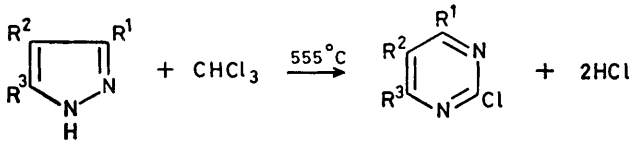
Reactions of Halogenomethanes in the Vapour Phase. Part 3.[1,2] Reactions of Chloroform with Pyrazoles, Indazole, and Other Heterocycles at 555 °C

By **Reginald E. Busby,* John Parrick, S. Mumtaz H. Rizvi,** and **C. J. Granville Shaw,** School of Chemistry Brunel University, Uxbridge, Middlesex UB8 3PH

A mixture of chloroform and either pyrazole (1) or a *C*-methylpyrazole [(2)—(6)] in a continuous-flow vapour-phase reactor at 555 °C gives a high yield (51—89%) of a 2-chloropyrimidine [(7)—(12)] as the only product. Indazole (13) similarly gives only 2-chloroquinazoline (14). These results contrast with the known formation of mixtures of products from the corresponding pyrroles and indoles, and the present finding that a number of heterocycles which do not contain the NH group give only carbon under similar conditions.

THE reactions of chloroform in a continuous-flow vapour phase system at 550 °C with pyrroles [1] and indoles [2] as substrates have been reported. We now describe work with pyrazoles as substrates. Previously, Jones and Rees [3] had treated 3,4,5-trimethylpyrazole with chloroform in the liquid phase (*a*) under basic conditions to give 4-dichloromethyl-3,4,5-trimethyl-4*H*-pyrazole (10.4%), and (*b*) under neutral conditions to give tris-(3,4,5-trimethylpyrazol-1-yl)methane (3.1%), 4-chloro-3,5,6-trimethylpyridazine (0.5%), 2-chloro-4,5,6-trimethylpyrimidine (0.4%), and 1-trichlorovinyl-3,4,5-pyrazole (0.1%). More recently,[4] yields of some of the compounds previously formed from 3,4,5-trimethylpyrazole and chloroform [3] under neutral conditions were increased by using benzyltriethylammonium chloride as a phase-transfer catalyst in reaction with chloroform under basic conditions. The yields reported [4] were 63% of tris-(3,4,5-trimethylpyrazol-1-yl)methane, 2.7% of 4-chloro-3,5,6-trimethylpyridazine, and 3.2% of 4-dichloromethyl-3,4,5-trimethyl-4*H*-pyrazole. By analogy with our results when pyrroles [1] and indoles [2] reacted with chloroform in the vapour phase, pyrazoles were expected similarly to give moderate to high yields of a mixture of 2-chloropyrimidines and 3- and 5-chloropyridazines. Surprisingly, the pyrolysis of a mixture of pyrazole (1) or a *C*-methylpyrazole [(2)—(6)] and chloroform in a vapour-phase flow reactor gave only one product, a 2-chloropyrimidine [(7)—(12)], in high yield (*cf.* the



(1) $R^1 = R^2 = R^3 = H$
(2) R^1 = Me, $R^2 = R^3 = H$
(3) $R^1 = R^3 = H$, R^2 = Me
(4) $R^1 = R^2$ = Me, $R^3 = H$
(5) $R^1 = R^3$ = Me, $R^2 = H$
(6) $R^1 = R^2 = R^3$ = Me
(7) $R^1 = R^2 = R^3 = H$
(8) R^1 = Me, $R^2 = R^3 = H$
(9) $R^1 = R^3 = H$, R^2 = Me
(10) $R^1 = R^2$ = Me, $R^3 = H$
(11) $R^1 = R^3$ = Me, $R^2 = H$
(12) $R^1 = R^2 = R^3$ = Me

liquid-phase reactions [3,4]). The method, therefore, affords a useful preparative route to these compounds, particularly as little or no unchanged material was recovered and isolation of the product was easy. The by-product in all cases is carbon, which by a mass balance of products and reactants was shown to account for >80% of that part of the substrate which is not converted into the 2-chloropyrimidine.

Details of the reaction conditions and the results obtained in studies with chloroform and pyrazole (1), 3-methylpyrazole (2), 4-methylpyrazole (3), 3,4-dimethylpyrazole (4), 3,5-dimethylpyrazole (5), 3,4,5-trimethylpyrazole (6), and indazole (13) are given in Table 1. The molar proportion of chloroform to the pyrazole was 5 : 1 except when 3,4,5-trimethylpyrazole (6) (6 : 1) and indazole (13) (18 : 1) were the reactants. Yields were highest with pyrazole (1) and 3-methyl- (2) and 3,5-dimethyl-pyrazole (5), and especially high in the last case. This suggests that the reaction is facilitated by a high electron availability in the region of one of the ring nitrogen atoms. Until a study of the kinetics of the reaction between chloroform and heterocycles at 460—555 °C (in progress) is complete, we prefer not to discuss the mechanism in detail.

TABLE 1

Yields of 2-chloropyrimidines from the reaction of pyrazoles with chloroform at 555 °C

Substrate		Wt. $CHCl_3$	Reaction time		Yield
No.	Wt. (g)	(g)	(min)	Product	(%)
(1)	10.00	88.0	40	(7)	80
(2)	10.00	73.0	45	(8)	77
(3)	10.07	73.0	32	(9)	67
(4)	4.53	28.0	12	(10)	70
(5)	10.00	62.0	35	(11)	89
(6)	10.97	71.5	37	(12)	51
(13)	4.00	75.0	30	(14)	68

The substrates furan, thiophen, benzoxazole, benzothiazole, and 2,1,3-benzothiadiazole yield only carbonaceous products when pyrolysed with chloroform in the flow system at 555 °C. Apparently, the presence of a reactive hydrogen atom attached to a ring nitrogen atom facilitates reaction to give a stable ring-expanded product.

Experiments designed to obtain the optimum conditions for the reaction of pyrazole with chloroform at 555 °C (molar ratios 1 : 4, 1 : 5, 1 : 6, and 1 : 12) showed that the highest yield was obtained with a 1 : 5 ratio.

The temperature of reaction was varied within the range 500—600° whilst the molar ratio of pyrazole to chloroform was kept constant at 1 : 5. A maximum yield was obtained at 555 °C. At 600 °C carbonisation

TABLE 2

Effect of variation of ' space time ' [a] on the yield of 2-chloropyrimidine from reaction of pyrazole with chloroform at 555 °C (wt. $CHCl_3$ 210.7 g; temp. of preheater 292 °C)

Wt. pyrazole (g)	Recovered pyrazole (g)	Space time (s)	Yield (%) [b]
3.33	0.01	7.99	31
	None	4.76	69
	None	3.11	80
	0.01	2.76	85
	None	2.40	65
6.66	0.05	7.69	50
	0.09	7.05	74
	0.06	6.74	81
	0.08	6.46	68
	0.02	5.85	85
	0.06	4.67	71
	0.03	3.68	77
	0.04	2.96	79
	0.02	2.34	80
10.00	0.08	7.59	70
	0.44	7.36	78 (81)
	0.54	6.82	74 (78)
	0.32	5.14	75 (77)
	0.10	2.83	77
15.00	1.64	9.50	73 (81)
	1.30	8.89	76 (83)
	0.85	7.45	64 (68)
	0.37	6.77	29 (30)

[a] Space time = (time of pyrolysis × volume of reactor tube)/(total volume of reactants and nitrogen at temperature and pressure of experiment). [b] Expressed as a percentage of the amount of pyrazole fed through the reactor tube. Figures in parentheses are based on the amount of pyrazole that has reacted and are quoted where such yields are significantly different from those based on the amount of pyrazole fed into the reactor tube.

was extensive, whereas at 500 °C 76% of pyrazole was recovered.

The effect of variation of ' space time ' on the yield of 2-chloropyrimidine obtained from pyrazole and chloroform at 555 °C was determined for four different ratios of pyrazole to chloroform (Table 2). A plot of the ' space time ' at which a maximum yield was observed ($\tau_{max.}$) against the logarithm of the weight of pyrazole (W) fed into the reactor could be represented by the relationship:

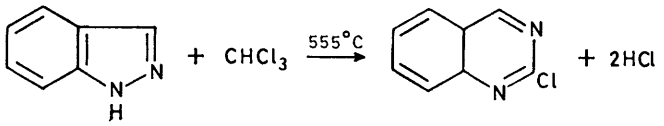
$$\tau_{max.} = -2.04 + 4.07 \ln W \text{ (standard error } \pm 0.16)$$

EXPERIMENTAL

4-Methylpyrazole,[5] 3,4-dimethylpyrazole,[6] 3,5-dimethylpyrazole,[7] and 3,4,5-trimethylpyrazole [8] were prepared by reported routes. Pyrazole, 3-methylpyrazole, indazole, and furan were supplied by Koch–Light Laboratories Ltd.; thiophen was supplied by B.D.H. Chemicals Ltd.; benzoxazole, benzothiazole, and 2,1,3-benzothiadiazole were supplied by Aldrich Chemical Co. Ltd.

Apparatus.—A silica reactor tube (75.5 × 2.1 cm i.d.) was placed in a horizontal Carbolite tube furnace tilted at 12° to the horizontal. Measurements showed little variation of temperature over the greater length of the tube when furnace temperature was 500, 550, 555, or 600 °C. During reaction a constant temperature was maintained over approximately one third of the length of the tube with a temperature gradient from 555 to 150 °C at the output end and a smaller region varying from 300 to 555 °C at the input end. A preheater (a Pyrex tube 64 cm long and 2.0 cm i.d. wrapped with heater tape) was fitted into the higher input end. The reactants addition assembly previously described [1] was placed at the higher input end of the preheater. Normally, substrates dissolved in or mixed with chloroform were simply placed in the addition assembly. When indazole was the substrate, however, the addition assembly was wrapped with heater tape in order to prevent deposition of indazole from the chloroform solution. The pyrolysis procedure was the same as that used in the reaction of chloroform with pyrroles.[1]

The product in each experiment was separated and analysed with the instruments specified.[1] A comparison of g.l.c. retention times for each product was made with that of an authentic sample whenever possible. An i.r. spectrum in each case of authentic samples of 2-chloropyrimidine, 2-chloro-4,6-dimethylpyrimidine, 2-chloro-4,5,6-trimethylpyrimidine, and 2-chloroquinazoline was identical with that of the product (7), (11), (12), or (14), respectively. ^1H



(13) (14)

N.m.r. data agreed with the assigned structures. The support material in the g.l.c. column was acid-washed and silanised Diatomite (100—120 mesh). All products exhibited a $(P + 2) : P$ ratio of 0.33 : 1.00 in their mass spectra which indicated one chlorine atom.

Further information about the product in each case is given in the following order: name of product, temperature used for g.l.c. OV17 column, m.p.

2-Chloropyrimidine (7) from pyrazole (1), 150°, m.p. 65—66° (lit., 63.6—64.5,[9,10] 64.5—65.5,[11] and 65—67° [12]); 2-chloro-4-methylpyrimidine (8) from 3-methylpyrazole (2), 150°, m.p. 47—48° (lit.,[13] 48—50°); 2-chloro-5-methylpyrimidine (9) from 4-methylpyrazole (3), 160°, m.p. 89—91° (lit., 92.5,[14] 92,[15] 91° [16]); 2-chloro-4,5-dimethylpyrimidine (10) from 3,4-dimethylpyrazole (4), 150°, m.p. 22—25° (lit.,[17] 22.5—26°), b.p. 89° at 4 mmHg (lit.,[17] 88° at 3 mmHg); 2-chloro-4,6-dimethylpyrimidine (11) from 3,5-dimethylpyrazole (5), 150°, m.p. 38—39° (lit.,[18] 38—39°), b.p. 210° (lit.,[18] 210—212°); 2-chloro-4,5,6-trimethylpyrimidine (12) from 3,4,5-trimethylpyrazole (6), 140°, m.p. 90—91° (lit.,[3] 91°); 2-chloroquinazoline (14) from indazole (13), 200°, m.p. 104—106° (lit.,[19] 108°).

In the optimisation of yield experiments the amounts of pyrazole and 2-chloropyrimidine were determined by interpolation from previously prepared linear peak area against weight calibration plots using a Pye–Unicam 105 Chromatograph fitted with a glass (5 ft × ¼ in) analytical column containing OV17 (3%) supported on Diatomite (100—120 mesh) at 150 °C.

We thank Dr. W. L. Armarego, Australian National University, Canberra, for the i.r. spectrum of 2-chloroquinazoline.

[9/399 *Received*, 12*th March*, 1979]

REFERENCES

[1] Part 1, R. E. Busby, M. Iqbal, M. A. Khan, J. Parrick, and J. C. G. Shaw, *J.C.S. Perkin I*, 1979, 1578.

[2] Part 2, R. E. Busby, S. M. Hussain, M. Iqbal, M. A. Khan, J. Parrick, and C. J. G. Shaw, *J.C.S. Perkin I*, preceding paper.
[3] R. L. Jones and C. W. Rees, *J. Chem. Soc.* (*C*), 1969, 2251.
[4] F. De Angelis, A. Gambacorta, and R. Nicoletti, *Synthesis*, 1976, 798.
[5] H. Bredereck, H. Herlinger, and E. H. Schweizer, *Chem. Ber.*, 1960, **93**, 1208.
[6] C. Alberti and G. Zerbi, *Farmaco* (*Pavia*) *Ed. Sc.*, 1961, **7**, 527.
[7] A. O. Fitton and R. K. Smalley, ' Practical Heterocyclic Chemistry,' Academic Press, London and New York, 1968, p. 23.
[8] B. Oettinger, *Annalen*, 1894, **279**, 244.
[9] N. Sperber, D. Papa, E. Schwenk, M. Sherlock, and R. Fricano, *J. Amer. Chem. Soc.*, 1951, **73**, 5752.
[10] K. L. Howard, U.S. P. 2 477 409/1949 (*Chem. Abs.*, 1949, **43**, 8105f).
[11] C. G. Overberger and I. C. Kogen, *J. Amer. Chem. Soc.*, 1954, **76**, 1065.
[12] T. E. Young and E. D. Amstutz, *J. Amer. Chem. Soc.*, 1951, **73**, 4773.
[13] J. M. Marshal and J. Walker, *J. Chem. Soc.*, 1951, 1004.
[14] O. Gerngross, *Ber.*, 1905, **38**, 3394.
[15] D. J. Brown and T.-C. Lee, *Austral. J. Chem.*, 1968, **21**, 243.
[16] D. J. Brown and P. Waring, *Austral. J. Chem.*, 1973, **26**, 443.
[17] S. Sugasawa, S. Yamada, and M. Narabishi, *J. Pharm. Soc. Japan*, 1951, **71**, 1345.
[18] G. M. Kosolapoff and C. H. Roy, *J. Org. Chem.*, 1961, **26**, 1895.
[19] M. T. Bogert and C. E. May, *J. Amer. Chem. Soc.*, 1909, **31**, 507.