HETEROCYCLES, Vol. 66, 2005, pp. 175 – 179. © The Japan Institute of Heterocyclic Chemistry
Received, 11th October, 2005, Accepted, 16th November, 2005, Published online, 18th November, 2005. COM-05-S(K)70

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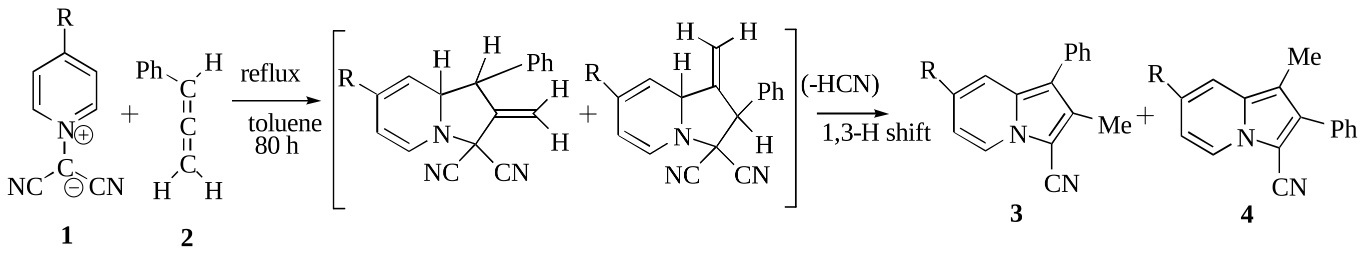
Dedicated to the memory of Professor Kenji Koga, Professor Emeritus of the University of Tokyo.

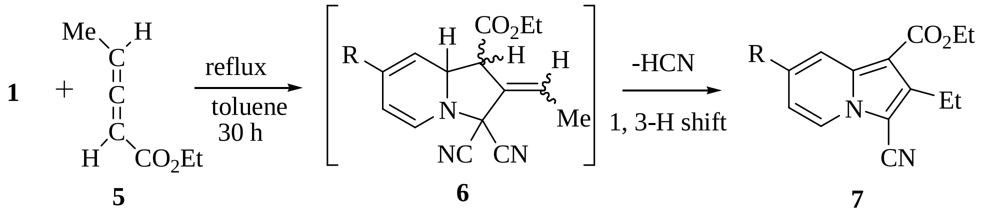
1-phenylpropyne, but the reaction was not regiospecific to give a mixture of 2-methyl-1-phenylindolizine-3-carbonitriles (**3**) and 1-methyl-2-phenylindolizine-3-carbonitriles (**4**), through dehydrocyanation and 1,3-sigmatropic hydrogen shift of the initial adducts. The regiochemical assignments were 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
$MeCO$ ...		

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.

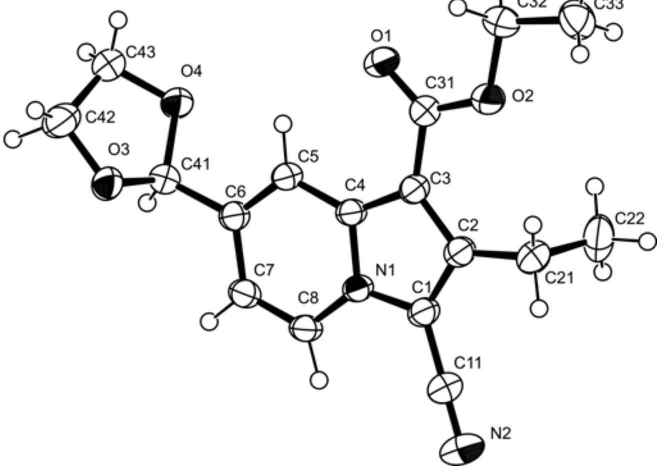


Figure 1. ORTEP Drawing of **7f**

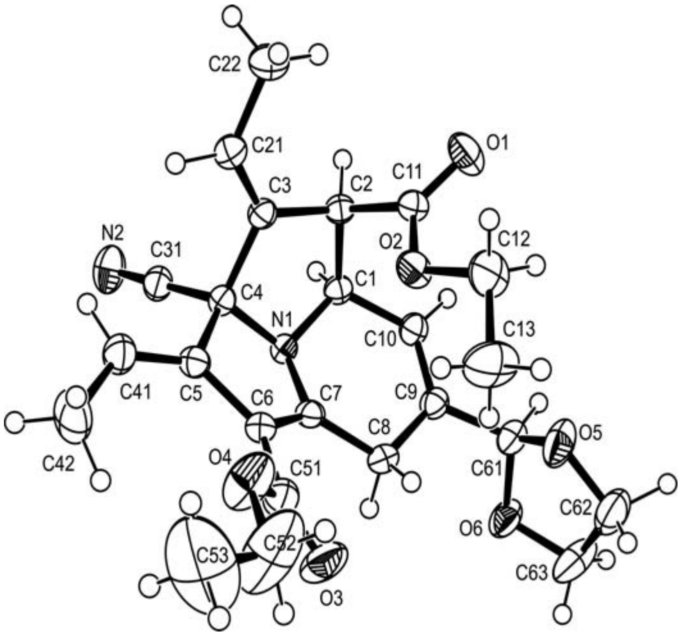
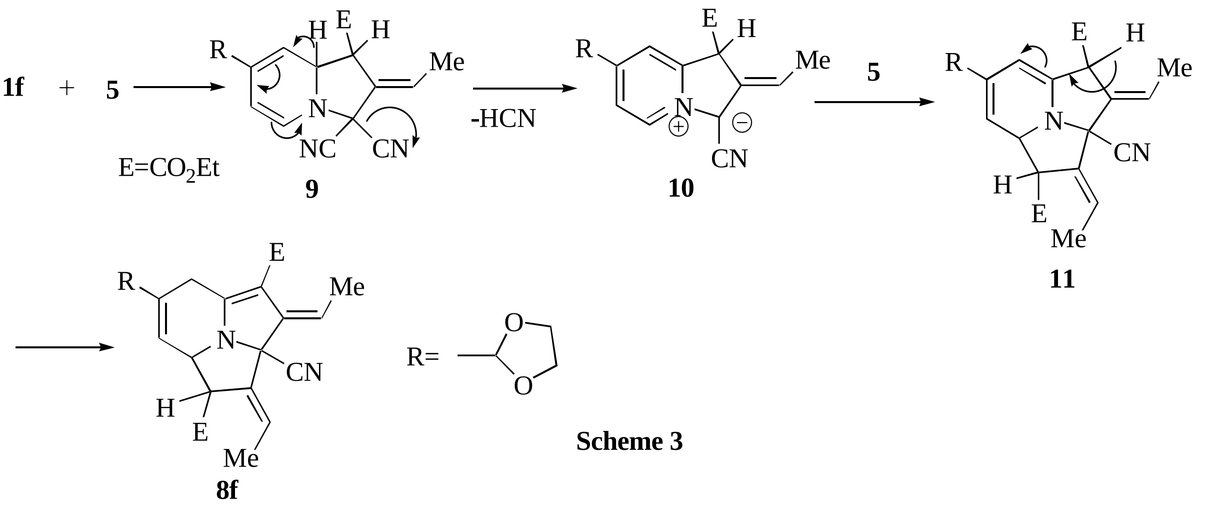


Figure 2 ORTEP Drawing of **8f**

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



Scheme 3

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (to NH and KM). The authors are also grateful to the Ministry of Education, Culture, Sports, Science, and Technology, Japan for purchasing the high-field NMR instruments (JEOL JNM-A500 and JNM-EX270) by the special fund to KM (Graduate School of Human and Environmental Studies, Kyoto University) in 1992. Generous and encouraging supports from the Chiba Institute of Science (CIS) are greatly acknowledged.

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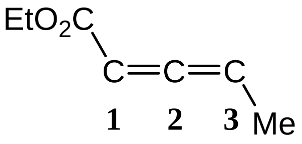
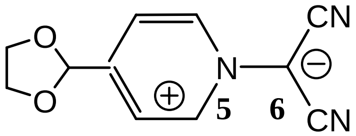
7. A typical experimental procedure and results: A mixture of **1f** (216 mg, 1.00 mmol) and **5** (252 mg, 2.00 mmol) in toluene (2 mL) was heated under reflux for 30 h. After evaporation of the solvent, the residue was subjected to chromatography on SiO_2 using hexane-ethyl acetate (3:1) as eluent. **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, β = 90.13(2)°, Z = 4, T = 203 K, D_c = 1.335 g cm^{-3}, $R1$ = 0.045 ($I > 2\sigma(I)$), w$R2$ = 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



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	C_4	C_6
HOMO	0.091	0.462
LUMO	0.055	0.096

9. **8f**: 14 % yield; mp 174-175 °C (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, α = 99.59(2)°, β = 95.39(2)°, γ = 98.40(2)°, Z = 2, T = 203 K, D_c = 1.269 g cm^{-3}, $R1$ = 0.053 ($I > 2\sigma(I)$), w$R2$ = 0.150 (all data).