ARTICLES

Preparation of 5-Substituted 2,3-Dimethylpyrazines from the Reaction of 2,3-Dimethyl-5,6-dihydropyrazine and Aldehydes or Ketones

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The dehydrogenation reaction of 2,3-dimethyl-5,6-dihydropyrazine produced 2,3-dimethyl-1,2,5,6-tetrahydropyrazine (25.4%) and 5-ethyl-2,3-dimethylpyrazine (2%) in addition to 2,3-dimethylpyrazine (26.7%) in a sodium ethoxide/ethanol solution. It was suspected that the carbanion of 2,3-dimethyl-5,6-dihydropyrazine was formed with the base and then reacted with acetaldehyde, which is present in ethanol in small quantities, to yield 5-substituted pyrazine. Six aldehydes and three ketones were reacted with 2,3-dimethyl-5,6-dihydropyrazine under basic conditions and the corresponding 5-substituted 2,3-dimethylpyrazine were obtained in high yields.

Pyrazines have received much attention in the last decade as the flavor chemicals which possess roasted or smoky odor (Watanabe and Sato, 1971; Buttery et al., 1971). Use of pyrazine compounds for flavor ingredients has, therefore, become increasingly popular recently. Various methods of pyrazine synthesis have also been reported (Tutin, 1910; Cormforth, 1958; Flament and Stoll, 1967; Bramwell et al., 1971). Ishiguruo and Matsumura (1958) obtained alkylpyrazines from corresponding 2,3-dihydropyrazines by heating in an ethanol–KOH solution under aerobic conditions. The yield of expected pyrazines by this method is, however, usually low. We found that dehydrogenation of dihydropyrazines also occurred in an ethanol–KOH solution or metal alkoxide solution under nitrogen stream. When 2,3-dimethyl-5,6-dihydropyrazine and 5-ethyl-2,3-dimethylpyrazine, which was expected to be formed from the reaction of carbanion and acetaldehyde (Shibamoto et al., 1979), were obtained as byproducts in addition to 2,3-dimethylpyrazine.

Following this procedure, the various 5-substituted 2,3-dimethylpyrazines were obtained in high yields from the reaction of 2,3-dimethyl-5,6-dihydropyrazines with aldehydes and ketones in a metal alkoxide solution.

EXPERIMENTAL SECTION

Materials. Diacetyl (Naarden Inc.) and ethylenediamine (Nakari Chemicals Ltd.) were used after distillation. 2,3-Dihydropyrazines were synthesized from corresponding dicarbonyls and diamines (Ishiguro and Matsumura, 1958). Methanol and ethanol were purified with magnesium under a nitrogen stream. Propanol, 2-propanol, and 2-methyl-2-propanol were purified with calcium hydride under a nitrogen stream. Aldehydes and ketones were obtained from reliable commercial sources and used after distillation. IR, NMR, and MS data were obtained on JASCO IR-S, JNM-PMX 60, and Hitachi Model RMU-6M, respectively.

Isolation of 2,3-Dimethylpyrazine (II), 2,3-Dimethyl-1,2,5,6-tetrahydropyrazine (III), and 5-Ethyl-2,3-dimethylpyrazine (IV) from the Reaction of 2,3-Dimethyl-5,6-dihydropyrazine (I) in a Sodium Ethoxide/Methanol Solution. Compound I (42 g) was dissolved into a mixture of methanol (200 mL) and sodium ethoxide (18 g of sodium metal in 360 mL of ethanol). The solution was refluxed for 4 h and vacuum distilled without stopping the reaction. Compounds II and III were isolated from the distillate by fractional distillation under reduced pressure [II, 75 °C (30 mmHg); III, 71–73 °C (20 mmHg)]. Compound IV was isolated from the residue of distillation using silica gel (Merk) thin-layer chromatography (developing agent, ethyl acetate/chloroform, 6:1). The spectral data of compounds are shown in Table I.

Formation of 2,3-Dimethyl-5-alkylpyrazines from I in an Alcohol–KOH Solution. Compound I was refluxed in three different alcohol solutions (propanol, 2-propanol, 2-methyl-2-propanol). Each alcohol solution contained 40 g of KOH, 400 mL of sodium isopropoxide (2 g of metal sodium in 400 mL of 2-propanol), and 80 g of potassium *tert*-butoxide. The reaction mixtures were treated according to the same procedure as that used in the isolation of compound IV.

Formation of 5-Substituted 2,3-Dimethylpyrazines from Compound I with Aldehydes or Ketones under Basic Conditions. Compound I (251 mg) was dissolved into 2 mL of methanol. Sodium methoxide (0.5 g of metal sodium in 10 mL of methanol) was added to the solution. Acetophenone (0.3 mL) was then added at 0 °C. The solution was stirred for 26 h at 25 °C. After the pH of the reaction mixture was adjusted to 1–2 with the addition of 4 mL of 6 N HCl solution, the solution was concentrated by distillation under reduced pressure. Ethyl acetate (30 mL) was added to the residue and the pH of the solution was adjusted to 8 with 1.5 mL of 50% NaOH solution. The ethyl acetate layer was separated and the aqueous layer extracted with two 30-mL portions of ethyl acetate. The ethyl acetate extract was washed with saturated brine water and dried over anhydrous sodium sulfate for 12 h. The solvent was removed by distillation under reduced pressure and the reaction product isolated using silica gel TLC. 2,3-Dimethyl-5-(α-methylbenzyl)pyrazine (V) was obtained (396 mg, yield, 81.9% relative to dihydropyrazine used). The experiments with other aldehydes and ketones were conducted using exactly the same procedure; the results are shown in Table II.

The identification of the products was conducted by IR, NMR, and MS analyses.

RESULTS AND DISCUSSION

2,3-Dimethylpyrazine (II), 2,3-dimethyl-1,2,5,6-tetrahydropyrazine (III), and 5-ethyl-2,3-dimethylpyrazine (IV) were obtained from 2,3-dimethyl-5,6-dihydropyrazine (I) when compound I was refluxed with sodium ethoxide in an ethanol solution under a nitrogen stream. The yield percentages of the above three compounds II, III, and IV

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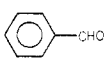
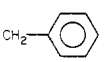
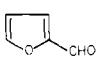
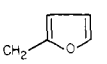
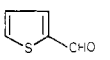
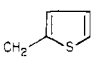
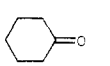
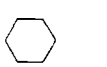
0021-8561/80/1428-0244$01.00/0

Table I. Spectral Data of the Products Obtained from 2,3-Dimethyl-5,6-dihydropyrazine

compound		spectral data
2,3-dimethylpyrazine	IR	1535, 1445, 1430, 1405, 1380 cm^{-1}
	NMR	δ 2.42, (s, 6 H), 8.13 (s, 2 H)
	MS	108 (95), 93 (4), 68 (8), 67 (100), 52 (10), 42 (25), 40 (20)
2,3-dimethyl-1,2,5,6-tetrahydropyrazine	IR	3300, 1660 cm^{-1}
	NMR	δ 1.18 (3 H, d, J = 7 Hz, $-CH_3$), 1.80 (3 H, t, J = 2 Hz, $CH_3C{=}N-$), 2.6-2.8 (2 H, m, $-C{=}NCH_2-$), 3.2-3.5 (3 H, m, $-CHNHCH_2-$), 1.10 (1 H, broad s, -NH-)
	MS	112 (45), 110 (35), 97 (16), 95 (8), 82 (24), 71 (63), 69 (55), 56 (51), 43 (47), 42 (100)
5-ethyl-2,3-dimethylpyrazine	IR	1535, 1480, 1420, 1395, 1370 cm^{-1}
	NMR	δ 1.26 (t, J = 7 Hz, 3 H), 2.43 (s, 6 H), 2.40 (q, J = 7 Hz, 2 H), 8.00 (s, 1 H)
	MS	136 (69), 135 (100), 108 (20), 107 (5), 80 (10), 54 (50)

Table II. Results Obtained from the Reaction of 2,3-Dimethyl-5,6-dihydropyrazine and Aldehyde or Ketones

aldehyde or ketone	reaction time, h	substituent at position 5	yield, %		spectral data of 5-substituted 2,3-dimethylpyrazine
CH_3CH_2CHO	24	$CH_2CH_2CH_3$	74.0	IR	1535, 1460, 1440, 1395, 1370 cm^{-1}
				NMR	δ 0.93 (t, J = 7 Hz, 3 H), 1.4-2.0 (m, 2 H), 2.38 (s, 6 H), 2.64 (t, J = 7 Hz, 2 H), 8.00 (s, 1 H)
				MS	150 (24), 135 (26), 122 (100), 121 (9), 80 (8), 42 (9)
$(CH_3)_2CHCHO$	12	$CH_2CH(CH_3)_2$	65.6	IR	1540, 1470, 1460, 1400, 1380 cm^{-1}
				NMR	δ 0.92 (d, J = 7 Hz, 6 H), 1.7-2.5 (m, 1 H), 2.40 (s, 6 H), 2.53 (d, J = 7 Hz, 2 H), 7.98 (s, 1 H)
				MS	164 (19), 149 (25), 123 (18), 122 (100), 121 (13), 107 (4), 80 (9), 42 (4)
$(CH_3)_2CHCH_2CHO$	24	$CH_2CH_2CH(CH_3)_2$	34.9	IR	1538, 1465, 1395, 1373 cm^{-1}
				NMR	δ 0.98 (d, J = 7 Hz, 6 H), 1.3-1.8 (m, 3 H), 2.37 (s, 6 H), 2.63 (t, J = 7 Hz, 2 H), 7.97 (s, 1 H)
				MS	178 (1), 163 (11), 136 (7), 135 (23), 123 (18), 122 (100), 121 (12), 80 (5)
			74.8	IR	3030, 1600, 1530, 1490, 1395, 1370 cm^{-1}
				NMR	δ 2.33 (s, 6 H), 3.90 (s, 2 H), 7.07 (s, 5 H), 7.92 (s, 1 H)
				MS	198 (76), 197 (100), 196 (6), 182 (5), 156 (5), 116 (7), 115 (17), 91 (5)
			78.8	IR	3165, 1600, 1510, 1400, 1375, 1015, 885, 790, 740 cm^{-1}
				NMR	δ 2.33 (s, 6 H), 3.97 (s, 2 H), 6.00 (m, 1 H), 6.12 (m, 1 H), 7.20 (m, 1 H), 8.00 (s, 1 H)
				MS	188 (90), 160 (23), 159 (100), 145 (7), 134 (4), 118 (12), 81 (20), 78 (17), 53 (6), 42 (3)
			80.0	IR	3100, 3000, 1540, 1465, 1400, 1370, 1070, 1045, 855, 830 cm^{-1}
				NMR	δ 2.42 (s, 6 H), 4.17 (s, 2 H), 6.7-6.9 (m, 2 H), 7.0-7.1 (m, 1 H), 8.10 (s, 1 H)
				MS	204 (100), 203 (27), 189 (7), 171 (22), 160 (8), 159 (53), 122 (12), 121 (12), 97 (79), 78 (3)
CH_3COCH_3	3	$CH(CH_3)_2$	72.5	IR	1530, 1470, 1450, 1420, 1395, 1370 cm^{-1}
				NMR	δ 1.28 (d, J = 7 Hz, 6 H), 2.44 (s, 6 H), 2.96 (m, J = 7 Hz, 1 H), 8.00 (s, 1 H)
				MS	150 (54), 149 (40), 136 (19), 135 (100), 123 (12), 122 (87), 121 (5), 109 (6), 108 (19), 107 (8), 99 (7), 94 (5), 80 (5), 67 (20), 53 (16), 42 (14)
$CH_3COCH_2CH_3$	24	$CH(CH_3)CH_2CH_3$	64.9	IR	1535, 1465, 1455, 1395 cm^{-1}
				NMR	δ 0.80 (t, J = 7 Hz, 3 H), 1.23 (d, J = 7 Hz, 3 H), 1.4-1.9 (m, 2 H), 2.40 (s, 6 H), 2.70 (m, 1 H), 8.01 (s, 1 H)
				MS	164 (28), 150 (11), 149 (58), 137 (23), 136 (100), 135 (70), 134 (12), 122 (47), 108 (11), 67 (6), 53 (6), 42 (6)
	24		79.5	IR	1535, 1465, 1395 cm^{-1}
				NMR	δ 1.3-2.0 (m, 10 H), 2.40 (s, 6 H), 8.03 (s, 1 H)
				MS	190 (27), 175 (7), 161 (17), 149 (29), 147 (13), 136 (25), 135 (100), 123 (8), 122 (64), 80 (1)

were 26.7, 25.4, and 2, respectively. Compound III oxidized to compound I quantitatively by air at room temperature. Compounds II and III may be formed by a disproportionation reaction of compound I.

The ethyl group of compound IV came from acetaldehyde, which is present in ethanol in very small quantities. 5-Propyl and 5-isopropyl derivatives were obtained with yields of 2% when propanol and 2-propanol, respectively, were used instead of ethanol. Shibamoto et al. (1979) proposed that the corresponding alcohol is oxidized to aldehyde, then reacts with dihydropyrazine to give 5-substituted pyrazine. The 2-methyl-2-propyl derivative was not formed when 2-methyl-2-propanol was used. This may be due to the fact that 2-methyl-2-propanol is not oxidized to an aldehyde or ketone. In order to investigate this proposed reaction mechanism, various aldehydes and ketones, such as acetophenone, were reacted with compound I. The pyrazine derivatives which possess a cor-

responding substituent at the 5 position were obtained in high yield. Results are shown in Table II.

The results indicate that the method developed in this study is useful in obtaining various alkylpyrazines.

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Received for review July 9, 1979. Accepted September 25, 1979.

Pyrethroid Photochemistry: *S*-Bioallethrin

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Photodecomposition of *S*-bioallethrin, the 1*R*,3*R*,4'*S* isomer of the insecticide allethrin, in the solid phase or in solution by sunlight or ultraviolet light (λ 360 nm) yields the following major products at <50% conversion: *cis*-allethrin, the di-π-methane rearrangement product at the allyl substituent, the allylic alcohol and epoxides from the isobutenyl group, and chrysanthemic acid. Triplet intermediates are involved in the cyclopropane isomerization reactions and the di-π-methane rearrangement, with the latter process predominating. The yield of epoxides formed by triplet oxygen is considerably enhanced with benzil as a mediator. Oxidation at the allylic position of the chrysanthemate moiety results from radical reactions of ground-state oxygen. Many other products obtained in low yields (<1%) presumably arise from further reactions of the primary photoproducts.

S-Bioallethrin (1 or Esbiol) is the most insecticidal isomer (1*R*,3*R*,4'*S*; 1*R*,trans,4'*S*) of allethrin, the first potent synthetic pyrethroid (Schechter et al., 1949). The uses of *S*-bioallethrin and various allethrin isomer mixtures are similar to those of pyrethrum. These compounds are less photostable as thin films than most other insecticidal chrysanthemates lacking an alkenylrethronyl substituent (Chen and Casida, 1969; Miskus and Andrews, 1972). The only identified photoproduct of 1 is the cyclopropylrethronyl derivative formed in solution (Bullivant and Pattenden, 1976). The chrysanthemate isobutenyl substituent undergoes photooxidation at the methyl group trans to the cyclopropane and at the double bond (Chen and Casida, 1969; Ueda et al., 1974). Photodecomposition of simple derivatives of the acid and alcohol components of 1 has been studied (Bullivant and Pattenden, 1971; Ueda and Matsui, 1971).

This work examines the photoisomerization and photooxidation of *S*-bioallethrin under a variety of irradiation conditions in the presence and absence of sensitizers, quenchers, and oxygen-transfer agents.

MATERIALS AND METHODS

Spectroscopy. Nuclear magnetic resonance (NMR) spectra were obtained as previously reported (Ruzo and Casida, 1980). Chemical ionization–mass spectra (CI-MS) were recorded with the Finnigan 1015D instrument equipped with a System Industries Model 150 computer using isobutane as the reagent gas at a CI source pressure of 0.3–0.5 torr at 70 eV and 60–140 °C.

Chromatography and Analyses. Gas–liquid chromatography (GLC) analysis utilized the Hewlett-Packard Model 5830A gas chromatograph with a ^{63}Ni electron-capture detector and an open tubular column (0.25 mm i.d. × 30 m) coated with SE-30 (4 μg/mL). The operating temperatures were as follows: injector, 250 °C; oven, 200 °C; detector, 350 °C. Helium was the carrier gas at a split ratio of 1:120 and argon–methane (95:5) was the makeup gas for the detector. An online computer calculated the retention time (t_R) of each peak and the normalized area as percentage of total peak area. Responses were calibrated by use of authentic standards where possible and in other cases by assuming similar electron-capture sensitivities to available standards.

Thin-layer chromatography (TLC) employed precoated 20 × 20 cm silica gel 60 F-254 chromatoplates (EM Laboratories, Inc., Elmsford, NY) with 0.25-mm gel thickness for analytical studies and 0.5 mm for preparative isolations. Three TLC solvent systems were used for one- and two-dimensional developments: hexane–ether (1:1, HE), tol-

Table I. Photoproducts of *S*-[^{14}C]Bioallethrin from Sunlight Irradiation of Thin Films

	yield, %[a]		R_f[b]		
product	1 h	3 h	TE	HE	t_R, min[b]
1	(33.0)[c]	(55.6)[c]	0.58	0.59	7.9
2	1.0	1.2	0.62	0.61	7.6
3	3.0	3.8	0.66	0.64	10.5
4	11.8	7.9	0.44	0.52	dec
5	4.2	3.2	0.35	0.45	9.9
6	5.2	6.7	0.27	0.39	9.9
7	3.6	2.9	0.40	0.48	13.0
8	3.0	3.2	0.31	0.42	13.0
9	25.2	14.7	0.38	0.52	3.3
10	0.9	1.5	0.47	0.55	7.0
11[d]	<0.1	nd	0.66	0.64	nd
unident[e]	42.0	54.9			

[a] Yields of 25 μg/cm² deposits are given as percent of [^{14}C]allethrin reacted. [b] For conditions, see the Methods section. [c] Values in parentheses are percent reaction at the indicated time. [d] Separated in CE (R_f 0.41) from 1-3 (R_f 0.35). [e] Unidentified products at R_f 0.0 in each solvent system.

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0021-8561/80/1428-0246$01.00/0