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CONDENSATION OF ACYL CHLORIDE ON SODIUM CYANATE : PREPARATION OF ACYL ISOCYANATES

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Abstract : The catalytic effects of various metal halides and solvents on the reaction of benzoyl chloride with sodium cyanate were studied. It has been found that $SnCl_4$, and $ZnCl_2$. catalyze the reaction to give the corresponding acyl isocyanates in good yields. The scope of the reaction was studied and a number of aroyl isocyanates and their derivatives were prepared. A few non aromatic isocyanates and their derivatives were also prepared.

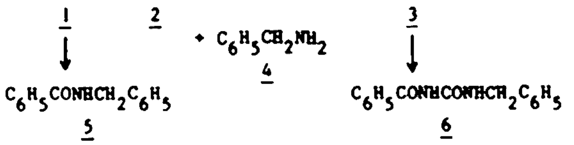
Acyl ureas and acyl carbamates play a considerable role in phytochemistry[1,2,3] as well as in medicinal chemistry[4]. Interested in the synthesis of a number of such derivatives we were confronted with the preparation of acyl isocyanates which are among their best precursors.

A number of acyl isocyanate preparations have been reported in the literature[5,6,7]. However none of them was completely satisfactory for our purposes. We therefore decided to study the synthesis of acyl isocyanates and we wish to report in the present publication the results obtained concerning the condensation of acyl halides with sodium cyanate.

Condensation of aroyl chlorides on sodium cyanate : influence of the catalysts and solvents

Aroyl isocyanates can be prepared by the condensation of aroyl chlorides with sodium cyanates in general. However, special catalysts and solvents must be used for receiving satisfactory yields.

For searching the best conditions the condensation of benzoyl chloride 1 (1 eq.) with sodium isocyanate 2 (1.3 eq.) in an acetonitril-benzene mixture (45:55) was studied at 78°C (reaction time 8 h) in detail. Instead of the isolation of the formed benzoyl isocyanate 3 the reaction mixture was quenched by the addition of benzylamine 4 after 8 hours. The added 4 gives raise to the formation of N-benzyl benzamide 5 and 1-benzoyl-3-benzyl urea 6 from the starting benzoyl chloride 1 and the resulting benzoyl isocyanate 3, respectively.



$$\begin{tikzcd}
\underset{1}{C_6H_5COCl} + \underset{2}{NaOCN} \arrow[rr] \arrow[dd] & & \underset{3}{C_6H_5CO\text{-}N{=}C{=}O} \arrow[dd] \\
 & + \underset{4}{C_6H_5CH_2NH_2} & \\
\underset{5}{C_6H_5CONHCH_2C_6H_5} & & \underset{6}{C_6H_5CONHCONHCH_2C_6H_5}
\end{tikzcd}$$

The results obtained are listed in Table I and Table II.

Without a catalyst, no reaction was observed and 1 was recovered as benzyl benzamide 5. Among the catalysts studied, $ZnCl_2$ led to good results. However, $SnCl_4$ appeared as the best reagent and we used it to perform the experiments described below. It is clear that the catalytic effects are the expression of an electrophilic assistance to the nucleophilic condensation.

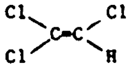
TABLE I : Effect of catalyst on the reaction of 1 with 2

Run	Catalyst (0.05 eq.)	Yield (%)	
		5(a)	6(b)
1	-	91	0
2	$SnCl_4$	0	87
3	$ZnCl_2$	20	71
4	$CdCl_2$	73	16
5	BF_3-Et_2O	90	0
6	$FeCl_3$	87	0
7	$TiCl_4$	80	0
8	$AlCl_3$	95	0

(a) m.p. of 5 was 104°C (lit.[9] 104°C)

(b) m.p. of 6 was 166°C (lit.[8] 165-166°C).

TABLE II : Effect of solvents on the reaction of 1 with 2 in presence of $SnCl_4$ (0.05 eq.)

Run	Solvent	Temp. (°C)	Time (h)	Yield (%)	
				5	6
9	CCl_4	70	8	76	0
10	THF	70	8	83	0
11	C_6H_6	78	8	68	19
12	$C_6H_5CH_3$	116	8	62	27
13	CH_3CN	70	8	0	26(a)
14	CH_3CN-C_6H_6 (45:55)	78	8	0	87
15	CH_3CN-CCl_4	78	8	0	88
16	$ClCH_2CH_2Cl$	83	8	78	0
17		85	8	20	68
18	Glyme	95	8	21	53
19	Diglyme	145	2	7	84
20	Dioxane	96	8	0	95
21	o-Dichlorobenzene	130	8	0	81
22	Chlorobenzene				

(a)In addition to 6, there was 59 % benzoyl isocyanate polymer.

From the data reported in Table II it appears that acetonitrile alone is a good solvent for the condensation. However it considerably favorises the polymerization of acyl isocyanates and must be discarded.

Mixtures of acetonitrile and non polar solvents, as well as diglyme and dioxane led to very good yields. However these solvents are not convenient for large scale preparations. Fortunately we found that the inexpensive 1,2-dichlorobenzene constituted an excellent reaction medium and we decided to use it for the synthesis of acyl isocyanates.

Preparation of aroyl isocyanates

With the above results in hand, we condensed sixteen representative aroyl chlorides on sodium cyanate in 1,2-dichlorobenzene in the presence of catalytic amounts of $SnCl_4$. The results obtained are reported in Table III. In a number of cases the aroyl isocyanates have been isolated in order to show that the yields obtained for the derivatives were close to those of the aroyl isocyanates themselves.

It clearly appears from these data that the method described is very general.

However we must indicate that we never succeeded in the condensation of orthophenoxybenzoyl chloride on sodium cyanate. Indeed, under our conditions, the only product isolated was 9-xanthenone formed by an internal Friedel Craft condensation.

Preparation of non aromatic acyl isocyanates

We are able to extend the above results to a few non aromatic acyl chlorides. The results obtained are reported in Table IV (the characteristics of the products are also given in this Table).

Interestingly it must be noted that if $SnCl_4$ was necessary to the condensation of acetyl and propionyl chloride, it was of no interest in the condensation of trichloroacetyl chloride since destruction of the starting compound was observed. On the contrary without catalyst the yield was very good. Incidently we found that 1,2,4-trichlorobenzene was a better solvent than 1,2-dichlorobenzene, because trichloroacetyl isocyanate was easily separated from 1,2,4-trichlorobenzene by distillation. Obviously the electronwithdrawing effect of the chlorine atoms sufficiently increase the reactivity of the carbonyl group of the acyl chloride to allow the condensation without catalyst.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. The IR spectra of acyl isocyanate were taken in solutions of CCl_4 or o-dichlorobenzene and the IR spectra of ureas were taken in KBr pellets on a Perkin Elmer 580 B spectrometer. ^1H NMR spectra were recorded using a Brucker AW 80 spectrometer. Solutions in $CDCl_3$ with TMS as internal standard were used. All experiments were carried out under argon and monitored by IR. Solvents for reactions were purified before use by distillation from suitable drying agents. $SnCl_4$, $TiCl_4$, BF_3-Et_2O, and all acyl chlorides were distilled under argon before use. $ZnCl_2$, $CdCl_2$, $FeCl_3$, and $AlCl_3$ were dried at 110°C in vacuum overnight before use.

Preparation of benzoyl isocyanate using the mixture of CH_3CN and C_6H_6 as a solvent

To a suspension of NaOCN (1.69 g ; 0.026 mol) in 10 ml of dry CH_3CN and 12.5 ml of dry C_6H_6 were added benzoyl chloride (2.81 g ; 0.02 mol) in 10 ml of CH_3CN and 12,5 ml of C_6H_6 and $SnCl_4$ (0.26 g ; 0.001 mol) under argon with stirring. The mixture was refluxed for 8 h after which the reaction was complete. In order to estimate the isocyanate yield , benzylamine (2.14 g ; 0.02 mol) in 10 ml of C_6H_6 was dropped into the mixture at room temperature. After stirring for half an hour, 100 ml of water were added to dissolve the salts. The mixture was filtered to give a white solid, which was recrystalized from ethanol to give (6) (4.42 g ; 87 %). m.p. 166°C (lit. m.p. 165-166°C).[8]

General method of the preparation of aroyl isocyanate in o-dichlorobenzene

A typical procedure is described for the reaction of o-chlorobenzoyl chloride with NaOCN. To a suspension of NaOCN (8.45 g ; 0.13 mol) in 20 ml of dry o-dichlorobenzene was added o-chlorobenzoyl chloride (17.5 g ; 0.1 mol) in 20 ml of o-dichlorobenzene and $SnCl_4$ (1.3 g ; 0.005 mol) under argon with stirring.

TABLE III - PREPARATION OF VARIOUS AROYL ISOCYANATES AND THEIR UREAS OF ANILINE

$$\underset{(1\ \text{eq.})}{\text{ArCOCl}} + \underset{(1.3\ \text{eq})}{\text{NaOCN}} \xrightarrow[\substack{\text{SnCl}_4\ (0.05\ \text{eq.})\\ \sim 180°\text{C},\ 2\ \text{h}}]{\text{o-dichlorobenzene}} \text{ArCONCO} \xrightarrow[\substack{(1\ \text{eq.})\\ \text{rt},\ 30\ \text{mn}}]{C_6H_5NH_2} \text{ArCONHCONHC}_6\text{H}_5$$

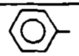
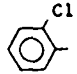
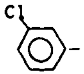
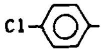
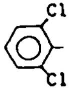
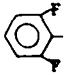
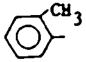
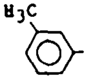
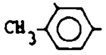
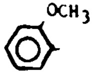
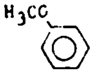
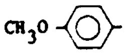
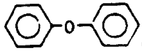
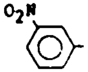
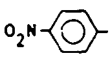
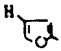
	ArCONCO				$ArCONHCONHC_6H_5$											
Run	Ar	b.p. (°C)	Yield[a] (%)	νNCO (cm^{-1})	m.p. (°C)	m.p. lit. (°C)	νC=O (cm^{-1})	^{1}H NMR δ (ppm)	Found (%)				Calcd. (%)			
									C	H	N	Cl	C	H	N	Cl
24		74-76/ 10 mm	83(88)	2230	209-10	208-9[10]	1710 1690	7.1-7.6 (10H,m,Ar) 9.7 (1H,s,NHC_6H_5) 10.9 (1H,s,CONHCO)	-				-			
25		98-101/ 2 mm	80(87)	2240	168-69	-	1710 1680	7.3-7.8 (9H,m,Ar) 9.7 (1H,s,NHC_6H_5) 10.9 (1H,s,CONHCO)	60.86	3.99	10.14	13.08	61.20	4.01	10.20	13.10
26		103-107/ 5 mm	81(79)	2250	194-95	-	1710	7.1-8.1 (9H,m,Ar) 9.9 (1H,s,NHC_6H_5) 10.9 (1H,s,CONHCO)	60.75	4.07	10.20	13.10	61.20	4.01	10.20	13.10
27		92-95/ 2 mm	85(86)	2250	242	243[11]	1710 1680	7.1-8.0 (9H,m,Ar) 9.9 (1H,s,NHC_6H_5) 10.9 (1H,s,CONHCO)	60.85	4.02	9.97	13.17	61.20	4.01	10.20	13.10
28		123-126/ 1-1.5 mm	87(92)	2240	193-94	-	1715 1690	7.2-7.4 (8H,m,Ar) 9.8 (1H,s,NHC_6H_5) 10.4 (1H,s,CONHCO)	54.13	3.28	9.03	23.29	54.37	3.24	9.06	22.98
29		83-88/ 9-10 mm	70(73)	2260	191-92	191-92[2]	1705 1695	6.9-7.6 (8H,m,Ar) 9.3 (1H,s,NHC_6H_5) 10.4 (1H,s,CONHCO)	-				-			
30			(85)	2240	183-84	-	1710 1675	2.41 (3H,s,CH_3) 7.0-7.6 (9H,m,Ar) 9.1 (1H,s,NHC_6H_5) 10.7 (1H,s,CONHCO)	70.71	5.55	10.82	-	70.87	5.51	11.02	-
31		84-86/ 2 mm	80(83)	2240	157.5-8.5	-	1710 1670	2.38 (3H,s,CH_3) 7.0-7.8 (9H,m,Ar) 9.7 (1H,s,NHC_6H_5) 10.9 (1H,s,CONHCO)	70.60	5.42	11.06	-	70.87	5.51	11.02	-
32		82-84/ 1.6 mm	81(85)	2240	208.5-9.5	-	1705 1670	2.40 (3H,s,CH_3) 7.05-8.1 (9H,m,Ar) 9.8 (1H,s,NHC_6H_5) 10.9 (1H,s,CONHCO)	70.55	5.96	11.08	-	70.87	5.51	11.02	-

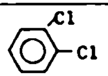
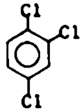
TABLE III (continued)

	ArCONCO				ArCONHCONHC$_6$H$_5$											
									Found (%)				Calcd. (%)			
Run	Ar	b.p. (°C)	Yield[a] (%)	νNCO (cm^{-1})	m.p. (°C)	m.p. lit. (°C)	νC=O (cm^{-1})	^{1}H NMR δ (ppm)	C	H	N	Cl	C	H	N	Cl
33		115-117/ 1 mm	67	2240	129-30	131[12]	1693 1675	4.0 (3H,s,CH$_3$O) 6.9-8.2 (9H,m,Ar) 9.9 (1H,s,NHC$_6$H$_5$) 10.9 (1H,s,CONHCO)	66.69	5.23	10.52	-	66.67	5.19	10.37	-
34		104-107/ 2 mm	76(80)	2240	168-69	-	1700 1670	3.8 (3H,s,CH$_3$O) 7.0-7.7 (9H,m,Ar) 9.7 (1H,s,NHC$_6$H$_5$) 10.9 (1H,s,CONHCO)	66.85	5.24	10.34	-	66.67	5.19	10.37	-
35			(73)	2240	200-1	201-1.4[12]	1700 1670	3.9 (3H,s,CH$_3$O) 7.0-7.8 (9H,m,Ar) 9.7 (1H,s,NHC$_6$H$_5$) 10.9 (1H,s,CONHCO)	66.63	5.22	10.30	-	66.67	5.19	10.37	-
36		131-135/ 0.5-0.7mm	76(78)	2240	209-10	-	1700 1670	6.9-8.1 (14H,m,Ar) 9,9 (1H,s,NHC$_6$H$_5$) 10.9 (1H,s,CONHCO)	72.01	4.83	8.25	-	72.28	4.82	8.43	-
37		103-7/ 0.5 mm	78(82)	2245	224	224[13]	1700 1690	7.0-7.8 (9H,m,Ar) 9.7 (1H,s,NHC$_6$H$_5$) 10.9 (1H,s,CONHCO)		-				-		
38		120-3/ 1.5 mm	84(87)	2245	224-5	-	1725 1695	7.0-8.0 (9H,m,Ar) 9.7 (1H,s,NHC$_6$H$_5$) 10.9 (1H,s,CONHCO)	58.84	3.63	14.38	-	58.95	3.96	14.74	-
39		80-83/ 15 mm	71	2240	191-2	193[14]	1710 1665	6.6 (1H, m, ) 7.1-7.6 (7H,m  and Ar) 8.9 (1H,s,NHC$_6$H$_5$) 10.5 (1H,s,CONHCO)		-				-		

(a) Figures in parentheses represent the urea yields

TABLE IV : Preparation of RCONCO and $RCONHCONHCH_2C_6H_5$

$$\underset{(1.0\ eq)}{RCOCl} + \underset{(1.3\ eq)}{NaOCN} \xrightarrow{SnCl_4} RCONCO \xrightarrow[r.t.\ 30\ min]{C_6H_5CH_2NH_2(1\ eq)} RCONHCONHCH_2C_6H_5$$

Run	RCONCO								$RCONHCONHCH_2C_6H_5$			
	R	Solvent	$SnCl_4$ (eq)	Temp. (°C)	Time (h)	b.p. (°C)	Yield (%)	νNCO (cm^{-1})	m.p. (°C)	m.p. lit. (°C)	νC=O (cm^{-1})	^1H NMR
40	CH_3-		0.05	80	8	78-80	36	2235	131	130-131[15]	1720 1700	2.2 (3 H, s, CH_3) ; 4.5 (2 H, d, $-CH_2Ar$) ; 7.1-7.6 (5 H, m, Ar) ; 10.0 (1 H, t, $-NHCH_2Ar$) ; 10.75 (1 H, s, -CONHCO-)
41	CH_3CH_2-	"	0.05	80	8	96-98	52	2235	118.5-119	118-119[15]	1720 1700	1.0 (3 H, t, CH_3) ; 2.6 (2 H, q, CH_2) ; 4.4 (2 H, d, CH_2Ar) ; 7.0-7.6 (5 H, m, Ar) ; 10.0 (1 H, t, $NHCH_2Ar$) ; 10.8 (1 H, s, -CONHCO-)
42	Cl_3C-	"	0.05	114	8	-	0	-	-	-	-	-
43	Cl_3C-	"	-	130-170	8	-	87[a]	-	106	106[16]	1725 1705	4,6 (2 H, d, CH_2Ar) ; 7.1-7.6 (5 H, m, Ar) ; 9.4 (1 H, t, $-NHCH_2Ar$) ; 10.0 (1 H, s, CONHCO-)
44	Cl_3C-		-	130-170	7	135-140	92	2250	106	106[16]	1725 1705	"

(a) Isolated as N-benzylurea.

The mixture was stirred for 2 hours at the refluxing temperature (180°C). After cooling to room temperature, the mixture was filtered under argon. The filtrate was distilled under reduced pressure to give o-chlorobenzoyl isocyanate (14.5 g ; 80 %) (b.p. 98-101°C/2 mm) which reacted with aniline in benzene at ambient temperature to give the corresponding urea ; the IR, ^1H NMR, m.p. and microanalysis of which are summarized in Table III.

General procedure for preparing non aromatic acyl isocyanates

A typical procedure is described for the reaction of acetyl chloride(15.9 g ; 0.2 mol) with NaOCN (16.9 g ; 0.26 mol) and $SnCl_4$ (2.6 g ; 0.01 mol) in 15 ml of o-dichlorobenzene. The mixture was stirred for 8 hours at 80°C and filtered under argon. The filtrate was distilled under nitrogen to give acetyl isocyanate (6.12 g ; 36 %) (b.p. 78-80°C). The isocyanate reacted with benzylamine in benzene at ambient temperature to give the corresponding urea ; the IR and ^1H NMR spectra as well as m.p. of which are given in Table IV.

Preparation of Cl_3CONCO

To a dry flask were added NaOCN (12.68 g ; 0.195 mol), 40 ml of 1,2,4-trichlorobenzene and Cl_3COCl (27.3 g ; 0.15 mol) under argon. The mixture was heated with stirring. The temperature of the reaction mixture increased from 130°C to 170°C in about 7 hours. It was seen that the reaction was complete when the temperature of the mixture reached about 170°C. After completion of the reaction, the mixture was distilled under argon to give Cl_3CONCO (26 g ; 92 %) (b.p. 135-140°C) which reacted with benzylamine in benzene at ambient temperature to give the corresponding urea. The IR and ^1H NMR spectra as well as m.p. are given in Table IV.

ACKNOWLEDGEMENTS

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