Pyrimidine Synthesis - A New Method

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A new one-step-method for the synthesis of 2-phenylpyrimidines of type I was developed by reacting benzotrichloride with various nitriles in the presence of aluminum chloride.

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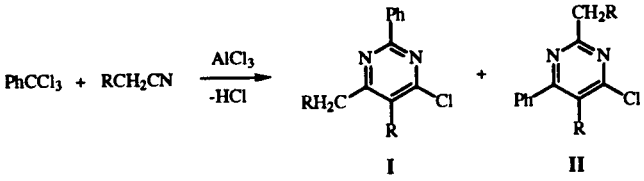
The structural diversity of the pyrimidine ring system brought about numerous synthetic methods which are well documented in the chemical literature, thus addressing the structural variety of this heterocycle [1]. In the present work we wish to report on a new synthetic methodology for a specifically substituted 2-phenylpyrimidine ring system. Certain 2-phenylpyrimidines function as growth hormones [2] as well as protecting agents for crop plants against phytotoxic damage caused by herbicide [3].

In connection with another study we have discovered that 4-chloro-2-phenylpyrimidines of type I can be synthesized in one step by Lewis acid treatment of benzotrichloride, and nitriles having an α-methylene group. The general transformation is depicted below.



I II

The nature of the R substituent on the pyrimidine rings depends on the structure of the nitrile used. With acetonitrile a mixture of isomers I and II was obtained. The ratio I/II depends on the reaction conditions, particularly on the Lewis acid used. With other nitriles, only pyrimidines of type I were formed.

The above reaction was discovered upon an attempt to couple benzotrichloride to give dichloro stilbene with Iron(0) in acetonitrile (Experiment 1, Table I). The selectivity was found to be temperature dependent, in as much as below 100° only dichlorostilbene was formed, while conducting the reaction above 100° led to the formation of a mixture of dichlorostilbene and pyrimidine. We have assumed that the ferric chloride formed in the stilbene reaction had induced pyrimidine formation (Experiment 2).

It has been reckoned that the formation of pyrimidines will be favored by using a Lewis acid better than ferric chloride. Thus, aluminum chloride (50 mole%) in acetonitrile at 140° resulted in 100% conversion and 73% yield of a 17:1 mixture of pyrimidines I and II respectively (Experiment 5; Table I). Inferior conversion and yield of pyrimidines were obtained with hexacarbonyl molybdenum(0) as a Lewis acid

Table I

Experimental Data for the Formation of Pyrimidines [a]

Experiment No.	Nitrile	Lewis Acid (% mole)	Time (hours)	Conv (%)	Pyrimidine gc Area (%)	Pyrimidine Yield (%) [b]	Stilbene gc Area %
1	acetonitrile	Fe (100)	1.5	100	I. R = H (28) 13 (*trans*)		59 (*cis*)
2	acetonitrile	$FeCl_3$ (10)	19	65	I. R = H (52) II. R = H(11)	20 [c] 8.8 [c]	0
3	acetonitrile	HCl (g)	3.25	46	I. R = H (12) II. R = H (20)		5 (*cis*) 1 (*trans*)
4	acetonitrile	$AlCl_3$ (10)	18.5	46	I. R = H (24) II. R = H (12)		0
5	acetonitrile	$AlCl_3$ (50)	22.5	100	I. R = H (79) II. R = H (4.6)	73 (total)	0
6	acetonitrile	$Mo(CO)_6$ (10)	19	83	I. R = H (40) II. R = H (6.3)		5.5 (*cis*) 1.5 (*trans*)
7	acetonitrile	EPZ 10 [d]; (1.0 g)	22	19	I. R = H (19)		0
8	propionitrile	$AlCl_3$ (50)	20	100	I. R = CH_3 (99)	65	0
9	heptanenitrile	$AlCl_3$ (50)	20	100	I. R = C_5H_{11} (95)	64	0
10	benzylcyanide	$AlCl_3$ (50)	20	100	I. R = Ph (44)	1 [c]	0

[a] All the reactions were carried out at 140°C (oil bath temperature) in a sealed glass tube. [b] Yields were determined by an internal standard method after work-up of the reaction mixture (see experimental section). [c] Isolated yield after chromatography. [d] A trade mark for a solid supported acid, procured from Contract Chemicals Limited, Prescot, UK.

precursor (Experiment 6; Table I). No reaction was observed (Table I, Experiment 7) with EPZ10, a solid supported acid, known as a catalyst in Friedel-Crafts reactions [4]. With aluminum chloride, the formation of dichlorostilbene was suppressed, thus improving the selectivity and yield of the pyrimidines.

The isomeric pyrimidines, 4-chloro-6-methyl-2-phenyl, **I** [3], and 4-chloro-2-methyl-6-phenyl **II** [5], both originating from acetonitrile, were separated by column chromatography, and identified by comparing their physical and spectral properties with those of the two known compounds. The rest of the pyrimidines in Table I are new compounds. They were all assigned structure **I** by comparing their ^{1}H-nmr spectra with those of the known isomers: 4-chloro-6-methyl-2-phenylpyrimidine (**I**) and 4-chloro-2-methyl-6-phenylpyrimidine (**II**), for which differences of 0.94 and 0.55 ppm respectively in the chemical shifts of the two sets of the aromatic hydrogen signals were found. For the rest of the pyrimidines, the respective differences fall in the range of 0.94-0.98 ppm, in accord with structure **I** above. The lowest field signals (2H) were assigned to the *ortho* hydrogen atoms of the phenyl ring in all the pyrimidines. With 2-phenylpyrimidines (isomer I, the *ortho* hydrogen atoms are deshielded by the two flanking nitrogen atoms of the pyrimidine ring and consequently resonate at lower field (*ca.* 0.4 ppm) relative to the 6-phenylpyrimidine (**II**).

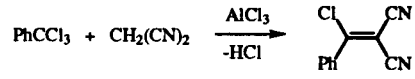
Although the yields are modest, the simplicity of obtaining the specific pyrimidines in a one-step-reaction, with good selectivity and purity, makes the above synthesis protocol an attractive one.

In an attempt to extend the scope of the starting material used in the pyrimidine forming reaction, benzotrichloride was replaced with benzoyl chloride. The reaction of benzoyl chloride with acetonitrile, propionitrile and heptanenitrile gave in all cases only trace amounts of the pyrimidines, but in every case benzonitrile was formed in small quantities. The formation of benzonitrile did not depend on the nitrile used, and its mode of formation is not clear.

The net pyrimidine ring formation involves the condensation of two nitrile molecules with benzotrichloride. The primary reaction step, under aluminum chloride catalysis, must involve formation of a carbon-nitrogen bond leading to an imine chloride:

$$PhCCl_3 + RCH_2CN + AlCl_3 \rightarrow PhC(Cl)_2\text{-}N{=}C(Cl)CH_2R$$

Having two types of chlorine atoms active towards aluminum chloride, the imine chloride may react with the nitrogen atom of a second nitrile molecule at either the benzylic or the imine carbon atom, leading eventually *via* a multistep process to the isomeric pyrimidines **I** and **II** respectively. The above proposed mechanism for the formation of pyrimidines, suggests the formation of 4,6-dichloro-2-phenylpyrimidine from malononitrile and benzotrichloride. Such reaction has been attempted under the standard reaction conditions with aluminum chloride. The only isolated product (47%) was 3-chloro-2-cyano-3-phenyl propenitrile, according to the following reaction.



Apparently, malononitrile is reacting as a carbon rather than a nitrogen nucleophile. The above compound was previously obtained (38%) by a different two-step reaction scheme [6,7].

EXPERIMENTAL

General Procedure.

A glass tube was charged with benzotrichloride (2.0 g, 0.0102 mole) and the appropriate nitrile (6.0 ml). The mixture was cooled in an ice bath, and the appropriate weight of Lewis acid (see Table I) was added. The tube was sealed and heated in an oil bath at 140° for the specified period of time (Table I). To the cooled reaction mixture there were added chloroform (40 ml) and water (40 ml), and the mixture was stirred for 15 minutes. The phases were separated, and the organic phase was further washed with 3 x 40 ml of water, dried over magnesium sulfate, evaporated and the residue chromatographed on Silica Gel 60 (70-230 mesh), using methylene chloride-pet ether mixtures. The purified pyrimidines served as standards for the determinations of yields by gc. Methyl trichloroacetate was used as an internal standard for the quantitative analyses of the reactions involving aceto and propionitrile, and benzotrichloride for the reaction of heptanenitrile.

4-Chloro-6-methyl-2-phenylpyrimidine.

This compound had mp 69° (lit [3] 71-72°); ir (potassium bromide): 1541, 1561 cm^{-1}; ms: m/z 206/204 (M^+), 169, 128, 104; ^{1}H-nmr (deuteriochloroform): δ 2.57 (s, 3H, Me), 7.10 (s, 1H, H5), 7.49 (m, 3H, aromatic H), 8.43 (m, 2H, aromatic H).

4-Chloro-2-methyl-6-phenylpyrimidine.

This compound had mp 53° (lit [5] 59°); ir (potassium bromide): 1558, 1533; ms: m/z 206/204 (M^+), 169, 128; ^{1}H-nmr (deuteriochloroform): δ 2.77 (s, 3H, Me), 7.50 (m, 5H, aromatic and pyrimidine H), 8.05 (m, 2H, aromatic H).

4-Chloro-6-ethyl-5-methyl-2-phenylpyrimidine.

This compound had mp 89°; ir (potassium bromide): 1404,1519, 1561 cm^{-1}; ms: m/z 234/232 (M^+), 217, 197, 169, 149, 115, 104; ^{1}H-nmr (deuteriochloroform): δ 1.36 (t, 3H, J = 7.5 Hz, Me), 2.39 (s, 3H, Me), 2.87 (q, 2H, J = 7.5, methylene H), 7.47 (m, 3H, aromatic H), 8.43 (m, 2H, aromatic H).

Anal. Calcd. for $C_{13}H_{13}N_2Cl$: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.24; H, 5.60; N, 12.07.

4-Chloro-6-hexyl-5-pentyl-2-phenylpyrimidine.

This compound is a liquid having ir (chloroform): 1401, 1467, 1519, 1557; ms: m/z 346/344 (M^+), 317, 315, 309, 301, 287, 276, 274, 259, 245, 239, 229, 220, 218, 104; ^{1}H-nmr (deuterio-

chloroform): δ 0.80-1.1 (m, 6H, 2Me), 1.2-1.9 (m, 14H, methylene H), 2.75 (t, methylene H, J = 8.3 Hz), 2.83 (t, 2H, methylene H, J = 7.4 Hz), 7.45 (m, 3H, aromatic H), 8.41 (m, 2H, aromatic H).

Anal. Calcd. for $C_{21}H_{29}N_2Cl$: C, 73.13; H, 8.47; N, 8.12. Found: C, 73.28; H, 8.50; N, 8.01.

6-Benzyl-4-chloro-2,5-diphenylpyrimidine.

This compound had mp 82°; ir (chloroform): 1403, 1509, 1558 cm^{-1}; ms: m/z 358/356 (M^+), 355, 278, 241, 239, 224, 204, 177, 84; ^1H-nmr (hexedeuterioacetone): δ 4.01 (s, 2H, methylene H), 7.0-7.5 (m, 13H, aromatic H), 8.48 (m, 2H, aromatic H).

Anal. Calcd. for $C_{23}H_{17}N_2Cl$: C, 77.41; H, 4.80; N, 7.85. Found: C, 77.55; H, 4.92; N, 7.70.

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