ring but also other aromatic heterocycles containing nitrogen atom can be doubly functionalized through a sequence of reactions shown in Scheme 1: i) the conversion of the heterocycles into the corresponding azomethine ylide 1,3-dipoles (the first functionalization), ii) the 1,3-dipolar cycloaddition reactions leading to the collapse of aromatic character of the starting heterocycles (the second functionalization), and iii) the second cycloaddition reactions across the unsaturated system released on the heterocyclic rings.



X: hetero atom
or
-CH=CH-

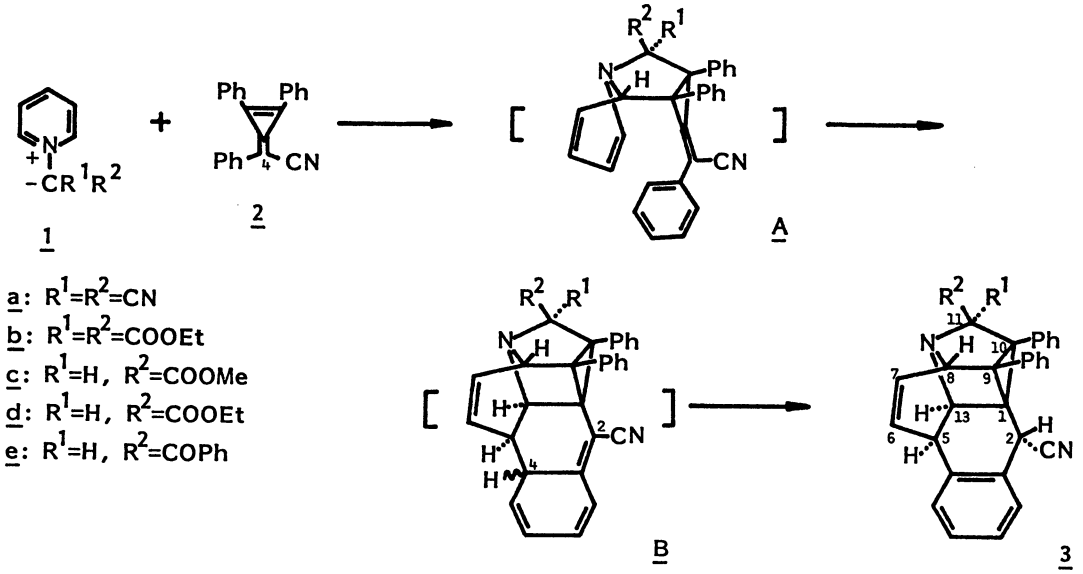
Scheme 1

In the present work, pyridine has been employed as a heterocycle which is to be doubly functionalized in the reactions with methylenecyclopropenes having unsaturated substituents at the 4-position. A few reactions of pyridinium[3] and quinolinium N-methylides[4] with methylenecyclopropenes are known; however, no successful examples of cycloaddition reaction have been reported so far.

Although no reaction took place under reflux in benzene, pyridinium N-dicyanomethylide 1a, an isolable pyridinium N-ylide, reacted with 2-phenyl-2-(2,3-diphenyl-2-cyclopropenylidene)acetonitrile

2 giving a colorless 1:1 adduct 3a as a sole product in 80 % yield when refluxed in xylene for 67 h.

Both the ^{1}H- and ^{13}C-NMR spectra as well as the other spectral data summerized in Table 1 and 2 indicate that 3a has a pentacyclic cage structure which includes a cyclopropane moiety (33.64s, 46.15s, and 47.14s ppm) and four methine hydrogens (4.67s, 4.30m, 4.28d, and 4.52dd ppm and 27.88d, 39.92d, 64.64d, and 67.52d ppm for the 2-, 5-, 8-, and 13-CH, respectively). The stereochemistry at the 2-position was determined on the basis of the chemical shift of 2-H and of the confirmed stereochemistry at the 2-position of the similar cage compounds obtained from the reaction between thiazolium N-dicyanomethylide and 2.[5]



1

a: $R^1=R^2=CN$
b: $R^1=R^2=COOEt$
c: $R^1=H$, $R^2=COOMe$
d: $R^1=H$, $R^2=COOEt$
e: $R^1=H$, $R^2=COPh$

A

B

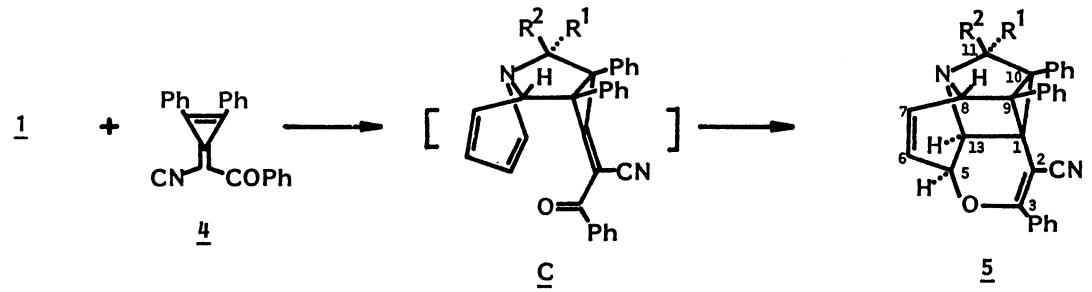
3

a: $R^1=R^2=CN$
b: $R^1=R^2=COOEt$
c: $R^1=H$, $R^2=COOMe$
d: $R^1=H$, $R^2=COOEt$
e: $R^1=H$, $R^2=COPh$

Scheme 2

Similarly, pyridinium N-bis(ethoxycarbonyl)- 1b, N-methoxycarbonyl- 1c, N-ethoxycarbonyl- 1d, and N-benzoylmethylide 1e reacted with 2 under the reaction conditions shown in Table 1 yielding the corresponding cage compounds 3b, 3c, 3d, and 3e, respectively, whose spectral data were consistent with the cage structures (Table 1 and 2). The stereochemistry of the 11-position for the products 3c, 3d, and 3e, which were obtained as the single products from the pyridinium N-methylides with an electron-withdrawing substituent at the ylide carbon, were tentatively assigned as shown in Scheme 2 on the ground of the possible similarity of the stereochemical reaction course to that observed in the case of thiazolium N-phenacylide.[6]

The formation of the cage compounds 3 is well understood by the following reaction paths: the stereoselective 1,3-dipolar cycloaddition reaction between 1 and 2 giving the endo [3 + 2] cycloadducts A, the intramolecular Diels-Alder reaction across one of the double bonds of the resulting dihydropyridine ring leading to B, and the hydrogen migration from the 4-position to the 2-position yielding the isolated cage compounds 3.



Scheme 3

Although the elimination of pyridine is the only route observed in the reaction of pyridinium N-phenacylide with 3-(2,3-diphenyl-2-cyclopropenylidene)pentane-2,4-dione,[3] it is still possible that methylenecyclopropenes with at least one carbonyl substituent at the 4-position would act as both a dipolarophile and a dienophile in the reaction with pyridinium N-methylides. Actually they yielded the cage compounds in the reaction with thiazolium N-methylides.[2]

The reaction of 1a with 2-benzoyl-2-(2,3-diphenyl-2-cyclopropenylidene)acetonitrile 4, under reflux in xylene for 72 h, afforded a poor yield of the cage compound 5a together with complex mixture of many unidentified products. Similarly the cage compounds 5b and 5c were obtained in fair yields in the reactions of 1b and 1e with 4, respectively, whereas in the latter case the pyridine-eliminated side product was isolated in 50 % yield. The reaction conditions are given in Table 1 and the spectral data which are consistent with the structures of 5 are listed in Table 1 and 2.

The formation of cage compounds 5 is explained by the participation of carbonyl group of the endo [3 + 2] cycloadducts C to the intramolecular Diels-Alder reaction.

Table 1. Reaction of Pyridinium N-Methylides 1 with Methylenecyclopropenes 2 and 4.

Reactants		Reaction Conditions[a]			Products[b]	Yield	mp	IR	MS
1	2 or 4	Solv.	Temp.	Time/h		%	°C	ν/cm^{-1}	m/e
1a	2	xy	reflux	67	3a	80	245-246	2225(CN)	448
1b	2	bz	reflux	69	3b	89	232-233	2250(CN) 1730(CO)	542
1c[c]	2	bz	reflux	48	3c	40	224-225	2240(CN) 1720(CO)	456
1d[c]	2	bz	reflux	42	3d	57	249-250	2250(CN) 1725(CO)	470
1e	2	bz	reflux	24	3e	64	286-290[d]	2300(CN) 1680(CO)	502
1a	4	xy	reflux	72	5a	16	238-240[d]	2200(CN)	476
1b	4	bz	rt	145	5b	60	188[d]	2200(CN) 1730(CO)	542
1e[c]	4	bz	rt	48	5c	49	176-177[d]	2250(CN) 1660(CO)	530

a) xy: xylene; bz: benzene
b) All the products gave satisfactory elemental analyses.
c) Generated in situ from the corresponding pyridinium bromides and triethylamine.
d) Melted with decomposition.

Table 2. NMR Spectral Data of Cage Compounds 3 and 5.

	^{1}H-NMR Spectra (in $CDCl_3$)												
	Chemical Shifts (δ/ppm)							Coupling Constants (J/Hz)					
	2-H	5-H	6-H	7-H	8-H	11-H	13-H	5-6	5-13	6-7	6-13	7-5	7-8
3a	[4.67s 4.27s	4.30m 4.24	5.88ddd 5.83	5.57ddd 5.53	4.28d 4.23	- -	4.52dd] a) 4.50	3.3	6.3	9.4	1.2	1.7	6.4
3b	4.23s	4.03-4.40m	5.72dd	5.54dd	4.03-4.40m	-	4.57d	3.0	6.2	9.6	0	0	6.0
3c	4.17s	4.09m	5.69ddd	5.41ddd	3.93d	4.61s	3.55dd	3.1	6.0	9.3	1.0	1.8	6.1
3d	4.12s	4.18m	5.72ddd	5.47ddd	3.93d	4.41s	3.78dd	3.4	6.0	9.4	1.0	1.6	6.0
3e	4.17s	4.10m	5.72ddd	5.41ddd	3.57d	5.27s	4.02dd	3.8	6.1	9.2	1.1	1.7	6.0
5a	-	5.71dd	5.94ddd	6.17dd	4.54d	-	4.36dd	3.1	6.0	9.0	1.0	0	5.8
5b	-	5.66dd	5.83ddd	5.99ddd	4.11d	-	4.58dd	2.8	6.0	9.5	1.2	0.8	5.2
5c	[-	5.70-5.90m	5.64ddd	5.70-5.90m	3.98d	5.23d	3.72dd] a)	2.8	4.8	6.0	1.2	-b)	5.7

	^{13}C-NMR Spectra (in $CDCl_3$, δ/ppm)								
	1-C	2-C	2-CN	3-C	5-C	8- and 13-C	9- and 10-C	11-C	11-R
3a	33.64s	27.88d	121.65s	-	39.92d	64.64d, 67.52d	46.15s, 47.14s	64.64s	111.61s, 112.25s
3b	34.64s	29.48d	119.71s	-	40.04d	63.47d, 66.58d	45.09s, 47.73s	85.37s	166.67s, 167.38s
3c	31.00s	29.65d	117.19s	-	40.51d	68.63d, 68.75d	39.57s, 46.26s	75.80d	169.67s
3d	29.65s	28.36d	118.65s	-	40.45d	65.93d, 67.16d	40.74s, 46.56s	73.09d	169.38s
3e	33.88s	28.53d	118.89s	-	40.69d	66.34d, 66.99d	40.28s, 46.85s	74.91d	195.45s
5b	29.65s	79.55s	116.60s	166.15s	75.27d	62.17d, 65.93d	48.44s, 49.08s	88.36s	167.14s
5c	29.35s	80.20s	116.07s	166.56s	80.61d	65.52d, 66.75d	44.85s, 46.85s	75.74d	194.33s

a) Measured in CD_3CN. b) No coupling constant was given because of the signal overlapping.

References

1) O. Tsuge, H. Shimoharada, M. Noguchi, and S. Kanemasa, Chem. Lett., 1982, 711.
2) O. Tsuge and H. Shimoharada, Chem. Pharm. Bull., 30, 1903 (1982).
3) Th. Eicher, E. v. Angerer, and A.-M. Hansen, Liebigs Ann. Chem., 746, 102 (1971).
4) Th. Eicher and V. Schafer, Tetrahedron Lett., 1975, 3919.
5) Two stereoisomers with different configuration at the 2-position were isolated in the reaction of thiazolium N-dicyanomethylide with 2 (see ref. 1). The isomer which shows a methine hydrogen at the 2-position at 4.29 ppm is more stable than the other isomer which shows the methine hydrogen at 5.03 ppm, the latter being converted into the former in the presence of triethylamine. All the cage compounds 3 show the 2-methine hydrogens at 4.12 to 4.27 ppm (see Table 2).
6) The reaction of thiazolium N-phenacylide with 2 at room temperature gave the stereselective [3 + 2] cycloadduct that was thought to be formed through the endo approach of anti form of the ylide to 2 (see ref. 1). In the present case, the endo approach of anti form of 1 and 2 is most likely to have occurred giving the stereoselective cycloadducts A as the intermediates of cage compounds 3.

(Received February 1, 1983)