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A Convenient Synthesis of Alkyl- and Arylpyrazinyl Ketones

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ABSTRACT

Besides alkylpyrazines, pyrazinyl ketones occur as trace constituents in foodstuffs. In addition to other general syntheses of these compounds, a route was explored by which pyrazinecarboxylic esters were reacted with alkyl- and aryl-lithium and magnesium compounds, forming pyrazinyl alkyl and aryl ketones in moderate yields. Although some by-products were formed, the method is direct and convenient. Huang-Minlon reduction of the ketones afforded alkyl and alkaryl-substituted pyrazines.

INTRODUCTION

Pyrazines are important trace constituents in foodstuffs, which have been reviewed extensively in recent years (Maga, 1982; Shibamoto, 1980; Ohloff & Flament, 1979; Maga & Sizer, 1973*a*,*b*). While most of the derivatives described have been the alkyl-substituted pyrazines, in a number of investigations pyrazinyl ketones were also identified (see, for example, Ohloff & Flament, 1979; Mussinan & Walradt, 1974).

Two general routes to the synthesis of pyrazinyl ketones have been described in the literature: conversion of a pyrazine-carboxylic acid or ester via the amide to the corresponding nitrile, followed by a reaction of the latter with an organomagnesium compound ((Kushner *et al.*, 1952; Schwaiger & Ward, 1972). The methyl methylpyrazinyl ketone described as the 2,6-isomer was shown to be the 2,5-isomer by Schwaiger & Ward

(1972). Compare Mussinan & Walradt (1974), where no mass spectroscopic distinction is made and α-bromination of an alkyl side-chain on the pyrazine ring with *N*-bromosuccinimide, followed by an oxidation step (Mookherjee & Klaiber, 1972). Neither method is as direct or convenient as the reaction of pyrazinecarboxylic esters with organolithium and organomagnesium compounds (Jorgenson, 1970). Although yields are modest, this method has the advantage of starting from commercially available pyrazinecarboxylic acid and methyl- and butyllithium.

MATERIALS AND METHODS

Materials

Pyrazinecarboxylic acid, methyllithium and butyllithium were commercial products. Light petroleum refers to a fraction, boiling point 40–60 °C. The isomeric 5-methyl- and 6-methylpyrazinecarboxylic acids were prepared from methylquinoxaline, as described earlier (Schwaiger & Ward, 1972), and by $KMnO_4$ oxidation of 2,5- and 2,6-dimethylpyrazine (Pitré *et al.*, 1966). Methyl esters were prepared in methanol/sulphuric acid; 2,5-isomer, melting point, 94–95 °C; 2,6-isomer, melting point 67–69 °C. 2,3-Dimethylpyrazine (Ishiguro & Matsumura, 1958; Pages & Spoerri, 1963) was oxidized similarly to crude 3-methylpyrazinecarboxylic acid, which was esterified directly (methanol/sulphuric acid). The methyl ester was obtained in 33% overall yield after crystallization from light petroleum; melting point, 42–43 °C. A sample of pure 3-methylpyrazinecarboxylic acid had a melting point of 165–167 °C.

Analysis

Products were identified by IR, NMR, UV, mass spectroscopy and, in some cases (e.g. ethylpyrazine from methyl pyrazinyl ketone), by comparison with authentic specimens. IR spectroscopy of pyrazines has been described earlier (Bus *et al.*, 1973). TLC was on silica gel plates using mixtures of light petroleum and diethyl ether as eluents. The most polar compounds found were the carbinol by-products, and the least polar components resulted from substitution on the pyrazine ring. With light petroleum/diethyl ether (1/1, v/v) methyl pyrazinyl ketone had an R_f of 0·5.

RESULTS

General

The results have been summarized in Tables 1 to 3. Corresponding reaction schemes and structure formulae are given in Figs 1 to 3. Three representative experiments (A, B and C) are described in detail.

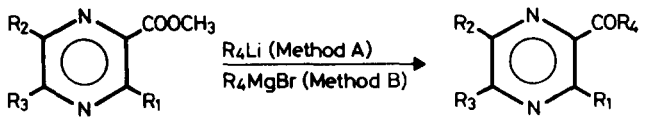

Fig. 1. Synthesis of pyrazinyl ketones via R_4Li (method (A)) or R_4MgBr (method B)).

The yields of ketone (Fig. 1, Table 1) were lowered by the formation of hydroxy compounds by reaction of the ketones with a further mole of metal–organic compound. Substitution products on the pyrazine ring were also found in minor amounts. For example, with *p*-anisylmagnesium

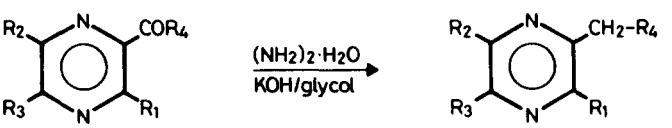

Fig. 2. Synthesis of alkyl- and arylpyrazines.

bromide and methyl pyrazinecarboxylate, two minor products isolated by TLC were identified as *p*-anisyl 2-(3-*p*-anisyl)pyrzinyl ketone and methyl 2-(3-*p*-anisyl)pyrazinecarboxylate.

The pyrazinyl ketones were reduced by the method of Huang-Minlon

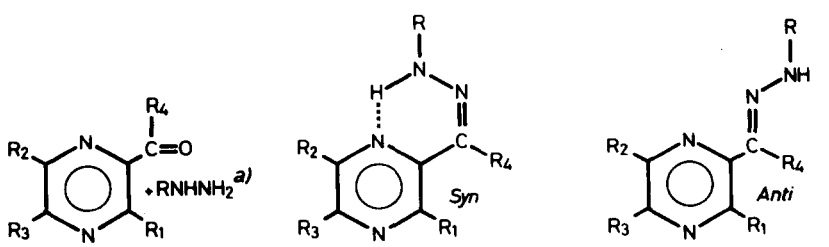

Fig. 3. *Syn*- and *anti*-DNPH of pyrazinyl ketones. (a): R = 2,4-dinitrophenyl.

TABLE 1

Data of Pyrazinyl Ketone Synthesis According to Fig. 1

Method	R_1	R_2	R_3	R_4	*Yield* (%)	*Melting point* (°C)	*Boiling point* (°C at p/kPa)		n_D^{20}	λ_{max} (nm)	log ε	*Reference*	*Lit. melting point* (°C)
(A)	H	H	H	Methyl	50	76	—			269	3·91*	Kushner *et al.* (1952)	76–78
										217	3·78		
(B)	H	H	H	Methyl	23	76	—			269	3·90*	Kushner *et al.* (1952)	
										218	3·76		
(A)	CH_3	H	H	Methyl	60	—	86	3·46	1·519 5	275	3·83	Mookherjee & Klaiber (1972)	(boiling point,
										220	3·67		56 °/67 Pa
(A)	H	CH_3	H	Methyl	57	32–34	—			276	3·87	Schwaiger & Ward (1972)	32–34
										223	3·60		
(A)	H	H	CH_3	Methyl	46	57	—			275	3·95	Schwaiger & Ward (1972)	57
										229	3·86		
(A)	H	H	H	Butyl	13	—	105	1·06	1·504 5	269	3·91*	—	
										217	3·78		
(B)	H	H	H	Phenyl	42	47–49	—			270	4·17	Smith & Kushner (1954)	(boiling point,
													190–200 °/2·7 kPa)
(B)	H	H	H	*p*-Tolyl	34	62·5	—			275	4·17	—	
										305	4·13		
(B)	H	H	H	*p*-Anisyl	29	125·6	—			272	4·02	—	
										227	3·99		

* Shoulders at 262 and 276 nm.

TABLE 2

Data of Aklyl- and Arylpyrazine Synthesis According to Fig. 2

R_1	R_2	R_3	R_4	*Yield* (%)	*Melting point* (°C)	*Boiling point* (°C at p/kPa)	n_D^{20}	λ_{max}/nm	log ε	*Reference*	*Lit. boiling point* (°C at p/kPa)
H	H	H	Methyl	68	—	—	1·4969	266·5 sh 260 272	3·74	Goldman *et al.* (1967)	155/101
CH_3	H	H	Methyl	52	—	59 1·6	1·5031	269 273 203·5	3·78 3·77 3·82	Rizzi (1968)	69–70/2·1
H	H	CH_3	Methyl	45	—	—	1·4917	272 277 203	3·67 3·67 3·85	Schwaiger & Ward (1972) Goldman *et al.* (1967)	79–80/7·5; n_D^{25} 1·4925
H	H	H	Butyl	55	—	96 2·0	1·4885	267 sh 260 273	3·84	Behun & Levine (1961)	95–98/0·8
H	H	H	Phenyl	68	—	103 0·05	1·5826	267·5 sh 262 274	3·83	Behun & Levine (1961)	120–124/0·2
H	H	H	*p*-Tolyl	68	66–68	—	—	267·5 sh 261 276	3·85	—	
H	H	H	*p*-Anisyl	65	29–30	148 0·05		269·5 224	3·91 3·93	—	

TABLE 3
Data of *Syn-* and *Anti*-DNPHs of Pyrazinyl Ketones

R_1	R_2	R_3	R_4	syn-*isomer*				anti-*isomer*				
				Melting point (°C)	λ_{max}(*nm*)	*log* ε	*IR NH-stretch* (cm^{-1})	*Melting point* (°C)	λ_{max}(*nm*)	*log* ε	*IR NH-stretch* (cm^{-1})	
H	H	H	H	256–264	374	3·63	3 120	238–40	370	4·37	3 240	3 110
H	H	H	Methyl	185	384	3·10	3 120	212–3	369	4·39	3 310	3 120
CH_3	H	H	Methyl		not formed			194–5	366	4·45	3 320	3 110
H	CH_3	H	Methyl		not formed			232–4	371	4·33	3 320	3 120
H	H	CH_3	Methyl		not formed			216–8	371	4·45	3 320	3 120
H	H	H	Butyl	—	384	2·94	3 100	153	370	4·22	3 320	3 110
H	H	H	Phenyl	235–6	392	3·93	3 120	235–8	372·5	4·14	3 280	3 120
H	H	H	*p*-Tolyl	252–4	395	4·09	3 100	238–40	377	4·33	3 290	3 120

(1946) in yields of about 60 % to alkyl- and alkaryl-substituted pyrazines (Table 2), providing an alternative route to these compounds.

A number of the ketones formed mixtures of stereoisomeric 2,4-dinitrophenyl-hydrazones (Fig. 3, Table 3), which could be separated readily by preparative TLC (silica gel/chloroform). The *syn* isomer gave only one NH-stretching frequency in the IR at about 3100 cm^{-1}. The *anti* isomer had an additional one in the 3200–3300 cm^{-1} region. In the UV, λ_{max} for the *syn* isomer was about 20 nm higher (390 nm) than that of the *anti* isomer (370 nm). The three isomeric methyl methylpyrazinyl ketones formed only *anti* DNPHs. Comparable results for the phenylhydrazones of phenyl and methyl 2-pyridinyl ketones (2-benzoyl- and 2-acetyl-pyridine) were described by Kuhn & Münzing (1952).

(A) Alkyl pyrazinyl ketones via organolithium compounds. In a three-necked 2-litre flask fitted with stirrer, thermometer and condenser, a solution of 27·6 g (0·2 mole) methyl pyrazinecarboxylate in 1750 ml sodium-dried diethyl ether was cooled to −30 °C. A hundred millilitres of methyllithium solution in ether (2 mole/litre) was added dropwise with stirring in 20 min. A dark-yellow precipitate formed. Stirring was continued at −30 °C for 30 min. Then the temperature was allowed to rise to 0 °C in about 45 min, and 200 ml HCl (1 mole/litre) was added. After stirring, the ether layer was separated and the practically neutral aqueous layer extracted three times with 500 ml diethyl ether. The combined ether layers were washed, dried (Na_2SO_4) and evaporated, leaving 18·4 g crude product. GLC showed methyl pyrazinyl ketone and 2(2-pyrazinyl)-2-propanol in the ratio 73:27. These were separated by column chromatography on silica gel (200 g). Light petroleum/diethyl ether mixtures were used as eluent, with the ether content increased stepwise from 5 % (v/v) to 25 %, after which 12·3 g methyl pyrazinyl ketone (50 % of theory) was obtained as colourless needles from light petroleum (melting point, 70 °C). The hydroxy compound was obtained in 16 % of theory; boiling point, 94 °C; n^{20}, 1·5149.

In the case of butyllithium, as well as the ketone (Table 1), impure 5-(2-pyrazinyl)-5-nonanol was obtained in 1·3 % of theory, melting point, 47–54 °C. Trace amounts of butyl 3-butylpyrazinyl ketone and butyl 6-butylpyrazinyl ketone (GLC, MS, IR) were isolated by preparative TLC as oils after chromatography on plates of silica gel (200 × 200 × 2 mm). With light petroleum/diethyl ether (3/1, v/v) the spots had R_f values of about 0·6.

(B) Alkyl pyrazinyl ketones via organomagnesium compounds. A

solution of 6·9 g (0·05 mole) methyl pyrazinecarboxylate in 600 ml sodium-dried diethyl ether was cooled to −30 °C, after which 0·05 mole phenylmagnesium bromide in diethyl ether was added under nitrogen in 10 min with stirring. A yellow precipitate formed at once. The work-up was analogous to that of example (A). A mixture of phenyl pyrazinyl ketone and diphenylpyrazinylmethanol was obtained, from which the ketone was obtained pure by crystallization (1 g/15 ml) from a mixture of light petroleum and diethyl ether (1/1, v/v) at −70 °C; yield 42%, melting point, 47–49 °C. The residue from the mother liquor was chromatographed on 60 g silica gel, whereby biphenyl (melting point, 68 °C), formed in the Grignard reaction, was first eluted with light petroleum/diethyl ether mixtures, initially with 5% ether (v/v), increasing stepwise to 20%. The hydroxy compound was obtained from the eluates after concentration and decolorization with animal charcoal; yield 5% (based on the pyrazinyl ester), melting point, 115–116 °C. When *p*-anisylmagnesium bromide was used, as well as the expected ketone (Table 1), the corresponding hydroxy compound was obtained as an oil (n^{20}, 1·5898) in 2% yield and, together with milligram amounts of the substitution product, *p*-anisyl 2-(3-*p*-anisyl)pyrazinyl ketone (MS, IR, NMR), melting point, 168–171 °C, and methyl 2-(3-*p*-anisyl)pyrazine carboxylate, melting point, 138–140 °C. These were isolated by preparative TLC of the mother liquor on silica gel plates (200 × 200 × 2 mm) using light petroleum/chloroform as eluent (1/1, v/v); R_f of about 0·6.

(C) Reduction of methyl pyrazinyl ketone to 2-ethylpyrazine. *CAUTION:* Hydrazine hydrate is highly toxic. The following reduction should be carried out in an efficient hood, taking all precautions against skin contact or inhalation. A mixture of 3·0 g (0·025 mole) methyl pyrazinyl ketone, 7·5 g KOH, 10 ml 80% hydrazine hydrate and 125 ml ethylene glycol was heated slowly to 140 °C in a 250-ml three-necked flask fitted with thermometer, stirrer and condenser, After 1 h at 140 °C, the condenser was set for distillation and the temperature raised slowly until ethylpyrazine distilled over with some water and ethylene glycol. The distillate and residue in the flask were extracted with ether, the extracts dried (Na_2SO_4) and evaporated. 2-Ethylpyrazine was obtained as a pale-yellow liquid; yield, 68%.

In some cases, the boiling points of the pyrazine compounds described in Table 2 were higher than that of ethylene glycol. The products were then extracted with ether from residue in the distillation flask and worked up as above.

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