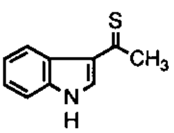
SYNTHESIS OF THIAPYRANO[4,3-*b*]INDOLES BY THE HETERO DIELS-ALDER REACTION USING 3-THIOACETYLINDOLES AS A DIENE

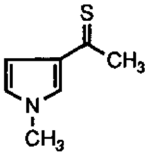
Masayuki Murase, Noriaki Nishino, Norichika Nara, Yoshimi Nakanishi, and Seisho Tobinaga*

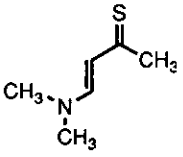
Showa College of Pharmaceutical Sciences, Machida, Tokyo 194 , Japan

Abstract-A new synthesis of thiapyrano[4,3-*b*]indoles by the hetero Diels-Alder reactions of 3-thioacetylindoles (**1**) with dienophiles is described.

A large number of reports of the hetero Diels-Alder reactions using heterobutadienes including thiobutadienes have been published to date.[1] On the other hand, we reported that 3-thioacetylindole (**1**), 3-thioacetylpyrrole (**2**) and the acyclic thioketone (**3**) yield dienes by alkylation reactions, and the resulting dienes undergo the Diels-Alder reactions with appropriate dienophiles to give the functionalized carbazoles and indoles.[2]

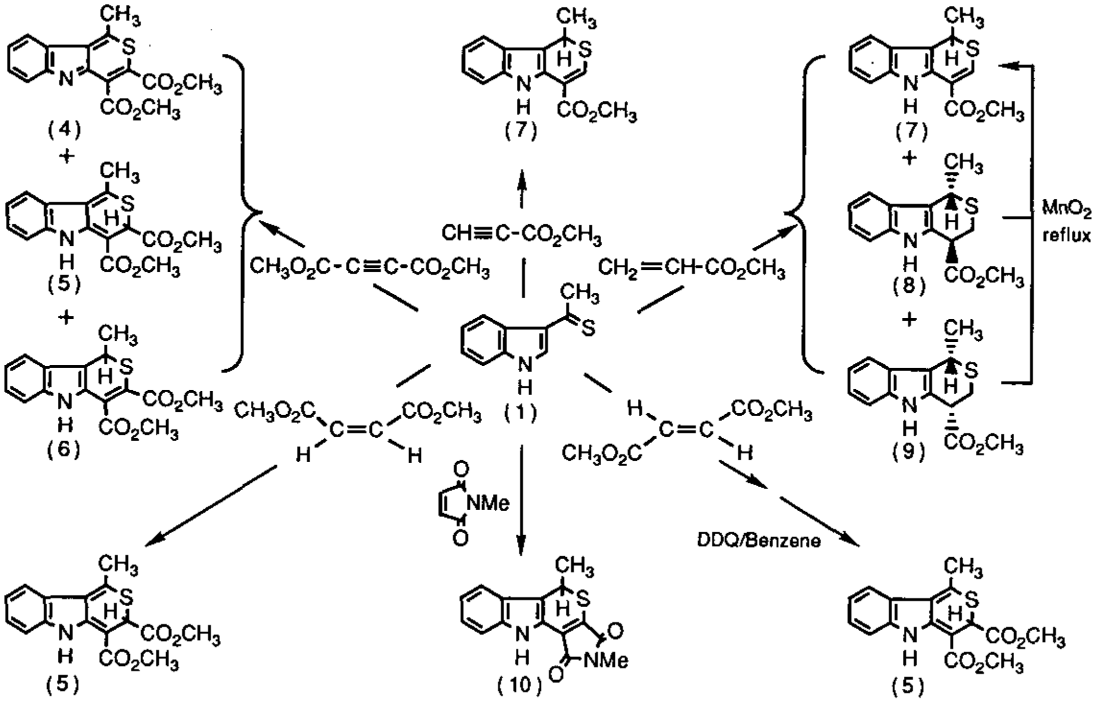

(1)


(2)


(3)

This paper describes an efficient method for the synthesis of thiapyrano[4,3-*b*]indoles by means of the hetero Diels-Alder reactions of 3-thioacetylindole (**1**) as a heterodiene with several dienophiles.

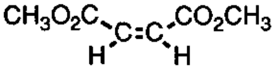
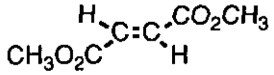
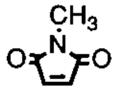
A general cycloaddition reaction with a dienophile was carried out as the following manner. A mixture of **1** (525 mg, 3 mmol) and dienophile (3.3 mmol) in CH_3CN (7.5 ml) was treated in a fused glass tube under the appropriate conditions. After the reaction, the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography using an appropriate solvent. The obtained results of the cycloaddition reactions of **1** with several dienophiles are summarized in Scheme 1 and Table 1.



Schme 1

Reaction of **1** with dimethyl acetylenedicarboxylate (run 1) gave dimethyl 1-methylthiapyrano[4,3-*b*]indole-3,4-dicarboxylate (**4**), which was precipitated as yellow crystals from the solvent, dimethyl 3,5-dihydro-1-methylthiapyrano[4,3-*b*]indole-3,4-dicarboxylate (**5**), and dimethyl 1,5-dihydro-1-methylthiapyrano[4,3-*b*]indole-3,4-dicarboxylate (**6**) respectively.[3] Other related experimental results by the general procedure are summarized in Scheme 1. The structures of **8** and **9**[5] (run 5) were confirmed by the chemical transformation to give **7**[4] by the treatment of each compounds with

Table 1 Cycloaddition Reaction of the Diene (1) with Dienophile

Run	Dienophile	temp (°C)	time (h)	product	Yield	mp (°C)
1	$CH_3O_2CC\equiv CCO_2CH_3$	room temperature	2	(4)	22.2	213 (decomp.)
				(5)	4.5	167~169
				(6)	33.4	oil
2	 $CH_3O_2C(H)C{=}C(H)CO_2CH_3$	110	48	(5)	47	
3	 $(H)(CH_3O_2C)C{=}C(CO_2CH_3)(H)$	110	48	(5)	25.2[a)]	
4	$CH\equiv CCO_2CH_3$	room temperature	72	(7)	67.2	103~104
5	$CH_2{=}CHCO_2CH_3$	110	48	(7)	18.5	
				(8)	32.6	111~113
				(9)	36.4	oil
6		room temperature	1	(10)	5.0	oil

a) Obtained by the oxidation of the cycloaddition product without purification.

active MnO_2 in refluxing benzene for 1 h. Also the structures of **8** and **9** were assigned to trans and cis isomers from the ^1H-nmr studies in which the C-4 proton of the compound (**9**) was observed as ABX type signal but the C-4 proton signal of the compound (**8**) as triplet. Additionaly, the NOE experiments of the compounds (**8**) and (**9**) support these assignments.

Further studies on the application of this reaction for related thiobutadienes are now under way.

REFERENCES AND NOTES

1) a) D. L. Boger and S. M. Weinreb., "Hetero Diels-Alder Methodology in Organic Synthesis", Academic Press, Inc., San Diego, 1987, Chap. 8; b) T. Karakasa and S. Motoki, *J. Org. Chem.*, 1979, **44**, 4151; 1978, **43**, 4147; c) K. R. Lawson, A. Singleton, and G. H. Whitham., *J. Chem. Soc.*, Perkin Trans. I, **1984**, 859; d) K. Kanakarajan and H. Meier., *J. Org. Chem.*, 1983, **48**, 881; e) B. M. Trost, and I. Fleming., "Comprehensive Organic Synthesis", Vol. 5, Pergamon Press, Inc., Oxford, 1991, p. 468.

2) a) M. Murase, T. Hosaka, T. Koike, and S. Tobinaga., *Chem. Pharm. Bull.*,

1989, **37**, 1999; b) M. Murase, S. Yoshida, T. Hosaka, and S. Tobinaga, *Chem. Pharm. Bull.*, 1991, **39**, 489; c) M. Murase, T. Hosaka, S. Yoshida, and S. Tobinaga, *Chem. Pharm. Bull.*, 1992, **40**, 1343.

3) **4**: Ms m/z 315 (M$^+$); ^{1}H-nmr (CDCl$_3$) δ: 3.14 (3H, s, C-1Me), 4.02 (3H, s, -CO$_2$Me), 4.16 (3H, s, -CO$_2$Me), 7.48 (1H, t, J=7.6 Hz, C-7 or 8H), 7 .66 (1H, t, J=7.6 Hz, C-7 or 8H), 8.08 (1H, d, J=7.6 Hz, C-6H), 8.10 (1H, d, J=7.6 Hz, C-9H). **5**: Ms m/z 317 (M$^+$); ^{1}H-nmr (CDCl$_3$) δ: 2.45 (3H, s, C-1Me), 3.70 (3H, s, -CO$_2$Me), 3.78 (3H, s, -CO$_2$Me), 4.86 (1H, s, C-3H), 6.97 (1H, t, J=7.6 Hz, C-8H), 6.97 (1H, d, J=7.6 Hz, C-6H), 7.19 (1H, t, J=7.6 Hz, C-7H), 7.48 (1H, d, J=7.6 Hz, C-9H), 9.70 (1H, br, NH). **6**: Ms m/z 317 (M$^+$); ^{1}H-nmr (CDCl$_3$) δ: 1.50 (3H, d, J=6.7 Hz, C-1Me), 3.83 (3H, s, -CO$_2$Me), 3.87 (3H, s, -CO$_2$Me), 4.80 (1H, q, J=6.7 Hz, C-1H), 7.10 (1H, t, J=7.6 Hz, C-7 or 8H), 7.20 (1H, t, J=7.6 Hz, C-7 or 8H), 7.48 (1H, d, J=7.6 Hz, C-6H), 7.63 (1H, d, J=7.6 Hz, C-9H), 10.36 (1H, br, NH).

4) **1,5-Dihydro-1-methylthiapyrano[4,3-*b*]indole-4-carboxylate 7**: Ms m/z 259 (M$^+$); ^{1}H-nmr (CDCl$_3$) δ: 1.53 (3H, d, J=1.2 Hz, C-1Me), 3.88 (3H, s, -CO$_2$Me), 4.72 (1H, q, J=1.2 Hz, C-1H), 7.11 (1H, t, J=7.9 Hz, C-7 or 8H), 7.19 (1H, t, J=7.9 Hz, C-7 or 8H), 7.36 (1H, d, J=7.9 Hz, C-6H), 7.48 (1H, d, J=7.9 Hz, C-9H), 7.61 (1H, s, C-3H), 9.77 (1H, br, NH).

5) **trans-1,3,4,5-Tetrahydro-1-methylthiapyrano[4,3-*b*]indole-4-carboxylate 8**: Ms m/z 261 (M$^+$); ^{1}H-nmr (CDCl$_3$) δ: 1.73 (3H, d, J=7.0 Hz, C-1Me), 3.28 (1H, d, J=4.6 Hz, C-3Ha), 3.30 (1H, d, J=4.6 Hz, C-3Hb), 3.78 (3H, s, -CO$_2$Me), 4.00 (1H, t, J=4.6 Hz, C-4H), 4.22 (1H, q, J=7.0 Hz, C-1H), 7.11 (1H, t, J=7.0 Hz, C-7 or 8H), 7.19 (1H, t, J=7.0 Hz, C-7 or 8H), 7.35 (1H, d, J=8.2 Hz, C-6H), 7.53 (1H, d, J=8.2 Hz, C-9H), 8.38 (1H, br, NH). **cis-1,3,4,5-Tetrahydro-1-mehtylthiapyrano[4,3-*b*]indole-4-carboxylate 9**: Ms m/z 261 (M$^+$); ^{1}H-nmr (CDCl$_3$) δ: 1.74 (3H, d, J=7.0 Hz, C-1Me), 3.09 (1H, dd, J=14 and 4.9 Hz, C-3Ha), 3.43 (1H, dd, J=14 and 10 Hz, C-3Hb), 4.07 (1H, dd, J=10 and 4.9 Hz, C-4H), 4.17 (1H, q, J=7.0 Hz, C-1H), 7.1 (1H, t, J=7.6 Hz, C-7 or 8H), 7.18 (1H, t, J=7.6 Hz, C-7 or 8H), 7.34 (1H, d, J=7.6 Hz, C-6H) 7.51 (1H, d, J=7.6 Hz, C-9H).

6) **5,10-Dihydro-2,5-dimethylpyrrolo[3,4-*b*]indole[2,3-*d*]thiapyran-1,3-dione 10**: MS m/z 236 (M$^+$); ^{1}H-nmr (CDCl$_3$) δ: 1.62 (3H, d, J=6.7 Hz, C-5Me), 3.10 (3H, s, N-Me), 4.98 (1H, q, J=6.7 Hz, C-5H), 7.16 (1H, t, J=8.2 Hz, C-7 or 8H), 7.25 (1H, t, J=8.2 Hz, C-7 or 8H), 7.40 (1H, d, J=8.2 Hz, C-9H), 7.53 (1H, d, J=8.2 Hz, C-6H), 8.65 (1H, br, NH).

Received, 30th September, 1993