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1,3-DIPOLAR CYCLOADDITION OF ETHYL 2,3-PENTADIENOATE WITH PYRIDINIUM DICYANOMETHYLIDES: REGIOSPECIFIC FORMATION OF ETHYL 3-CYANO-2-ETHYLINDOLIZINE-1-CARBOXYLATES AND A NOVEL FORMATION OF TRICYCLIC COMPOUNDS[†]

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Abstract – Pyridinium dicyanomethylides underwent site- and regioslective 1,3-dipolar cycloaddition with ethyl 2,3-pentadienoate to give ethyl 3-cyano-2-ethylindolizine-1-carboxylates in moderate yields. In two cases, a novel type of the tricyclc compounds, in addition to indolizines, were obtained whose structure was established by a single crystal X-Ray analysis. A plausible mechanism for its formation is also presented.

INTRODUCTION

The 1,3-dipolar reaction, whether concerted or not, undoubtedly rivals Diels-Alder reactions in ubiquity as well as in synthetic utility.[1] Both intermolecular and intramolecular version of this cycloaddition represents an efficient method for the syntheses of a wide variety of carbocycles as well as heterocycles, including natural products; their synthetic potential is far from exhausted. Among the unsaturated compounds capable of behaving as dipolarophiles, allenes exhibit some peculiarities.[2] Previously, we have briefly reported 1,3-dipolar cycloaddition of pyridinium dicyanomethylides (**1**) with 1-phenylpropa-1,2-diene (**2**) and found that this allene has served as an synthetic equivalent of

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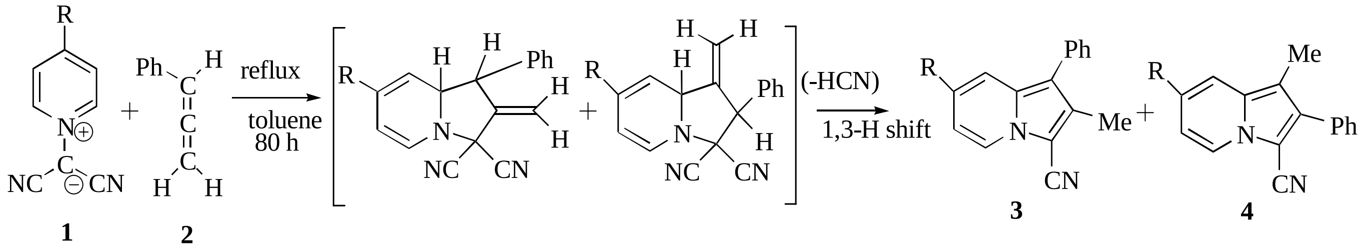
Dedicated to the memory of Professor Kenji Koga, Professor Emeritus of the University of Tokyo.

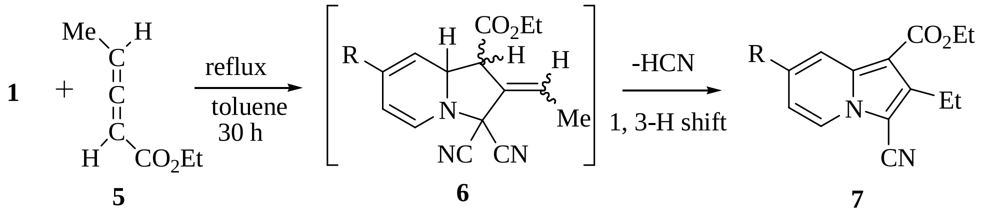
1-phenylpropyne, but the reaction was not regiospecific to give a mixture of 2-methyl-1-phenylindolizine-3-carbonitriles (**3**) and 1-methyl-2-phenylindolizine-3-carbonitriles (**4**), through dehydrocyanation and 1,3-sigmatropic hydrogen shift of the initial adducts. The regiochemical assignments were established by X-Ray analyses.[3] In order to explore further generality of this reaction using allenes, we chose ethyl 2,3-pentadienoate (**5**)[4] having an electron deficient group this time and below describe briefly the results of the reactions with pyridinium dicyanomethylides (**1**).[5]



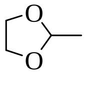
Scheme 1

RESULTS AND DISCUSSION

The reaction of pyridinium dicyanomethylide (**1a**) with **5** in refluxing toluene for 30 h afforded site- and regioselectively ethyl 2-ethyl-3-cyanoindolizine-1-carboxylate (**7a**) in 50% yield. Analogous reactions of several 4-substituted pyridinium dicyanomethylides (**5b-g**) gave the corresponding indolizines (**7b-g**) in low to moderate yields. Among them, ethyl 3-cyano-7-(1,3-dioxolan-2-yl)-2-ethyl-1-indolizine carbonitrile (**7f**) is especially required for further investigation on synthesis of porphyrin-linked indolizines since the 1,3-dioxolan-2-yl group has proven to serve as a formyl equivalent.[6] In general, pyridinium ylides having an electron donating group at 4 position gave better yields than those possessing an electron withdrawing group. The structure, *e.g.* regiochemistry, was established by X-ray analyses.[7] For instance, the ORTEP drawing of **7f** is shown in Figure 1.



Scheme 2

R		Yield (%)
H	**a**	50
Me	**b**	54
PhCO	**c**	19
$MeCO_2$	**d**	21
MeCO	**e**	26
	**f**	61
Isoq	**g**[a]	45

[a]Isoquinolinium dicyanomethylide

It is passing note that the regiochemical results are in good agreement with HOMO-LUMO density interaction (frontier orbital theory).[8]

In some cases, *e.g.* in the reactions with **1c** and **1f**, there were found additional compounds to the indolizines (**7**) whose ^{1}H and ^{13}C NMR spectra did not permit us to illuminate any structure but a single crystal X-Ray analysis established the structure as **8f** (Figure 2).[9] A plausible mechanism for the formation of **8f** is depicted in Scheme 3; an initial 1,3-dipolar cycloaddition of **1f** to **5** affords the 1:1 adduct (**9**) followed by elimination of HCN to give a new ylide (**10**) which underwent 1,3-dipolar cycloaddition with another molecule of **5** giving **11** followed by 1,3-hydrogen shift finally to form **8f**. All the attempts to aromatize **8f** to the corresponding cycl[2.2.3]azine were unsuccessful in our hands.

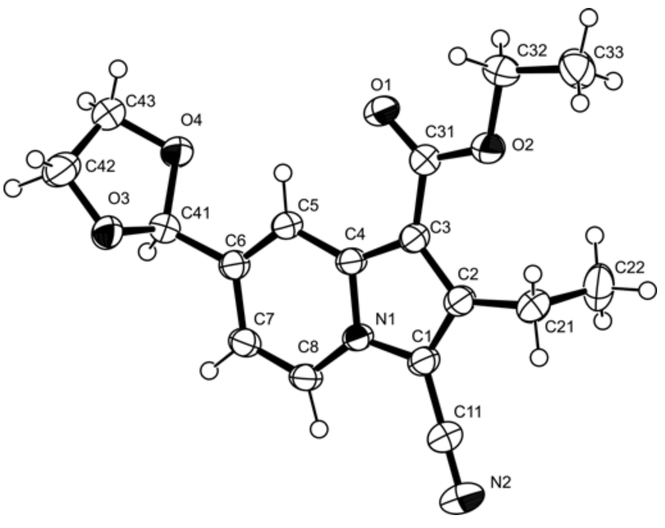


Figure 1. ORTEP Drawing of **7f**

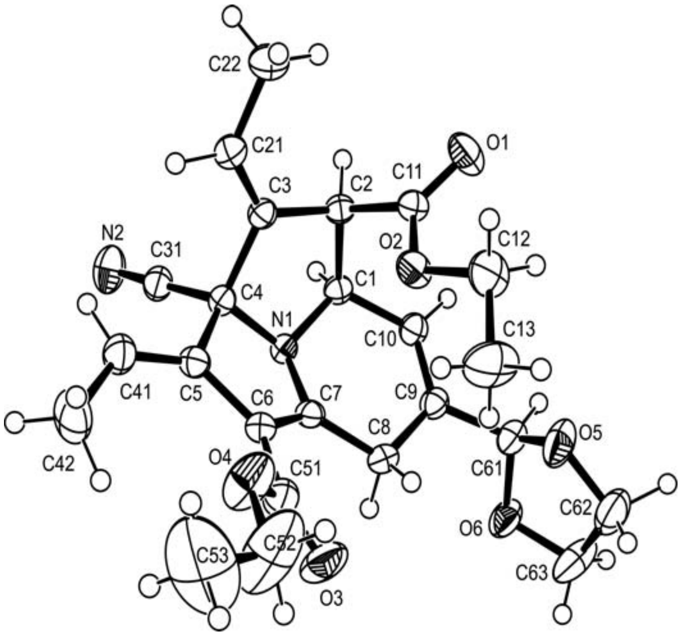
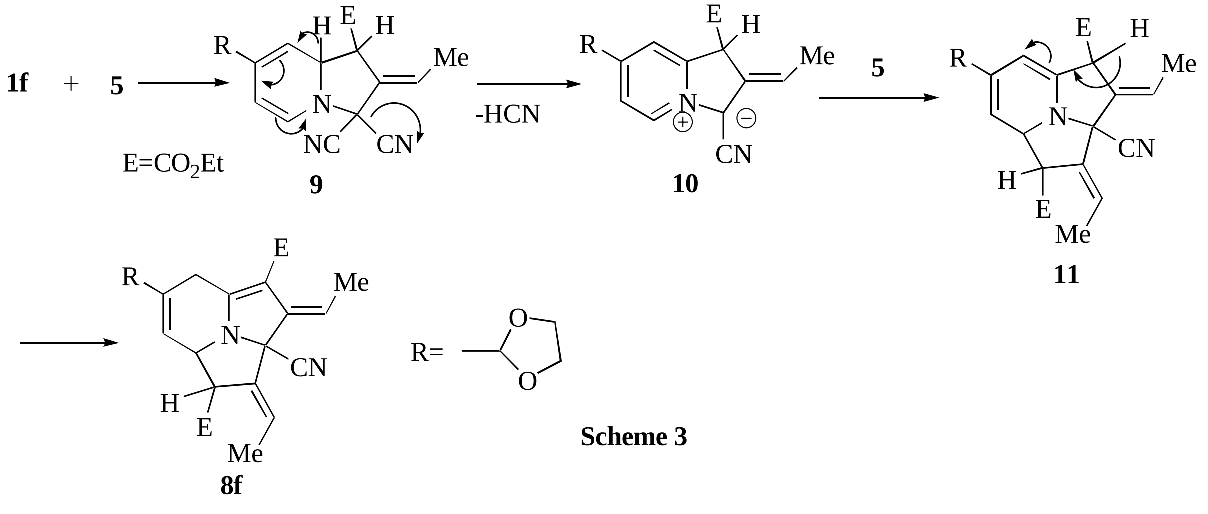


Figure 2 ORTEP Drawing of **8f**

Further studies employing other allenes as dipolarophiles are now in progress.



Scheme 3

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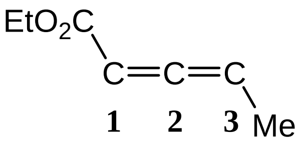
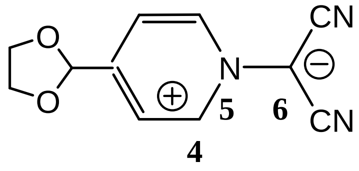
6. K. Matsumoto, A. Ogasawara, S. Kimura, N. Hayashi, and T. Machiguchi, *Heterocycles*, 1998, **48**, 861.
7. A typical experimental procedure and results: A mixture of **1f** (216 mg, 1.00 mmol) and **5** (252 mg, 2.00 mmol) in toluene (2 mL) was heated under reflux for 30 h. After evaporation of the solvent, the residue was subjected to chromatography on SiO_2 using hexane-ethyl acetate (3:1) as eluent. **7f**: mp 96-97 ºC (hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7.6 Hz), 1.44 (3H, t, J = 7.0

Hz), 3.10 (2H, q, *J* = 7.6 Hz), 4.04-4.17 (4H, m), 4.40 (2H, q, *J* = 7.3 Hz), 5.85 (1H, s), 7.07 (1H, dd, *J* = 1.9, 7.0 Hz), 8.23 (1H, dd, *J* = 1.2, 6.9 Hz), 8.36-8.37 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.40, 15.22, 20.24, 60.03, 65.52, 97.09, 102.40, 112.65, 118.30, 125.42, 136.64, 137.75, 145.32, 162.40, 163.54; *Anal.* Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.93; H, 5.74; N, 8.84. Crystal data: $C_{17}H_{18}N_2O_4$, MW = 314.33, monoclinic, $P2_1/c$, $a = 10.922(2)$, $b = 4.402(4)$, $c = 32.524(7)$ Å, $\beta = 90.13(2)^\circ$, $Z = 4$, $T = 203$ K, $D_c = 1.335$ g cm^{-3}, $R1 = 0.045$ ($I > 2\sigma(I)$), $wR2 = 0.144$ (all data).

8. For example, the HOMO and LUMO densities of **1f** and **5** were obtained using CAChe systems (Version 4.1.1, CAChe Scientific, Oxford Molecular Group, PM3: J. J. Stewart, *J. Comp. Chem.*, 1989, **10**, 209.).



	C_1	C_2	C_3
HOMO	0.041	0.341	0.346
LUMO	0.246	0.412	0.005



	C_4	C_6
HOMO	0.091	0.462
LUMO	0.055	0.096

9. **8f**: 14 % yield; mp 174-175 ºC (hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.06 (3H, t, *J* = 7.3 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 1.69 (2H, dd, *J* = 1.3, 7.0 Hz), 1.90 (2H, d, *J* = 7.3 Hz), 3.26 (1H, m), 3.55 (1H, dt, *J* = 12.4 Hz), 4.03-3.79 (4H, m), 4.15-4.31 (4H, m) 4.53 (1H, m), 5.75 (1H, q, *J* = 7.3 Hz), 6.01-6.03 (1H, m), 6.20 (1H, dq, *J* = 2.2, 7.1Hz); ^{13}C NMR ($CDCl_3$) δ 13.53, 14.40, 15.18, 15.46, 24.65, 52.09, 59.46, 59.86, 61.14, 65.48, 72.56, 103.73, 105.86, 119.05, 119.49, 126.06, 134.63, 136.85, 138.30, 160.33, 164.59, 169.80. *Anal.* Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.33; H, 6.38; N, 6.34. Crystal data: $C_{24}H_{28}N_2O_6$, MW = 440.48, triclinic, P-1, $a = 11.719(4)$, $b = 12.741(4)$, $c = 7.973(2)$ Å, $\alpha = 99.59(2)^\circ$, $\beta = 95.39(2)^\circ$, $\gamma = 98.40(2)^\circ$, $Z = 2$, $T = 203$ K, $D_c = 1.269$ g cm^{-3}, $R1 = 0.053$ ($I > 2\sigma(I)$), $wR2 = 0.150$ (all data).