STEREOSELECTIVE SYNTHESES OF SPICY COMPONENTS IN PEPPERS

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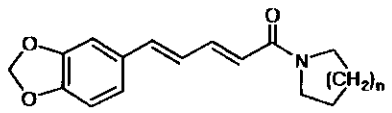
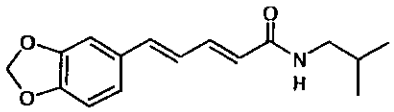
Abstract---The syntheses of (E)-α,ß-unsaturated amides were accomplished from chloroacetamides and alkyl halides *via* ß-elimination of the pyrazinylsulfinyl group, and some of the products are spicy components of piperaceous plants.

Many piperaceous plants contain various (E)-α,ß-unsaturated amides as spicy components (Figure 1). One of the amides, piperine, has recently attracted attention as a bioactive compound[1] and reports concerning the synthesis of piperine and its analogues have often been presented.[2] Most of the syntheses are carried out *via* the Wittig reaction while Tsuboi *et al.*[3] recently reported the way *via* Claisen rearrangement of ketene acetals. However, the yield of the undesired (Z)-isomer cannot be avoided by these procedures. We have reported the efficient and highly stereoselective syntheses of (E)-olefins by applying ß-elimination of the pyrazinylsulfinyl group which is faster than that of phenylsulfinyl group.[4,5] Generally, α,ß-unsaturated amides are synthesized from the corresponding esters and amines. We gave no attention to the preparation of the esters and researched the conditions to obtain the present amides from chloroacetamides and alkyl halides by applying our previous procedure.[4]

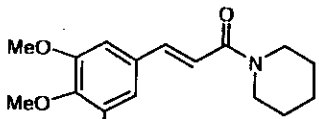
Figure 1



Piperyline (5e: n = 1)
Piperine (5f: n = 2)
(*Piper nigrum* L.)



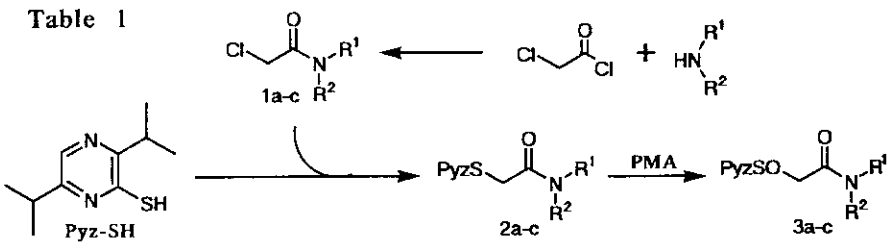
Piperlongumine
(*Piper longum* L.)



Piplartine
(*Piper longum* L.)

The preparation of chloroacetamides (1a-c) was carried out using the Schotten-Baumann reaction between chloroacetyl chloride and amines (pyrrolidine, piperidine and isobutylamine) according to the procedure developed by Pinchard et al.[6] The resulting 1a-c were reacted with 3,6-diisopropyl-2-pyrazinethiol (PyzSH) to give the corresponding sulfides (2a-c), which upon oxidation with permaleic acid (PMA) gave 1-[1-oxo-2-(3,6-diisopropylpyrazin-2-ylsulfinyl)ethyl]-amines (3a-c). The results are shown in Table 1.

Table 1

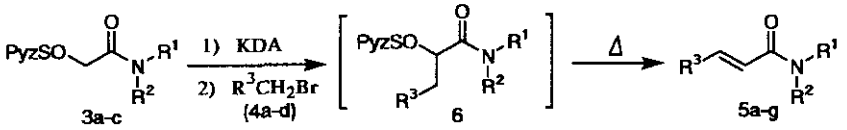


Entry No.	Amines R^1	Amines R^2	Chloroacetamides (Yields %)	Compd. No. (Yields %) Sulfides	Sulfoxides
1	$-(CH_2)_4-$		**1a** (73)	**2a** (70)	**3a** (89)
2	$-(CH_2)_5-$		**1b** (74)	**2b** (95)	**3b** (95)
3	H	iso-Bu	**1c** (58)	**2c** (84)	**3c** (72)

The α-hydrogen to the pyrazinylsulfinyl group on 3a-c was deprotonated with the hybrid base, called KDA,[7] prepared from lithium diisopropylamide (LDA) and potassium tert-butoxide. The nucleophilic substitution of the resulting carbanion to various alkyl halides (4a-d) was examined. The conditions used in the previous studies were available for the present work to give various α,ß-unsaturated amides

(5a-g) in good yields as shown in Table 2. When the reaction of 3c with 4c was also carried out in order to obtain pipelongumine,[8] many by-products were, however, produced and the desired compound could not be isolated in spite of the use of 2 eq. of KDA. The alkyl halides (4c) and (4d) were prepared according to the method shown in Scheme 1. All of 5a-g were determined to have the (E)-form from the corresponding J values of the olefinic protons in their ^{1}H-nmr spectra. Melting points of 5e-g agreed with those of naturally occurring compounds (5e: piperine[9], 5f: piperyline[9], 5g: piplartine[10]).

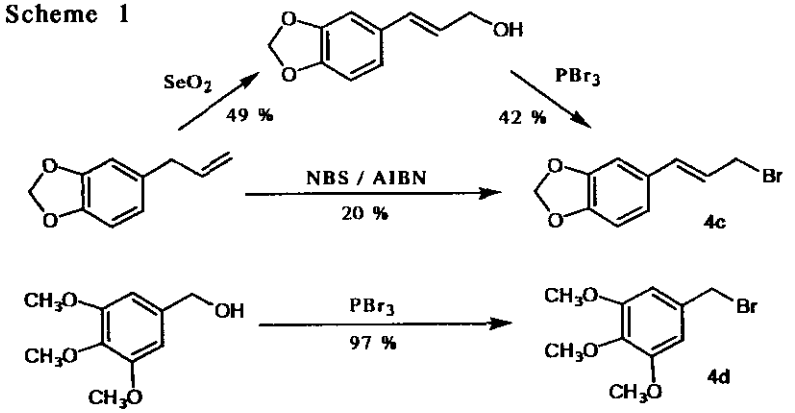
Table 2



Entry No.	Sulfoxides	R^3CH_2Br R^3 (Compd)	Products (Yields %)	mp [lit.] (°C)
1	3a	Ph (4a)	5a (95)	94-95 [100-100.5][12]
2	3b	Ph (4a)	5b (56)	114-117 [118.5-119.5][13]
3	3a	PhCH=CH (4b)	5c (82)	118-119
4	3b	PhCH=CH (4b)	5d (89)	89-94 [93][14]
5	3a	3,4-(OCH_2O)-PhCH=CH (4c)	5e*(99)	141-143 [142][9]
6	3b	3,4-(OCH_2O)-PhCH=CH (4c)	5f*(77)	126-127 [129][9]
7	3b	3,4,5-(CH_3O)$_3$-Ph (4d)	5g*(89)	98-100 [101-102][10]
8	3c	3,4-(OCH_2O)-PhCH=CH (4c)	not obtained	

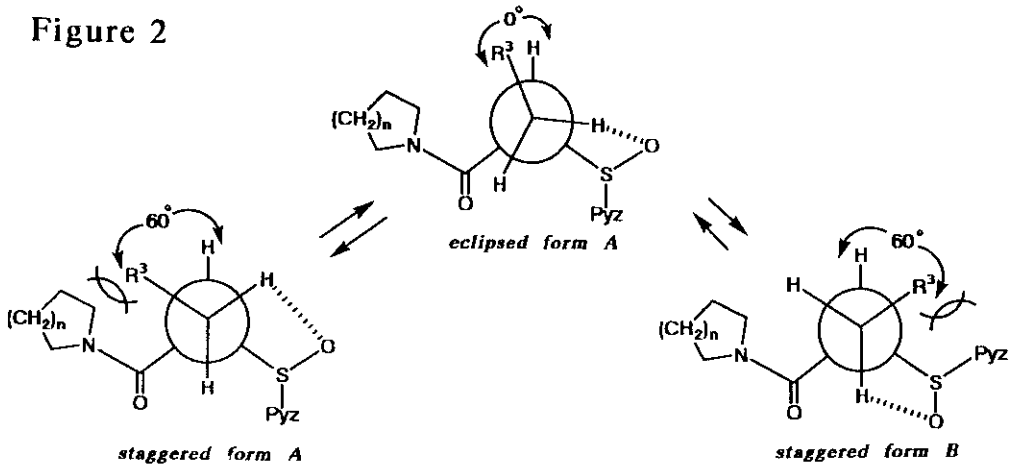
* Naturally occurring compounds.

Scheme 1



Exclusive formation of (E)-olefins can be explained by assuming the prefered conformation of a sulfoxide (6) as shown in Figure 2. Thus, the eclipsed form A seems to be favorable to the others by the steric hindrance between R^3 and $CONR_2$ or between R^3 and PyzSO. The elimination of 6, therefore, takes place predominantly via eclipsed form A giving the (E)-olefin. If this mechanism is correct, 3,6-diisopropyl-2-pyrazinylsulfinyl group should be an efficient leaving group for obtaining the (E)-olefin by the steric bulkiness effect. These points are now being studied.

Figure 2



It is known that the ß-elimination of an arylsulfinyl group is accelerated in the presence of bases. Pyrazine is a very weak base (pKa = 0.65)[11] by comparison with pyridine (pKa = 5.17)[11] and other diazines, pyridazine (pKa = 2.33)[11] and pyrimidine (pKa = 1.30),[11] so that the basicity seems to only slightly affect to the rate of such an elimination. However, the rate of the elimination using the pyrazinylsulfinyl group as the leaving group is obviously faster than that using phenylsulfinyl group as described in our previous paper.[4] We suggest the facts are based on the strength of the electron withdrawing effect of the pyrazine ring as estimated from the unstability of acyloxypyrazines for water in comparison with phenyl carboxylate. Anyway, the characteristics of the pyrazinylsulfinyl group as a leaving group for ß-elimination gave us good results for the syntheses of naturally occurring α,ß-unsaturated amides.

EXPERIMENTAL

The melting and boiling points are uncorrected. ^{1}H-Nmr spectra were obtained using Varian EM-390 (90 MHz) and Brucker AM-400 (400 MHz) with TMS as the internal standard and $CDCl_3$ as the solvent. Other spectral data were obtained by the following instruments: ir spectra; Japan Spectroscopic Co. A100, ms; Hitachi M-80B spectrometer.

General Procedure for the Preparation of Chloroacetamides (1a-c)

To a solution of amines (pyrrolidine, piperidine or isobutylamine; 0.2 mol) in dry Et_2O (150 ml) was added dropwise a solution of chloroacetyl chloride (11.3 g; 0.1 mol) in dry Et_2O (150 ml) at -5°C over 1 h with stirring. The mixture was stirred for 1 h at room temperature and the depositing salt was filtered off. The solvent of the filtrate was evaporated and the residual colorless oil was purified by vacuum distillation to give **1a-c**. The melting and boiling points were agreed with those of the corresponding reported compounds.

Pyrrolidine Chloroacetamide (1a):

Colorless prisms; mp 48-49°C (after the distillation) [lit., 48-50°C].[15]

Piperidine Chloroacetamide (1b):

Colorless oil; bp 135-137°C/9 torr [lit., 149-153°C/17 torr].[16]

Isobutylamine Chloroacetamide (1c):

Colorless oil; bp 117-120°C/18 torr [lit., 117-118°C/18 torr].[17]

General Procedure for the Condensation of 3,6-Diisopropyl-2-pyrazinethiol with Chloroacetamides (1a-c)

This condensation was carried out according to the procedure described in the previous paper[4] to obtain the corresponding sulfides (**2a-c**).

N-[1-Oxo-2-(3,6-diisopropyl-2-pyrazinylthio)ethyl]pyrrolidine (2a):

Colorless needles; mp 76-77°C (n-hexane); ms: m/z 307 (M^+); ir (KBr): 1640 (νCO) cm^{-1}; ^{1}H-nmr: δ 1.24 (d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.26 (d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.63-2.10 (m, 4H, pyrrolidine H), 2.82-3.46 (m, 2H, $C\underline{H}(CH_3)_2$ X 2), 3.46-3.70 (m, 4H, pyrrolidine H), 4.03 (s, 2H, SCH_2CO), 8.10 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{16}H_{25}N_3OS$: C, 62.50; H, 8.20; N, 13.67. Found: C, 62.29; H, 8.47; N, 13.67.

N-[1-Oxo-2-(3,6-diisopropyl-2-pyrazinylthio)ethyl]piperidine (2b)

Colorless needles; mp 62-63°C (n-hexane); ms: m/z 321 (M^+); ir (KBr): 1640 (νco) cm^{-1}; ^{1}H-nmr: δ 1.18 (d, J = 7 Hz, 12H, $CH(C\underline{H}_3)_2$ X 2), 1.50-1.63 (m, 6H, piperidine H), 2.80-3.30 (m, 2H, $C\underline{H}(CH_3)_2$ X 2), 3.40-3.63 (m, 4H, piperidine H), 4.10 (s, 2H, SCH_2CO), 8.03 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{17}H_{27}N_3OS$: C, 63.51; H, 8.47; N, 13.07. Found: C, 63.43; H, 8.48; N, 13.22.

N-[1-Oxo-2-(3,6-diisopropyl-2-pyrazinylthio)ethyl]-N-isobutylamine (2c)

Colorless needles; mp 74-76°C (n-hexane); ms: m/z 309 (M^+); ir (KBr): 1650 (νco) cm^{-1}; ^{1}H-nmr: δ 0.72 (d, J = 7 Hz, 6H, $NCH_2CH(C\underline{H}_3)_2$), 1.26 (d, J = 7 Hz, 12H, $CH(C\underline{H}_3)_2$), 1.45-1.83 (m, 1H, $NCH_2C\underline{H}(CH_3)_2$), 2.96 (t, J = 7 Hz, 2H, $NC\underline{H}_2CH(CH_3)_2$), 2.70-3.30 (m, 2H, $C\underline{H}(CH_3)_2$), 3.77 (s, 2H, SCH_2CO), 8.08 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{16}H_{27}N_3OS$: C, 62.10; H, 8.79; N, 13.58. Found: C, 62.17; H, 8.93; N, 13.58.

General Procedure for the Oxidation of 2a-c

Oxidation of **2a-c** was carried out with permaleic acid (PMA) to give the corresponding sulfoxides (**3a-c**) and the procedure was in accord with it described in the previous report.[4]

N-[1-Oxo-2-(3,6-diisopropyl-2-pyrazinylsulfinyl)ethylpyrrolidine (3a)

Colorless needles; mp 83-84°C (n-hexane); ms: m/z 323 (M^+); ir (KBr): 1030 (νso), 1640 (νco) cm^{-1}; ^{1}H-nmr: δ 1.31 (d, J = 6.6 Hz, 3H, $CH(C\underline{Ha}_3)CHb_3$), 1.33 (d, J = 6.6 Hz, 3H, $CH(CHa_3)C\underline{Hb}_3$), 1.34 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.74-2.13 (m, 4H, pyrrolidine H), 3.00-3.33 (m, 1H, $C\underline{H}(CH_3)_2$), 3.23-3.63 (m, 4H, pyrrolidine H), 3.63-3.93 (m, 1H, $C\underline{H}(CH_3)_2$), 4.19 (d, J = 15 Hz, 1H, SCHaCO), 4.61 (d, J = 15 Hz, 1H, SCHbCO), 8.53 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{16}H_{25}N_3O_2S$: C, 59.41; H, 7.79; N, 12.99. Found: C, 59.41; H, 7.45; N, 13.03.

N-[1-Oxo-2-(3,6-diisopropyl-2-pyrazinylsulfinyl)ethyl]piperidine (3b)

Colorless needles; mp 102-103°C (n-hexane); ms: m/z 337 (M^+); ir (KBr): 1040 (νso), 1640 (νco) cm^{-1}; ^{1}H-nmr : δ 1.26 (d, J = 6.6 Hz, 3H, $CH(C\underline{Ha}_3)CHb_3$), 1.27 (d, J = 6.6 Hz, 3H, $CH(CHa_3)C\underline{Hb}_3$), 1.34 (d, J = 6.6 Hz, $CH(C\underline{H}_3)_2$), 1.53-1.73 (m, 6H, piperidine H), 2.93-3.33 (m, 1H, $C\underline{H}(CH_3)_2$), 3.30-3.58 (m, 4H, piperidine H), 3.67-3.96 (m, 1H, $C\underline{H}(CH_3)_2$), 4.22 (d, J = 15 Hz, 1H, SCHaCO), 4.85 (d, J = 15 Hz, 1H, SCHbCO), 8.55 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{17}H_{27}N_3O_2S$: C, 60.50; H, 8.06; N, 12.45. Found: C, 60.54; H, 7.84; N, 12.39.

N-[1-Oxo-2-(3,6-diisopropyl-2-pyrazinylsulfinyl)ethyl]-N-isobutylamine (3c)

Colorless needles; mp 85-88°C (n-hexane); ms: m/z 325 (M^+); ir (KBr): 1040 (νso), 1640 (νco) cm^{-1}; ^{1}H-nmr : δ 0.86 (d, J = 6.7 Hz, 6H, $NCH_2CH(C\underline{H}_3)_2$), 1.31 (d, J = 6.7 Hz, 3H, $CH(C\underline{H}a_3)CHb_3$), 1.35 (d, J = 6.7 Hz, 9H, $CH(CHa_3)C\underline{H}b_3$ and $CH(C\underline{H}_3)_2$), 1.70-1.80 (m, 1H, $NCH_2C\underline{H}(CH_3)_2$), 3.01-3.21 (m, 3H, $NC\underline{H}_2CH(CH_3)_2$ and $C\underline{H}(CH_3)_2$), 3.62-3.69 (m, 1H, $C\underline{H}(CH_3)_2$), 3.79 (d, J = 15 Hz, 1H, SCHaCO), 4.05 (d, J = 15 Hz, 1H, SCHbCO), 8.58 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{16}H_{27}N_3O_2S$: C, 59.04; H, 8.36; N, 12.91. Found: C, 59.16; H, 8.08; N, 12.85.

Synthesis of 5-(3-Bromo-1-propenyl)-1,3-dioxaindan (4c)

To a solution of 5-(3-hydroxy-1-propenyl)-1,3-dioxaindan (17.8 g, 0.1 mol) in CH_2Cl_2 (500 ml) was added dropwise a solution of PBr_3 (7.0 ml, 74 mmol) in CH_2Cl_2 (10 ml) at -5°C over 1 h with stirring and the mixture was stirred for 30 min at -5°C. The reaction mixture was poured into ice water (200 ml) and neutralized with powdered $KHCO_3$ with stirring. The organic layer was separated by a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (200 ml X 2). The combined extracts were washed with water (200 ml X 2). After drying over dry Na_2SO_4, the CH_2Cl_2 solution was evaporated to give crude 5-(3-bromo-1-propenyl)-1,3-dioxaindan (**4c**; 10.0 g, 42 mmol; 42 %). The resulting crude product was purified by reflux with active carbon and the following recrystallization from Et_2O. The melting point of **4c** was agreed with one of the product obtained by bromination of safrole with NBS.

Colorless needles; mp 69-70°C (Et_2O) [lit., 69°C].[18]

Synthesis of 3,4,5-Trimethoxybenzyl Bromide (4d)

This preparation was carried out according to the procedure for the synthesis of **4c** using 3,4,5-trimethoxybenzyl alcohol (17.9 g, 0.1 mol) as the starting material.

Colorless needles; mp 71-73°C (n-hexane) [lit., 71-72°C].[19]

General Procedure of the Metalation of 3a-c with KDA and the Following Reaction with 4a-d

To a suspension of tert-BuOK (264 mg, 2.4 mmol) and diisopropylamine (0.32 ml, 2.4 mmol) in dry THF (20 ml) was added 1.6 M n-BuLi hexane solution (1.5 ml, 2.4 mmol) at -78°C under Ar stream. After stirring for 15 min, a solution of

3a-c (2 mmol) in dry THF (10 ml) was added to the previous mixture and the resulting solution was stirred for 1 h at room temperature. The solvent was removed *in vacuo* and the residue was extracted with Et_2O. The Et_2O solution was washed with 5 % HCl (50 ml X 3) and brine (50 ml X 1), and dried over Na_2SO_4. After removal of the solvent, the residue was applied to the chromatography (Kieselgel 60, 230-400 mesh, n-hexane:AcOEt = 8:2) to give α,β-unsaturated amides (**5a-f**). All melting points of **5a-f** are shown in Table 2 and were agreed with reported data except **5c** to be unreported compound. The spectroscopic data and elemental analysis of **5c** are as following:

Colorless needles; ms: m/z 227 (M^+); ir (KBr): 1640 (νco) cm^{-1}; ^{1}H-nmr: δ 1.85-2.00 (m, 4H, pyrrolidine H), 3.54-3.59 (m, 4H, pyrrolidine H), 6.31 (d, J = 15 Hz, 1H, Ar-CH=CH-CH=C<u>H</u>), 6.86 (d, J = 15 Hz, 1H, Ar-C<u>H</u>=CH-CH=CH), 6.92 (dd, J = 8.9 and 16 Hz, Ar-CH=C<u>H</u>-CH=CH), 7.26-7.36 (m, 5H, benzene H), 7.47 (dd, J = 10 and 15 Hz, 1H, Ar-CH=CH-C<u>H</u>=CH) ppm; *Anal.* Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.21; H, 7.22; N, 6.29.

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