

HETEROCYCLIC SYNTHESIS WITH MALONYL DICHLORIDE AND NITRILES

N.A. Zaidi, J.M. Al-Katti and F.H. Saeed

Chemistry Department, Faculty of Science, Benghazi, Libya

(Received May 24, 1981; revised October 2, 1982)

Reaction of malonyl dichloride with cyclopropane carbonitrile yielded 2-chloro-3-(2'-chloroethyl) 4-hydroxy-6-pyridone which on recrystallization from ethanol converted to 2-chloro-1,6,4',5'-tetrahydro-6-oxo-furano-(3',2'-3,4) pyridine. Cyclohexane carbonitrile with malonyl dichloride yielded the mixture of 2-cyclohexyl-4-chloro-6-pyrimidone and 2-cyclohexyl-7-chloro-4,5-dioxopyrano - [3,4-e] - [1,3] - oxazine. Reactions of malonyl dichloride with 1-phenylcyclopentane carbonitrile and pivalonitrile gave the corresponding bicyclic oxazines. Malonyl dichloride with pyruvonitrile yielded most probably a four membered heterocyclic compound.

INTRODUCTION

Malonyl dichloride has been reported to react with nitriles to produce different heterocyclic compounds depending upon the nature of nitrile and conditions of the reaction. Malonyl dichloride reacts with some nitriles at 100° yielding bicyclic heterocycles (chloro-oxopyrano-oxazines)[1]. Some nitriles react with malonyl dichloride at room temperature producing 3-substituted-2-chloro-4-hydroxy-6-pyridones[2]. Formation of 2-substituted-3-chloro-6-pyrimidones has been reported in some reactions of malonyl dichloride and nitriles [3,4,5]. The reactions of malonyl dichloride with cyclopropane carbonitrile, cyclohexane carbonitrile, 1-phenylcyclopentane carbonitrile, pivalonitrile and pyruvonitrile are reported in the present studies.

EXPERIMENTAL

Infrared and ultraviolet spectra, and nuclear magnetic resonance were recorded employing Pye Unicam SP 1200 spectrophotometer, Pye Unicam SP 800 spectrophotometer, and Varian EM-390 90MHZ spectrometer respectively. Mass spectra were run by Morgan MS Schaffer Corporation, Canada. Infrared spectral data were measured in KBr discs and ultraviolet spectra of all pyridine and pyrimidine derivatives were run in ethanol solutions. Ultraviolet spectra of compounds VI and VIII were recorded in cyclohexane solution while that of compound VII in chloroform.

General Procedure for the Reactions of Malonyl Dichloride with Nitriles. Mixture of malonyl dichloride and nitrile was kept at room temperature under anhydrous con-

ditions for an appropriate time. The reaction product was triturated with a mixture of dry ether and dry dioxane except in the reaction of pyruvonitrile where chloroform was used for trituration (Table. 1). Analytical and spectroscopic data of the compounds are presented in Tables 2 and 3.

Nitration of Compound IA. Compound IA (0.57g) and 50% nitric acid (5ml) were heated at 75° on a water bath for 25 minutes. The contents of the flask were then poured on crushed ice and the yellow crystalline product (0.55g, 79%) was collected. On sublimation bright yellow crystals of 2-chloro-3-(2'-chloroethyl)-5-nitro-4-hydroxy-6-pyridone (II) were obtained, m.p 162-3°.

Bromination of Compound IB. The mixture of compound IB (0.5g) in ethanol (5ml) and bromine (0.3ml) was heated under reflux for half an hour. The reaction mixture was cooled and filtered. Recrystallization of the product from aqueous ethanol gave white needles of 5-bromo-2-chloro-1,6,4',5'-tetrahydro-6-oxo-furano(3',2'-3,4)pyridine (IV) (0.5g, 75%) melting at 239-41°.

RESULTS AND DISCUSSION

Reaction of Malonyl Dichloride and Cyclopropane Carbonitrile. Reaction of malonyl dichloride and cyclopropane carbonitrile yielded a solid crystalline product. Repeated recrystallization from ethanol gave a mixture of two compounds. These two compounds (IA and IB) were separated on the basis of their solubilities in chloroform. Compound IA(m.p 190-2°) was completely insoluble in chloroform while compound IB (m.p 264°) was soluble in chloroform. Attempt of recrystallization of compound IA from ethanol again yielded the mixture of compounds IA

Table 1. Experimental details of reactions of malonyl dichloride and nitriles.

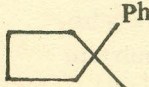
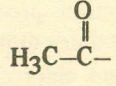
R in RCN	R C N	Malonyl dichloride	Reaction time	Recrystallizing solvent	Product (% yield) (m.p.)
1. Cyclopropyl	8.8ml (0.12 mole)	6 ml (0.06 mole)	3 hours	Ethanol	IA (80%) (190-2°C)
2. Cyclohexyl	9.6ml (0.08 mole)	3.9ml (0.04 mole)	10 days	Ethanol for V Pet. ether for VI	V (7%) (222-4°C) VI (27%) 151-2°C
3. 	10ml (0.06 mole)	3ml (0.03 mole)	½hour on boiling w/b	Pet. ether + benzene	VII (71%) (145-6°C)
4. (CH ₃) ₃ C-	3.3ml (0.04 mole)	2.0ml (0.02 mole)	3 days	Pet. ether + benzene	VIII (52%) (99-100°C)
5. 	5.6ml (0.08 mole)	7.8ml (0.08 mole)	2 days	Acetonitrile	IX (35%) (160°C- decomposition)

Table 2. Elemental analysis and important features of IR,UV and mass spectra.

Com- pound	% of elements Found (calculated)	IR absorption cm ⁻¹	UV absorption λ max. (ε max.)	Mass spectra m/e (%)
IA	C,40.5(40.6);H,3.5(3.4); N,6.8(6.8),Cl,34.1(33.8)	Reference 5	275(5205)	209(P+2,10),207(P,15),171(50), 158(82),136(B,100).
IB	C,49.1(49.1);H,3.6(3.5);N,8.2 (8.2); Cl,20.8(20.5)	Reference 5	289(5329)	173(P+2,37),171(P,B,100), 136(62).
II	C,33.2(33.3);H,2.2(2.4);N,11.2 (11.1),Cl,27.8(27.8)	3200-2200(b),1670(s). 1595-1560,1480,1350	347(4945)	254(P+2,5),252(P,8),216(B,100), 203(30),158(41).
III	C,50.15(50.47); H,3.2(3.7); N,6.71(6.55); Cl, 16.46 (16.57)	3100-2300(b),1675(s),1605 1560,1470	295(5785)	215(P+2,2.6),213(P,6), 171(85),136(100)
IV	C,33.44(33.59);H,1.96(1.99); N,5.76(5.6);Cl,14.36(14.18); Br, 31.89(31.9)	3100-2300(b), 1640,1600 (s),1400,1140,800	298(5678)	244(P+2,32),242(P,25),216 (20),173(17),171(50),136 (B,100)
V	C,56.5(56.6);H,6.1(6.1); N,13.3 (13.2); Cl,16.6(16.5)	3220-2210 (b),1680 (s),1578,1462,1440	280(4777) 288(1060)	214(P+2,11),212(P,30),183 (22),159(33),157(B,100)
VI	C,56.2(55.5);H,4.8(4.3),N,4.5 (4.9);Cl,11.9(12.4)	1750(s),1603,1520 1462.	273(4250), 330(5480)	281,(P,17),41(B,100).

(Continued.....)

Table 2. Continued.

VII	C,63.9(62.8);H,4.0(4.1);N,3.9 (4.1);Cl,9.8(10.2)	1772(s),1642(s),1584, 1543,1504,1402.	268(10976) 331(10290)	343(P,18),145(B,100)
VIII	C,51.8(51.8);H,4.0(3.9);N,5.4 (5.5);Cl,13.6(13.7)	1778(s),1717(s),1620 1525,1500,1422.	257(7520) 308(8670).	255(P,0.8),57,(B,100).
IX	C,37.8(37.7);H,3.1(3.1);N,7.5 (7.3);Cl,18.4(18.3)	3400,3300-2350(b), 1760(s),1663,1560,1464		190(P,30),43(B,100).

b = broad, s = strong, P = Parent peak, B = base peak

Table 3. ^1H Nuclear magnetic resonance results at 90 Mc/sec.

Compound (solvent)	Chem. shift (δ)	Intensity	Multiplicity J in c/sec.	Assignment
IA (DMSO- d_6)	3.0	2	t	Pyr-CH ₂
	3.57	2	t	-CH ₂ -Cl
	6.3	1	s	5-H
	10.97	2	b	NH/OH
IB (DMSO- d_6)	3.1	2	t	Pyr-CH ₂ -
	4.7	2	t	C-CH ₂ -
	6.0	1	s	5-H
	11.1	1	b	NH/OH
II (DMSO- d_6)	3.15	2	t	Pyr-CH ₂ -
	3.75	2	t	-CH ₂ Cl
	11.8	2	b	NH/OH
III (DMSO- d_6)	2.3	3	s	-O-CO-CH ₃
	3.15	2	t	Pyr-CH ₂ -
	4.72	2	t	-CH ₂ -O-
	6.58	1	s	5-H
IV (DMSO- d_6)	3.25	2	t	Pyr-CH ₂ -
	4.8	2	t	-CH ₂ -O-
	12.22	1	b	NH/OH
V (CDCl ₃)	1.7	10	c	-CH ₂ -of cyclohexane
	2.6	1	c	-CH-of cyclohexane
	4	1	s	5-H
	13	1	b	NH/OH

(Continued)

Table 3. Continued.

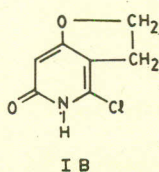
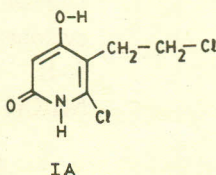
VI (DMSO-d ₆)	1.4	10	c	-CH ₂ -of cyclohexane
	2.1	1	c	-CH-of cyclohexane
	6.45	1	s	8-H
VII (CDCl ₃)	2.4	8	c	-CH ₂ - of cyclopentane
	6.45	1	s	8-H
	7.45	5	s	Ar-H
VIII (DMSO-d ₆)	1.2	9	s	-CH ₃
	6.43	1	s	8-H
IX (DMSO-d ₆)	1.8	3	s	-CO-CH ₃
	8.5	~3	b	NH/OH
	9.3			

*s = singlet, t = triplet; b = broad; c = complex.

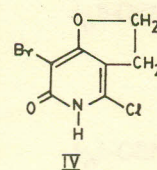
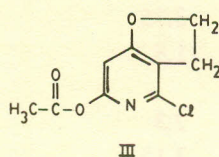
and IB. The compound IB could be recrystallized from ethanol. From their microanalyses and mass spectra the compositions of compounds IA and IB appeared to be C₇H₇Cl₂NO₂ and C₇H₆ClNO₂ respectively.

From spectroscopic evidence compound IA appeared to be 2-chloro-3-(2'-chloroethyl)-4-hydroxy-6-pyridone. This compound was unexpected in this reaction as it has been reported that cyanomethyl group was necessary for the formation of pyridine derivative from malonyl dichloride and nitriles [2]. Formation of compound IA in the reaction of malonyl dichloride and 4-chlorobutyronitrile has been reported earlier [2,6]. Synthesis of compound IA according to this procedure furnished a product which was found to be identical (mixed m.p, IR and ¹H-NMR spectra) with a sample of compound IA obtained from malonyl dichloride and cyclopropane carbonitrile. However, we differ from the reported m.p (255-7°). Compound IA on nitration yielded 2-chloro-3-(2'-chloroethyl)-5-nitro-4-hydroxy-6-pyridone(II).

On the basis of its elemental analysis and its spectroscopic studies compound IB was found to be 2-chloro-1,6,4',5-tetrahydro-6-oxo-furano(3',2'-3,4) pyridine.



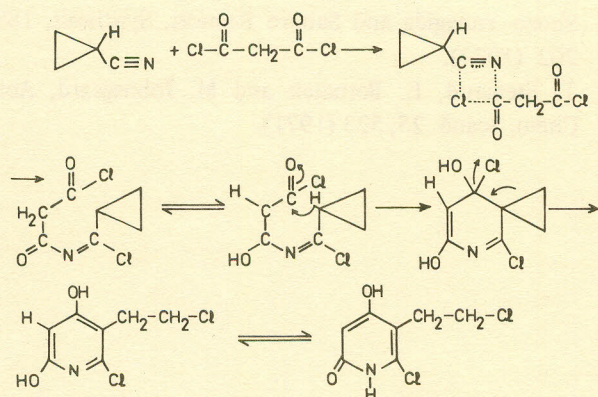
Compound IB was acetylated to its 6-acetoxy derivative (III) and was brominated to its unreported 5-bromo derivative (IV). Elvidge [2] has also reported compound IB and its acetylated derivative. The variously prepared samples of compounds IB and those of compound (III) were found identical (mixed m.p and IR spectrum). We present here the unreported NMR spectra of compounds IB and III.



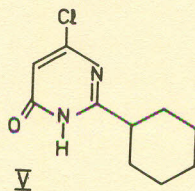
The presence of compound IB could not be detected in the crude product of the reaction. Therefore, it is concluded that IA is converted to IB during the recrystallization of the former from ethanol. The conversion of IA to IB had also been observed by refluxing compound IA with absolute ethanol, methanol and with water but with chloroform and with nitromethane no such conversion could be observed. It was also noted that compound IA could be recrystallized to almost pure compound IA by using excess of ethanol without much heating.

It was thought that hydrogen chloride might have opened cyclopropane carbonitrile to 4-chlorobutyronitrile and then later might have reacted with malonyl dichloride to yield IA. In fact it is not so because the reaction of 4-

chlorobutyronitrile with malonyl dichloride yields IA in six days while cyclopropane carbonitrile under similar conditions yields IA only in three hrs. Moreover, the ring of cyclopropane carbonitrile could not be opened by passing dry hydrogen chloride through it. Therefore, opening of cyclopropane ring should take place at some stage after nitrile reacts with malonyl dichloride. The following mechanism is suggested:



Reaction of Malonyl Dichloride and Cyclohexane Carbonitrile. This reaction at room temperature yielded a mixture of two compounds, which were isolated on the basis of their solubilities in petroleum ether. The compound insoluble in petroleum ether had the composition $C_{10}H_{13}ClN_2O$ while the composition of petroleum ether-soluble compound was $C_{13}H_{12}ClNO_4$. The infrared and ultraviolet spectra of compound $C_{10}H_{13}ClN_2O$ closely resembled those of 2-substituted-4-chloro-6-pyrimidones reported by Elvidge and Zaidi [3]. The NMR and mass spectra of this compound were also in complete accord with the corresponding pyrimidine structure. This compound, therefore, appeared to be 2-cyclo-hexyl-4-chloro-6-pyrimidone(V).

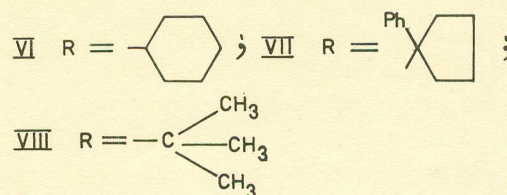
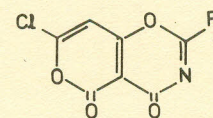


The infrared spectrum of compound $C_{13}H_{12}ClNO_4$ showed a strong band at 1770 cm^{-1} but no absorption of OH or NH groups. On the basis of its microanalysis and spectroscopic studies this compound was found to be 2-cyclohexyl-7-chloro-4,5-dioxopyrano [3,4-e]-[1,3]-oxazine (VI). Such bicyclic compounds have been reported by Davis *et al.* [1] from the reactions of malonyl dichloride with some

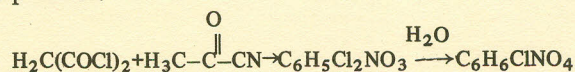
nitrile at 100° . Infrared and ultraviolet spectra of compound (VI) are in complete agreement with the spectra reported by those workers for such chloro-oxopyrano oxazines.

Reactions of Malonyl Dichloride with 1-Phenylcyclopentane Carbonitrile and Pivalonitrile. The mixture of malonyl dichloride and 1-phenyl cyclopentane carbonitrile at room temperature resulted in very low yield a solid compound of composition $C_{18}H_{14}ClNO_4$. The same compound was obtained in good yield at 100° . On the basis of its spectroscopic studies this compound was assigned the structure of 7-chloro-2-(1'-phenylcyclopentyl)-4,5-dioxopyrano-[3,4-e]-[1,3]-oxazine (VII).

The product obtained from malonyl dichloride and pivalonitrile had the composition $C_{11}H_{10}ClNO_4$. From its spectroscopic analysis this compound appeared to be the corresponding bicyclic compound (VIII).

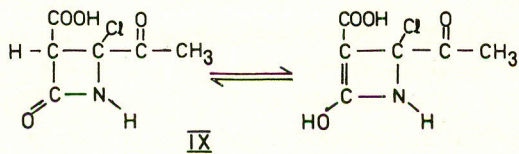


Reaction of Malonyl Dichloride with Pyruvonitrile. The reaction of malonyl dichloride with pyruvonitrile yielded a solid product of composition $C_6H_6ClNO_4$. Its infrared spectrum indicated the presence of carboxyl, OH/NH and keto groups. Chemical tests also supported the presence of carboxyl and acetyl groups. Its ultraviolet spectrum did not show any strong absorption above 180 nm. In its mass spectrum parent peak appeared at m/e 190 and a very strong peak at m/e 43 indicating the presence of acetyl group. The nuclear magnetic resonance spectrum of this compound gave a singlet at δ 1.8 (3H) and two broad signals at δ 8.5 and δ 9.3 (~3H). Last two signals disappeared on deuteration. It seems that the reaction produces some acid chloride which is hydrolysed during working up the product.



On the basis of its various spectra and chemical tests

the following structure (IX) (3-carboxy-4-acetyl-4-chloro-azetidine-2-one) is tentatively suggested but further work is being carried out to confirm the structure.



Acknowledgement. The authors thank University of Sulaimanyiah, Iraq, for providing the necessary facilities for this work.

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