Cycloaddition Reactions of Dicyanomethylids with Triphenylcyclopropene. A Simple Route to 1,2,3-Triphenylindolizines

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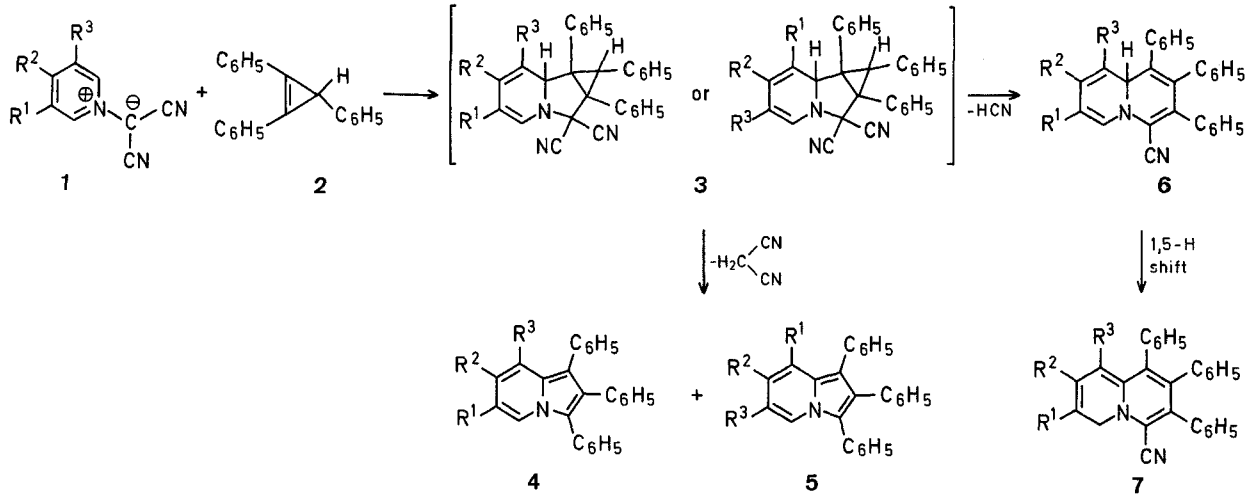
Cycloaddition reactions of substituted cyclopropenes to dienes and 1,3-dipoles have provided a facile synthetic entry into the five-, six-, or seven-membered carbo- or heterocyclic ring systems[1,2]. In this paper, we report a further application of this principle to provide a new route to indolizines[3]. Arylindolizines are of some medical interest[4].

Dicyanomethylids (**1a–g**)[5] reacted with triphenylcyclopropene (**2**) in refluxing dimethylformamide to give the corresponding 1,2,3-triphenylindolizines (**4** and **5**) with formal elimination of malononitrile. Depending on the structures of **1**, the formation of 5-cyano-6,7,8-triphenyl-4*H*-quinolizines (**7**) may predominate. This may be due to less steric effect in the intermediates **6**.

A possible mechanism for the formation of **7** involves a cycloaddition of **1** to **2** to give an initial 1,3-dipolar adduct **3**[6] which produces indolizine **4** (and **5**) with extrusion of malononitrile, followed by elimination of hydrogen cyanide, and a thermally allowed 1,5-hydrogen shift. In fact, stable dehydrocyanated adducts **6b** and **6e** in which 1,5-hydrogen shift is possibly obstructed by the adjacent methyl group, were isolated.

A limitation of the present method lies in the unavailability of 2-substituted pyridinium dicyanomethylids; for instance, reaction of 2-methylpyridine with tetracyanooxirane does not give the corresponding dicyanomethylid. No indolizine was obtained when an electron-withdrawing substituent such as a cyano group is present in the pyridine ring. The nature of products formed in the presence of an electron-withdrawing substituent is under investigation.

This type of reaction can be applied to the preparation of azaindolizines, as exemplified by the synthesis of **9** from



	R^1	R^2	R^3
a	H	H	H
b	H	H	CH_3
c	H	CH_3	H
d	CH_3	H	CH_3
e	H	CH_3	CH_3
f	H	$CH_2C_6H_5$	H
g	—CH=CH—CH=CH—		H

Table. Preparation and Physical and Analytical Data of 1,2,3-Triphenylindolizines and 4*H*- and 9a*H*-Quinolizines

Product	Yield [%]	m.p.	Molecular formula[a]	M.S. *m/e* for M$^+$	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4a[b]	25	195–196°	$C_{26}H_{19}N$ (345.4)	345	1600, 1430	8.01 (d, 1H, J=7 Hz); 6.2–7.7 (m, 18H)
7a	37	96–98°	$C_{28}H_{20}N_2$ (384.5)	384	1600, 1435, 2260	3.98 (s, 2H); 6.21 (d, 1H, J=4 Hz); 6.6–7.5 (m, 17H); 7.78 (s, 1H)
4b+5b[c]	35	167–168°	$C_{27}H_{21}N$ (359.5)	359	1600, 1438	2.01 (s, 2.73H); 2.17 (s, 0.27H); 6.3–6.5 (m, 2H); 6.9–7.5 (m, 15H); 7.9–8.1 (m, 1H)
6b	13	217–218°	$C_{29}H_{22}N_2$ (398.5)	398	1600, 1435, 2250	2.15 (s, 3H); 5.87 (s, 1H); 6.68 (d, 1H, J=9 Hz); 7.1–7.5 (m, 16H); 7.59 (d, 1H, J=9 Hz)
4c	24	157–158°	$C_{27}H_{21}N$ (359.5)	359	1600, 1435	2.25 (s, 3H); 6.1–6.4 (m, 2H); 6.7–7.5 (m, 15H); 7.91 (d, 1H, J=7 Hz)
7c[d]	45	173–174°	$C_{29}H_{22}N_2$ (398.5)	398	1603, 1435, 2260	2.28 (s, 3H); 3.96 (bs, 2H); 6.08 (bs, 1H); 6.6–7.5 (m, 15H); 7.82 (s, 1H)
4d	55	141–142°	$C_{28}H_{23}N$ (373.5)	373	1603, 1430	1.98 (s, 3H); 2.10 (s, 3H); 6.25 (s, 1H); 6.8–7.4 (m, 15H); 7.69 (s, 1H)

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Table. (Continued)

Product	Yield [%]	m.p.	Molecular formula[a]	M.S. *m/e* for $M^{\oplus}$	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
7d (6d)	0	—	—	—	—	—
4e+5e[e]	41	134–137°	$C_{28}H_{23}N$ (373.5)	373	1600, 1435	1.96 (s, 2.25H); 2.12 (s, 0.75H); 2.18 (s, 2.25H); 2.23 (s, 0.75H); 6.28 (d, 0.75H, J=6.5 Hz); 6.2–7.8 (m, 15.5 H); 7.90 (d, 0.75H, J=6.5 Hz)
6e	24	251–253°	$C_{30}H_{24}N_2$ (412.5)	412	1603, 1440, 2250	2.06 (s, 3H); 2.21 (s, 3H); 5.84 (s, 1H); 7.0–7.8 (m, 17H)
4f	27	155–156°	$C_{33}H_{25}N$ (435.5)	435	1602, 1433	3.87 (s, 2H); 6.28 (d, 1H, J=8 Hz); 6.9–7.6 (m, 21H); 7.99 (d, 1H, J=8 Hz)
7f	31	87–89°	$C_{35}H_{26}N_2$ (474.6)	474	1603, 1435, 2260	3.86 (s, 2H); 4.03 (bs, 2H); 6.16 (bs, 1H); 6.6–7.6 (m, 20H); 7.83 (s, 1H)
4g[f]	44	172–173°	$C_{30}H_{21}N$ (395.5)	395	1605, 1435	6.59 (d, 1H, J=8 Hz); 6.8–7.5 (m, 19H); 7.76 (d, 1H, J=8 Hz)
7g (6g)	0	—	—	—	—	—
9	47	203–205°	$C_{25}H_{18}N_2$ (346.4)	346	1603, 1440	6.7–7.79 (m, 16H); 7.92 (d, 1H, J=6 Hz); 9.00 (s, 1H)

[a] All products gave satisfactory microanalyses (C ±0.25%, H ±0.26%, N ±0.35%).

[b] Lit.[4] m.p. 196–197°.

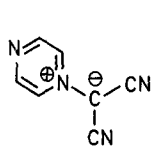
[c] **4b/5b**=91:9 from ^{1}H-N.M.R. analysis.

[d] ^{13}C-N.M.R. of **7c** ($CDCl_3$): δ=11.65 (q, —$\underline{C}H_3$); 13.48 (t, —$\underline{C}H_2$—); 101.85 (d, =$\underline{C}$H); 108.18 (s, =$\underline{C}$—CH_3); 115.49 (s, —$\underline{C}$≡N); 120.08 (d, =$\underline{C}$H); 125–140 ppm (complex peaks due to olefinic quaternary and aromatic carbons).

[e] **4e/5e**=75:25 from ^{1}H-N.M.R. analysis.

[f] For orientation of cycloaddition, see Ref.[7].

ylid **8** (Table). Thus, cyclopropenes may be employed as reagents for the synthesis of indolizines.



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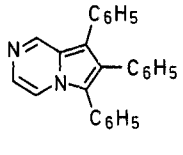

9

Cycloaddition of Dicyanomethylids (1a–g, 8) and Triphenylcyclopropene (2); General Procedure:

A mixture of the dicyanomethylid (3 mmol) and triphenylcyclopropene (3 mmol) in dry dimethylformamide (15 ml) is heated under reflux with stirring for 4–8 h, during which time the dicyanomethylid goes into solution. The solvent is removed from the resulting dark red solution in vacuo to leave a deep red oil. Chromatography of this oil on silica gel (Wakogel C-100, Wako Pure Chemical Industries, Ltd.) with hexane gives as the first fraction the indolizine which is recrystallized from hexane. Further elution of the column with hexane/benzene (1:1) gives the 4*H*- or 9a*H*-quinolizine as an oil, which is purified by recrystallization from hexane/benzene; see Table.

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[6] When reaction of **1a** with **2** was carried out in refluxing acetonitrile (3 days), a 1:1 adduct (**3**; $R^1=R^2=R^3=H$) was obtained in a low yield (7%) and no indolizine was detected.

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