

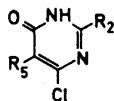
## Heterocyclic Compounds from Malonyl Chlorides and Nitriles

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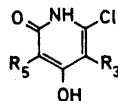
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The formation of pyridones and pyrimidones from nitriles and substituted malonyl chlorides has been investigated from a synthetic point of view. Some comments are made on the limitations of the reaction.

The reaction between malonyl chloride and nitriles has been reported<sup>1-3</sup> to give pyrimidones and pyridones. The present work was aimed at a more thorough investigation of the scope and limitations of the reaction, with special emphasis on the use of substituted malonyl chlorides. The new 4-chloro-6-pyrimidones and 2-chloro-4-hydroxy-6-pyridones of the types (I) and (II) are listed in Tables 1 and 2.



(I)



(II)

In addition, a few substances were prepared, which had been reported in the literature, but with incomplete data. These substances are found in Table 3.

The synthesis of pyrimidones and pyridones from nitriles and malonyl chlorides is from the present point of view fairly wide in scope. It is, however, limited in several directions, and the synthetic value, which depends on the yield and reaction time, varies considerably with the nitriles employed, as well as with the substituent in the malonyl chloride.

An obvious condition is that the nitrile must contain no other groups which react with acid chlorides. Further, the presence of unsaturation, carbonyl (keto and aldehyde) groups and ether linkages in the nitrile seems to be detrimental to a successful reaction. The presence of halogen in the vicinity

Table 1. 4-Chloro-6-pyrimidones.

R <sub>2</sub>	R <sub>5</sub>	React. time (days)	Yield raw product (%)	Subl. (°C)	M.p. (°C)	τNH/OH	τR <sub>2</sub>	τR <sub>5</sub>
CH <sub>2</sub> C <sub>6</sub> H <sub>11</sub>	H	18	28	140	160–164		7.55, 8.6	3.66
CH <sub>3</sub>	Cl	10	39	200	245–251	–3.2, 6	7.68	
C <sub>2</sub> H <sub>5</sub>	Cl	20	35	170	217–223	–1.6	7.35, 8.78	
n-C <sub>3</sub> H <sub>7</sub>	Cl	6	19	150	185–192		7.45, 8.32	
							9.08	
i-C <sub>3</sub> H <sub>7</sub>	Cl	65	8	130	227–230	–3.4	7.0, 8.76	
n-C <sub>4</sub> H <sub>9</sub>	Cl	12	23		158–167		7.42, 8.5,	
							9.1	
CH <sub>2</sub> C <sub>6</sub> H <sub>11</sub>	Cl	60	12	160	174–178	–1.0	7.53, 8.6	
(CH <sub>2</sub> ) <sub>2</sub> Cl	Cl	15	20	170	211–215	1.7	6.03, 6.9	
(CH <sub>2</sub> ) <sub>3</sub> Cl	Cl	17	27		147–155	–2.5	6.3, 7.25,	
							7.87	
CH <sub>2</sub> OCH <sub>3</sub>	Cl	15	14	160	196–201	–1.2	5.68, 6.63	
CH <sub>2</sub> OCCCH <sub>3</sub>	Cl	7	54	190	203–208	1.5	5.06, 7.87	
CH <sub>2</sub> OCC <sub>6</sub> H <sub>5</sub>	Cl	10	60		208–213		2.17, 4.76	
C <sub>6</sub> H <sub>5</sub>	Cl	45	17	200	280–287	3.9	2.3	
C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> (4)	Cl	27	12	230	286–290		2.0, 2.67,	
							7.61	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>3</sub> ) <sub>3</sub> (2,4,6)	Cl			260	284–293	6.7	3.15, 6.05,	
							7.8	
CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Cl	14	21	190	203–206	1.1	2.67, 6.1	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> (4)	Cl	68	22	170	212–218		2.8, 6.11,	
							7.7	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> (4)	Cl	18	4.6	200	215–220	5.1	2.95, 6.25,	
							6.65	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Br(4)	Cl	60	22	200	238–245	–3.4,	2.55, 6.06	
						6.5		
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> F(4)	Cl	55			205–217	–3	2.75, 6.05	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Cl(2)	Cl	18	37	215	253–270	–3.6	2.6, 5.87	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Cl(3)	Cl	60	47	180	210–214	5	2.56, 2.65,	
							6.04	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Cl(4)	Cl	14	44	190	230–238	–0.3	2.62, 6.03	
CH <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Cl <sub>2</sub> (2,4)	Cl	12	25	190	273–276		2.49, 5.87	
CH <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Cl <sub>4</sub> (2,6)	Cl	13	37	190	288–292		2.52, 5.67	
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> (4)	Cl	100	low				2.1, 5.86	
CH <sub>2</sub> OC <sub>6</sub> H <sub>5</sub>	Cl	18	29	220	270–272	–2.9	2.87, 5.0	
2-C <sub>4</sub> H <sub>9</sub> S	Cl			200	295–302		1.8, 2.05,	
							3.75	
CH <sub>3</sub>	CH <sub>3</sub>	80	19	130	225–229	0.5	7.7	8.01
C <sub>2</sub> H <sub>5</sub> <sup>a</sup>	CH <sub>3</sub>	80	4	120	197–201	–2.1	7.42, 8.82	8.02
CH <sub>2</sub> Cl	CH <sub>3</sub>	45		170	209–212	–2.6	5.53	7.96
(CH <sub>2</sub> ) <sub>3</sub> Cl	CH <sub>3</sub>	127	13		180–	–0.9	6.3, 7.3,	8.01
					230 d		7.85	
CH <sub>2</sub> OCC <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	12	9		200–205	–0.8	2.2, 4.75	7.98
CH <sub>2</sub> OC <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	4		170	232–242	–1.5	2.87, 5.04	7.98
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	142	12		198–205	–2.6	7.7	7.5,
								8.95
CH <sub>2</sub> OCC <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	148	17		163–168	–1.8	2.2, 4.78	7.47,
								8.94
CH <sub>2</sub> Cl	C <sub>6</sub> H <sub>5</sub>	3	47	160	176–182	–2.2	5.36	2.6

Table 1. Continued.

CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	100	3.3	190	200-204	-2.8, 6.5	7.69	2.75, 6.17
CH <sub>2</sub> Cl	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	31	17	190	213-218	-2.1	5.04, 7.89	2.73, 6.14
CH <sub>2</sub> OOCCH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>		64	170	175-180			
CH <sub>2</sub> OOCCH <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	31	50		191-198	-1.1	2.2, 4.75	2.71, 6.12
CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Cl(4)	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	76	10	230	253-259	-2.2	2.6, 6.02	2.78, 6.41
CH <sub>2</sub> OC <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	10	48		203-206	-1.0	2.75, 5.0	2.75, 6.13

<sup>a</sup> Reported by Yanagida *et al. Tetrahedron Letters* **19** (1968) 2351, after the completion of our synthesis.

of the nitrile group has a more ambiguous effect. Chloroacetonitrile reacts readily with the tested malonyl chlorides (except with ethylmalonyl chloride). Bromoacetonitrile evidently reacts more tardily and gives no product with chloromalonyl chloride. Dichloroacetonitrile, trichloroacetonitrile, and 4,4,4-trichlorobutyronitrile give either no products or intractable mixtures. 3-Chloropropionitrile and 4-chlorobutyronitrile react with some but not all the investigated malonyl chlorides. Aromatic bound halogen has in our experience improved the yield of pyrimidones. (In Table 1 is, *e.g.*, seen that with chloromalonyl chloride, phenylacetonitrile yields 21 % of product, while 2,6-dichlorophenylacetonitrile yields 37 %.)

Cyanogen bromide and chloromalonyl chloride react to give unidentified products, which apparently are not pyrimidones.

Table 2. 2-Chloro-4-hydroxy-6-pyridones.

R <sub>3</sub>	R <sub>5</sub>	React. time (days)	Yield raw product (%)	Subl. (°C)	M.p. (°C)	τNH/OH	τR <sub>3</sub>	τR <sub>5</sub>
OOCCH <sub>3</sub>	H	4	34	160	224-228	-1.1	7.7	3.85
OOCCH <sub>2</sub> H <sub>5</sub>	H	6	20		230-232	-0.6	2.15	3.74
C <sub>6</sub> H <sub>5</sub> (CH <sub>3</sub> ) <sub>3</sub> (2, 4, 6)	H	39	49	220	320-326	-0.8	3.1, 7.74 8.04	3.8
C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> (4)	H	14	low	230	305-306	-0.74	2.87, 6.22	3.87
COOC <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	70	33	160	235-327	0.8	5.65, 8.66	8.03
COOC <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	147	14	130	200-205	-0.6	5.64, 8.65	7.46, 8.93
COOC <sub>2</sub> H <sub>5</sub>	Cl	91	5	175	240-245	-0.2	5.65, 8.64	
COOC <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	53	69	180	250-253	1.1	5.64 8.68	2.64
COOC <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	150			217-226	-1	5.64, 8.7	2.75, 6.14

Table 3. Additional data on literature compounds.

	M.p. (°C)	$\tau_{\text{NH/OH}}$	$\tau_{\text{R}_2}$	$\tau_{\text{R}_3}$	$\tau_{\text{R}_5}$
2-Benzoyloxymethyl-4-chloro-6-pyrimidone <sup>3</sup>	170–175	–3.17	2.2, 4.75		3.51
2-Chloro-3-(2-chloroethyl)-4-hydroxy-6-pyridone <sup>1</sup>	255–257 (dec.)	–0.2		6.31, 7.0	3.92
2-Chloro-4-hydroxy-3-propyl-6-pyridone <sup>1</sup>	308–316	0.2		7.46, 8.5, 9.1	3.96
2-Chloro-4-hydroxy-3-phenyl-6-pyridone <sup>1</sup>	322–324	0.9, 6.42		2.65	3.8

Allyl cyanide, cyanoacetic acid, and triethylammoniumacetonitrile chloride induced the self-condensation of malonyl chloride to 6-chloro-4-hydroxy-2-pyrone-3-carbonyl chloride.<sup>4</sup>

Diethyl cyanamide is only slightly reactive with acid chlorides in general, but reacts vigorously with malonyl chlorides with the formation of tarry matter.

Thiocyanates react with malonyl chlorides to give pyrimidones with a 2-alkylthio or 2-arylthio group.

Results from this work will be published shortly.

The following substituted malonyl chlorides have been investigated in this work: chloromalonyl, methylmalonyl, ethylmalonyl, phenylmalonyl, and benzylmalonyl chloride. In general, chloromalonyl chloride has proved to be the best reagent, as it reacts relatively rapidly with a majority of the tested nitriles and gives reasonably pure products. Malonyl chloride itself also reacts with a fairly wide range of nitriles, and is comparable to the chlorosubstituted reagent in this respect. The products were, however, usually more impure. The other acid chlorides react more tardily and give products with considerably fewer nitriles.

Dichloromalonyl and diethylmalonyl chloride did not react with any of the nitriles investigated.

As a comment to the  $\tau$ -values in the tables, we should like to emphasize that the very broad NH/OH bands usually are hard to observe, unless the concentration in the samples is above 10 %.

#### EXPERIMENTAL

Procedures for the preparation of malonyl chlorides found in the literature do not always give the expected yield and purity of the products. Our adapted procedures are therefore given here.

*Malonyl chloride.* To malonic acid (180 g), which is moistened with phosphorus oxychloride, is added in portions phosphorus pentachloride (700 g). No external cooling is necessary. When the mixture is completely liquified, it is set aside for about half an

hour and fractionated in subdued light at 20–22 mmHg. The fractions 28–37°C and 37–60°C are collected in receivers, cooled with solid carbon dioxide. The second fraction must be distilled rapidly, in order to avoid formation of tar. Both fractions are redistilled to b.p.<sub>15</sub> 40–45°C, or b.p.<sub>28</sub> 50–56°C. The average yield is 48 % of a pale yellow liquid, which is almost unchanged after several months at –20°C.

In this procedure it is essential to avoid an excess of phosphorus pentachloride; if not, tar formation during distillation occurs.

*Chloromalonyl chloride.* Sulphuryl chloride (200 g) is added dropwise to dry malonic acid (104 g) under anhydrous ether (500 ml) during 4–5 h. When the evolution of gas has ceased, the ether is evaporated (bath temperature not above 50–55°C), and the residue kept at 0°C overnight when it crystallises. The mother liquor is filtered thoroughly off by suction, leaving by average 105 g (83 %) of crude chloromalonic acid (hygroscopic!). To this is added, with stirring and cooling in portions during 1–2 h, 516 g (2 mol) of phosphorus pentachloride. Fractionation of the liquid mixture yields by average 75 g of a colourless liquid; b.p.<sub>15</sub> 38–45°C, or b.p.<sub>30</sub> 40–48°C. The product is reasonably free from malonyl chloride (as controlled by NMR), which is important in avoiding mixtures when reacted with nitriles.

*Phenyl- and benzylmalonyl chloride.* Attempts to distil these products (made with phosphorus pentachloride or thionyl chloride) invariably led to evolution of hydrogen chloride. The distillates showed very strong IR-absorption in the region 2130–2120 cm<sup>-1</sup>. (A weak absorption at 2130 cm<sup>-1</sup> was also found in distilled ethylmalonyl chloride.) In the NMR-spectra of the distillates, the methine signal (4.65  $\tau$ ) in phenylmalonyl chloride was very weak. The CH<sub>2</sub>–CH bands in benzylmalonyl chloride were also weak, and a singlet at 6.5  $\tau$  (just below the CH<sub>2</sub> doublet) appeared. This signal increased in intensity the more the product had been heated. Probably these results indicate a conversion to ketenes.<sup>5</sup> Integration of the NMR diagrams indicated a 80–90 % conversion of phenylmalonyl chloride and a 60–80 % conversion of benzylmalonyl chloride. A sample of distilled benzylmalonyl chloride had a chlorine content of 21.3 % (calculated 35.2 %), which indicates 79 % conversion. These acid chlorides reacted tardily with nitriles, giving low yields of pyrimidones/pyridones.

To obtain active reagents, the best procedure was to treat the acids with thionyl chloride for 18–22 h at 45–50°C and to strip the excess thionyl chloride at the same temperature and 10 mmHg. These products had the expected spectral properties and gave products with nitriles as recorded in the tables.

*Condensation. General procedure.* The acid chloride and a small excess of nitrile were mixed in a glass-stoppered flask and left at room temperature. After a variable time (from a few hours to several weeks) a crystalline precipitate appeared. When this was judged no longer to increase in amount, it was collected and washed (usually with acetonitrile). The calculated yields are based on the washed and dried crude products. These were purified for analysis by recrystallisation and sublimation (10–12 mmHg) when possible. Small amounts of decomposition products in the sublimates were removed by a final recrystallisation (from acetonitrile, ethanol or 60–100 % acetic acid). The elemental analyses (C, H, Cl, N) were all satisfactory.

*Deviations from the general procedure.* With 4-nitrobenzylcyanide the acid chloride was used in excess. The nitrile was pulverised, and the reaction mixture stirred from time to time. Undissolved nitrile was extracted from the product with hot benzene.

With benzylmalonyl chloride, acetonitrile had to be used in great excess to avoid intractable contaminations in the product. Benzylmalonyl chloride (15 g) and acetonitrile (100 g) gave after 100 days a brown crude product (0.5 g), yielding a fairly pure sublimate.

Lithium perchlorate was added to some reaction mixtures in order to promote pyridone formation.<sup>3</sup> Lithium perchlorate (1 g) was dissolved in chloroacetonitrile (3 g), malonyl chloride (2.5 g) was added, and the pyridone was collected after 4 days. Perchlorate (1 g) in benzyloxyacetonitrile (8 g) was mixed with malonyl chloride (7 g). The pyridone was collected after 6 days.

With charges of more than a few grams, the heat of reaction may cause the temperature to rise uncontrollably if no external cooling is applied, and formation of other heterocyclic products will occur.<sup>4</sup> This was especially conspicuous when chloro- and acetoxyacetonitrile reacted with malonyl chloride. Cooling the reaction mixtures below room temperature or changing the molar ratio between the reactants had effects only on reaction time and yield.

Sublimation temperatures and melting points were determined on a Kofler micro hot-stage. Several substances suffered some decomposition near the melting point. Rapid heating was necessary in these cases and the melting points are consequently somewhat uncertain.

The NMR-spectra were recorded on a Varian A-60A spectrometer. Dimethyl sulphoxide- $d_6$  was used as a solvent throughout with a concentration of substance of 10–20 % when possible.

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