Communications to the Editor

[Chem. Pharm. Bull.
31(9)3342—3345(1983)]

A NOVEL METHOD FOR SYNTHESIZING CONDENSED [hi]INDOLIZINES

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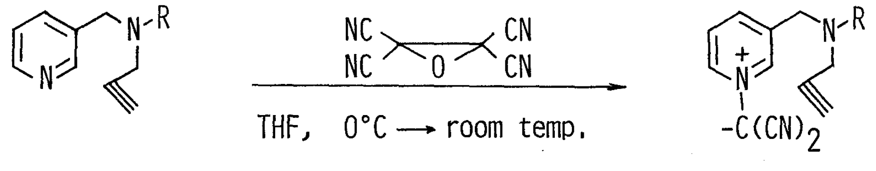
Some pyrido-, azepino-, and azocino[3,4,5-hi]indolizines were obtained in excellent yields by the intramolecular 1,3-dipolar addition of pyridinium dicyanomethylides having non-activated acetylenic dipolarophiles in the same molecules.

KEYWORDS —— indolizine; condensed [hi]indolizine; 1,3-dipolar addition; intramolecular reaction

Recently, much attention has been paid to the synthesis of aminoalkylindolizines, owing to their pharmacological activities.1) For instance, the synthesis of pyrrolo[3,2,1-gh]-4,7-phenanthololine as an indolizine analogue of ergoline, reported by Claudi et al.,2) is expected to provide a biologically active potentiality. However, the preparation of the [hi]indolizines condensed with benzene, naphthalene, and quinoline rings are not generally practicable because they are based on the inaccessible condensed pyridines as starting materials.2)

In this communication, we describe a novel and effective method of preparing condensed [hi]indolizines via the intramolecular 1,3-dipolar addition of pyridinium *N*-methylides.

At first, 3-substituted pyridinium *N*-dicyanomethylides (1a - 1e) were prepared in moderate yields by Linn's method,3) whose structures were determined based on the spectral data.4)



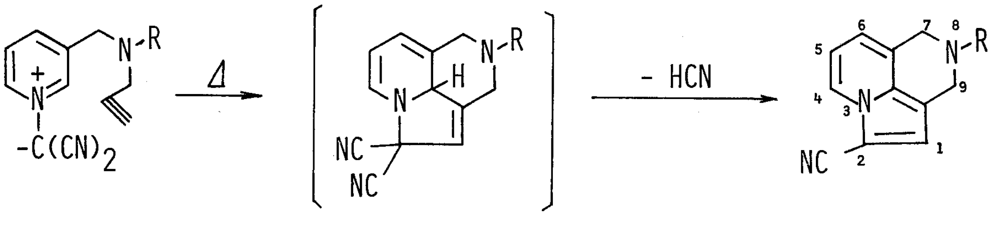
(1) Y. 40-66%

a: R= CH_3; b: R= CH_2-C≡CH; c: R= CH_2Ph; d: R= SO_2CH_3; e: R= $COCH_3$

When a solution of dicyanomethylide (1a)(300 mg, 1.34 mmol) in dry toluene (30 ml) was heated at 110°C for 24 h under nitrogen atmosphere and the resulting small amount of polymeric products was filtered off, a 2-cyano-8,9-dihydro-7*H*-pyrido[3,4,5-hi]indolizine (2a) was isolated in 91% yield as yellow prisms. The compound (2a) was identified as the expected indolizine derivative from the following analytical and spectral data.

2a: mp 92-93°C; Formula: $C_{12}H_{11}N_3$(197, 1a - HCN); IR(KBr): no νC≡CH, 2200 (CN) cm^{-1}; ^{1}H-NMR($CDCl_3$)δ: 2.26(3H, s, >N-CH_3), 3.78, 3.84(each 2H, s, -CH_2-), 6.6-6.8(2H, m, =CH-), 7.04(1H, s, =CH-), 8.04(1H, d, J=6 Hz, =CH-).

Similarly, the heating of dicyanomethylides (1b - 1e) and the successive purification with alumina chromatography gave the indolizine derivatives (2b - 2e) in excellent yields (Table I and Table II).



(1) (2)

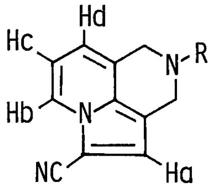
Table I. Conversion of Dicyanomethylides (1) to Indolizines (2)

	R	Time(h)[a)]	2			
			Yield(%)	mp (°C)	MS(M/e) M^+	IR(KBr) cm^{-1}
a	CH_3	T (24)	91 [b)]	92-93	197	2200(CN)
b	CH_2-C≡CH	T (18)	quant.	122-123.5	221	3250(C≡CH), 2190(CN, C≡C)
c	CH_2Ph	T (11)	97	85-87	273	2200(CN)
d	SO_2CH_3	D (9)	97	186-187	261	2215(CN), 1325, 1155(SO_2)
e	$COCH_3$	T (7)	68 [b)]	164-165	225	2200(CN), 1660(CO)
		B (70)	72 [b)]			

a) Performed under nitrogen atmosphere in the following solvents at reflux.
B: benzene; T: toluene; D: dioxane.

b) Also polymeric products were obtained.

Table II. ^{1}H-NMR Spectral Data of 8-Substituted-8,9-dihydro-7*H*-pyrido[3,4,5-hi]-indolizines (2)



(2)

δ [a)]	Ha	Hb	Hc, Hd	-CH_2-		Jbc(Hz)
a	7.04^s	8.04^d	$6.7\text{-}6.8^m$	3.78^s	3.84^s	6
b	7.14^s	8.14^d	$6.7\text{-}7.0^m$	4.00^s	4.04^s	7
c	7.08^s	8.12^d	$6.6\text{-}6.9^m$	3.90^s	3.94^s	6
d [b)]	7.56^s	8.46^{br}	$7.1\text{-}7.2^m$	4.76^{br}		—
e	7.10^s	8.05^d	$6.7\text{-}6.9^m$	4.78^s	4.98^s	6

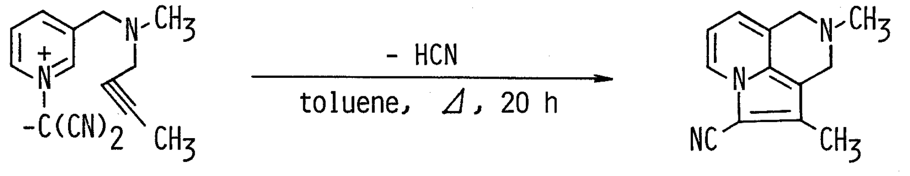
a) Measured in $CDCl_3$ except 2d.

b) Measured in $(CD_3)_2SO$.

The pyridinium dicyanomethylide unit in 1 added very smoothly on the non-activated acetylenic bond because of the enhanced reactivity by the intramolecular reaction. These reactions were analyzed by TLC and ended at the point of the disappearance of 1. Thus, the reaction times described in Table I correspond roughly with the reactivities of dicyanomethylides (1). It is pointed out that the spatial size of the *N*-substituent influences the reactivity owing to the entropic effect, i.e., reactivity (spatial size of *N*-substituent): 1d > 1c > 1b > 1a. A similar result was reported in the intramolecular Diels-Alder reaction of furn systems by Parker and his coworker.5)

Next, in order to examine the introduction of alkyl group at C-1 of the pyrido[hi]indolizine system, 3-[*N*-(2-butynyl)-*N*-methylaminomethyl]pyridinium dicyanomethylide (3) was prepared and its cyclization to indolizine was attempted.

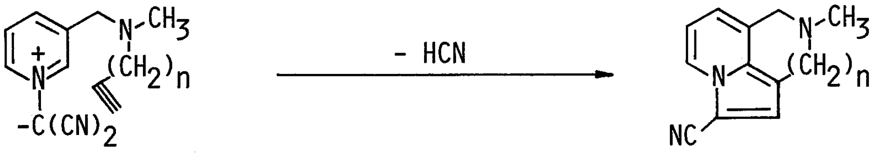
The compound (3) afforded a pyridoindolizine (4)6) in 88% yield, when heated in toluene at reflux for 20 h. This proved that 1-alkylated pyrido[hi]indolizines can be obtained using appropriate internal acetylenes as dipolarophiles instead of the terminal one.



(3) (4) Y. 88%

Finally, two other dicyanomethylides (5, 7) were prepared to apply this method to the preparation of azepino- and azocino[hi]indolizines.

3-[*N*-(3-Butynyl)-*N*-methylaminomethyl]pyridinium dicyanomethylide (5: n=2) was converted to an azepino[hi]indolizine (6)7) in 91% yield. On the other hand, the reactivity of 3-[*N*-(4-pentynyl)-*N*-methylaminomethyl]pyridinium dicyanomethylide (7: n=3) dropped significantly in comparison with 1a or 5. Thus, the heating of 7 in toluene at reflux for 8 days did not show any change. The desired azocino[3,4,5-hi]indolizine (8)8) was obtained in 52% yield by heating 7 in xylene at reflux for 64 h, together with a 6% yield of bimolecular adduct (9).9)



1a (n= 1)	toluene, Δ, 24 h	2a (n= 1)	Y. 91%
5 (n= 2)	toluene, Δ, 20 h	6 (n= 2)	Y. 91%
7 (n= 3)	xylene, Δ, 64 h	8 (n= 3)	Y. 52%

The intramolecular 1,3-dipolar addition of pyridinium dicyanomethylides with non-activated acetylenes proved to be a novel method for preparing pyrido-, azepino-, and azocino[3,4,5-hi]indolizines. Indolizines condensed with rings with more than eight members could be prepared in the above described method.

Further investigations on similar systems now continue in this laboratory.

ACKNOWLEDGEMENT We would like to express our thanks to Prof. Otohiko Tsuge, Research Institute of Industial Science, Kyushu University, for his valuable advices and encouragement.

REFERENCES AND NOTES

1) I. Antonini, F. Claudi, U. Gulini, L. Micossi, and F. Venturi, J. Pharm. Sci., 68, 321 (1979).
2) M. Cardellini, G.M. Cingolani, F. Claudi, G. Cristalli, U. Gulini, and S. Martelli, J. Org. Chem., 47, 688 (1982).
3) W.J. Linn, O.W. Webster, and R.E. Berson, J. Am. Chem. Soc., 87, 3651 (1965).
4) All new compounds in this communication gave satisfactory analytical values.
5) K.A. Parker and M.R. Adamchuk, Tetrahedron Lett., 1978, 1689.
6) **4**: yellow prisms; mp 142.5-144°C; IR(KBr): 2180(CN) cm^{-1}; ^1H-NMR($CDCl_3$)δ: 2.30(3H, s, $=\underset{|}{C}-C\underline{H}_3$), 2.54(3H, s, $>N-C\underline{H}_3$), 3.68(4H, br s, $-C\underline{H}_2-$), 6.5-6.6(2H, m, ring-H), 7.80(1H, d, J=6 Hz, ring-H); MS(m/e): 211(M^+).
7) **6**: yellow prisms; mp 79.5-81.5°C; IR(KBr): 2190(CN) cm^{-1}; ^1H-NMR($CDCl_3$)δ: 2.46(3H, s, $>N-C\underline{H}_3$), 3.08(4H, br s, $-C\underline{H}_2-$), 4.02(2H, s, $-C\underline{H}_2-$), 6.5-6.6(2H, m, ring-H), 7.04 (1H, s, ring-H), 8.02(1H, d, J=6 Hz, ring-H); MS(m/e): 211(M^+).
8) **8**: colorless prisms; mp 82-87°C; IR(KBr): 2170(CN) cm^{-1}; ^1H-NMR($CDCl_3$)δ: 1.7-2.1 (2H, m, $-C\underline{H}_2-$), 2.41(3H, s, $>N-C\underline{H}_3$), 2.5-2.7(2H, m, $-C\underline{H}_2-$), 3.1(2H, t, J=7 Hz, $-C\underline{H}_2-$), 4.06(2H, s, $-C\underline{H}_2-$), 6.7(2H, m, ring-H), 6.99(1H, s, ring-H), 8.09(1H, t(p), J=4 Hz, ring-H); MS(m/e): 225(M^+).
9) **9**: yellow prisms; mp 260°C(dec.); IR(KBr): 2180(CN) cm^{-1}; MS(m/e): 450(M^+). The investigation concerning the structure will be reported elsewhere.

(Received July 13, 1983)