Studies on pyrazines. Part 32.[1] Synthesis of trisubstituted and tetrasubstituted pyrazines as ant pheromones

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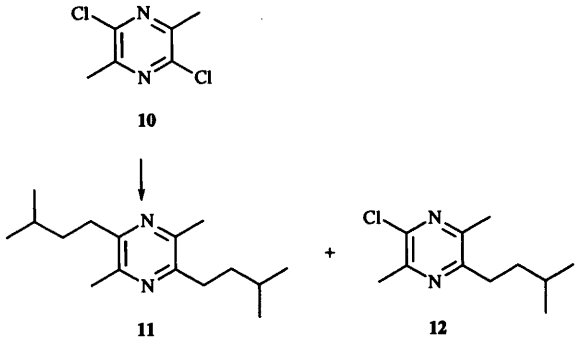
The synthesis of trialkylpyrazines having methyl groups on C-2 and C-5 is described, which is completed by the cross-coupling reaction of 2-chloro-3,6-dimethylpyrazine with dialkylzinc in the presence of [1,3-bis(diphenylphosphino)propane] nickel(II) chloride. Similarly, 2,5-diisobutyl-, -diisopropyl- and -di-*sec*-butyl-3-methylpyrazines are prepared from the corresponding dialkyl chloropyrazines. The dimethyl products are acylated with an α-keto acid under the Minisci radical conditions providing 2-acyl-5-alkyl-3,6-dimethylpyrazines. Several compounds obtained in this study prove to be active as components of pheromones in ants.

Insect pheromones are an exciting and vigorous subject for synthesis as well as for biological studies. This unique form of communication is effected by a single chemical or a mixture of chemicals. Numerous alkylpyrazines have been recognized as the components of trail-laying[2] or alarm pheromones[3] in various species of ants, and have been verified to be either trialkylpyrazines possessing *meta*- or *para*-dimethyl substituents or the 2-alkenyl-5-methyl derivatives.[4] A variety of novel pheromones were recently detected in certain ants,[5] and were identified as tetrasubstituted pyrazines bearing an alkyl, alkenyl, acyl or α-hydroxyalkyl group along with the trialkyl substituents. This report concerns an efficient synthetic pathway to those pheromones, in which trialkylpyrazines are prepared by the nickel-catalysed cross-coupling reaction of 2-chloro-3,6-dialkylpyrazines with dialkylzinc. The major aim of this work is the transformation of trialkylpyrazines to 2-acyl-3,5,6-trialkylpyrazines, which is achieved by the Minisci-type radical reaction. In addition, the scope of each reaction step was examined by utilization of higher-alkyl substituted chloropyrazines.

Conventionally, alkylpyrazines are synthesized by condensation of α-diketones with 1,2-diamines followed by dehydrogenation. However, this method suffers from poor regioselectivity in the preparation of unsymmetrically substituted pyrazines. Nucleophilic addition of alkyllithium to pyrazines was employed for the preparation of alkylpyrazines, but methylpyrazines underwent competitive alkylation either on the pyrazine ring or on the side chain, leading to some products in low yield.[6] Recently, several 2-alkyl-3,6-dimethylpyrazines were prepared by thermal electrocyclization[7] or zirconium-mediated alkenylation of 2,5-dimethylpyrazine with acetylenes.[8] Being apparently attractive for the synthesis of trialkylpyrazines, the latter method is of little practical value because the requisite zirconium catalyst is so air-sensitive that preparation of the cationic complex needs extreme care. Meanwhile, transition metal-mediated reaction of halogenopyrazines, *e.g.* with organometallic reagents in the presence of tetrakis(triphenylphosphine)palladium(0)[9] or [1,3-bis(diphenylphosphino)propane] nickel(II) chloride,[10] allows the preparation of alkylpyrazines. Compared with the palladium complex, the nickel catalyst is easier to handle due to its stability in air. We undertook the nickel-catalysed cross-coupling reaction of 2-chloro-3,6-dialkylpyrazine with dialkylzinc.

The starting 2-chloro-3,6-dialkylpyrazines **1**–**4** were prepared by self-condensation of the corresponding α-amino acids, followed by chlorination of the resulting piperazine-2,5-diones with refluxing phosphoryl chloride, in which 2,5-dichloro-3,6-dialkylpyrazines were formed as minor products.[11] Reaction of



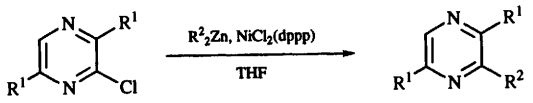
Scheme 1 *Reagents:* isopentylmagnesium bromide or diisopentylzinc

chloropyrazine **1** with 1.2 equiv. of diethylzinc in THF proceeded smoothly in the presence of 5 mol% of [1,3-bis(diphenylphosphino)propane] nickel(II) chloride at room temperature to produce 2,5-dimethyl-3-ethylpyrazine **5** in 71% yield (entry 1, Table 1); without the catalyst the coupling did not occur. The use of ethylmagnesium chloride in place of diethylzinc decreased the yield of the product **5** to 17% even after reaction for 8 h, when a 46% yield of the starting chloride was recovered. Diisopentylzinc, which was generated *in situ* from isopentylmagnesium bromide and zinc bromide, also induced cross-coupling with **1** to afford isopentylpyrazine **6** (entry 2, Table 1). When chloropyrazines **2**, **3** and **4**, having more bulky alkyl groups, were employed, the coupling reaction did not ensue at room temperature, but it did proceed at 45–50 °C to provide the corresponding trialkylpyrazines **7**–**9** in excellent yields (entries 3, 4 and 5, Table 1). Although dimethylpyrazine **1** was completely consumed after 2 h at 45 °C, the yield of **5** was surprisingly reduced to 57%.

Symmetrically-substituted tetraalkylpyrazines could be similarly prepared *via* the coupling reaction, but the displacement of halogeno groups with alkyl groups was suppressed when compared with the above monoalkylation. Thus, when 2,5-dichloro-3,6-dimethylpyrazine **10** was treated with 2.4 equiv. of diisopentylzinc under the nickel-catalysed conditions, a 37% yield of the unreacted starting material **10** was recovered and the monoalkylated material, 2-chloro-3,6-dimethyl-5-isopentylpyrazine **12**, was formed in 29% yield, while the desired 2,5-diisopentylpyrazine **11** was obtained in only 7% yield (Scheme 1). When isopentylmagnesium bromide was used instead of the zinc reagent, the dichloropyrazine **10** was completely consumed and the yields of products **11** and **12** were increased to 29 and 53%, respectively.

Of the trialkylpyrazines synthesized above, 3-isopentyl-2,5-

Table 1 Synthesis of trialkylpyrazines **5–9** from 2-chloro-3,6-dialkylpyrazines **1–4** with dialkylzincs in the presence of $NiCl_2(dppp)$[a,b]



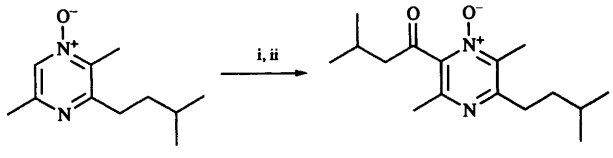
1–4 **5–9**

Entry	Starting material	R^1	T/°C	t/h	Product	R^2	Yield (%)
1	**1**	Me	Room temp.	3	**5**	Et	71
2	**1**	Me	Room temp.	2.5	**6**	Isopentyl	70
3	**2**	Bu^i	45	3.5	**7**	Me	93
4	**3**	Pr^i	50	7	**8**	Me	75
5	**4**	Bu^s	45	19	**9**	Me	87[c]

[a] dppp = $Ph_2P(CH_2)_3PPh_2$. [b] A 5 mol% of the catalyst was used. [c] A 12% yield of **4** was recovered.

dimethylpyrazine **6** is one of the most widespread pheromones,[4a,4c] and the 3-ethyl analogue **5** has been proved to be the major component of the trail pheromone of the South America leaf-cutting ant.[2] Tetraalkylpyrazine **11** has been also found in some species of worker ants collected in New Zealand.

A noteworthy feature of a number of pheromones identified recently is the oxygen-containing side chains attached to the pyrazine core, such as acyl and α-hydroxyalkyl groups. The synthesis of these compounds, however, is not straightforward, because Friedel–Crafts reactions cannot be used for the acylation of nitrogen heteroaromatics, due to the electron-deficient nature of the ring system. Substitution of pyrazines has sometimes been achieved by other methodologies, *e.g.* lithiation of pyrazines having two electron-withdrawing groups[12] or 2,5-dialkylpyrazine 1-oxides,[13] followed by treatment with an ester. For the synthesis of acylpyrazines, the route from the *N*-oxide seemed to be adequate. However, metallation of 2,5-dimethyl-3-isopentylpyrazine 1-oxide **13**[1] with lithium 2,2,6,6-tetramethylpiperidine (LTMP) at −78 °C and then treatment with methyl 3-methylbutyrate resulted in incomplete conversion, giving only 5% yield of acylpyrazine *N*-oxide **14**, while 56% of the unreacted starting substrate **13** was recovered (Scheme 2).

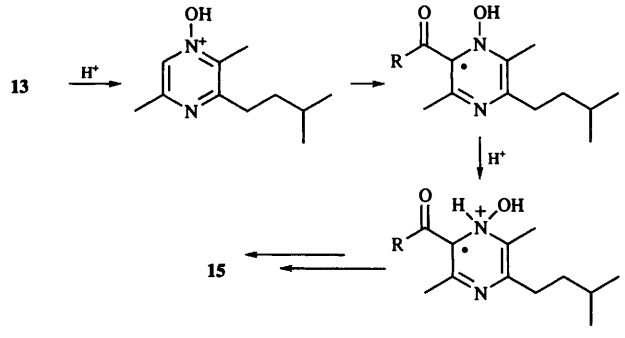


13 **14**

Scheme 2 *Reagents and conditions:* i, LTMP, −78 °C; ii, Bu^iCO_2Me

Synthesis of acylpyrazines can also be effected by homolytic acylation of protonated pyrazines, but acylation of alkylpyrazines gives rise to poor yields and nonregioselective formation of acylpyrazines.[14] Hence there is scope for a new approach to the homolytic synthesis of acylpyrazines to improve the yields. Acyl radicals are formed by the redox decomposition of an aldehyde using *tert*-butyl hydroperoxide and an Fe^{II} salt, or by the silver-catalysed decarboxylation of an α-keto acid with persulfate. It has been shown that these radicals behave as a nucleophile, so that electron-withdrawing functionality on the heteroaromatics activates the substitution.[15,16] In this respect, the *N*-oxide **13** bearing a cationic ring nitrogen was expected to be the precursor of choice for the synthesis of acylpyrazines. The radical substitution, however, did not occur when *N*-oxide **13** was treated with isovaleraldehyde in aqueous acetonitrile at 3 °C (entry 1, Table 2). In contrast, acylation in sulfuric acid proceeded with loss of the *N*-oxide oxygen to afford acylpyrazine **15** in 27% yield (entry 2, Table 2). The failure of the acylation in the absence of acidic media could be due to the back-donation of electrons from the *N*-oxide oxygen towards the ring, which might suppress the electron-withdrawing effect. Addition of sulfuric acid protonates the *N*-oxide oxygen, leading to *N*-hydroxypyrazinium intermediates which facilitate the nucleophilic radical substitution. The hydroxy group is finally removed as a hydroxyl radical or water to form the unexpected acylpyrazine (Scheme 3). On the other hand, the acylation of *N*-oxide **13** by 4-methyl-2-oxovaleric acid in the absence of sulfuric acid at 62–65 °C also yielded acylpyrazine **15** (entry 3, Table 2). This reaction probably also follows the same pathway as above because the reaction mixture is strongly acidic due to protons generated in the oxidative decarboxylation of the α-keto acid by persulfate (*vide infra*).[16]

As can be seen from the acylation of *N*-oxide **13**, the key factor in promoting the substitution reaction is the pyrazinium nitrogen in the initial intermediate, as shown in Scheme 3. This

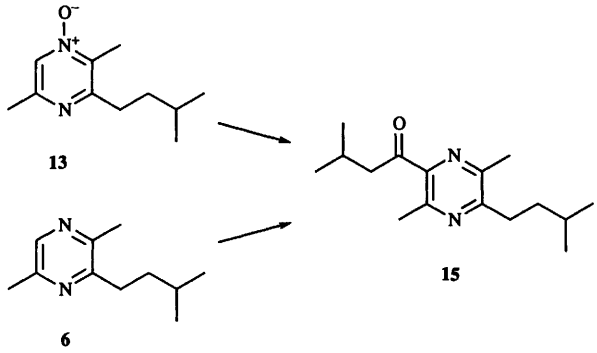


Scheme 3

kind of species is easily formed from alkylpyrazines in acidic solution, and this method is now commonly employed for acylation. In fact, the effect of protonation with sulfuric acid is evident when compared with the acylation of 2,5-dimethyl-3-isopentylpyrazine **6** by isovaleraldehyde in the absence of the acid (entries 5 *vs.* 4, Table 2). To our surprise, the outcome of the acylation using 4-methyl-2-oxovaleric acid was entirely different, *i.e.* substitution under the conditions without sulfuric acid proceeded more efficiently to yield quantitatively acylpyrazine **15** (entries 7 *vs.* 6). As described above, the keto acid is a strong proton donor, and the reaction solution containing 4-methyl-2-oxovaleric acid has a pH of approximately 1.7 (entry 7, Table 2). This value is not significantly different to that (pH 0.3) of the sulfuric acid solution (entry 6, Table 2), indicating that the decreased yield is caused by other factors. One possibility is decomposition of the keto acid in warm sulfuric acid solution, but this is excluded by NMR studies, which show no reduction of a model compound (pyruvic acid) in sulfuric acid under the conditions used in the above acylation.

We have successfully adapted this facile acylation procedure

Table 2 Preparation of acylpyrazine **15**

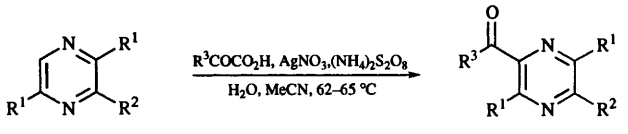


13 **6** **15**

Entry	Starting material	Radical source[a]	Solvent	Yield (%)	Recovered (%)
1	**13**	A	H_2O–MeCN[b]	0	61
2	**13**	A	3 mol dm^{-3} H_2SO_4–MeCN[b]	27	13
3	**13**	K	H_2O–MeCN[c]	50	0
4	**6**	A	H_2O–MeCN[b]	31	51
5	**6**	A	3 mol dm^{-3} H_2SO_4–MeCN[b]	63	0
6	**6**	K	0.5 mol dm^{-3} H_2SO_4–MeCN[c]	53	0
7	**6**	K	H_2O–MeCN[c]	100	0

[a] A: isovaleraldehyde, K: 4-methyl-2-oxovaleric acid. [b] At 3 °C to room temperature for 3 h. [c] At 62–65 °C for 0.5 h.

Table 3 Preparation of acylpyrazines

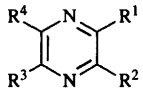


5–9, 16 **15, 17–27**

Entry	Starting material	*t*/h	Product	R^1	R^2	R^3	Yield (%)
1	**16**[a]	0.5	**17**	Me	Me	Et	75
2	**16**[a]	0.5	**18**	Me	Me	Bu^i	99
3	**5**	0.5	**19**	Me	Et	Et	83
4	**5**	0.5	**20**	Me	Et	Bu^i	97
5	**6**	0.5	**21**	Me	Isopentyl	Et	86
6	**6**	0.5	**15**	Me	Isopentyl	Bu^i	100
7	**7**	1	**22**	Bu^i	Me	Et	46[b]
8	**7**	1	**23**	Bu^i	Me	Bu^i	58[c]
9	**8**	3	**24**	Pr^i	Me	Et	34[d,h]
10	**8**	3	**25**	Pr^i	Me	Bu^i	30[e,i]
11	**9**	3	**26**	Bu^s	Me	Et	34[f,j]
12	**9**	3	**27**	Bu^s	Me	Bu^i	35[g,k]

[a] 2,3,5-Trimethylpyrazine. [b–g] Byproducts: (*b*) 2-ethyl-3,6-diisobutyl-5-methylpyrazine **28** (13%), (*c*) 2,3,5-triisobutyl-6-methylpyrazine **29** (17%), (*d*) 2-ethyl-3,6-diisopropyl-5-methylpyrazine (22%), (*e*) 2-isobutyl-3,6-diisopropyl-5-methylpyrazine (17%), (*f*) 2,5-di-*sec*-butyl-3-ethyl-6-methylpyrazine (19%), (*g*) 2,5-di-*sec*-butyl-3-isobutyl-6-methylpyrazine (17%). The ratios were determined from ^1H NMR spectra. [h–k] Unreacted starting materials were isolated in (*h*) 12, (*i*) 28, (*j*) 17 and (*k*) 35% yields.

using 2-oxobutyric acid or 4-methyl-2-oxovaleric acid and 3-alkyl-2,5-dimethylpyrazines **5**, **6** and **16**, and the results are listed in Table 3. Higher yields were obtained of isovalerylpyrazines than of the propionyl homologues (entries 2 *vs.* 1, 4 *vs.* 3 and 6 *vs.* 5, Table 3) and the yields probably reflect the stability of acyl radicals. For the acylation of 2,5-diisobutylpyrazine **7**, complete consumption of the starting substrate required a doubling of the reaction time, and the yields of acylpyrazines **22** and **23** were markedly reduced (entries 7 and 8, Table 3). Additionally, 2,5-diisobutyl-3-ethyl-6-methyl- or 2,3,5-triisobutyl-6-methyl-pyrazines **28** and **29** were formed as byproducts, as confirmed by NMR spectroscopy. It is conceivable that their formation is due to ethyl or isobutyl



28 $R^1 = R^3 = Bu^i$, $R^2 = Et$, $R^4 = Me$
29 $R^1 = R^2 = R^3 = Bu^i$, $R^4 = Me$
30 $R^1 = CH(OH)Bu^i$, $R^2 = R^4 = Me$, R^3 = isopentyl
31 $R^1 = R^3 = COBu^i$, $R^2 = R^4 = Me$

radicals generated by partial decarbonylation of the acyl radicals. Such alkylation competing with acylation has been observed in the radical reaction of various heteroaromatics with isobutyraldehyde.[17] When the R^1 substituents are the more bulky isopropyl or *sec*-butyl groups, only modest yields of the starting materials were recovered even after 3 h. In other words, the acylation is influenced by steric factors due to the substituent adjacent to the ring carbon available for the substitution. The acylpyrazines obtained in that case were also contaminated with the corresponding alkylpyrazines in sizeable proportions. Separation of the two products, alkyl- and acyl-pyrazines, could not be accomplished, either by HPLC or fractional distillation. In conclusion, the current methodology is seen to be limited to synthesis of *para*-dimethyl substituted acylpyrazines.

As cited above, several alkylpyrazines have been subjected to acylation using an aldehyde in the presence of sulfuric acid, and the reactivity order has been shown to follow the series: trialkyl > dialkyl > monoalkyl > the parent pyrazines. Since the best yield in that case was 48%, the outcome of the acylation of **6** leading to a 63% yield of acylpyrazine **15** (entry 5, Table 2) is moderately satisfactory. Despite the nucleophilic character of the acyl radical, the excellent accessibility of trialkylpyrazines to radical attack could be suggested to result from easier protonation, as electron-donating alkyl substituents enhance the basicity of the ring nitrogen. Generally, acylation with a keto acid is more effective, as exemplified by formation of **15** (entries 7 *vs.* 5, Table 2). Another opportunity for comparison is the acylation of 2,3,5-trimethylpyrazine **16** with 2-oxobutyric acid, which gave a 75% yield of acylpyrazine **17** in the present study while it was previously obtained in 48% yield by reaction with propionaldehyde.[14] A drawback of the radical acylation method is the difficulty in stopping reaction at the monoacylation stage, there being multiple positions

Table 4 Preparation of chloropyrazines from piperazine-2,5-diones

Substituent R[1]	Products and yield (%)	
	Monochloropyrazine	Dichloropyrazine
Me	**1** 61	**10** 21
Bu[i]	**2** 36	27
Pr[i]	**3** 26	19
Bu[s]	**4** 51	15

available for the substitution.[16] Conversely this polyacylation was advantageous for the synthesis of 3,6-dimethyl-2,5-diisovalerylpyrazine **31**, one of our target pheromones, which was synthesized through homolytic acylation of 2,5-dimethylpyrazine with 4-methyl-2-oxovaleric acid in 83% yield.

Finally, we achieved the reduction of acylpyrazine **15** by treating it with sodium borohydride in propan-2-ol, obtaining 2-(1-hydroxyisopentyl)-3,6-dimethyl-5-isopentylpyrazine **30** in 84% yield. This product also functions as a form of ant pheromone. It has been reported that diacylpyrazine **31** is reduced in the same manner to give monohydroxy and dihydroxypyrazines.[5]

Experimental

Melting points were determined using a Büchi 535 apparatus and are uncorrected. Boiling points were oven temperatures for Kugelrohr distillation and are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrometer. NMR spectra were obtained with a JEOL JNM EX270 (270 MHz ^{1}H, 67.8 MHz ^{13}C) instrument using solutions in $CDCl_3$, unless otherwise noted, containing Me_4Si as internal standard. *J* Values are given in Hz. THF was used after distillation over lithium aluminum hydride. Isopentyl bromide and propan-2-ol were dried over 4 Å molecular sieves and then distilled prior to use. Acetonitrile was also used after distillation.

Chloropyrazines 1–4, 10

These compounds were prepared by chlorination of the corresponding piperazine-2,5-diones with phosphoryl chloride by the procedure of Blake and Sammes.[11b] The results are collected in Table 4.

Zinc and Grignard reagents

Diethylzinc (1.0 mol dm^{-3} solution in hexane), dimethylzinc (1.0 mol dm^{-3} solution in hexane) and ethylmagnesium chloride (2.0 mol dm^{-3} solution in THF) were purchased from commercial suppliers. Diisopentylzinc was prepared *in situ* by mixing zinc bromide with isopentylmagnesium bromide. This Grignard reagent was prepared from isopentyl bromide (4.8 cm^3, 40 mmol) and magnesium (1.2 g, 48 mmol) in THF (24 cm^3) in the usual manner. Anhydrous zinc bromide (4.1 g, 18 mmol) was placed under argon and THF (30 cm^3) was added. The isopentylmagnesium solution (26 cm^3, 36 mmol) was added *via* a syringe with stirring at 0–5 °C. The mixture was then slowly warmed to room temperature for 1 h.

General procedure for Ni-catalysed cross-coupling of chloropyrazines with zinc and Grignard reagents

A mixture of chloropyrazine (**1–4**, **10**) (10 mmol) and [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (0.300 g, 0.50 mmol, 5 mol%) was placed under argon, and THF (80 cm^3) and zinc or Grignard reagent (12 mmol) were added *via* a syringe. The mixture was stirred under the conditions given in Table 1, and then ice–water was added to quench the reaction. After filtration, the solution was neutralized with $NaHCO_3$ solution, extracted with ethyl acetate (2 × 100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil, which was purified by column chromatography (SiO_2, 40 g; hexane–ethyl acetate 9:1 to 3:1), then HPLC (10 μm SiO_2, 2.2 × 30 cm; hexane–ethyl acetate 9:1) in the cases of **8**, **9**, **11** and **12** and finally vacuum distilled. The yields of trialkylpyrazines **5–9** are summarized in Table 1. The following compounds were obtained by the above procedure.

3-Ethyl-2,5-dimethylpyrazine 5. An oil, bp 79–82 °C/19 mmHg (lit.,[18] 80–81 °C/19 mmHg); δ_H 1.27 (3 H, t, *J* 7.6), 2.49 (3 H, s), 2.53 (3 H, s), 2.80 (2 H, q, *J* 7.6), 8.15 (1 H, s); δ_C 13.3, 21.7, 28.9, 141.3, 149.0, 150.8, 156.4.

3-Isopentyl-2,5-dimethylpyrazine 6. An oil, bp 90–96 °C/7 mmHg (Found: C, 74.1; H, 10.4; N, 15.5. $C_{11}H_{18}N_2$ requires C, 74.1; H, 10.2; N, 15.7%); δ_H 0.97 (6 H, d, *J* 6.6), 1.50–1.59 (2 H, m), 1.63–1.73 (1 H, m), 2.48 (3 H, s), 2.52 (3 H, s), 2.73–2.80 (2 H, m), 8.14 (1 H, s); δ_C 21.7, 21.8, 23.1, 29.0, 33.9, 38.3, 141.3, 149.1, 150.7, 155.8.

2,5-Diisobutyl-3-methylpyrazine 7. An oil, bp 86–89 °C/5 mmHg (Found: C, 75.7; H, 10.8; N, 13.5. $C_{13}H_{22}N_2$ requires C, 75.7; H, 10.75; N, 13.6%); δ_H 0.93 (6 H, d, *J* 6.3), 0.96 (6 H, d, *J* 6.6), 2.02–2.19 (2 H, m), 2.54 (3 H, s), 2.59 (2 H, d, *J* 7.3), 2.66 (2 H, d, *J* 7.3), 8.16 (1 H, s); δ_C 22.6, 23.1, 23.2, 29.1, 29.7, 44.0, 44.9, 141.9, 152.0, 152.8, 153.5.

2,5-Diisopropyl-3-methylpyrazine 8. An oil, bp 64–67 °C/5 mmHg (Found: C, 74.2; H, 10.2; N, 15.6. $C_{11}H_{18}N_2$ requires C, 74.1; H, 10.2; N, 15.7%); δ_H 1.27 (6 H, d, *J* 6.6), 1.31 (6 H, d, *J* 6.9), 2.57 (3 H, s), 2.97–3.07 (1 H, m), 3.17–3.27 (1 H, m), 8.25 (1 H, s); δ_C 22.1, 22.2, 23.0, 31.7, 34.4, 139.7, 150.4, 157.8, 158.8.

2,5-Di-*sec*-butyl-3-methylpyrazine 9. An oil, bp 83–86 °C/18 mmHg (Found: C, 75.7; H, 10.8; N, 13.5. $C_{13}H_{22}N_2$ requires C, 75.7; H, 10.75; N, 13.6%); δ_H 0.84 (3 H, t, *J* 7.6), 0.86 (3 H, t, *J* 7.6), 1.24 (3 H, d, *J* 6.9), 1.28 (3 H, d, *J* 7.3), 1.57–1.69 (2 H, m), 1.71–1.86 (2 H, m), 2.56 (3 H, s), 2.71–2.79 (1 H, m), 2.94–3.01 (1 H, m), 8.21 (1 H, s); δ_C 12.7, 12.9, 20.2, 20.6, 22.4, 29.8, 30.3, 38.6, 41.5, 140.6, 151.1, 157.2, 157.8.

2,5-Diisopentyl-3,6-dimethylpyrazine 11. An oil, bp 131–133 °C/4 mmHg (lit.,[19] 96–98 °C/0.45 mmHg); δ_H 0.97 (12 H, d, *J* 6.6), 1.48–1.57 (4 H, m), 1.59–1.71 (2 H, m), 2.49 (6 H, s), 2.69–2.75 (4 H, m); δ_C 21.7, 23.2, 29.0, 33.5, 38.6, 148.4, 152.7.

2-Chloro-5-isopentyl-3,6-dimethylpyrazine 12. An oil, bp 83–85 °C/5 mmHg (Found: C, 62.4; H, 8.1; N, 12.8. $C_{11}H_{17}N_2Cl$ requires C, 62.1; H, 8.05; N, 13.2%); δ_H 0.97 (6 H, d, *J* 6.3), 1.49–1.57 (2 H, m), 1.61–1.71 (1 H, m), 2.50 (3 H, s), 2.58 (3 H, s), 2.71–2.77 (2 H, m); δ_C 20.9, 21.7, 22.6, 28.4, 32.5, 37.8, 144.8, 148.8, 149.1, 154.0.

General procedure for acylation of alkylpyrazines with isovaleraldehyde

In a typical reaction a mixture of alkylpyrazine (0.50 mmol) and isovaleraldehyde (0.22 cm^3, 3.0 mmol) in acetonitrile (2.0 cm^3) was stirred and 3 mol dm^{-3} sulfuric acid (0.5 cm^3) was added at 3 °C. To the mixture 80% *tert*-butyl hydroperoxide (0.21 cm^3, 2.1 mmol) and a solution of $FeSO_4 \cdot 7H_2O$ (0.834 g, 3.0 mmol) in water (1.5 cm^3) were added simultaneously. The resulting mixture was stirred for 3 h, during which time the temperature was raised to 27 °C. After dilution with a small amount of H_2O, $NaHSO_3$ was added until a test with starch–iodide paper was negative. The mixture was extracted with ethyl acetate (2 × 20 cm^3). The extracts were washed with $NaHCO_3$ solution and then H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 7 g; hexane–ethyl acetate 6:1 in most cases) and vacuum distilled.

General procedure for acylation of alkylpyrazines with α-keto acids

In a typical reaction a mixture of $(NH_4)_2S_2O_8$ (2.28 g, 10 mmol) and $AgNO_3$ (0.052 g, 0.30 mmol) was placed under argon, and a solution of alkylpyrazine (2.0 mmol) in acetonitrile (16 cm^3) was added with stirring. To the mixture were added a solution

of α-keto acid (6.0 mmol) in H_2O (20 cm^3) and acetonitrile (4 cm^3). The resulting mixture was stirred under argon at 62–65 °C (internal temperature) for the time given in Tables 2 and 3. After cooling to room temperature, the mixture was diluted with H_2O and extracted with ethyl acetate (2 × 80 cm^3) and the extracts were worked up as described above. The following compounds were obtained by the above procedure.

1-(5-Isopentyl-3,6-dimethylpyrazin-2-yl)-3-methylbutan-1-one 15. A pale yellow oil, bp 105–110 °C/4 mmHg (Found: C, 73.4; H, 10.1; N, 10.3. $C_{16}H_{26}N_2O$ requires C, 73.2; H, 10.0; N, 10.7%); ν_{max}(neat)/cm^{-1} 1695 (C=O); δ_H 0.98 (12 H, d, *J* 6.3), 1.53–1.61 (2 H, m), 1.64–1.73 (1 H, m), 2.20–2.30 (1 H, m), 2.57 (3 H, s), 2.73 (3 H, s), 2.78–2.84 (2 H, m), 3.03 (2 H, d, *J* 6.9); δ_C 21.8, 23.1, 23.4, 23.5, 25.6, 29.0, 34.0, 38.0, 48.9, 144.5, 148.3, 151.0, 158.5, 204.4.

1-(3,5,6-Trimethylpyrazin-2-yl)propan-1-one 17. Pale yellow needles, mp 65.5–68 °C (from hexane) (lit.,[14] 65–67 °C); ν_{max}(neat)/cm^{-1} 1700 (C=O); δ_H 1.18 (3 H, t, *J* 7.3), 2.54 (3 H, s), 2.56 (3 H, s), 2.74 (3 H, s), 3.18 (2 H, q, *J* 7.3); δ_C 8.2, 21.7, 22.4, 23.0, 33.0, 143.8, 148.5, 150.4, 154.3, 204.5.

1-(3,5,6-Trimethylpyrazin-2-yl)-3-methylbutan-1-one 18. A pale yellow oil, bp 84–87 °C/5 mmHg (Found: C, 70.0; H, 8.9; N, 13.4. $C_{12}H_{18}N_2O$ requires C, 69.9; H, 8.8; N, 13.6%); ν_{max}(neat)/cm^{-1} 1695 (C=O); δ_H 0.98 (6 H, d, *J* 6.6), 2.19–2.29 (1 H, m), 2.55 (3 H, s), 2.56 (3 H, s), 2.73 (3 H, s), 3.03 (2 H, d, *J* 6.9); δ_C 22.2, 22.8, 23.4, 25.6, 48.9, 144.7, 148.9, 150.9, 154.7, 204.3.

1-(5-Ethyl-3,6-dimethylpyrazin-2-yl)propan-1-one 19. A pale yellow oil which crystallized on standing, bp 78–81 °C/5 mmHg; mp 22 °C (Found: C, 68.8; H, 8.5; N, 14.4. $C_{11}H_{16}N_2O$ requires C, 68.7; H, 8.4; N, 14.6%); ν_{max}(neat)/cm^{-1} 1700 (C=O); δ_H 1.18 (3 H, t, *J* 7.3), 1.30 (3 H, t, *J* 7.3), 2.57 (3 H, s), 2.75 (3 H, s), 2.85 (2 H, q, *J* 7.6), 3.19 (2 H, q, *J* 7.3); δ_C 8.7, 12.9, 21.7, 23.5, 29.0, 33.4, 144.1, 148.3, 151.0, 159.1, 205.0.

1-(5-Ethyl-3,6-dimethylpyrazin-2-yl)-3-methylbutan-1-one 20. A pale yellow oil, bp 86–89 °C/5 mmHg (Found: C, 70.95; H, 9.3; N, 12.5. $C_{13}H_{20}N_2O$ requires C, 70.9; H, 9.15; N, 12.7%); ν_{max}(neat)/cm^{-1} 1700 (C=O); δ_H 0.98 (6 H, d, *J* 6.6), 1.30 (3 H, t, *J* 7.6), 2.20–2.30 (1 H, m), 2.57 (3 H, s), 2.74 (3 H, s), 2.85 (2 H, q, *J* 7.6), 3.03 (2 H, d, *J* 6.9); δ_C 12.9, 21.7, 23.4, 23.5, 25.6, 29.0, 48.9, 144.5, 148.3, 151.0, 159.0, 204.4.

1-(5-Isopentyl-3,6-dimethylpyrazin-2-yl)propan-1-one 21. A pale yellow oil, bp 84–87 °C/5 mmHg (Found: C, 71.45; H, 9.4; N, 12.0. $C_{14}H_{22}N_2O$ requires C, 71.8; H, 9.5; N, 11.95%); ν_{max}(neat)/cm^{-1} 1695 (C=O); δ_H 0.98 (6 H, d, *J* 6.3), 1.17 (3 H, t, *J* 7.3), 1.52–1.61 (2 H, m), 1.63–1.73 (1 H, m), 2.56 (3 H, s), 2.74 (3 H, s), 2.78–2.84 (2 H, m), 3.18 (2 H, q, *J* 7.3); δ_C 9.2, 22.3, 23.6, 24.0, 29.5, 33.9, 34.4, 38.5, 144.5, 148.8, 151.5, 159.1, 205.5.

The following materials could not be isolated so only their ^1H NMR spectral data are given.

1-(3,6-Diisobutyl-5-methylpyrazin-2-yl)propan-1-one 22. δ_H 0.91 (6 H, d, *J* 6.9), 0.99 (6 H, d, *J* 6.6), 1.17 (3 H, t, *J* 7.3), 2.03–2.13 (1 H, m), 2.15–2.28 (1 H, m), 2.57 (3 H, s), 2.68 (2 H, d, *J* 7.3), 2.99 (2 H, d, *J* 7.3), 3.17 (2 H, q, *J* 7.3).

1-(3,6-Diisobutyl-5-methylpyrazin-2-yl)-3-methylbutan-1-one 23. δ_H 0.91 (6 H, d, *J* 6.6), 0.98 (6 H, d, *J* 6.9), 0.99 (6 H, d, *J* 6.6), 2.05–2.18 (2 H, m), 2.21–2.28 (1 H, m), 2.57 (3 H, s), 2.69 (2 H, d, *J* 7.3), 2.99 (2 H, d, *J* 7.3), 3.00 (2 H, d, *J* 6.9).

1-(3,6-Diisopropyl-5-methylpyrazin-2-yl)propan-1-one 24. δ_H 1.18 (3 H, t, *J* 7.3), 1.25 (6 H, d, *J* 6.9), 1.28 (6 H, d, *J* 6.9), 2.60 (3 H, s), 3.13–3.29 (1 H, m), 3.18 (2 H, q, *J* 7.3), 3.75–3.85 (1 H, m).

1-(3,6-Diisopropyl-5-methylpyrazin-2-yl)-3-methylbutan-1-one 25. δ_H 0.98 (6 H, d, *J* 6.6), 1.25 (6 H, d, *J* 6.6), 1.28 (6 H, d, *J* 6.9), 2.20–2.25 (1 H, m), 2.60 (3 H, s), 3.01 (2 H, d, *J* 6.9), 3.20–3.26 (1 H, m), 3.76–3.81 (1 H, m).

1-(3,6-Di-*sec*-butyl-5-methylpyrazin-2-yl)propan-1-one 26. δ_H 0.79 (3 H, t, *J* 7.3), 0.84 (3 H, t, *J* 7.6), 1.17 (3 H, t, *J* 7.3), 1.24 (3 H, d, *J* 6.6), 1.25 (3 H, d, *J* 7.2), 1.54–1.63 (2 H, m), 1.74–1.85 (2 H, m), 2.59 (3 H, s), 2.94–3.04 (1 H, m), 3.15 (2 H, q, *J* 7.3), 3.55–3.62 (1 H, m).

1-(3,6-Di-*sec*-butyl-5-methylpyrazin-2-yl)-3-methylbutan-1-one 27. δ_H 0.78 (3 H, t, *J* 7.3), 0.84 (3 H, t, *J* 7.6), 0.93 (6 H, d, *J* 6.9), 1.24 (3 H, d, *J* 6.6), 1.25 (3 H, d, *J* 6.6), 1.54–1.63 (2 H, m), 1.78–1.82 (2 H, m), 2.18–2.20 (1 H, m), 2.58 (3 H, s), 2.89–3.01 (1 H, m), 2.98 (2 H, dd, *J* 6.9, 1.3), 3.59–3.51 (1 H, m).

2,5-Diisobutyl-3-ethyl-6-methylpyrazine 28. δ_H 0.93 (6 H, d, *J* 6.6), 0.94 (6 H, d, *J* 6.6), 1.24 (3 H, t, *J* 7.6), 2.03–2.13 (2 H, m), 2.49 (3 H, s), 2.63 (4 H, d, *J* 7.3), 2.78 (2 H, q, *J* 7.6).

2,3,5-Triisobutyl-6-methylpyrazine 29. δ_H 0.92 (6 H, d, *J* 6.6), 0.93 (6 H, d, *J* 6.6), 0.94 (6 H, d, *J* 7.6), 2.21–2.28 (3 H, m), 2.49 (3 H, s), 2.62 (2 H, d, *J* 7.3), 2.63 (2 H, d, *J* 7.3), 2.64 (2 H, d, *J* 7.3).

3-Methyl-1-[5-(3-methylbutanoyl)-3,6-dimethylpyrazin-2-yl]-butan-1-one 31

This compound was prepared according to the above procedure using 2,5-dimethylpyrazine (0.11 cm^3, 1.0 mmol), 4-methyl-2-oxovaleric acid (0.520 g, 4.0 mmol), $(NH_4)_2S_2O_8$ (1.14 g, 5.0 mmol) and $AgNO_3$ (26 mg, 0.15 mmol); yield 0.230 g (83%) as pale yellow needles, mp 39–41.5 °C (from hexane) (lit.,[5] 39.5–41 °C); ν_{max}(neat)/cm^{-1} 1695 (C=O); δ_H 0.99 (12 H, d, *J* 6.9), 2.20–2.30 (2 H, m), 2.78 (6 H, s), 3.04 (4 H, d, *J* 7.0); δ_C 23.3, 23.4, 25.5, 49.1, 147.8, 150.3, 203.8.

1-(5-Isopentyl-3,6-dimethylpyrazin-2-yl)-3-methylbutan-1-ol 30

A solution of ketone **15** (0.131 g, 0.50 mmol) in propan-2-ol (3 cm^3) was added to a stirred suspension of $NaBH_4$ (0.038 g, 1.0 mmol) in the same solvent (2 cm^3) at 0–2 °C under argon. The mixture was stirred for 10 min, slowly warmed to room temperature for a period of 2 h, neutralized with 1 mol dm^{-3} hydrochloric acid and extracted with ethyl acetate (2 × 20 cm^3). The extracts were washed with H_2O, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography (SiO_2, 10 g, hexane–ethyl acetate 4:1) to give the alcohol **30** (0.111 g, 84%), which was distilled to afford an oil, bp 94–96 °C/5 mmHg (Found: C, 72.7; H, 10.6; N, 10.5. $C_{16}H_{28}N_2O$ requires C, 72.7; H, 10.7; N, 10.6%); ν_{max}(neat)/cm^{-1} 3450 (O–H); δ_H 0.95 (3 H, d, *J* 6.6), 0.97 (6 H, d, *J* 6.3), 1.06 (3 H, d, *J* 6.6), 1.36–1.43 (2 H, m), 1.49–1.58 (2 H, m), 1.62–1.72 (1 H, m), 2.00–2.10 (1 H, m), 2.46 (3 H, s), 2.52 (3 H, s), 2.73–2.79 (2 H, m), 4.19 (1 H, d, *J* 7.9), 4.84 (1 H, dt, *J* 8.4, 4.0); δ_C 20.8, 21.6, 22.1, 23.2, 24.5, 25.6, 29.0, 33.4, 38.4, 48.0, 68.4, 146.7, 147.7, 152.2, 154.4.

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