DIELS-ALDER REACTION OF 3-(2-PYRIDYLSULFINYL)ACRYLATES ----- THE ENHANCEMENT OF THE REACTIVITY AND THE DIASTEREOSELECTIVITY BY THE INTRODUCTION OF ELECTRON-WITHDRAWING SUBSTITUENTS ON THE PYRIDINE RING

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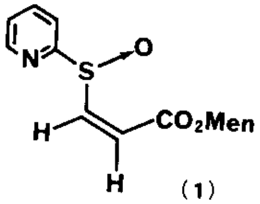
Abstract——The introduction of nitro or trifluoromethyl group at C_3 position on pyridine ring enhanced the reactivity and the diastereoselectivity of 3-(2-pyridylsulfinyl)acrylate in the Diels-Alder *reaction with furan.*

Asymmetric Diels-Alder(D-A) reaction using chiral sulfinylacrylates has recently received a considerable attention.[1] The application of this new methodology to asymmetric organic synthesis, however, has been limited only to chiral synthesis of bicyclo[2.2.1]heptenes owing to the low reactivity of these chiral dienophiles. Very recently we have developed new chiral dienophiles, $(\mathbf{S})_S$- and $(\mathbf{R})_S$-menthyl 3-(2-pyridylsulfinyl)acrylates (**1**), and achieved the first efficient asymmetric synthesis of 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate derivatives.[2] The use of 2-pyridyl group, which has a stronger inductive electron-withdrawing effect than the p-tolyl group, enhanced the dienophilic reactivity considerably. However, the D-A reaction of (**1**) with furan, which is known to be one of the low reactive dienes, proceeded rather sluggishly and the use of diethylaluminum chloride was essential for the realization of high diastereoselectivity. Therefore the



(**1**)

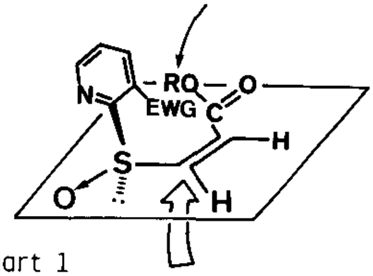
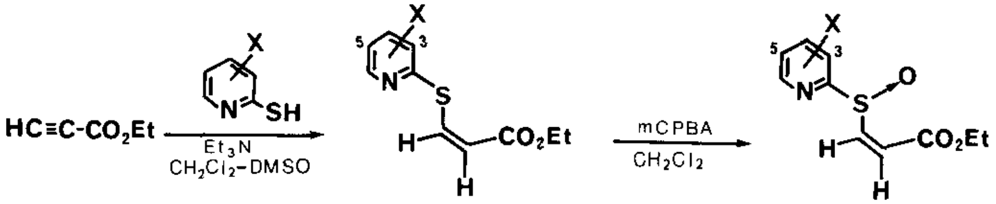


Chart 1

development of those new dienophiles is strongly required, which react smoothly and diastereoselectively with less-reactive dienes even in the absence of Lewis acid. The introduction of electron-withdrawing group (EWG), such as nitro or trifluoromethyl group, at the α position of the sulfinyl group on pyridine ring in compound (**1**) could enhance both the dienophilic reactivity and the diastereofacial selectivity by the electronic and steric effects of the substituent **EWG** during the cycloaddition process (Chart 1). Bearing these consideration in mind, we investigated the D-A reaction of 3-(2-pyridylsulfinyl)acrylates (**2**)-(**5**) with furan. The present communication describes the results along this line which would lead one to expect the development of new and efficient dienophiles.

The requisite dienophiles (**2**)-(**5**)[3] were prepared as follows. Triethylamine-catalysed Michael addition of 2-mercaptopyridine, 3-nitro-2-mercaptopyridine[4], and 3- and 5-trifluoromethyl-2-mercaptopyridine[5] to ethyl propiolate afforded preferentially the cis-sulfides (**6**)-(**9**)[6], which were then oxidized with m-chloroperbenzoic acid(mCPBA) to give the corresponding sulfoxides (**2**)-(**5**)[7], in high yields (Scheme 1).

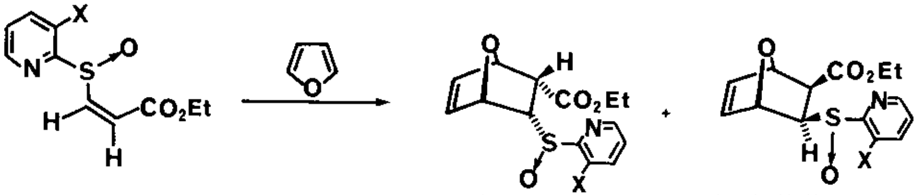


(**6**) X=H
(**7**) $X=3\text{-}NO_2$
(**8**) $X=3\text{-}CF_3$
(**9**) $X=5\text{-}CF_3$

(**2**) X=H
(**3**) $X=3\text{-}NO_2$
(**4**) $X=3\text{-}CF_3$
(**5**) $X=5\text{-}CF_3$

Scheme 1

The D-A reaction of the sulfoxides was carried out with a large excess furan in a sealed tube under argon atmosphere (Scheme 2). The condition and the results on the diastereomeric products were summarized in Table 1. The cycloaddition of (**4**) with furan proceeded at room temperature to give the endo adducts (**14**) predominantly. Moreover, high diastereoselectivity was observed (entry 2 and 3) without employing any Lewis acid. In case of the nitro derivative (**3**), only the single diastereomer was detected both in the endo and exo products, as checked by the ^1H(200MHz)- and ^{13}C-NMR analysis. The D-A reaction of 5-trifluoromethyl derivative (**5**) with furan proceeded at ambient temperature, but the diastereoselectivity was low compared with that observed in the case of (**4**).



(2) X=H
(3) X=NO_2
(4) X=CF_3

(10) X=H
(12) X=NO_2
(14) X=CF_3

(11) X=H
(13) X=NO_2
(15) X=CF_3

Scheme 2

Table 1. Diels-Alder Reaction of 3-(2-Pyridylsulfinyl)acrylates with Furan.

entry	dienophiles	condition temp.	condition days	endo adducts[8] yield	endo adducts[8] diastereoselectivity(a:b)[9]	exo adducts[8] yield	exo adducts[8] diastereoselectivity(a:b)[9]
1	(2) X=H	50°C	6	(10) 49%	(55:45)	(11) 13%	(93:7)
2	(3) X=NO_2	50°C	6	(12) 56%	(>98:2)	(13) 16%	(>98:2)
3	(4) X=CF_3	rt	7	(14) 63%	(92:8)	(15) 7%	(93:7)

[endo adducts; diastereoselectivity (80:20), exo adducts; diastereoselectivity (83:17)]. This result implies that the presence of a substituent at the α position of the sulfinyl group is essential for the realization of high diastereoselectivity.

In conclusion, we have found that the introduction of electron-withdrawing substituent at C_3 position on pyridine ring considerably enhanced the reactivity and the diastereoselectivity of 3-(2-pyridylsulfinyl)acrylate (**2**) in the D-A reaction. The preliminary experiments for the optical resolution of menthyl 3-(3-trifluoromethylpyrid-2-ylsulfinyl)acrylates was undertaken to afford $(S)_S$ sulfoxide in a diastereomerically pure state.[10] The D-A reaction of this chiral dienophile with furans proceeded highly diastereoselectively as the racemic derivative (**4**). The optimization of the yields of the above optical resolution and the asymmetric synthesis of optically active natural products employing these dienophiles are in progress in this laboratory, and the results will be reported in due course.

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2. H. Takayama, A. Iyobe, and T. Koizumi, J.Chem.Soc., Chem.Commun., in press.
3. All new compounds reported here gave satisfactory spectroscopic and analytical data.
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5. 3-Trifluoromethyl-2-mercaptopyridine(mp 160-162°C) was prepared from 2-chloro-3-trifluoromethylpyridine according to the method of literature (reflux in ethanol with thiourea for 39h then alkaline hydrolysis, yield 76%). T. Haga, K. Fujisawa, T. Koyanagi, T. Nakajima, and K. Hayashi, Heterocycles, 1984, 22, 117.
6. (**6**):mp 68°C, yield 82%. (**7**):mp 136-137°C, yield 77%. (**8**):mp 60-62°C, yield 86%. (**9**):mp 119-119.5°C, yield 59%.
7. (**2**):gummy oil, yield 97%. (**3**):mp 84-85°C, yield 71%. (**4**):mp 58-59°C, yield 99%. (**5**):mp 69-69.5°C, yield 67%.
8. The structures of the cycloadducts were respectively determined by chemical transformation to *endo*- and *exo*-2-carbethoxy-7-oxabicyclo[2.2.1]heptane (W. L. Nelson and D. R. Allen, J. Heterocycl. Chem., 1972, 9, 561). (**10**):(major diastereomer), mp 64-65°C, ^{1}H-NMR(CDCl$_3$) δ; 4.20(dd,J=9 and 4.5Hz), 3.59(dd,J=9 and 4.5Hz). (**11**):(major diastereomer), ^{1}H-NMR δ; 3.49(d,J=8Hz), 2.89(d,J=8Hz). (**12**):mp 133-134 °C, ^{1}H-NMR δ; 4.76(1H,dd,J=9 and 4Hz), 3.54(1H,dd,J=9 and 4Hz). (**13**):mp128-129°C, ^{1}H-NMR δ; 3.92(d,J=8Hz), 2.85(d,J=8Hz). (**14**):(major diastereoisomer) mp 119-121 °C, ^{1}H-NMR δ; 5.01(dd,J=9 and 4Hz), 3.59(dd,J=9 and 4Hz) (**15**):(major diastereoisomer) ^{1}H-NMR δ; 4.18(d,J=8Hz), 2.89(d,J=8Hz).
9. Notation **a** and **b** refer to diastereomeric cycloadducts derived from the attack of furan on the *re* or *si* face of the acrylate. The ratio of diastereoisomer was determined by ^{1}H-NMR(200MHz) analysis. The diastereoisomeric relationship concerning the sulfoxide was confirmed as follows. The TiCl$_3$ reduction of the sulfoxides (**10**, **11**, **14** , and **15**) gave the single sulfide, respectively, which afforded a mixture of diastereoisomeric sulfoxides again in a ratio of about 1:1 by mCPBA oxidation. (The treatment of compounds **12** and **13** with TiCl$_3$ gave 3-aminopyridine derivatives).
10. mp 148-149°C, $[\alpha]_D^{24}$ +189°(c1.08,CHCl$_3$).

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