EFFICIENT MICHAEL ADDITION REACTIONS OF THE *N*-ARYLSULFONYL-3-PHENYLTHIOPIPERIDONES. SYNTHESIS OF 3-SUBSTITUTED DIHYDROPYRIDINONES †

Masako Nakagawa*, Yasuhiro Torisawa, Toshihiro Hosaka, Kiyoshi Tanabe, Fabrice Tavet, Maki Aikawa, and Tohru Hino*

Faculty of Pharmaceutical Sciences, Chiba University
1-33, Yayoi-cho, Inage-ku, Chiba-shi, 263 Japan

Abstract- Efficient methods for the Michael addition reactions of *N*-arylsulfonyl-3-phenylthiopiperidones (**1**) with both the protected amidoacrylates (**4, 9**) and the simple acrylates (**12**) have been developed. These reactions offer an efficient route to the 3-alkyl-substituted dihydropyridinones (**3, 11**), the dienophiles employed in the natural product synthesis.

During the course of our synthetic study on the antitumor marine alkaloid manzamine A,[1] it was necessary to prepare various derivatives of *N*-arylsulfonyl-3-alkyl-3-phenylthiopiperidones (**2**) starting from *N*-arylsulfonyl-3-phenylthiopiperidones (**1**).[2] These compounds served as effective precursors to *N*-arylsulfonyl-3-alkyldihydropyridinones (**3**), the dienophile employed in the Diels-Alder reaction with Danishefsky diene.[2,3] Although conventional α-alkylation of **1a** with methyl iodide proceeded without event, alkylation with slightly bulky alkyl halides (EtI, *n*-BuI, *i*-BuI, ICH_2CH_2Br) were unsuccessful.

---

† This paper is dedicated to Professor E. C. Taylor, Princetone University, on the occasion of his 70 th birthday.

Scheme I

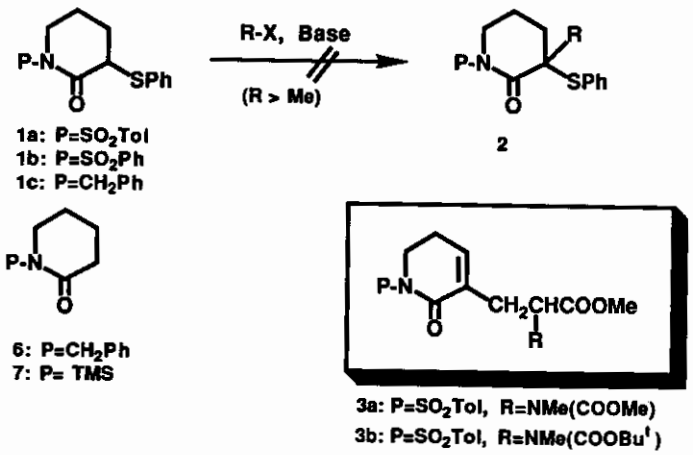
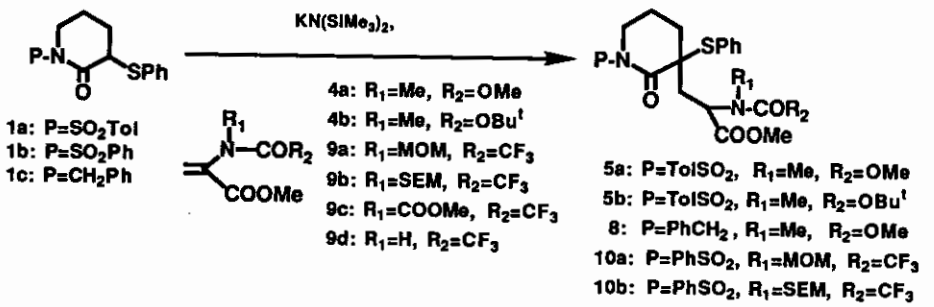


Table I. The Michael Reactions with Some Amidoacrylates



run	substrate	equiv. of base	acrylate	conditions	product	yield (%)
1)	1a	0.5	4a	-60°~-20°C, 2 h	5a	72[2c]
2)	1a	0.5	4b	-25° C, 1 h	5b	90[2c]
3)	1c	0.8	4a	-78° C, 15 min	8a	68
4)	1b	0.1	9a	-78° C, 15 min	10a	95
5)	1b	0.1	9b	-78° C, 0.5 h	10b	quant
6)	1b	0.8	9c	-78° C ~ room temperature	No Reaction	
7)	1b	0.8	9d	-78° C ~ room temperature	No Reaction	

The fact that α-dialkylation occurred quite smoothly in the case of *N*-CH_2Ph[4] and *N*-TMS[5] piperidones (**6**, **7**) suggested the difficulty might stem from the electron-withdrawing character of *N*-*p*-toluenesulfonyl (Ts) group and hence the susceptibility of the piperidone ring to the nucleophilic attack. To overcome these problems, the Michael addition reactions of *N*-arylsulfonyl-3-phenylthiopiperidones to various acrylate derivatives have been surveyed, especially to amidoacrylates (dehydroalanine derivatives, e.g. **4** and **9**) in order to obtain a suitable intermediate for our synthesis. Herein, we describe the details of these survey showing the effectiveness of these reactions in the catalytic C-C bond forming process.

We initiated our survey on the Michael addition between **1a** and two amidoacrylate (**4a**, **4b**) to clarify the effect of the substituents (especially the *N*-protecting groups in the Michael acceptor). As expected these acrylates reacted smoothly with **1a** in the presence of the weakly nucleophilic base $KN(TMS)_2$ in THF (Table I). The use of this base was critical, because we had already observed that $KN(TMS)_2$ was superior to LDA for the anion generation from **1**.

As shown in the Table I, initial results obtained with *N*-Ts-piperidone (**1a**, run 1, 2)[2c] and *N*-benzylpiperidone (**1c**, run 3) were quite satisfactory. A slight difference in the reactivity of these two differently *N*-protected piperidones (**1a** and **1c**) was observed; *N*-benzylpiperidone (**1c**) reacted at -78°C within 15 min to afford **8**, while *N*-Ts derivative (**1a**) required slightly higher temperature and longer reaction time. These Michael adducts obtained were successfully converted to the 3-substituted dihydropyridinones (**3a**, **3b**) by mCPBA oxidation and subsequent PhSOH elimination (Scheme I).[2c]

Encouraged by these initial success, we tried to search more mild and practical conditions for this Michael reaction especially in view of the amount of base and reaction temperature. Thus, various amidoacrylate derivatives were prepared in order to obtain a more reactive and suitable Michael acceptor for a catalytic process. Amidoacrylate derivatives with different *N*-protecting groups were obtained from DL-serine methyl ester hydrochloride by the reported procedure.[6] Among the derivatives prepared, *N*-$COCF_3$ compounds such as **9a** and **9b** showed an extraordinal reactivity as shown in the Table I. The Michael reaction of *N*-benzenesulfonylpiperidone (**1b**) with the *N*-MOM derivative (**9a**) proceeded at -78 °C with a catalytic (0.1 equiv.) amount of base in 95% yield. The more easily deprotective *N*-SEM derivative (**9b**) also reacted with **1b** quantitatively.

Scheme II

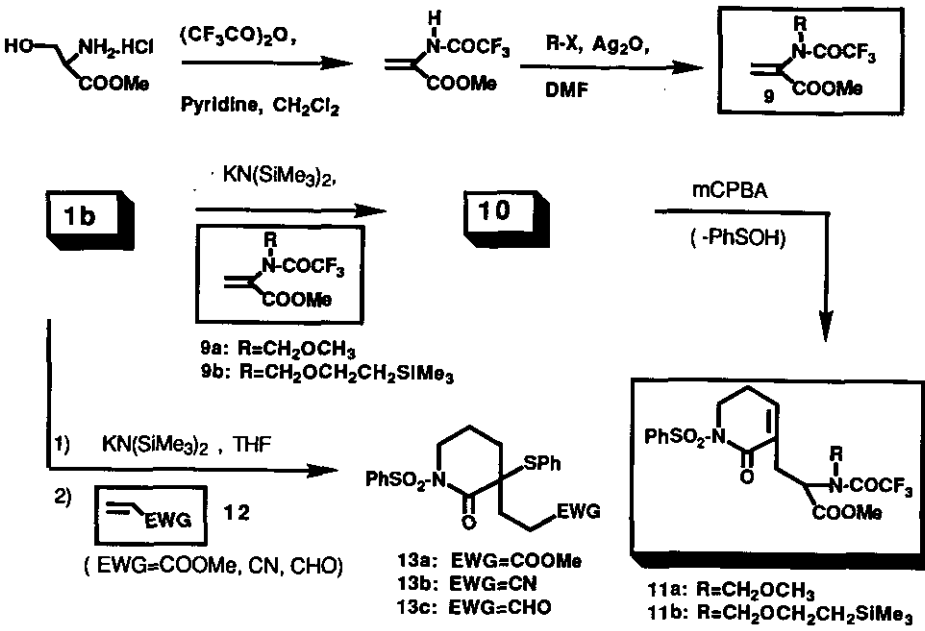
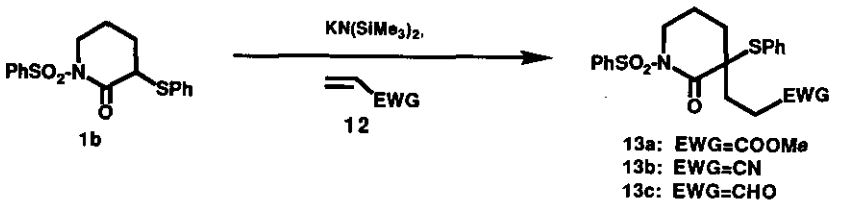


Table II. The Michael Reactions with Simple Acrylates



run	substrate	equiv. of base	12	conditions	product	yield (%)
1)	1b	0.6	Methyl acrylate	-15° C, 2 h	13a	84
2)	1b	0.3	Acrylonitrile	0° C, 2 h	13b	60
3)	1b	0.02	Acrolein	-5° C, 1 h	13c	72

In addition, we have developed an efficient two-step preparation method (Scheme II) for **9**, which proved more convenient than the previously reported procedure.[6]

As a suitable *N*-protecting group for these Michael acceptors, a combination of $COCF_3$ and MOM (as in **9a**) or $COCF_3$ and SEM (as in **9b**) was found to be the best; namely one is electron-donating and the other is electron-withdrawing. Reaction did not occur at all in the case of $NCOCF_3$(COOMe) derivative (**9c**) or $NHCOCF_3$ derivative (**9d**).

These Michael adducts (**10a**, **10b**) were successfully converted to the 3-substituted dihydropyridinones (**11a**, **11b**) by *m*CPBA oxidation and subsequent PhSOH elimination.

We next turned our attention to the more simple but none the less important acrylate derivatives (**12**). Because of the intrinsic lability of these compounds towards base (polymerization), the reaction conditions were carefully optimized. Among the three typical compounds (**12**) examined, acrylonitrile showed modest reactivity (Table II, run 2), while in the case of methyl acrylate a milder condition was required (Table II, run 1) but the yield was quite satisfactory (84 %). In the case of acrolein, similar reaction conditions were ineffective to result in a messy mixture, because of the polymerization. After several attempts, it was found that the amount of the base employed was crucial. Thus, in the presence of minimum base (0.02 equiv.), acrolein was added to the diluted solution of **1b** in THF at 0°C to afford the fairly stable adduct in 72% yield (Table II, run 3).

The product obtained here was served as a useful intermediate in our synthetic approach to manzamine B.

In summary, efficient methods for the Michael addition reactions of *N*-arylsulfonyl-3-phenylthio-piperidones (**1**) have been developed with some suitably protected amidoacrylates (**4**, **9**) and simple acrylates (**12**). These reactions offer both an efficient route toward functionalized amino acid derivatives and an alternative mild method for α-alkylation of some carbonyl compounds in which direct alkylation was unsuccessful. Of special interest is an asymmetric version of these catalytic C-C bond forming processes, which is now being explored.

EXPERIMENTAL

General. Melting points are uncorrected. Unless otherwise noted, ir spectra were measured as a KBr disk, and ^{1}H- and ^{13}C nmr spectra were measured as a solution in $CDCl_3$. Preparation of the *N*-*p*-toluenesulfonyl-3-phenylthiopiperidone (**1a**) and the *N*-BOC and *N*-COOMe amidoacrylates (**4a, 4b**), as well as the Michael addition reactions of **1a** with these two amidoacrylates (**4a, 4b**) and further conversion to the dienophiles (**3a, 3b**) have already been reported.[2c]

N-Benzenesulfonyl-3-phenylthio-2-piperidone (1b)

1b was prepared as follows according to the method previously reported for *N*-*p*-toluenesulfonyl-3-phenylthiopiperidone (**1a**).[2c]

N-Benzenesulfonyl-2-piperidone. To a stirred solution of 2-piperidone (6.0 g, 60.0 mmol) in THF (100 ml) was added slowly a *n*-BuLi solution (40 ml, 1.6M hexane solution, 60 mmol) at -60 °C and the resulting mixture was kept stirring for 20 min. Benzenesulfonyl chloride (10.5 g, 60 mmol) was added dropwise by syringe and the mixture was kept stirring for 30 min at this temperature. The mixture was then warmed to 0 °C over 2 h and quenched by the addition of sat NH_4Cl (30 ml) and extarcted with AcOEt (200 ml x3). The combined AcOEt layer was washed with water (50 ml) and brine (50 ml). After drying over $MgSO_4$, the solvents were removed under reduced pressure to afford the crude product, which was recrystalized from MeOH/Et_2O (2/1) to afford the pure *N*-benzenesulfonyl-2-piperidone (10.6 g, 73.6 g) as colorless crystals: mp 72~73°C (MeOH/ Et_2O); ir 3050, 2950, 2900, 1700, 1580, 1480, 1460, 1400, 1370, 1360, 1330, 1300, 1260 cm^{-1}; ^{1}H nmr (500 MHz) δ 1.76-1.81 (2H, m, CH_2), 1.89-1.94 (2H, m, CH_2), 2.42 (2H, t, *J*=6.75 Hz, 3-CH_2), 3.92 (2H, t, *J*=5.95 Hz, 6-CH_2), 7.26-7.63 (3H, m, aromatic), 8.02 (2H, d, *J*=7.5 Hz, aromatic); LRFABms *m/z* (%): 240 (MH^+, 100), 154 (18), 137 (13). Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.23; H, 5.44; N, 5.86; Found: C, 54.97; H, 5.35: N, 5.72.

N-Benzenesulfonyl-3-phenylthio-2-piperidone (1b). To a cooled (-78 °C) and stirred mixture of *N*-benzenesulfonyl-2-piperidone (10.9 g, 45.6 mmol) and diphenyldisulfide (8.37g, 45 mmol) in dry THF (450 ml) was added $KN(TMS)_2$ (0.5 M soln in toluene, 185 ml, 92.5 mmol) dropwise by syringe. The resulting mixture was then kept stirring at this temperature for 0.5 h. After tlc analysis (AcOEt/ *n*-hexane=1/1), the mixture was quenched by the addition of sat. NH_4Cl (100 ml) and further with ether-

AcOEt (1/1, ~300 ml). The organic layer was separated and aqueous layer was extracted with AcOEt (200 mlx2). The combined organic layers were washed with brine (100 mlx2) and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was recrystalized from MeOH to furnish the pure *N*-Benzenesulfonyl-3-phenylthio-2-piperidone (**1b**, 8.82 g, 69.8%) as a white solid: mp 105 °C (MeOH); ir 3050, 2950, 1690, 1580, 1480, 1450, 1390, 1360, 1340, 1280, 1260, 1170 cm^{-1}; ^1H nmr (500 MHz) δ 1.84-1.98 (2H, m, CH_2), 2.00-2.20 (2H, m, CH_2), 3.70 (1H, t, *J*=5.91 Hz, 3-H), 3.88-4.10 (2H, m, CH_2), 7.16-7.29 (5H, m, aromatic), 7.51-7.55 (2H, m, aromatic) 7.60-8.00 (1H, m, aromatic), 8.03 (2H, d, *J*=6.80 Hz, aromatic); LRFABms *m/z* (%): 348 (MH^+, 100). Anal. Calcd for $C_{17}H_{17}NO_3S_2$: C, 58.77; H, 4.93; N, 4.03; Found: C, 58.52; H, 4.80: N, 3.93.

N-Benzyl-3-phenylthio-2-piperidone (1c)

N-Benzyl-2-piperidone . To a stirred solution of 2-piperidone (560 mg, 5.60 mmol) in DMSO (5 ml) was added KOH powder (0.64 g, 5.60 mmol) and benzyl chloride (0.65 ml, 5.60 mmol) at room temperature and the resulting mixture was kept stirring for 2.5 h at room temperature. The mixture was quenched by pouring into water (30 ml) and extarcted with CH_2Cl_2 (100 ml x2). The combined CH_2Cl_2 layer was washed with 5% HCl (20 ml), sat. $NaHCO_3$ (20 ml) and finally with brine (10 ml). After drying over Na_2SO_4, the solvent was removed under reduced pressure to afford the crude product, which was purified by SiO_2 column chromatography (20 g, AcOEt/ *n*-hexane, 1/1) to afford *N*-benzylpiperidone (970 mg, 91.0 %) as a colorless oil: Ir 2900, 1640 cm-1; ^1H nmr (400 MHz) δ 1.78 (4H, m, CH_2) 2.47 (2H, t, *J*=6.40 Hz, CH_2), 3.19 (2H, t, *J*=6.40 Hz, *N*-CH_2), 4.60 (2H, s, PhCH_2), 7.29 (5H, m, aromatic); LREIms *m/z* (%): 189 (M^+, 100), 160 (12), 105 (31).

N-Benzyl-3-phenylthio-2-piperidone (1c). To a cooled (-78 °C) and stirred solution of LDA [2.1 equiv., prepared from *n*-BuLi (2.0 ml of 1.5 M hexane solution) and i-Pr_2NH (0.40 ml) in THF (8 ml)] was added a THF (10 ml) solution of *N*-benzyl-2-piperidone (270 mg, 1.40 mmol) dropwise by syringe. The resulting mixture was then kept stirring at this temperature for 0.5 h and to this enolate solution was added phenyl disulfide (311mg, 1.40 mmol) solution in THF (10 ml)-HMPA (0.24 ml). Resulting mixture was kept stirring at this temperature for 0.5 h and warmed to room temperature over 1 h. After tlc analysis (AcOEt/ *n*-hexane=1/1), the mixture was quenched by the addition of sat. NH_4Cl (10 ml) and further with ether-AcOEt (1/1, ~100 ml). The organic layer was separated and aqueous

layer was extracted with AcOEt (100 ml). The combined organic layers were washed with brine (30 mlx2) and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by SiO_2 column chromatography (20g, AcOEt/ *n*-hexane, 1/3) to furnish the pure **1c** (8.82 g, 69.8%) as a faint yellow oil: Ir (neat) 3050, 2900, 1640 cm^{-1}; ^1H nmr (500 MHz) δ 1.78 (4H, m, CH_2), 2.47 (1H, t, *J*=6.4 Hz, CH), 3.19 (2H, t, *J*=6.4 Hz, 6-H),4.60 (2H, s, $PhCH_2$), 7.29 (5H, m, aromatic), 7.51-7.55 (3H, m, aromatic) 7.60-8.00 (1H, m, aromatic), 8.03 (2H, d, *J*=6.80 Hz, aromatic); LREIms *m/z* (%): 297 (M^+, 10), 160 (12), 105 (31); HREIms *m/z* calcd for $C_{18}H_{19}NOS$ (M^+) 297.1183, found 297.1188.

_N_-Methoxymethyl-_N_-trifluoroacetyl-dehydroalanine methyl ester (9a)

To a cooled (0 °C) and stirred solution of DL-serine methyl ester hydrochloride (3.50 g, 22.6 mmol) in CH_2Cl_2 (35 ml) was added pyridine (11 ml, 133 mmol) and trifluoroacetic anhydride (16 ml, 112 mmol) and the mixture was stirred at room temperature for 4.5 h. After tlc analysis, the mixture was diluted with CH_2Cl_2 (300 ml) and washed with water (100 ml). The organic layer was separated and washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by SiO_2 column chromatography (120 g, AcOEt/ *n*-hexane, 1/4) to afford the NH-dehydroalanine methyl ester (3.50 g, 80.2 %) as a colourless liquid: Ir 3700-3100, 2950, 1720, 1640, 1550, 1440, 1390, 1340, 1300, 1220, 1160, 1100 cm^{-1}; ^1H nmr (60 MHz) δ 3.80 (3H, s, OMe), 6.10 (1H, s, olefinic), 6.70 (1H, s, olefinic), 8.30-8.90 (1H, br, NH).

To a stirred solution of the above prepared $NHCOCF_3$-dehydroalanine methyl ester (3.50 g, 18.1 mmol) and Ag_2O (18 g, 77.9 mmol) in DMF (100 ml) was added methoxymethyl chloride (3.60 g, 45.0 mmol) at room temperature and the mixture was kept stirring for 1 h. After tlc analysis (AcOEt/ *n*-hexane), a further amount of MOM chloride (3.60 g, 45.0 mmol) was added to ensure the completion of the reaction. The mixture was stirred at room temperature for 1 h and diluted with Et_2O (150 ml) and solid mass was filtered by the aid of added MgSO4 to obtain a clear yellow organic filtrate. The filtrate was diluted with water (150 ml), extracted with ether (300 mlx2). The organic layer was washed with brine (150 ml) and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by SiO_2 column chromatography (120 g, AcOEt/ *n*-hexane, 1/4) to afford the *N*-methoxymethyl-*N*-trifluoroacetyl-dehydroalanine methyl ester (**9a**, 3.05 g, 71.3 %) as a faint yellow oil: Ir (neat) 3700-

3100, 2950, 1720, 1640, 1550, 1450, 1440, 1390, 1340, 1300, 1220, 1160, 1100 cm^{-1}; ^1H nmr (500 MHz) δ 3.41 (3H, s, OMe), 3.83 (3H, s, OMe), 4.60 (1H, br, CH), 5.36 (1H, br, CH), 5.93 (1H, s, vinyl), 6.62 (1H, s, vinyl).

_N_-Trifluoroacetyl-_N_-[(β-trimethylsilylethoxy)methyl]dehydroalanine methyl ester (9b)

To a stirred solution of the above prepared $NHCOCF_3$-dehydroalanine methyl ester (1.77 g, 9.0 mmol) and Ag_2O (6.26 g, 27.0 mmol) in DMF (10 ml) was added dropwise β-trimethylsilylethoxymethyl chloride (SEM chloride, 3.20 ml, 18.0 mmol) in DMF (5 ml) over 10 min at room temperature and the mixture was kept stirring for 1 h. The mixture was diluted with Et_2O (80 ml) and solid mass was filtered through a pad of celite to obtain a clear yellow organic filtrate. The filtrate was diluted with brine (50 ml) and extracted with AcOEt (200 mlx2). The organic layer was washed with brine (50 ml) and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by SiO_2 column chromartography (110 g, $CHCl_3$/ *n*-hexane, 3/2) to afford crude *N*-SEM-*N*-trifluoroacetyl-dehydroalanine methyl ester (**9b**, 3.91 g, 133 %) as a faint yellow oil, which was contaminated with b-trimethylsilylethanol and other by product (we could not further purify this material but it was sufficient to use in the next step) **9b**: ^1H Nmr (60 MHz) δ 0.05 (9H, s, TMS), 1.00 (2H, t, *J*=8.0 Hz, CH2), 3.80 (2H, t, *J*=8.0 Hz, CH_2), 3.90 (3H, s, OMe), 5.05 (2H, m, CH_2), 6.00 (1H, s, vinyl), 6.60 (1H, s, vinyl)

Michael addition reaction of 1b with 9a

To a cooled (-60 °C) and stirred solution of the 3-phenylthiopiperidone (**1b**, 1.04 g, 3.00 mmol) in THF (30 ml) was added $KN(TMS)_2$ solution (0.6 ml, 0.5 M solution in toluene, 0.3 mmol) and stirring was continued at this temperature for 10 min. To this solution was added dropwise a THF (20 ml) solution of **9a** (723 mg, 3.0 mmol). After stirring for additional 1 h, the mixture was quenched by the addition of sat. NH_4Cl (20 ml) and warmed to room temperature. The mixture was then diluted with AcOEt (~150 ml) and the organic layer was separated. After washing with brine (10 ml x2), the organic layer was dried ($MgSO_4$) and concentrated . The residue thus obtained was purified by SiO_2 column chromatography (60 g, AcOEt/*n*-hexane, 4/1) to afford the Michael adduct (**10a**, 1.67 g, 95 %) as a colorless amorphous: Ir 2950, 1740, 1700, 1660, 1470, 1450, 1420, 1170 cm^{-1}; ^1H nmr (500 MHz)

δ 1.93-2.31 (4H, m, CH_2), 2.75 (1H, dd, *J*=15.4, 4.6 Hz, CH), 3.26 (3H, s, OMe), 3.62 (3H, s, OMe) 3.84 (1H, m, $CHNSO_2$), 4.15 (1H, m, $CHNSO_2$), 4.59 (1H, t, *J*=5.5 Hz, CHN), 4.66 (2H, s, CH_2O), 7.06-8.03 (10H, m, aromatic); LRFABms *m/z* (%): 589 (MH^+, 13), 557 (100); HRFABms *m/z* calcd for $C_{25}H_{28}N_2O_7F_3S_2$ (MH^+): 589.1290, found 589.1282.

Michael addition reaction of 1b with 9b

To a cooled (-78 °C) and stirred solution of the 3-phenylthiopiperidone (**1b**, 2.43 g, 7.00 mmol) in THF (50 ml) was added $KN(TMS)_2$ solution (1.4 ml, 0.5 M solution in toluene, 0.7 mmol) and stirring was continued at this temperature for 10 min. To this solution was added dropwise a THF (20 ml) solution of the *N*-SEM-*N*-trifluoroacetyl-dehydroalanine methyl ester (**9b**, 3.91 g, 9.0 mmol). After stirring for additional 1 h, the mixture was quenched by the addition of sat. NH_4Cl (20 ml) and warmed to room temperature. The mixture was then diluted with AcOEt (~150 ml) and the organic layer was separated. After washing with brine (10 ml x2), the organic layer was dried ($MgSO_4$) and concentrated . The residue thus obtained was purified by SiO_2 column chromatography (60 g, AcOEt/*n*-hexane, 1/5) to afford the Michael adduct (4.75 g, quant) as a colourless amorphous: Ir 2950, 1740, 1690 cm^{-1}; ^1H nmr (500 MHz) δ 0.00 (9H, s, TMS), 0.85 (2H, m, CH_2Si) 2.02-2.31 (5H, m), 2.73 (1H, dd, *J*=15.48, 4.31 Hz) 3.44 (1H, m, OCH_2) 3.53 (1H, m, OCH_2), 3.61 (3H, s, OMe), 3.85 (1H, m, NCH), 4.17 (1H, m, NCH), 4.64-4.73 (3H, m, NCH_2, CH), 7.10 (2H, d, *J*=7.32 Hz, aromatic), 7.17 (2H, m, aromatic), 7.32 (1H, m, aromatic), 7.55 (2H, t, *J*=7.88 Hz, aromatic), 7.67 (1H, m, aromatic), 8.04 (2H, d, *J*=7.32, aromatic); LRFABms *m/z* (%): 697(MNa^+, 39), 617 (100); HRFABms *m/z* calcd for $C_{29}H_{37}N_2O_7F_3NaSiS_2$ (MNa^+): 697.1661, Found: 697.1649.

Michael addition reaction of 1c with 4a

To a cooled (-78 °C) and stirred solution of *N*-benzyl-3-phenylthio-2-piperidone (**1c**, 445 mg, 1.50 mmol) in THF (30 ml) was added a THF (10 ml) solution of $KN(TMS)_2$ (150 mg, 0.8 equiv.) and the mixture was kept stirring at this temperature for 10 min. A THF (5 ml) solution of the *N*-COOMe amidoacrylate (**4a**, 260 mg, 1.50 mmol) was added and the mixture was stirred at this temperature for 15 min. After checking by tlc, the mixture was diluted with sat. NH_4Cl (3 ml) at this temperature and extracted with CH_2Cl_2 (150 ml). The organic layer was separated, washed with brine and dried over

Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by SiO_2 column chromatography (50 g, AcOEt/*n*-hexane. 2/3) to afford the Michael adduct (**8**, 470 mg, 68.0 %) as a colorless amorphous solid: Ir 2900, 1740, 1700, 1640 cm^{-1}; ^1H nmr (500MHz) δ as a mixture of diastereomers; 1.40-1.50 (~8.5H, m), 1.60 (2.5H, m), 1.90-2.00 (3.5H, m), 2.24-2.47 (6H, Me x2), 2.65 (2H, m), 3.58-4.38 (1H, m), 7.30-7.90 (10H, m, aromatic); LREIms *m/z* (%): 470 (M^+, 2), 361 (65), 297 (100).

_N_-Benzenesulfonyl-3-[2-methoxycarbonyl-2-[_N_-(trifluoroacetyl)-_N_-(methoxymethyl)-amino]ethyl-5,6-dihydro-2(1_H_)-pyridinone (11a)

To a cooled (0° C) and stirred suspension of the above Michael adduct (**10a**, 1.30 g, 2.21 mmol) in CH_2Cl_2 (40 ml) and sat. $NaHCO_3$ (15 ml) was added slowly a CH_2Cl_2 (40 ml) solution of mCPBA (80 %, 850mg, 4.3 mmol) over 30 min with ice-cooling (0°C). After tlc analysis, the mixture was diluted with AcOEt (~200 ml)-sat. $NaHCO_3$ (20 ml) and the organic layer was separated. The organic extracts were washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a residue, which was purified by SiO_2 column chromatography (100 g, AcOEt/*n*-hexane, 1/4) to afford the dienophile (**11a**, 1.06 g, quant.)as a colorless amorphous solid: Ir 2950, 1740, 1700, 1450, 1400, 1360, 1280, 1150 cm^{-1}; ^1H nmr (500 MHz) δ 2.50 (2H, m, CH_2), 2.86 (1 H, m, CH), 3.01 (1H, m, CH), 3.21 (3 H, s, OMe), 3.69 (3 H, s, OMe), 3.85 (1H, m, $CHNSO_2$), 4.15 (1H, m, $CHNSO_2$), 4.42 (1 H, dd, *J*=10.2, 5.7 Hz, CHN), 4.50 (2H, d, *J*=10.6 Hz, CH_2O), 6.56 (1H, t like, *J*=4.2 Hz, olefinic), 6.61 (0.5H, t like, olefinic), 7.53 (2H, t like, aromatic), 7.63 (1H, m, aromatic), 8.04 (2 H, d, *J*=7.7 Hz, aromatic); ^{13}C nmr (125.65 MHz) δ 25.25, 29.86, 44.04, 52.65, 56.00, 59.09, 79.78, 128.44, 128.87, 131.01, 133.72, 139.02, 142.68, 163.86, 169.13; LRFABms *m/z* (%):479 (MH^+, 28), 447 (100) ; HRFABms *m/z* calcd for $C_{19}H_{22}N_2O_7F_3S$ (MH^+): 479.1100 , found: 479.1105.

_N_-Benzenesulfonyl-3-[2-methoxycarbonyl-2-[_N_-(trifluoroacetyl)-_N_-[β-(trimethylsilyl)ethoxymethyl]amino]ethyl-5,6-dihydro-2(1_H_)-pyridinone (11b)

To a cooled (0° C) and stirred suspension of the above Michael adduct (**10b**, 6.14 g, 9.11 mmol) in CH_2Cl_2 (300 ml) and sat. $NaHCO_3$ (70 ml) was added slowly a CH_2Cl_2 (200 ml) solution of mCPBA (80 %, 2.63 g, 10.93 mmol) over 1 h under ice-cooling. After tlc analysis, the mixture was diluted with

CH_2Cl_2 (~200 ml) - sat. $NaHCO_3$ (20 ml) and the organic layer was separated. The organic extracts were washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a residue, which was purified by SiO_2 column chromatography (240 g, $CHCl_3$) to afford the dienophile (**11b**, 4.64 g, 90 %) as a faint yellow oil: Ir (neat) 2950, 1740, 1690 cm^{-1}; ^1H nmr (500 MHz) δ 0.00 (9H, s, TMS), 0.90 (2H, m, CH_2Si), 2.51 (2H, m, CH_2), 2.81 (1 H, dd, *J*=14.1, 9.53 Hz,,CH), 3.09 (1H, dd, *J*=14.1, 5.9 Hz, CH), 3.45 (1H, m, OCH_2), 3.59 (1 H, m, OCH_2), 3.68 (3H, s, OMe), 4.04 (2H, m, $CHNSO_2$), 4.30 (1H, d, *J*=10.1 Hz, NCH_2O), 4.47 (1 H, dd, *J*=9.5, 5.8 Hz, CHN), 4.62 (1H, d, *J*=10.1 Hz, NCH_2O), 6.61 (1H, t like, *J*=4.1 Hz, olefinic), 7.53 (2 H, m, aromatic), 7.63 (1 H, m, aromatic), 8.03 (2H, m, aromatic); ^{13}C nmr (125.65 MHz) δ -1.53, 17.64, 25.15, 29.89, 44.05, 52.51, 58.43, 66.01, 112.39, 114.68, 116.97, 119.25, 128.34, 128.76, 130.89, 133.64, 138.89, 142.85, 156.58, 156.87, 157.17, 163.79, 169.71 ; LRFABms *m/z* (%): 565 (MH^+, 10), 447 (100) ; HRFABms *m/z* calcd for $C_{23}H_{32}N_2O_7F_3SSi$ (MH^+): 565.1651, found: 565.1660.

Michael addition reaction of 1b with methyl acrylate

To a cooled (-15 °C) and stirred solution of the 3-phenylthiopiperidone (**1b**, 1.74 g, 5.00 mmol) in THF (40 ml) was added $KN(TMS)_2$ (0.6 g, 3.0 mmol) and stirring was continued at this temperature for 10 min. To this solution was added dropwise methyl acrylate (0.50 ml, 5.5 mmol). After stirring for 2 h under cooling, the mixture was quenched by the addition of sat. NH_4Cl (50 ml) and warmed to room temperature. The mixture was then diluted with AcOEt (100 ml x3) and the organic layer was separated. After washing with brine (50 ml), the organic layer was dried ($MgSO_4$) and concentrated . The residue thus obtained was purified by SiO_2 column chromatography (AcOEt/*n*-hexane, 2/1) to afford the Michael adduct (1.83 g, 84 %) as a colorless amorphous. **13a:** Ir 2950, 1738, 1680, 1345, 1180 cm^{-1}; ^1H nmr (500 MHz) δ 1.89-2.03 (5H, m, CH_2), 2.19-2.32 (2H, m, CH_2) , 2.42 (1H, m, H-4), 3.59 (3H, s, OMe), 3.84 (1H, m, $CHNSO_2$), 4.27 (1H, m, $CHNSO_2$), 6.98-7.00 (2H, m, aromatic), 7.12-7.15 (2H, m, aromatic), 7.26-7.32 (1H, m, aromatic), 7.54-7.57 (2H, m, aromatic), 7.65-7.68 (1H, m, aromatic), 8.04-8.06 (2H, m, aromatic); ^{13}C nmr (125.65 MHz) δ 20.18, 28.93, 31.07, 31.10, 46.26, 51.71, 55.55, 128.66, 128.68, 128.76, 128.99, 129.81, 133.52, 137.45, 138.98, 169.15, 173.09; LREIms *m/z* (%): 433 (M^+, 10), HRFABms *m/z* calcd for $C_{21}H_{24}NO_5S_2$ (MH^+): 434.1098, found: 434.1098.

Michael addition reaction of 1b with acrylonitrile

To a cooled (0 °C) and stirred solution of the 3-phenylthiopiperidone (**1b**, 1.75 g, 5.0 mmol) in THF (50 ml) was added $KN(TMS)_2$ (0.5 g, 1.5 mmol) and stirring was continued at this temperature for 10 min. To this solution was added dropwise a THF (20 ml) solution of the acrylonitrile (0.40 ml, 5.5 mmol) over 10 min. After stirring for 20 h at room temperature, the mixture was quenched by the addition of sat. NH_4Cl (50 ml). The mixture was then diluted with AcOEt (100 ml) and the organic layer was separated. After washing with brine (50 ml), the organic layer was dried ($MgSO_4$) and concentrated . The residue thus obtained was purified by SiO_2 column chromatography (CH_2Cl_2) to afford the Michael adduct (**13b**, 2.42 g, 60.0 %) as a colorless amorphous: Ir 2950, 1740, 1700, 1660, 1470, 1450, 1420, 1380, 1350, 1310, 1280, 1240, 1200 cm^{-1}; ^1H nmr (500 MHz) δ 1.97-2.35 (8 H, m, CH_2), 3.99 (1H, m, $CHNSO_2$), 4.30 (1H, m, $CHNSO_2$), 6.98 (2H, d, *J*=7.5 Hz, aromatic) 7.17 (2H, t, *J*=7.5 Hz, aromatic), 7.35 (1H, t, *J*=7.3 Hz, aromatic), 7.57 (2H, t, *J*=7.6 Hz, aromatic), 7.69 (1H, *J*=7.3 Hz, aromatic), 8.05 (2H, d, *J*=7.6 Hz); ^{13}C nmr (125.65 MHz) δ 12.39, 20.05, 30.89, 31.83, 46.08, 55.07, 119.12, 128.06, 128.77, 129.00, 130.24, 133.75, 137.31, 138.75, 168.62; LREIms *m/z* (%): 534 (M^+, 10), 503 (15).

Michael addition reaction of 1b with acrolein

To a cooled (-5 °C) and stirred solution of the 3-phenylthiopiperidone (**1b**, 5.21g, 15.0 mmol) in THF (150 ml) was added $KN(TMS)_2$ (75 mg, 0.375 mmol, 0.02 equiv.) and stirring was continued at this temperature for 10 min. To this solution was added dropwise a THF (5 ml) solution of acrolein (2.0 ml, 30.1 mmol, 2.0 equiv.). After stirring for 2 h, the mixture was quenched by the addition of sat. NH_4Cl (10 ml) and warmed to room temperature. The mixture was then diluted with AcOEt (100 ml x3) and the organic layer was separated. After washing with brine (50 ml), the organic layer was dried ($MgSO_4$) and concentrated . The residue thus obtained was purified by SiO_2 column chromatography (AcOEt/*n*-hexane, 1/1) to afford the Michael adduct (**13c**, 4.36 g, 72.1 %) as a colorless amorphous: Ir (KBr) 2950, 2900, 2250, 1680, 1480, 1460, 1350, 1270, 1170, 1100, 765.cm^{-1}; ^1H nmr (500 MHz) δ 1.88-2.15 (m, 5H, CH_2), 2.30-2.45 (m, 3H, CH_2), 3.90 (m, 1H, NCH), 4.25 (m, 1H, NCH), 6.97 (m, 2H, aromatic), 7.15 (m, 2H, aromatic), 7.25 (m, 1H, aromatic), 7.57 (m, 2H, aromatic), 7.67 (m, 1H, aromatic), 8.05 (m, 2H, aromatic); ^{13}C nmr (125.65 MHz) δ 20.14, 28.40, 31.35, 38.79, 46.27,

55.46, 126.97, 128.69, 128.76, 128.97, 129.88, 133.60, 137.34, 138.89, 169.27, 200.64; LREIms *m/z* (%): 403 (M^+, 10), HRFABms *m/z* calcd for $C_{20}H_{22}NO_4S_2$ (MH^+): 404.0990, Found: 404.0990.

ACKNOWLEDGMENTS

Financial support by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture and Uehara Memorial Foundation is gratefully acknowledged. We also thank Mrs. H. Seki, Miss R. Hara, Mr. T. Kuramochi, and Dr. K. Ogata in the Analytical Center of Chiba University for spectral data and elemental analysis.

REFERENCES

1. (a) R. Sakai, T. Higa, C. W. Jefford, and G. Bernardinelli, *J. Am. Chem. Soc.*, 1986, **108**, 6404; (b) R. Sakai, S. Kohmoto, T. Higa, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.*, 1987, **28**, 5493; (c) T. Ichiba, R. Sakai, S. Kohmoto, G. Sausy, and T. Higa, *ibid.*, 1988, ***29***, 3083; (d) H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotake, Y. Matsuzaki, and Y. Hirata, *Tetrahedron Lett.*, 1987, ***28***, 621.

2. (a) M. Nakagawa, Z. Lai, Y. Torisawa, and T. Hino, *Heterocycles*, 1990, **32**, 999 ; (b) Y.Torisawa, M. Nakagawa, H. Arai, Z. Lai, T. Hino, T. Nakata, and T. Oishi, *Tetrahedron Lett.*, 1990, **31**, 3195; (c) Y. Torisawa, M. Nakagawa, T. Hosaka, K. Tanabe, Z. Lai, K. Ogata, T. Nakata, T. Ohishi, and T. Hino, *J. Org. Chem.*, 1992, **57**, 5741.

3. (a) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807; (b) S. Danishefsky, T. Kitahara and P. F. Shuda, *Org. Synth., Coll. Vol.* **7**, 312 (1990).

4. (a) P. A. Zoretic and P. Soja, *J. Org. Chem.*, 1976, **41**, 3587.

5. M. J. Fisher and L. E. Overmann, *J. Org. Chem.*, 1990, **55**, 1447.

6. (a) G. A. Flynn and D. W. Beight, *Tetrahedron Lett.*, 1984, **25**, 2655; (b) R. K. Olsen, *J. Org. Chem.*, 1970, **35**, 1912.

Received, 10th December, 1992