Direct Aminolysis of Nonactivated and Thermally Unstable Esters at High Pressure

Kiyoshi Matsumoto*[a], Shiro Hashimoto[a], Takane Uchida[b], Tadashi Okamoto*[c], and Shinichi Otani[a]

College of Liberal Arts and Sciences, Kyoto University[a], Kyoto 606, Japan

Faculty of Education, Fukui University[b], Fukui 910, Japan

Institute for Chemical Research, Kyoto University[c], Uji 611, Japan

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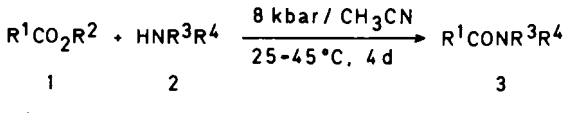
The preparation of the amides 3 from a wide variety of nonactivated esters 1 and secondary amines 2 has been achieved at 8 kbar and around 45°C; scope and limitations are discussed. The method was also successfully applied for the aminolysis of alkyl 2-arylsulfinylacetates 7 that are relatively sensitive to heat.

Direkte Aminolyse von nichtkonjugierten und thermisch instabilen Estern bei hohem Druck

Die Darstellung der Amide **3** von einer Vielzahl nichtaktivierter Ester **1** und sekundärer Amine **2** gelang bei 8 kbar um 45°C; Anwendungsbreite und Grenzen werden aufgezeigt. Die Methode wurde auch erfolgreich auf die Aminolyse von Alkyl-2-arylsulfinylacetate **7** angewandt, die relativ hitzeempfindlich sind.

High-pressure apparatuses now are only moderately expensive[1], and the knowledge of the volume profile of chemical reactions is now reaching the stage of application in the synthetic laboratory[2]. Indeed, the high-pressure technique has proven useful to surmount the energy barrier imposed by electronic and steric effects in many kinds of addition reactions such as Diels-Alder, Michael, aldol, and related reactions[3]. The aminolysis of unactivated esters is known to be a difficult reaction[4], though it potentially constitutes a useful synthetic method as shown by the number of ways devised to facilitate it[5–8]. It is particularly difficult with substituted amines, where uncatalysed aminolysis by primary amines requires temperatures higher than 200°C[9], whereas the corresponding reaction with secondary amines has never been reported.



1	R^1	R^2
a	$H(CH_2)_8CH{=}CH(CH_2)_7$	Me
b	$c\text{-}C_6H_{11}$	Me
c	$NCCH_2CH_2$	Me
d	$o\text{-}CH_3OC_6H_4$	Me
e	$p\text{-}O_2NC_6H_4$	Me
f	Ph	Et
g	$PhCH_2$	Me
h	PhCH(OH)	Me

2	R^3	R^4
a	$-(CH_2)_4-$	
b	$-(CH_2)_5-$	
c	Et	Et
d	$PhCH_2$	H
e	$-(CH_2)_2O(CH_2)_2-$	
f	$-(CH_2)_2N(Me)(CH_2)_2-$	
g	$-(CH_2)_2S(CH_2)_2-$	
h	n-Bu	H

We now describe full details on our findings that even secondary amines **2** react in moderate to high yields at room temperature or 35–45°C with a wide variety of unactivated esters **1** to give the acid amides **3** if the reactions are performed at 8 kbar[10].

The results are summarized in Table 1. Of course, the method is also applicable to primary amines as exemplified by the reaction with benzyl amine (**2d**). The structures of the amides **3** thus obtained were derived from their analytical and spectroscopic data, especially from their ^{1}H- and ^{13}C-NMR spectra (see Experimental). Neither an inert atmosphere nor dry solvents are required. The reaction was extremely clean and therefore the workup procedure is straightforward; the hydrolysis procedure used in the excellent method with alkylaluminum amide reagents[7b] is unnecessary. Usually, the solution of the products **3** contains only the esters **1**, if the yield is not quantitative, and excess amine **2**.

Whereas at 1 bar methyl oleate (**1a**) reacted only at 230°C with octyl amine[9], **1a** with pyrrolidine (**2a**) produced a quantitative yield of the amide **3aa**, the isolated double bond being unaffected. Similarly, no reaction of methyl cyclohexanecarboxylate (**1b**) with pyrrolidine (**2a**) was observed under vapor-phase condition at 190°C[8], while at 8 kbar and 45°C **1b** with **2a** afforded the amide **3ba** in 66% yield.

Some advantages and disadvantages over other reagents and/or catalysts such as dialkylaluminum amides and boron tribromide deserve to be mentioned. One of the most versatile reagents for direct and mild aminolysis of esters are dialkylaluminum amides[7b]. The only drawback is apparently that they often react with a cyano group[11] (and possibly with a nitro group, see below), while a cyano group

*) Present address: Ibaraki Research Laboratory, Hitachi Chemical Co., Ltd., Hitachi, Ibaraki 317, Japan.

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Table 1. Aminolysis of nonactivated esters **1** to acid amides **3** at 8 kbar

3	Temp.[°C]	Time[d]	Yield[%]	M.p.[°C]
aa	35	3	100	oil
ab	35	4	100	oil
ba	35	4	66	67-68
bb	45	4	66	oil
ca	35	4	100	oil
cb	35	4	100	oil
da	35	4	100	oil
ea	35	4	71	81-82
fa	room temp.	4	100	oil
fb	35	4	81	oil
fc	45	4	10	oil
fd	35	3	97	105-106
ga	35	3	100	oil
gb	45	3	100	oil
gc	45	3	46	oil
gd	35	3	100	118-119
ha	35	4	96	94.5-95
hb	35	3	63	77
hc	45	4	46	oil
hd	35	3	90	99.5-100

Table 2. Aminolysis of alkyl 2-arylsulfonylacetates **7** at 8 kbar and 40°C, for 4 d

8	Yield[%]	M.p.[°C]
aa	90	119-120
ab	94	56- 57
ae	93	125-126
af	86	73.5-74.5
ag	87	141-142
ba	100	163-164
bb	100	138-139
bc	83	oil
be	91	140-141
bf	100	135-136
bg	95	160-161
bh	100	136-137

is inert to the high-pressure method (Table 1: **3ca, 3cb**). On the other hand, a high-pressure reaction of methyl γ-chlorobutyrate (**4**) with **2a** produced a complex mixture of products, though a chloro group is inert, towards dialkylaluminum amides. Furthermore, this type of reagents does not attack a conjugated double bond, whereas ethyl cinnamate (**5**) underwent a high-pressure Michael reaction[12] with **2b** to give the adduct **6** in 89% yield. This reaction has been elegantly applied for the enantioselective synthesis of β-aminoesters[13].

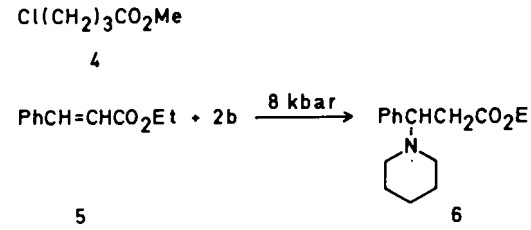


Table 3. Analytical data of **3**

3	Method of Purif.	Molecular Formula	Calcd/Found[%] C	H	N
aa	A	$C_{22}H_{41}NO$	78.72 78.56	12.34 12.30	4.17 4.33
ab	A	$C_{23}H_{43}NO$	79.00 78.89	12.41 12.52	4.01 4.05
ba	B	$C_{11}H_{19}NO$	72.86 73.00	10.58 10.73	7.73 7.60
bb	B	$C_{12}H_{21}NO$	73.78 73.39	10.86 10.75	7.17 7.08
ca	B	$C_8H_{12}N_2O$	63.12 62.85	7.96 8.10	18.41 17.93
cb	B	$C_9H_{14}N_2O$	65.02 64.75	8.51 8.69	16.85 16.66
da	B	$C_{12}H_{15}NO_2$	70.21 69.67	7.38 7.47	6.82 6.77
ea	B	$C_{11}H_{12}N_2O_3$	59.99 60.25	5.49 5.53	12.72 12.52
fa	A	$C_{11}H_{13}NO$	75.38 75.57	7.49 7.74	7.99 7.88
fb	B	$C_{12}H_{15}NO$	76.16 75.83	8.00 8.06	7.40 7.25
fc	B	$C_{11}H_{15}NO$	74.52 74.50	8.55 8.54	7.90 7.88
fd	B	$C_{14}H_{13}NO$	79.58 79.76	6.21 6.17	6.63 6.62
ga	A	$C_{12}H_{15}NO$	76.14 76.27	8.00 8.24	7.40 7.37
gb	A	$C_{13}H_{17}NO$	76.79 76.65	8.45 8.69	6.89 6.86
gc	B	$C_{12}H_{17}NO$	75.34 74.81	8.98 9.07	7.32 7.01
gd	B	$C_{15}H_{15}NO$	79.96 79.44	6.72 6.55	6.22 6.37
ha	A	$C_{12}H_{15}NO_2$	70.21 70.23	7.38 7.42	6.82 6.66
hb	A	$C_{13}H_{17}NO_2$	71.19 71.09	7.83 7.94	6.39 6.20
hc	B	$C_{12}H_{17}NO_2$	69.52 69.52	8.28 8.42	6.76 6.52
hd	B	$C_{15}H_{15}NO_2$	74.66 74.89	6.28 6.26	5.81 5.87

Boron tribromide constitutes one of the mildest catalysts for direct conversion of esters to amides, though the generality has not well been tested[6b]. This reagent often cleaves an alkoxy group; indeed, BBr_3 has been successfully employed to remove methyl protecting groups in the synthesis of a free catecholate macrocycle[14]. In contrast, methyl *o*-anisate (**1d**) underwent high-pressure aminolysis to produce the amide **3da** quantitatively. The present method also did not affect a nitro group (Table 1: **3ea**) that probably reacts with metal amides as well as with some of the strong alkali metal catalysts such as NaH[5d], $LiAlH_4$[5e], and $RMgX$[5f]. Finally, an attempted amidation of ethyl benzoate (**1f**) with **2b** by the recently reported method utilizing K_2CO_3/DMSO[15] failed at 1 bar and 25°C (and 80°C).

It is apparent that this technique is amenable to those cases, where either reactants or products are sensitive to heat, reagents, or even catalysts since requisite reactions often take place at lower temperatures and/or under milder catalysis when performed at high pressures. Since some alkyl arylsulfinylacetates are sensitive to heat, it seemed desirable to realize the direct aminolysis at lower temperature.

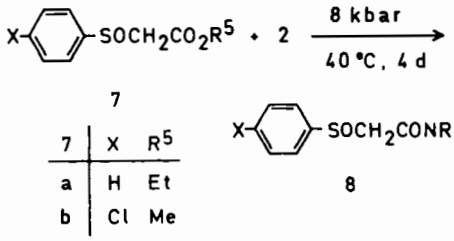
This was indeed achieved as summarized in Table 2. The yields were excellent. For example, high-pressure aminolysis of ethyl phenylsulfinylacetate (**7a**) with **2b** afforded the amide **8ab** in 94% yield, whereas **7a** only sluggishly underwent aminolysis with **2b** at 1 bar and 80°C in acetonitrile to give 2% yield of **8ab**, probably due to the instability of **7a**; **7a** slowly decomposes even at room temperature. Methyl

Table 4. ^{1}H-NMR spectral data of **3**

3	δ (in $CDCl_3$)
aa	0.88(t, J=6.0 Hz, 3H, CH_3), 1.20-1.45(m, 20H, CH_2x10), 1.55-1.73(m, 2H, CH_2), 1.80-2.08(m, 8H, CH_2x4), 2.26(t, J=7.6 Hz, 2H, $COCH_2$), 3.42, 3.46 (each t, J=6.8 Hz, 4H, NCH_2x2), 5.34(t, J=5.0 Hz, 2H, CH=CH)
ab	0.87(t, J=6.0 Hz, 3H, CH_3), 1.19-1.42(m, 19H, CH_2x19.5), 1.45-1.70(m, 8H, CH_2x4), 2.0(br-s, 3H, CH_2x1.5), 2.30(br-t, J=7.0 Hz, 2H, $COCH_2$), 3.38, 3.53(each br-s, 4H, NCH_2x2), 5.33(br-s, 2H, CH=CH)
ba	1.0-2.4(m, 15H, Cyclohexyl + CH_2x2), 3.2-3.5(m, 4H, NCH_2x2)
bb	1.0-2.7(m, 17H, Cyclohexyl + CH_2x3), 3.3-3.7(m, 4H, NCH_2x2)
ca	1.80-2.10(m, 4H, Pyrrolidinyl-CH_2x2), 2.58-2.80(m, 4H, $NCCH_2CH_2$), 3.37-3.56(m, 4H, NCH_2x2)
cb	1.46-1.74(m, 6H, Piperidino-CH_2x3), 2.69(s, 4H, $NCCH_2CH_2$), 3.35-3.41, 3.53-3.59(each m, 4H, NCH_2x2)
da[a]	1.72-1.97(m, 4H, CH_2x2), 3.17(br-t, J=7.2 Hz, 2H, NCHH), 3.59(br-t, J=6.3 Hz, 2H, NCHH), 3.81(s, 3H, OCH_3), 6.77-7.31(m, 4H, C_6H_4)
ea[a]	1.64-2.30(m, 4H, CH_2x2), 3.37, 3.64(each br-t, J=6.3 Hz, 4H, NCH_2x2), 7.61, 8.18(ABq, J=9.4 Hz, 4H, C_6H_4)
fa[a]	1.7-2.1(m, 4H, CH_2x2), 3.42, 3.65(each t, J=7.2 Hz, 4H, NCH_2x2), 7.3-7.6(m, 5H, C_6H_5)
fb	1.54, 1.66(each br-s, 6H, CH_2x3), 3.33, 3.69(each br-s, 4H, NCH_2x2), 7.38 (br-s, 5H, C_6H_5)
fc[a]	0.95-1.28(m, 6H, CH_3x2), 3.4-3.6(m, 4H, CH_2x2), 7.37(s, 5H, C_6H_5)
fd	4.56, 4.58(each d, J=5.6 Hz, 2H, Benzyl-CH_2), 6.85(br-s, 1H, NH), 7.2-7.5 (m, 8H, C_6H_5 + m,p-$COC_6H_3H_2$), 7.75-7.80(m, 2H, o-$COC_6H_3H_2$)
ga[a]	1.6-2.0(m, 4H, CH_2x2), 3.44(q, J=6.3 Hz, 4H, NCH_2x2), 3.64(s, 2H, Benzyl-CH_2), 7.27(s, 5H, C_6H_5)
gb[a]	1.2-1.6(m, 6H, CH_2x3), 3.36, 3.56(each br-t, J=5.5 Hz, 4H, NCH_2x2), 3.72 (s, 2H, Benzyl-CH_2), 7.24(s, 5H, C_6H_5)
gc	1.07, 1.11(each t, J=7.2 Hz, 6H, CH_3x2), 3.28, 3.38(each q, J=7.2 Hz, 4H, CH_2x2), 3.69(s, 2H, Benzyl-CH_2), 7.20-7.35(m, 5H, C_6H_5)
gd[a]	3.60(s, 2H, $COCH_2$), 4.36-4.43(m, 2H, $NHCH_2$), 7.1-7.4(m, 11H, NH + C_6H_5x2)
ha	1.65-1.9(m, 4H, CH_2x2), 2.75-2.9, 3.3-3.65(each m, 4H, NCH_2x2), 4.77, 5.03 (ABq, J=5.8 Hz, 2H, CHOH), 7.32(s, 5H, C_6H_5)
hb	0.78-0.95, 1.25-1.45, 1.4-1.6(each m, 6H, CH_2x3), 3.16(t, J=5.5 Hz, 2H, NCHHx2), 3.35-3.5, 3.7-3.85(each m, 2H, NCHHx2), 4.89, 5.20(each br-s, 2H, CHOH), 7.2-7.4(m, 5H, C_6H_5)
hc[a]	0.78, 1.13(each t, J=8.0 Hz, 6H, CH_3x2), 3.10, 3.42(each q, J=7.0 Hz, 4H, CH_2x2), 4.87, 5.15(ABq, J=6.3 Hz, 2H, CHOH), 7.32(s, 5H, C_6H_5)
hd[a]	4.0(br-s, 1H, NH), 4.33(d, J=5.4 Hz, 2H, Benzyl-CH_2), 4.96(br-d, J=4 Hz, 1H, CH), 6.6-6.9(br-s, 1H, OH), 7.1-7.35(m, 10H, C_6H_5x2)

[a] 90 MHz.

4-chlorophenylsulfinylacetate (**7b**) is more stable than **7a**. Thus, reaction of **7b** with **2b** in acetonitrile at 80°C and 1 bar for 12 h produced 36% of the amide **8bb**, **7b** being completely consumed, while at 8 kbar and 40°C a quantitative yield of **8bb** was obtained.



7

7	X	R^5
a	H	Et
b	Cl	Me

8

The high acceleration of the aminolysis of esters by application of pressure is not in disagreement with the rate-determining formation of a tetrahedral zwitterionic intermediate[4,16].

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Experimental

Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. – The high-pressure instrument

Table 5. ^{13}C-NMR spectral data of **3**

3	R^1	C=O	R^3, R^4
aa	34.6($CO\underline{C}H_2$), 22.4($\underline{C}H_2CH_3$), 13.8($CH_2\underline{C}H_3$), 129.5, 129.6(C̲H=C̲H) 31.7, 29.5, 29.3, 29.1, 28.9, 27.0, 24.7[a] ($\underline{C}H_2$)	171.4	45.3, 46.3(2-,5-$\underline{C}H_2$) 24.2,[a] 25.9[a] (3-,4-$\underline{C}H_2$)
ab	33.1($CO\underline{C}H_2$) 22.4($\underline{C}H_2CH_3$), 13.8($CH_2\underline{C}H_3$), 129.4, 129.4(C̲H=C̲H) 31.6, 29.4, 29.2, 29.0, 28.9 26.9 26.3 24.3[b] ($\underline{C}H_2$)	171.0	42.3, 46.4(2-,6-$\underline{C}H_2$), 24.3(4-$\underline{C}H_2$) 25.2,[b] 25.3[b] (3-,5-$\underline{C}H_2$)
ba	42.2(1-C̲H), 28.3(2-,6-$\underline{C}H_2$), 25.3(3-,4-,5-$\underline{C}H_2$)[c]	173.9	45.0, 45.7(2-,5-$\underline{C}H_2$) 23.7, 25.6(3-,4-$\underline{C}H_2$)[c]
bb	39.8(1-C̲H), 28.9(2-,6-$\underline{C}H_2$), 25.4(3-,4-,5-$\underline{C}H_2$)[d]	173.9	42.1, 45.9(2-,6-$\underline{C}H_2$),[d] 24.2(4-$\underline{C}H_2$) 26.3, 28.9(3-,5-$\underline{C}H_2$)[d]
ca	29.6($\underline{C}H_2CH_2CN$), 12.1($CH_2\underline{C}H_2CN$), 119.1(C̲N)	166.7	45.2, 45.7(2-,5-$\underline{C}H_2$), 23.7, 25.4(3-,4-$\underline{C}H_2$)
cb	28.5($\underline{C}H_2CH_2CN$), 12.6($CH_2\underline{C}H_2CN$), 119.2(C̲N)	166.5	42.4, 45.7(2-,6-$\underline{C}H_2$), 23.8(4-$\underline{C}H_2$) 24.9, 25.7(3-,5-$\underline{C}H_2$)
da	55.3($O\underline{C}H_3$), 129.9(1-C̲), 155.0(2-C̲), 110.9(3-C̲H), 127.3(4-C̲H) 120.5(5-C̲H), 127.4(6-C̲H)	167.4	45.2, 47.3(2-,5-$\underline{C}H_2$), 24.3 25.5(3-,4-$\underline{C}H_2$)
ea	142.9(1-C̲), 127.8(2-,6-C̲H), 123.2(3-,5-C̲H), 148.0(4-C̲)	166.9	46.0, 49.0(2-,5-$\underline{C}H_2$), 24.0, 26.0(3-,4-$\underline{C}H_2$)
fa	136.7(1-C̲), 127.6(2-,6-C̲H), 126.4(3-,5-C̲H), 129.1(4-C̲H)	168.9	45.5, 48.9(2-,5-$\underline{C}H_2$), 23.8, 25.7(3-,4-$\underline{C}H_2$)
fb	135.9(1-C̲), 127.8(2-,6-C̲H), 126.2(3-,5-C̲H), 128.7(4-C̲H)	169.6	42.6, 47.9(2-,6-$\underline{C}H_2$), 24.0(4-$\underline{C}H_2$) 25.5(3-,5-$\underline{C}H_2$)
fc	137.4(1-C̲), 128.4(2-,6-C̲H), 126.3(3-,5-C̲H), 129.1(4-C̲H)	171.3	41.3($\underline{C}H_2CH_3$), 13.6($CH_2\underline{C}H_3$)
fd	134.2(1-C̲), 128.3(2-,6-C̲H),[e] 127.5(3-,5-C̲H),[f] 131.2(4-C̲H)	167.5	43.7($\underline{C}H_2C_6H_5$), 138.3(1-C̲), 127.0(2-,6-C̲H),[f] 128.4(3-,5-C̲H),[e] 127.2(4-C̲H)
ga	41.8($\underline{C}H_2C_6H_5$), 134.6(1-C̲), 128.6(2-,6-C̲H), 128.1(3-,5-C̲H), 126.2(4-C̲H)	169.0	45.5, 46.4(2-,5-$\underline{C}H_2$) 23.9, 25.8(3-,4-$\underline{C}H_2$)
gb	40.9($\underline{C}H_2C_6H_5$), 135.2(1-C̲), 128.4(2-,3-,5-,6-C̲H), 126.3(4-C̲H)	169.0	42.6, 47.0(2-,6-$\underline{C}H_2$), 24.2(4-$\underline{C}H_2$) 25.3, 25.9(3-,5-$\underline{C}H_2$)
gc	40.5($\underline{C}H_2C_6H_5$), 135.2(1-C̲), 128.3(2-,6-C̲H), 128.2(3-,5-C̲H), 126.2(4-C̲H)	169.7	39.8, 42.0($\underline{C}H_2CH_3$), 12.6, 13.8($CH_2\underline{C}H_3$)
gd	43.6($\underline{C}H_2C_6H_5$), 134.8(1-C̲), 127.4(2-,6-C̲H), 129.0(3-,5-C̲H),[g] 128.6(4-C̲H)	170.9	43.8($\underline{C}H_2C_6H_5$), 138.2(1-C̲), 128.9(2-,6-C̲H),[g] 129.4(3-,5-C̲H),[g] 127.5(4-C̲H)
ha	72.2(C̲H(OH)C_6H_5), 138.7(1-C̲), 127.3(2-,6-C̲H), 128.4(3-,5-C̲H), 127.9(4-C̲H)	170.2	45.4, 46.1(2-,5-$\underline{C}H_2$), 23.3, 25.0(3-,4-$\underline{C}H_2$)
hb	71.0(C̲H(OH)C_6H_5), 139.5(1-C̲), 127.0(2-,6-C̲H), 128.6(3-,5-C̲H), 127.9(4-C̲H)	170.0	43.6, 45.4(2-,6-$\underline{C}H_2$), 23.8(4-$\underline{C}H_2$) 24.8, 25.4(3-,5-$\underline{C}H_2$)
hc	71.0(C̲H(OH)C_6H_5), 139.5(1-C̲), 127.0(2-,6-C̲H), 128.4(3-,5-C̲H), 127.8(4-C̲H)	170.9	40.2, 40.4($\underline{C}H_2CH_3$) 12.1, 12.5($CH_2\underline{C}H_3$)
hd	74.1(C̲H(OH)C_6H_5), 139.6(1-C̲) 126.7, 127.4, 128.2, 128.5(Aromatic-C̲H)	172.5	43.2($\underline{C}H_2C_6H_5$), 137.7(1-C̲)

[a] – [g] Assignment may be reversed.

Table 6. Analytical data of **8**

8	Method of Purif.	Molecular Formula	Calcd/Found[%] C	H	N
aa	A	$C_{12}H_{15}NO_4$	60.75 60.46	6.37 6.30	5.90 5.91
ab	A	$C_{13}H_{17}NO_2S$	62.14 61.89	6.82 6.82	5.57 5.56
ae	A	$C_{12}H_{15}NO_3S$	56.91 56.97	5.97 5.75	5.53 5.13
af	B	$C_{13}H_{18}N_2O_2S$	58.63 58.47	6.81 6.80	10.52 10.27
ag	A	$C_{12}H_{15}NO_2S_2$	53.53 53.23	5.62 5.56	5.20 5.25
ba	B	$C_{12}H_{14}NO_2SCl$	53.03 52.86	5.20 5.11	5.15 4.92
bb	B	$C_{13}H_{16}NO_2SCl$	54.64 54.54	5.65 5.64	4.90 5.00
bc	B	$C_{12}H_{16}NO_2SCl$	52.65 52.51	5.89 5.96	5.12 5.16
be	A	$C_{12}H_{14}NO_3SCl$	50.09 49.97	4.91 4.86	4.87 4.82
bf	B	$C_{13}H_{17}N_2O_2SCl$	51.92 51.85	5.70 5.67	9.32 9.39
bg	A	$C_{12}H_{14}NO_2S_2Cl$	47.45 47.22	4.65 4.58	4.61 4.72
bh	A	$C_{10}H_{16}NO_2SCl$	52.65 52.81	5.89 6.00	5.12 5.18

employed has already been described elsewhere[2]. – The ^{1}H-NMR spectra were measured either on a Hitachi R40 (90 MHz), a JEOL JNM FX90Q (90 MHz), or on a Varian VX200 (200 MHz) instrument. – ^{13}C-NMR spectra were recorded on a JEOL JNM FX90Q pulsed Fourier transform spectrometer operating at 22.49 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Partial proton decoupling was used to distinguish between individual carbon atoms. – Preparative medium-pressure liquid chromatography was carried out using a column (25 × 310 mm) prepacked with silica gel (Lobar, LiChroprep Si60, Merck). – All esters (except alkyl 2-arylsulfinylacetates **7**) employed are commercially available either from Woko Pure Chemical Industries, Ltd., Nakarai Tesque, Inc., or Aldrich Co., Inc. and were used as received.

General Procedure for the High-Pressure Reaction of Esters **1** *with Amines* **2**: A mixture of ester **1** (5 mmol) and amine **2** (10 mmol) was diluted with acetonitrile in an 8-ml PTFE capsule, which was stored for 3 or 4 d at 8 kbar. After evaporation of solvent and amine, the residue was either (Method A) dissolved in dichloromethane and extracted with dilute HCl (satd. with ammonium sulfate in the case of water-soluble amides) or (Method B) chromatographed on silica gel with benzene/ethyl acetate (1:1 or 4:1) as eluent. **3ha** and **3hb** were recrystallized from ethanol and ethanol/hexane, respectively. The results of microanalytical and ^{1}H- and ^{13}C-NMR spectroscopic data are collected in Tables 3, 4, and 5, respectively.

Reaction of Ethyl Cinnamate (**5**) *and Piperidine* (**2b**): The high-pressure reaction was performed as described above at 8 kbar and 35°C for 2 d. The reaction mixture was worked up by Method B to give ethyl 1-piperidino-1-phenylpropanoate (**6**) in 89% yield;

Table 7. ^{1}H-NMR spectral data of **8**

8	δ (in $CDCl_3$)
aa	1.70-1.95(m, 4H, CH_2x2), 3.06-3.17, 3.35-3.55(each m, 1H+3H, NCH_2x2), 3.65, 3.99(ABq, J=13.1 Hz, 2H, CH_2), 7.48-7.56, 7.70-7.77(each m, 3H+2H, C_6H_5)
ab	1.50-1.60(m, 6H, CH_2x3), 3.25-3.37, 3.45-3.55(each m, 4H, NCH_2x2), 3.72, 4.03(ABq, J=13.7 Hz, 2H, CH_2), 7.48-7.56, 7.69-7.77(each m, 3H+2H, C_6H_5)
ae	3.27-3.40, 3.45-3.81(each m, 8H, CH_2x4), 3.72, 3.97(ABq, J=13.5 Hz, 2H, CH_2), 7.50-7.62, 7.65-7.74(each m, 3H+2H, C_6H_5)
af	2.27(s, 3H, NCH_3), 2.20-2.37(m, 4H, CH_2x2), 3.24-3.38, 3.43-3.74(each m, 1H+3H, CH_2x2), 3.72, 4.01(ABq, J=13.6 Hz, 2H, CH_2), 7.51-7.57, 7.69-7.75 (each m, 3H+2H, C_6H_5)
ag	2.38-2.70(m, 4H, CH_2x2), 3.65-3.75(m, 2H, NCHHx2), 3.85(t, J=5.2 Hz, 2H, NCHHx2), 3.71, 3.99(ABq, J=13.7 Hz, 2H, CH_2), 7.50-7.58, 7.69-7.75(each m, 3H+2H, C_6H_5)
ba	1.74-1.98(m, 4H, CH_2x2), 3.11-3.25, 3.32-3.55(each m, 1H+3H, NCH_2x2), 3.67, 3.97(ABq, J=13.4 Hz, 2H, CH_2), 7.50, 7.69(ABq, J=8.7 Hz, 4H, C_6H_4)
bb	1.40-1.68(m, 6H, CH_2x3), 3.27-3.38, 3.48-3.55(each m, 2H+2H, NCH_2x2), 3.76, 4.03(ABq, J=13.8 Hz, 2H, CH_2), 7.50, 7.69(ABq, J=8.8 Hz, 4H, C_6H_4)
bc	1.08(t, J=7.2 Hz, 6H, CH_3x2), 3.12-3.43(m, 4H, CH_2x2), 3.72, 4.02(ABq, J=13.9 Hz, 2H, CH_2), 7.52, 7.72(ABq, J=8.8 Hz, 4H, C_6H_4)
be	3.32-3.74(m, 4H, CH_2x2), 3.77, 3.97(ABq, J=13.8 Hz, 2H, CH_2), 7.52, 7.66 (ABq, J=8.7 Hz, 4H, C_6H_4)
bf	2.30(s, 3H, NCH_3), 2.17-2.44(m, 4H, CH_2x2), 3.29-3.51, 3.52-3.67(each m, 2H+2H, CH_2x2), 3.75, 4.01(ABq, J=13.8 Hz, 2H, CH_2), 7.52, 7.68(ABq, J=8.6 Hz, 4H, C_6H_4)
bg	2.48-2.75(m, 4H, CH_2x2), 3.68-3.75(m, 2H, NCHHx2), 3.83-3.89(m, 2H, NCHH x2), 3.75, 3.99(ABq, J=14.0 Hz, 2H, CH_2), 7.53, 7.69(ABq, J=8.5 Hz, 4H, C_6H_4)
bh	0.90(t, 7.0 Hz, 3H, CH_3), 1.21-1.54(m, 4H, CH_2x2), 3.20(q, J=6.1 Hz, 2H, CH_2), 3.42, 3.70(ABq, J=14.2 Hz, 2H, CH_2), 6.72(br-s, 1H, NH), 7.53(s, 4H, C_6H_4)

Table 8. ^{13}C-NMR spectral data of **8**

8	$SOCH_2$	Aromatic-C	C=O	R^3, R^4
aa	63.3	143.8(1-C), 129.2(2-,6-CH), 124.2(3-,5-CH), 131.5(4-CH)	162.4	46.0, 47.3(2-,5-CH_2), 24.3, 25.9(3-,4-CH_2)
ab	62.0	144.0(1-C), 129.2(2-,6-CH), 124.4(3-,5-CH), 131.4(4-CH)	162.4	43.1, 47.6(2-,6-CH_2), 24.2(4-CH_2), 25.4, 26.4(3-,5-CH_2)
ae	61.0	143.6(1-C), 129.4(2-,6-CH), 124.2(3-,5-CH), 131.6(4-CH)	162.7	42.4, 47.0(2-,6-CH_2), 66.7(3-,5-CH_2)
af	61.4	143.6(1-C), 129.2(2-,6-CH), 124.2(3-,5-CH), 131.4(4-CH)	162.5	41.8, 46.3(2-,6-CH_2), 45.8(NCH_3), 54.3, 54.9(3-,5-CH_2)
ag	61.6	143.6(1-C), 129.3(2-,6-CH), 124.3(3-,5-CH), 131.6(4-CH)	162.8	44.7, 49.2(2-,6-CH_2), 27.3, 28.0(3-,5-CH_2)
ba	62.8	142.2(1-C), 129.2(2-,6-CH), 125.6(3-,5-CH), 137.2(4-C)	161.9	45.7, 46.9(2-,5-CH_2), 24.0, 25.7(3-,4-CH_2)
bb	62.0	142.5(1-C), 129.4(2-,6-CH), 126.0(3-,5-CH), 137.5(4-C)	162.2	43.0, 47.5(2-,6-CH_2), 24.1(4-CH_2), 25.4, 26.4(3-,5-CH_2)
bc	61.8	142.1(1-C), 129.0(2-,6-CH), 125.6(3-,5-CH), 137.1(4-C)	162.9	40.2, 42.3(CH_2CH_3), 12.6, 14.0(CH_2CH_3)
be	60.9	141.9(1-C), 129.6(2-,6-CH), 125.7(3-,5-CH), 137.8(4-C)	162.5	42.3, 46.8(2-,6-CH_2), 66.5(3-,5-CH_2)
bf	61.5	142.2(1-C), 129.6(2-,6-CH), 125.9(3-,5-CH), 137.8(4-C)	162.3	41.9, 46.4(2-,6-CH_2), 45.9(NCH_3), 54.4, 55.0(3-,5-CH_2)
bg	61.6	142.0(1-C), 129.6(2-,6-CH), 125.8(3-,5-CH), 137.8(4-C)	162.6	44.7, 49.1(2-,6-CH_2), 27.3, 28.0(3-,5-CH_2)
bh	59.1	140.3(1-C), 129.7(2-,6-CH), 125.5(3-,5-CH), 138.0(4-C)	163.1	39.6($CH_2CH_2CH_2CH_3$), 31.5($CH_2CH_2CH_2CH_3$), 20.1($CH_2CH_2CH_2CH_3$), 13.7($CH_2CH_2CH_2CH_3$)

m.p. 45–49°C (from dry hexane/benzene; hygroscopic). – ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, CH_3); 24.5, 26.3, and 50.8 (each t, piperidino CH_2); 38.0 (t, C-2); 60.1 (t, OCH_2), 66.3 (d, C-3), 127.1 (d, C-4′ of Ph), 127.7 (d, C-2′ of Ph), 128.3 (d, C-3′ of Ph), 138.6 (s, C-1′ of Ph), 171.8 (C=O).

$C_{16}H_{23}NO_2$ (261.4) Calcd. N 5.36 Found N 5.28

General Procedure for the High-Pressure Reaction of Alkyl 2-Arylsulfinylacetates **7** *with Amines* **2**: A mixture of ester **7**[17] (5 mmol) and amine **2** (10 mmol) was diluted with acetonitrile in an 8-ml PTFE capsule, which was kept for 4 d at 8 kbar and ca. 40°C. After evaporation of solvent and amine, the residue was either (Method A) crystallized from acetone or benzene/hexane or (Method B) subjected to chromatography on silica gel using benzene and benzene/ethyl acetate (2:1) as eluents. The results of microanalytical and ^{1}H- and ^{13}C-NMR spectral data are collected in Tables 6, 7, and 8.

Reaction of Ethyl Phenylsulfinylacetate (**7a**) *with Piperidine* (**2b**) *at 1 bar:* A mixture of ester **7a** (0.5 mmol) and amine **2b** (1 mmol) in acetonitrile (1 ml) was heated to 80°C for 12 h. **7a** was not detected by TLC, thus indicating almost complete consumption. The mixture was worked up by Method B as described above. Amide **8ab** was obtained in 2% yield.

Reaction of Methyl 4-Chlorophenylsulfinylacetate (**7b**) *with Piperidine* (**2b**) *at 1 bar:* The reaction was carried out and worked up in the same manner as above. Amide **8bb** was obtained in 36% yield.

CAS Registry Numbers

1a: 112-62-9 / **1b**: 4630-82-4 / **1c**: 4107-62-4 / **1d**: 606-45-1 / **1e**: 619-50-1 / **1f**: 93-89-0 / **1g**: 101-41-7 / **1h**: 771-90-4 / **2a**: 123-75-1 / **2b**: 110-89-4 / **2c**: 109-89-7 / **2d**: 100-46-9 / **2e**: 110-91-8 / **2f**: 109-01-3 / **2g**: 123-90-0 / **2h**: 109-73-9 / **3aa**: 4637-54-1 / **3ab**: 4637-46-1 / **3ba**: 68571-10-8 / **3bb**: 7103-46-0 / **3ca**: 102423-81-4 / **3cb**: 84732-51-4 / **3da**: 120173-04-8 / **3ea**: 53578-11-3 / **3fa**: 3389-54-6 / **3fb**: 776-75-0 / **3fc**: 1696-17-9 / **3fd**: 1485-70-7 / **3ga**: 3389-53-5 / **3gb**: 3626-62-8 / **3gc**: 2431-96-1 / **3gd**: 7500-45-0 / **3ha**: 57872-38-5 / **3hb**: 102423-80-3 / **3hc**: 2019-69-4 / **3hd**: 4410-32-6 / **5**: 103-36-6 / **6**: 120173-16-2 / **7a**: 54882-04-1 / **7b**: 73281-90-0 / **8aa**: 120173-05-9 / **8ab**: 120173-06-0 / **8ae**: 120173-07-1 / **8af**: 120173-08-2 / **8ag**: 120173-09-3 / **8ba**: 120173-10-6 / **8bb**: 120173-11-7 / **8bc**: 120173-12-8 / **8be**: 120173-13-9 / **8bf**: 120204-19-5 / **8bg**: 120173-14-0 / **8bh**: 120173-15-1

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