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 tricycle 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

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. In order to explore further generality of this reaction using allenes, we chose ethyl 2,3-pentadienoate (5) having an electron deficient group this time and below describe briefly the results of the reactions with pyridinium dicyanomethylides (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. 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. For instance, the ORTEP drawing of 7f is shown in Figure 1.

<table>
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<td>H</td>
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<tr>
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<tr>
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*Isoquinolinium dicyanomethylide*
It is passing note that the regiochemical results are in good agreement with HOMO-LUMO density interaction (frontier orbital theory). 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). 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. Further studies employing other allenes as dipolarophiles are now in progress.

![Figure 1. ORTEP Drawing of 7f](image1)

![Figure 2 ORTEP Drawing of 8f](image2)

![Scheme 3](image3)
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REFERENCES AND NOTES
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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 SiO2 using hexane-ethyl acetate (3:1) as eluent. 7f: mp 96-97 °C (hexane-ethyl acetate); 1H NMR (CDCl3) 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); 13C NMR (CDCl3) 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 C17H18N2O4: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.93; H, 5.74; N, 8.84. Crystal data: C17H18N2O4, MW = 314.33, monoclinic, P21/c, a = 10.922(2), b = 4.402(4), c = 32.524(7) Å, β = 90.13(2)º, Z = 4, T = 203 K, Dc = 1.335 g cm⁻³, R1 = 0.045 (I > 2σ(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.).

![HOMO and LUMO densities](image)

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9. 8f: 14 % yield; mp 174-175 ºC (hexane-ethyl acetate); 1H NMR (CDCl3) 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); 13C NMR (CDCl3) 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, 164.59, 169.80. Anal. Calcd for C24H28N2O6: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.33; H, 6.38; N, 6.34. Crystal data: C24H28N2O6, MW = 440.48, triclinic, P-1, α = 11.719(4), b = 12.741(4), c = 7.973(2) Å, α = 99.59(2)º, β = 95.39(2)º, γ = 98.40(2)º, Z = 2, T = 203 K, Dc = 1.269 g cm⁻³, R1 = 0.053 (I > 2σ(I)), wR2 = 0.150 (all data).