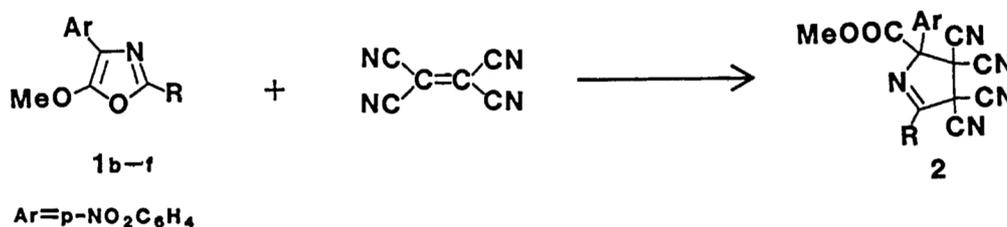


Anomalous Cycloaddition of Oxazoles with PTAD

Toshikazu IBATA,^{*} Yasushi ISOGAMI, and Hatsue TAMURA
 Institute of Chemistry, College of General Education,
 Osaka University, Toyonaka, Osaka 560

The reaction of various substituted oxazoles with 4-phenyl-1,2,4-triazole-3,5-dione gave anomalous cycloadducts, N-phenyl-5-acyl- Δ^3 -1,2,4-triazoline-1,2-dicarboximides in high yields through oxazole ring opening. The structure of one of the adducts was determined by a single-crystal X-ray analysis.

The previous paper of this series dealt with the formation of 3,3,4,4-tetracyano-4,5-dihydropyrrole derivatives (2) in the abnormal Diels-Alder reaction between oxazoles and tetracyanoethylene (TCNE).¹⁾ These results prompted us to reinvestigate the reaction of oxazoles with 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) reported before to give normal Diels-Alder adducts,²⁾ because PTAD has been recognized to have strong electron-acceptor character similar to TCNE and also to have a strong dienophilicity toward the various types of dienes.^{3,4)} In this paper, we report the results of detailed investigations of the products of many oxazoles with PTAD to give Δ^3 -1,2,4-triazoline derivatives and would like to correct the description in the previous paper suggesting the usual Diels-Alder adduct formation.²⁾



Treatment of ethyl 2-methyl-5-ethoxyoxazole-4-carboxylate (1a) with equimolar amount of PTAD in an acetonitrile solution at room temperature resulted in rapid disappearance of deep carmine color of PTAD in a few seconds and gave

a colorless crystalline product (3a) in high yield (99%) after evaporation of solvent. The results of elemental analysis revealed that 3a is an adduct of 1a with PTAD.⁵⁾ The ¹H NMR data of the adduct show the presence of two identical ethyl groups of ethoxycarbonyl in a molecule; [¹H NMR (CDCl₃) δ 1.33 (t, 2xCH₃), 2.50 (s, CH₃), 4.35 (q, 2xCH₂), 7.44 (s, Ph)]; ¹³C NMR δ 163.68 (ester C=O), 155.19, 152.27 (imide C=O), 147.98 (C=N), 130.51, 129.39, 129.12, 126.29 (Ph), 91.65 (quarternary-C), 63.86 (2xCH₂), 14.36 (CH₃), 13.91 (2xCH₃); IR (KBr) 1743 cm⁻¹ (broad, C=O)]. This indicates that the adduct does not have the normal Diels-Alder adduct structure (4a) but has a structure having two equivalent ethoxycarbonyl groups in a molecule. For the further definitive characterization of the structure, spectral data were found useless, and then the X-ray study was done as shown below.

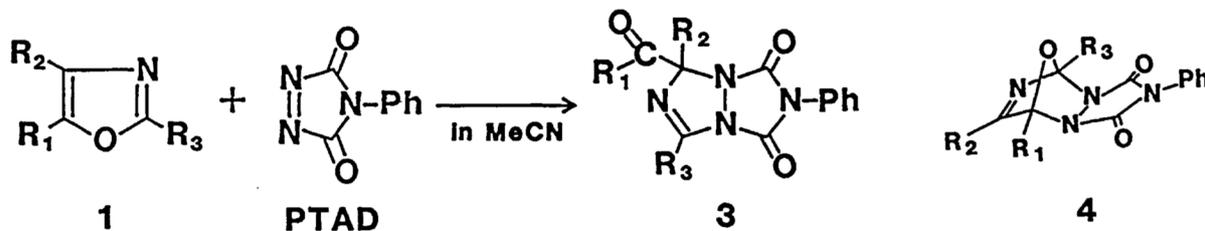


Table 1. Yields of Adduct 3^{a)}

Run	R ₁	R ₂	R ₃	Yield of <u>3</u> / % ^{b)}
a	EtO	EtOOC	Me	99
b	MeO	p-NO ₂ C ₆ H ₄	Me	94
c	"	"	Et	100
d	"	"	iso-Pr	99
e	"	"	t-Bu	98
f	"	"	Ph	99
g	"	Me	Me	88
h	"	"	p-tolyl	76
i	Ph	H	Ph	0 ^{c)}

- a) All reactions were carried out in an acetonitrile solution at room temperature using equimolar amount of oxazole and PTAD.
 b) Yields listed here are isolated yields based on the amount of oxazoles after flush column chromatography on silica gel.
 c) The reaction mixture was refluxed for 20 h.

Other oxazoles having various substituents on C_2 , C_4 , and C_5 were also confirmed to give similar type of adducts (3) in the reactions with PTAD in almost quantitative yields (Table 1).

In order to determine the structure of the adducts definitely, a single-crystal X-ray crystallography of the adduct (3h; $R_1=CH_3O$, $R_2=CH_3$, $R_3=p-MeC_6H_4$) of 5-methoxy-4-methyl-2-p-tolyloxazole (1h) with PTAD was undertaken and the Δ^3 -1,2,4-triazoline-1,2-dicarboximide structure was confirmed as shown in Fig. 1.⁶⁾ Each of the triazoline ring and urazole ring are almost planar, and two planes make a dihedral angle of 140.75° .

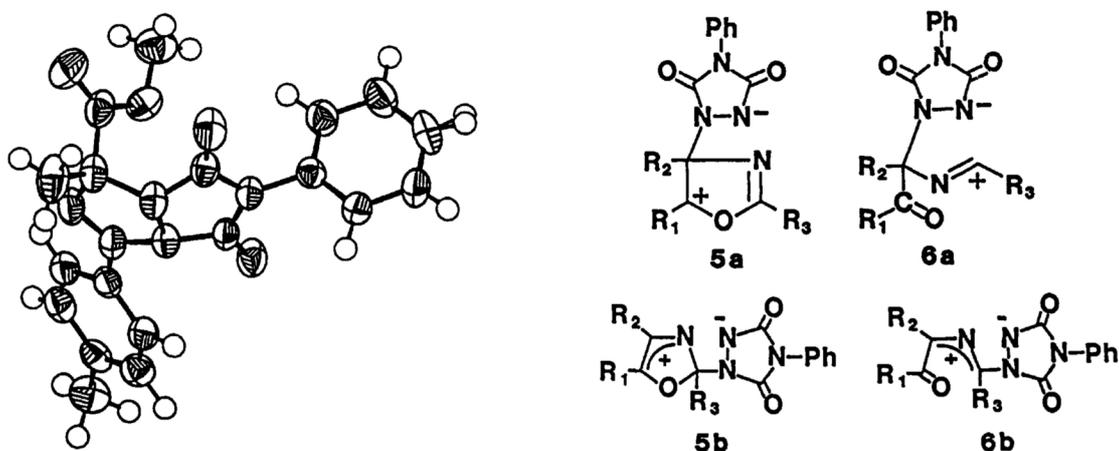


Fig. 1. ORTEP view of 3h.

The similarity of the structure of the adducts 3 with those of oxazoles and TCNE¹⁾ suggests that the reaction proceeds in a similar stepwise mechanism through zwitterion intermediates 5a or 5b followed by oxazole ring opening to give other type of zwitterions 6a or 6b, respectively, which cyclize to afford the adduct 3. However, a possibility of the process through ring opening of the normal Diels-Alder adduct 4 can not be eliminated.

Because of much higher dienophilic reactivity of PTAD than that of TCNE,⁷⁾ the reactions of PTAD with oxazoles are much faster than the cases of TCNE. Therefore, substituents on oxazoles are not so effective on the reactivity of oxazoles toward PTAD different from the reactions with TCNE.¹⁾ For example, a bulky *t*-butyl group on C_2 of oxazole depressed the reactivity toward TCNE, but gave no effect on the reaction with PTAD (run e). However, introduction of phenyl groups on C_2 and C_4 seems to lower the reactivity of oxazoles as seen in the reaction of 2,5-diphenyloxazole (1i) which shows no reaction even under reflux for 20 h in acetonitrile (run i).

As these reactions will open a new route to the synthesis of fungicidal Δ^3 -1,2,4-triazoline-1,2-dicarboximides,⁸⁾ experiments to confirm the generality of the reaction are now in progress together with the mechanistic studies.

References

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- 2) T. Ibata, S. Nakano, H. Nakawa, J. Toyoda, and Y. Isogami, *Bull. Chem. Soc. Jpn.*, **59**, 433 (1986); the reactions of 2-methyl-5-methoxy-4-(p-nitrophenyl)-oxazole (**1b**) with ethylenic, acetylenic and azo-type dienophiles were reported. In that paper we have tentatively assigned the structure of the reaction products of **1b** with PTAD as a formal Diels-Alder adduct (**4b**).
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- 4) C. J. Moody, *Adv. Heterocycl. Chem.*, **30**, 1 (1982).
- 5) All new compounds obtained show satisfactory elemental analysis.
- 6) Crystal data for **3h**: $C_{20}H_{18}N_4O_4$, $MW=378.39$, monoclinic, $a=16.267(2)$, $b=10.739(2)$, $c=11.133(1)$ Å, $\beta=103.036(9)^\circ$, space group $P2_1/n$, $Z=4$, $D_m=1.328$ g/cm³, $D_x=1.326$ g/cm³. Independent 3020 reflections were measured on a Rigaku four-circle diffractometer with Cu-K α radiation using the ω scan method for ($0^\circ < 2\theta < 60^\circ$) and $\omega - 2\theta$ scan method for ($60^\circ \leq 2\theta \leq 120^\circ$). The structure was solved by direct method (MULTAN 80) using 2379 reflections with $|Fo| > 2\sigma(Fo)$. The non-hydrogen atoms were refined anisotropically and hydrogen atoms isotropically to give $R=0.062$, $R_w=0.067$ ($w=1/(\sigma^2(Fo) + 0.0315Fo + 0.0001Fo^2)$). The hydrogen atom at para-position of N-phenyl group was disordered with occupancy factors 0.65 and 0.35. Atomic co-ordinates, bond lengths and angles, and thermal parameters will be deposited at the Cambridge Crystallographic Data Center.
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