April 1995 Communications to the Editor *Chem. Pharm. Bull.* **43**(4) 705—707 (1995)

STEREOSELECTIVE 1,4-DIPOLAR CYCLOADDITIONS OF 2-(METHYLTHIO)-3,6-DIHYDRO-3,5-DIMETHYL-6-OXO-1-SUBSTITUTED PYRIMIDINIUM-4-OLATES WITH ALKENES

Akihiro OHTA,*,[a] Fumiaki OKAZAKI,[a] Yoshiko YAMANOI,[a] Mikiko MAEDA,[a]
Yutaka AOYAGI,[a] Teruo KURIHARA[b] and Gui-Lin PANG[b]
Tokyo University of Pharmacy and Life Science, School of Pharmacy[a], 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan and Faculty of Science, Josai University[b], 1-1 Keyakidai, Sakado, Saitama 350-02, Japan

Reaction of 2-(methylthio)-3,6-dihydro-3,5-dimethyl-6-oxo-1-aryl- and alkyl-1-pyrimidinium-4-olates (**1a**-**d**) with alkenes carrying electron withdrawing groups gave 1,4-cycloadducts in good yields, demonstrating that 1,4-dipolar cycloaddition reaction proceeds with regio- and diastereoselectivity.

KEY WORDS 1,4-dipolar cycloaddition; 2-(methylthio)-3,6-dihydro-3,5-dimethyl-6-oxo-1-substituted-1-pyrimidinium-4-olate; dihydropyridine; stereoselectivity

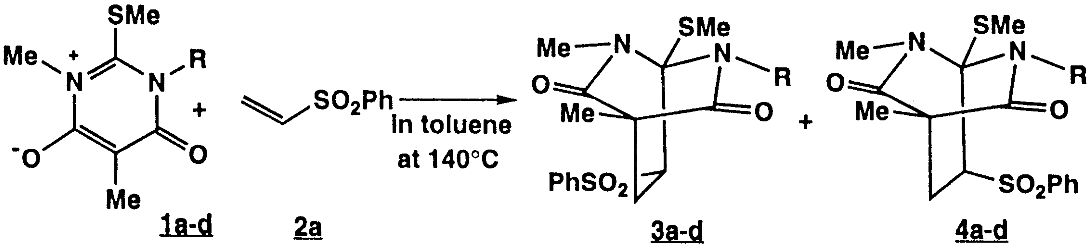
Cycloaddition reactions, such as 1,3-dipolar cycloaddition and hetero Diels-Alder reaction, have established effective strategies for the synthesis of heterocycles.1) Although 1,4-dipolar cycloaddition is known to be an efficient method for synthesis of heterocyclic systems, this reaction is much less often investigated.2) 3,6-Dihydro-6-oxo-1-pyrimidinium-4-olates are potential 1,4-dipoles, and there have been some reports on 1,4-dipolar cycloadditions of these compounds with alkynes.3) In this paper, we describe the 1,4-dipolar cycloaddition reaction to heating of 2-(methylthio)-3,6-dihydro-3,5-dimethyl-6-oxo-1-aryl or alkyl-1-pyrimidinium-4-olates (**1a**-**d**) with alkenes carrying electron withdrawing groups .

2-(Methylthio)-3,6-dihydro-3,5-dimethyl-6-oxo-1-substituted-1-pyrimidinium-4-olates (**1a**-**d**) were heated with phenylvinylsulfone (**2a**) at 140 °C in toluene in a sealed tube and yielded a cycloadduct mixture of **3a**-**d** and **4a**-**d**, which were separated easily from each other by column chromatography over silica gel. Since compounds **1a**-**d** are yellow and the reaction products are colorless, it was easy to pinpoint the end of the reaction. Especially good diastereoselectivity was observed with the reaction of **1b** and **1c** (Table 1).

---

* To whom correspondence should be addressed.

Table 1. Reactions of Several 1,4-Dipoles (1a-d) with Phenyl Vinyl Sulfone (2a)



Run	1,4-Dipole	Reaction time (h)	Yield(%) of (3+4)	Ratio (3:4)
1	1a (R=n-Pr)	8	Quantitative	47:53
2	1b (R=i-Pr)	10	Quantitative	91:9
3	1c (R=cyclohexyl)	10	96	93:7
4	1d (R=phenyl)	18	93	66:34

The structures of the products were determined by ^{1}H-^{1}H-NOESY. NOE was observed between the methyl protons on N-3 and the methine proton on the carbon attached to the electron withdrawing group (SO_2Ph) in 4d , but this NOE was not observed between the corresponding protons in 3d (Chart 1).

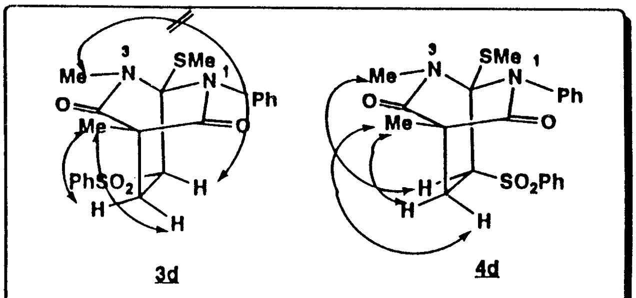


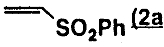
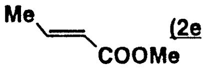
Chart 1

In the reactions of various alkenes (2b-f) with pyrimidinium-4-olates (1c,d) under heating, regio- and diastereoselective 1,4-dipolar cycloaddition was observed to have taken place in all cases (Table 2). This reaction seemed to be not a charge controlled reaction but a orbital controlled reaction, because only one kind of adduct (3 and 4, each) is obtained in runs 9-11. The regioselective [4+2] cycloadditions, presented by Padwa *et al.*,[4] proceed by the LUMO (dipole)-HOMO (dipolarophile) interactions.[5] On the other hand, in the present work, molecular orbital calculation with PM3 method confirmed that the reaction of these systems proceeds by the oposite interaction: the LUMO (dipolarophile)-HOMO (dipole) interaction.[6]

The thermolysis of 3d and 4d gave the identical plane dihydropyridine product (5) in 85 and 41 % yields, respectively (Chart 2).

The 1,4-dipolar cycloaddition reaction between pyrimidinium-olates and alkenes is being further studied on the basis of the MO theory. The thermolysis of cycloadducts to yield tetrahydropyridines directly is also being studied. These results will be reported elsewhere.

Table 2. Reactions of 1,4-Dipoles(1c and 1d) with Alkenes (2a-f)

Run[a]	1,4-Dipole	Alkene	Solvent	Reaction time(h)	Yield(%) of (3+4)[1]	Ratio (3+4)
1	1c	 (2a)	Toluene	10	96	93:7
2	1d	2a	Toluene	18	93	66:34
3	1c	 (2b)	Toluene	5	Quantitative	91:9
4	1d	2b	Toluene	5	Quantitative	80:20
5	1c	 (2c)	Toluene	5	87	88:12
6	1d	2c	Toluene	5	Quantitative	69:31
7	1c	N-Methyl-maleimide (2d)	Toluene	5	Quantitative	84:16
8	1d	2d	Toluene	5	Quantitative	76:24
9	1c	 (2e)	o-Dichloro-benzene	24	73	81:19
10	1d	2e	o-Dichloro-benzene	6	55	79:21
11	1c	Diethyl fumalate (2f)	o-Dichloro-benzene	8	85	77:23
12	1d	2f	o-Dichloro-benzene	24	61	77:23

a) The reactions were carried out at 140°C in Runs 1~8; at 200°C in Runs 9~12.

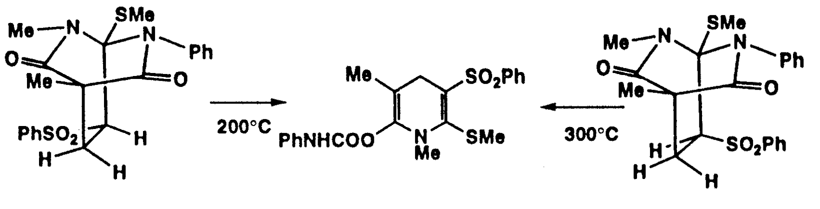


Chart 2

REFERENCES AND NOTES

1) Carruthers W., " Cycloaddition Reactions in Organic Synthesis," Vol. 8, ed. by Baldwin J. E., Pergamon Press, London, 1990.

2) Huisgen R., " The Adventure Playground of Mechanisms and Novel Reactions," ed. by Seeman J. I., American Chemical Society, Washington, DC, 1994.

3) a) Potts K. T., Dery M. O., *J. Org. Chem.*, **55**, 2884 (1990); b) Kappe T., Pocivalink D., *Heterocycles*, **20**, 1367 (1983); c) Gotthardt H., Schenk K. -H., *Chem. Ber.*, **119**, 1315 (1986).

4) Padwa A., Coats S. J., Semones M. A., *Tetrahedron Lett.*, **34**, 5405 (1993).

5) Sustmann R., *Tetrahedron Lett.*, 2717 (1971).

6) These detailed calculation results will be described in our articles in near future.

(Received December 19, 1994; accepted March 1, 1995)