[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, TOKYO INSTITUTE OF TECHNOLOGY]

Novel Method for the Preparation of Organic Isocyanates[1]

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Received March 13, 1961

A novel method for the preparation of organic isocyanates by the pyrolysis of acid amides has been studied. The pyrolysis of acetoacetamides, obtained from amines and ketene dimer, at a temperature range from 350° to 740° gave corresponding isocyanates in fairly good yields along with acetone. Similarly, the pyrolysis of α-trichloroacetanilide gave phenyl isocyanate, benzonitrile, hydrogen chloride, and phosgene. The pyrolysis of acid amides yielding isocyanates is considered to proceed through cyclic intermediates.

The mechanism of the thermal dissociation of ureas and urethanes into their component compounds, isocyanate and amine, and isocyanate and alcohol, respectively, has been described in the preceding papers.[2–4] It is the purpose of this paper to present data on the thermal dissociation of *N*-substituted acetoacetamides into isocyanates and acetone. The usual isocyanate generators[5,6] are unsatisfactory for the synthesis of isocyanate *per se*, since the acidic materials to which they decompose, such as phenols, alcohols, and enolizable hydrogen compounds with pK_a values of 9–14, react again with the isocyanate to give starting materials. The product acetone in the present work is such a weak acid, with pK_a value of 20, that it does not react at all with the isocyanate.

The same process of dissociation reactions of adducts of isocyanate with weak acids described above can be applied to adducts of isocyanate with chloroform, methylene chloride, chloromethane, etc., namely to α-trichloroacetamides, α-dichloroacetamides, α-chloroacetamides, etc.

What has prompted the whole idea expounded here are the results obtained in our laboratory from the pyrolysis of acetoacetylhydroxamates[7] at 300–400° to give isocyanates and acetone in high yields.

Acetoacetamides have two possible alternative pathways of dissociation as represented in the following scheme.

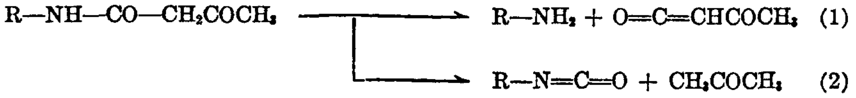
When acetoacetanilide as a model compound was heated directly in a Claisen flask at 180–200° under reduced pressure, a 60% yield of aniline was obtained along with a small amount of acetone and *sym*-diphenylurea *via* equation (1). The temperature was kept at the stated degree because acetoacetanilide decomposes at about 180°.

In order to carry out the dissociation of acetoacetanilide at a more elevated temperature, pyrolysis of acetoacetanilide through a quartz column packed with quartz chips was tried.

The results of these studies are given in Table I and generalizations may be made as follows. At low temperatures, that is, below 350°, the formation of phenyl isocyanate could not be observed, though the starting material was recovered. However, at 540° and over the phenyl isocyanate was formed along with acetone *via* equation (2).

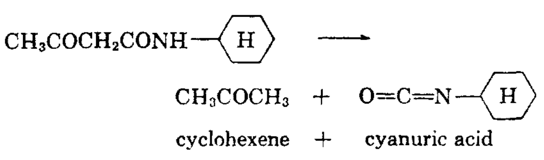
The amount of undesirable *sym*-diphenylurea and char deposited in the reaction tube increases as the temperature of pyrolysis rises.

The syntheses of aromatic isocyanates with electron-releasing substituents, according to this procedure, using approximately maximized reaction conditions, are shown in Table II. It is noteworthy that the three aliphatic *N*-substituted acetoacetamides also give the corresponding aliphatic isocyanates in somewhat reduced yields. In the case of *N*-cyclohexylacetoacetamide, 0.4 g. of cyclohexene is formed by the above mentioned thermal decomposition along with 0.9 g. of cyclohexyl isocyanate and 0.4 g. of acetone.



$$R{-}NH{-}CO{-}CH_2COCH_3 \longrightarrow R{-}NH_2 + O{=}C{=}CHCOCH_3 \quad (1)$$

$$\longrightarrow R{-}N{=}C{=}O + CH_3COCH_3 \quad (2)$$



But, acetoacet-*p*-nitroanilide and acetoacet-*p*-carboethoxyanilide gave only disubstituted urea along

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(1) T. Mukaiyama, H. Nohira, and M. Tokizawa, partly presented to Japanese Patent Office, January 11, 1960.

(2) T. Mukaiyama and M. Iwanami, *J. Am. Chem. Soc.*, **79**, 73 (1957).

(3) T. Mukaiyama, T. Akiba, and T. Asahi, *Bull. chem. soc. Japan*, **33**, 1137 (1960).

(4) T. Mukaiyama and T. Akiba, *Bull. chem. soc. Japan*, **33**, 1707 (1960).

(5) O. Bayer, *Angew. Chem.*, **A59**, 257 (1947).

(6) R. G. Arnold, *Chem. Revs.*, **57**, 47 (1957).

(7) T. Mukaiyama and H. Nohira, *J. Org. Chem.*, **26**, 782 (1961).

TABLE I

PYROLYSIS OF ACETOACETANILIDE UNDER VARIOUS CONDITIONS

Aceto-acetanilide Charged (G.)	Pyrolysis Conditions			Products (G.)			R.M.[a] (G.)
	Temp.	Pressure (mm.)	Time (min.)	Acetone	Iso-cyanate	Urea	
5.0	550	11		0.3	0.7		
5.0	550	19–20	27	0.2	1.3	1.1	
5.0	730–740	5.0	15	0.3	1.5	0.8	
2.8	620	5.0	5	0.2	0.9	0.6	
5.0	540–550	5.0	12	0.5	2.3	0.1	0.4
5.0	520	3.0	21	0.5	1.7	0.3	1.5
5.0	460	6.0	5	0.4	1.5	0.5	0.3
5.0	460	4.5	12	—	1.6	0.6	0.7
5.0	430–450	1.0–3.0	21	0.4	1.6	0.2	1.5
5.0	380–400	1.0–3.0	21	—	0.3	None	3.5
5.0	570	Atm.	20	—	1.5	0.5	0.3

[a] R.M. = amount of acetoacetanilide recovered.

TABLE II

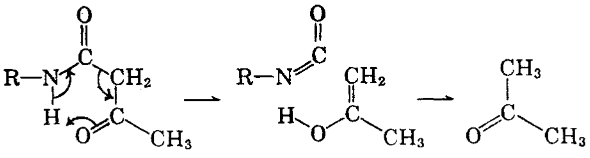
PYROLYSIS OF ACETOACETAMIDES

Aromatic Derivs. Charged (G.)	Pyrolysis Conditions		Products (G.)			R.M.[a] (G.)
	Temp.	Pressure (mm.)	Acetone	Isocyanate (b.p./mm.)	Urea	
Acetoacetanilide (5.0)	540–550	5.0	0.5	2.3 (50/11)	0.1	0.4
-*p*-Toluidide (5.0)	545	5.0	—	2.4 (84/23)	0.3	0.5
-*o*-Toluidide (5.0)	530–540	4.5–5.0	—	1.8 (85/27)	0.4	0.7
-*p*-Anisidide (5.0)	450	5.0	—	1.4 (72–73/2)	0.1	1.6
-*p*-Chloroanilide (5.0)	540–550	4.5–5.0	0.4	2.1 (90–95/20)	0.4	0.7
-*p*-Carboethoxyanilide (5.0)	450–460	3.5–7.0	S.M.[b]	None		S.M.
-*p*-Nitroanilide (5.0)	520	17.0	0.2	?	2.0	S.M.
Aliphatic Derivs.						
N-*n*-Hexylacetoacetamide (5.0)	550	6.5–7.0	0.3	1.4 (67–68/24)	S.M.	
N-Benzylacetoacetamide (5.0)	550	4.5	0.2	0.8 (51/13)	S.M.	0.8
N-Cyclohexylacetoacetamide (5.0)	550	5.0	0.4	0.9 (170–175)	S.M.	

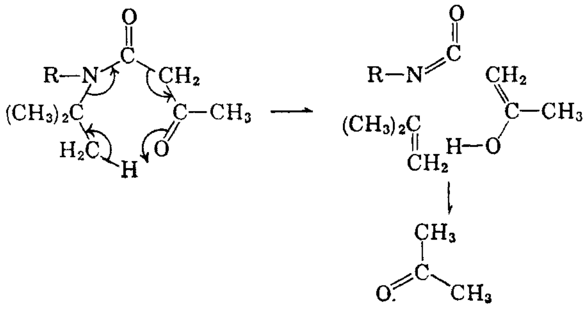
[a] R.M. = amount of acetoacetamides recovered. [b] S.M. = small amount.

with a small amount of acetone under the same condition, and *p*-nitrophenyl isocyanate and *p*-carboethoxyphenyl isocyanate, though expected theoretically, could not be obtained, presumably because of technical deficiencies. The best conditions to be selected for the pyrolysis, depending on the reaction temperature, the pressures, the flow rate of an inert gas and the amount, the type, shape, and size of the fillers are now being studied.

These results obtained by the gas phase decomposition of acetoacetamides at high temperature indicate that the course of the decomposition is dependent on the ease of the bond fission with which more stable ions, *i.e.*, $CH_3COCH_2^{\ominus}$ and R—NHCO$^{\oplus}$ are formed. The anion thus formed accepts hydrogen atom from the cation to form acetone and isocyanate. The pyrolysis of acetoacetamides is thus regarded as proceeding through the following cyclic intermediates, which are essentially the same *cis*-type elimination reaction as usual pyrolytic reaction of esters and xanthates.[8]



By the pyrolysis of *N*-*t*-butylacetoacetanilide, phenyl isocyanate, isobutylene, and acetone were obtained in good yields under the same conditions. The reaction may proceed through the same cyclic intermediate, which involves transfer of hydrogen from the *t*-butyl group to a negatively charged oxygen atom of the acetyl group as shown in the following scheme:



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(8) C. H. De Puy and R. W. King, *Chem. Revs.*, **60**, 431 (1960).

TABLE III

MELTING POINTS AND ANALYSIS FOR ACETOACETAMIDES

Derivs. of Acetoacetamide	Formula	M.P.	N, % Calcd.	N, % Found
Acetoacetanilide		85		
-*p*-Toluidide		95		
-*o*-Toluidide	$C_{11}H_{13}NO_2$	105–106	7.33	7.24
-*p*-Chloroanilide	$C_{10}H_{10}NO_2Cl$	131–132	6.62	6.53
-*p*-Methoxyanilide	$C_{11}H_{13}NO_3$	116–117	6.76	6.56
-*p*-Nitroanilide	$C_{10}H_{10}N_2O_4$	122	12.61	12.55
-*p*-Carboethoxyanilide	$C_{13}H_{15}NO_4$	122	5.62	5.44
N-*n*-Hexylacetoacetamide	$C_{10}H_{19}NO_2$	58	7.56	7.49
N-Cyclohexylacetoacetamide	$C_{10}H_{17}NO_2$	74	7.64	7.80
N-Benzylacetoacetamide	$C_{11}H_{13}NO_2$	101–102	7.33	7.28
N-*t*-Butylacetoacetanilide	$C_{14}H_{19}NO_2$	70–71.5	6.00	5.82
N-Ethylacetoacetanilide	$C_{12}H_{15}NO_2$	56	6.82	6.85

In contrast to *N*-*t*-butylacetoacetanilide, *N*-ethylacetoacetanilide did not give phenyl isocyanate under the same conditions, but starting material was recovered quantitatively. The results may be attributed to the difference, due to their electrical and structural effects, in the readiness with which *t*-butyl and ethyl groups form olefins.

In view of these results it is to be noted that acid amides containing atomic groups which are stable as anions in their acyl groups can be decomposed to produce isocyanates. In order to ascertain this hypothesis experimentally, the pyrolysis of α-trichloroacetanilide, which may produce $CCl_3^{\ominus}$ and C_6H_5—$NHCO^{\oplus}$ ions at an elevated temperature, was tried. By carrying out the pyrolysis of α-trichloroacetanilide at 520–530° under reduced pressure, phenyl isocyanate was obtained as expected. At the same time, however, hydrogen chloride, phosgene, and benzonitrile were unexpectedly obtained in higher yield than phenyl isocyanate.

$$C_6H_5NHCOCl_3 \longrightarrow \underset{\text{(minor)}}{C_6H_5{-}N{=}C{=}O} + \underset{\text{(major)}}{C_6H_5{-}C{\equiv}N} + COCl_2 + HCl$$

Further study of other acid amides, including α-halo compounds such as trichloroacetamides, dichloroacetamides, and monochloroacetamides, is now in progress.

EXPERIMENTAL

Materials. Aromatic amines, aliphatic amines, and ketene dimer were obtained from commercial sources and purified by distillation or by recrystallization. Acetoacetanilide was prepared according to the method of Kaslow and Sommer.[9] Similarly, the other acetoacetamides listed in Table III were prepared from ketene dimer and corresponding amines.

Decomposition of acetoacetanilide. Five grams (0.028 mole) of acetoacetanilide was heated in a Claisen flask at 3–4 mm. and 180–200°. Acetone and aniline produced were fractionated by distillation to give 0.2 g. (12%) of acetone and 1.6 g. (60%) of aniline. A crystalline substance deposited in the flask proved to *sym*-diphenylurea, m.p. 235–237°.

Pyrolysis under reduced pressure. The apparatus used for all pyrolyses consisted of a vertical quartz tube, 18 mm. in diameter and 120 cm. long, equipped with standard taper joint and a side-inlet tube near the top for the exchange of air with nitrogen and for the steady flow of the nitrogen. This tube was packed with quartz chips and externally heated with an electric furnace. The temperature was determined by a pyrometer, and the thermocouple was attached to the outside of the pyrolysis tube. During pyrolysis, a slow stream of dry nitrogen was introduced through the capillary under reduced pressure. By using the apparatus described above, 5.0 g. (0.028 mole) of acetoacetanilide was pyrolyzed at 540° over a period of 12 min. at 5 mm. pressure. The pyrolyzate was collected in a flask cooled in a Dry Ice–acetone bath and fractionated by distillation to yield 2.3 g. (68%) of phenyl isocyanate, b.p. 50°/11 mm., and 0.5 g. (31%) of acetone, b.p. 55°. The residue was washed with hot dry benzene and recrystallized from acetic acid to yield 0.1 g. of *sym*-diphenylurea, m.p. 237°. Four-tenths gram of acetoacetanilide was recovered from the filtrate.

Similarly, pyrolysis of acetoacetanilide under various conditions and of other derivatives of acetoacetamides are listed in Tables I and II.

Pyrolysis of acetoacetanilide under atmospheric pressure. (a)Using the apparatus described above, a solution of 5.0 g. (0.028 mole) of acetoacetanilide in 12 ml. of acetone was pyrolyzed at 550° under atmospheric pressure. A 33% yield (1.2 g.) of phenyl isocyanate was obtained along with 0.5 g. of *sym*-diphenylurea; 0.5 g. of acetoacetanilide was recovered.

(b) In a similar way, 5.0 g. (0.028 mole) of acetoacetanilide was fed to a reaction zone which was kept at 570° under atmospheric pressure. A 44% yield (1.5 g.) of phenyl isocyanate was obtained along with 0.5 g. of *sym*-diphenylurea and 0.3 g. of acetoacetanilide.

Pyrolysis of N-t-butylacetoacetanilide. Using the apparatus described above, 1.7 g. (0.0073 mole) of *N*-*t*-butylacetoacetanilide was fed to the reaction zone which was kept at 570–580° under reduced pressure (2.5 mm.) over a period of 15 min. Five-tenths gram of phenyl isocyanate and 0.1 g. of acetone were obtained along with a small amount of *sym*-diphenylurea. The yield of phenyl isocyanate was 54%.

Pyrolysis of N-ethylacetoacetanilide. In a similar way, 5.2 g. (0.025 mole) of *N*-ethylacetoacetanilide was fed to the reaction zone which was kept at 530–540° over a period of 15 min. at 4.5–5.0 mm. pressure. Phenyl isocyanate was not obtained, and *N*-ethylacetoacetanilide was recovered quantitatively.

Pyrolysis of α-trichloroacetanilide. By use of the same apparatus as employed in the cases of the pyrolysis of acetoacetamides, 5.0 g. (0.021 mole) of α-trichloroacetanilide was pyrolyzed at 520–530° over a period of 70 min. under reduced pressure (6.0 mm). Hydrogen chloride and phosgene in the pyrolysate were lead to a solution of aniline in ether, and

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[9] C. E. Kaslow and N. B. Sommer, *J. Am. Chem. Soc.*, **68**, 644 (1946); *Org. Syntheses*, **Coll. Vol. III**, 10 (1955).

1.8 g. of aniline hydrochloride and 0.6 g. of *sym*-diphenylurea, which is equivalent to 0.3 g. of phosgene (0.003 mole), were obtained. One and one-half grams of a mixture of phenyl isocyanate and benzonitrile was obtained by distillation (b.p., 50–74°/18 mm.), from which 0.4 g. of *sym*-diphenylurea was precipitated by addition of aniline (equivalent to 0.2 g. (9%) of phenyl isocyanate).

Acknowledgment. The authors wish to express their hearty thanks to Mr. Asaji Kondo for the microanalyses and to Dainippon Celluloid Co. Ltd. for the gift of ketene dimer.

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O-Alkyl- and Aryl-*N*,*N*-ethyleneurethans. II. Reaction with Thiophenol, Acids, and Phenols

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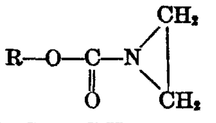
Received February 2, 1961

Reactions of *O*-alkyl- and aryl-*N*,*N*-ethyleneurethans with several nucleophilic reagents were investigated. *O*-Alkyl- and aryl-*N*,*N*-ethyleneurethans reacted with thiophenol or benzoic acid to give the addition products: *O*-alkyl- and aryl-*N*-(β-substituted ethyl)urethans. When a small amount of triethylamine and water was present in these reactions, *O*-aryl-*N*,*N*-ethyleneurethans gave *N*,*N'*-bis(β-substituted ethyl)ureas along with urethans. This urea formation was explained as proceeded *via* *O*-aryl-*N*-(β-substituted ethyl)urethans.

Ethylenimines are known to react with several nucleophilic reagents such as thiophenol,[1] phenols,[2] and acids[3] to give β-substituted ethylamines. We extended these studies to *N*-substituted ethylenimines such as *N*-alkoxycarbonyl and *N*-aryloxycarbonyl (I).


(I)

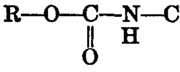
Ia. R = C_2H_5
b. R = n-C_4H_9
c. R = cyclohexyl
d. R = C_6H_5
e. R = p-$CH_3C_6H_4$
f. R = p-$C_2H_5OC_6H_4$
g. R = p-ClC_6H_4
h. R = p-$CH_3COC_6H_4$
i. R = p-$NO_2C_6H_4$

Thiophenol reacted with all these ethylenimino compounds at room temperature to give the addition products (Table I) in less than a day with good yields. Benzoic acid also reacted with these derivatives, but prolonged standing was required to give the products (Table II) at room temperature. Phenol, on the other hand, was found to be much less reactive. *O*-Cyclohexyl-*N*,*N*-ethyleneurethan (Ic) and phenol did not react after standing for a year at room temperature without a solvent, or by heating at 100° in excess phenol for four hours.

In the presence of a small quantity of water, thiophenol and crude *O*-phenyl-*N*,*N*-ethyleneurethan (Id) gave *N*,*N'*-bis(β-phenylthioethyl)urea in addition to *O*-phenyl-*N*-(β-phenylthioethyl)urethan. Reaction of Id with other nucleophilic reagents in the presence of water gave more complicated results. Benzoic acid and *p*-nitrobenzoic acid reacted with Id to give *N*,*N'*-bis(β-substituted ethyl)ureas along with *O*-phenyl-*N*-(β-substituted ethyl)urethans, while hydrochloric acid and picric acid gave only *O*-phenyl-*N*-(β-substituted ethyl)-

TABLE I

O-ALKYL- and ARYL-*N*-(β-PHENYLTHIOETHYL)URETHANS


$$R{-}O{-}\underset{\underset{O}{\|}}{C}{-}\underset{H}{N}{-}CH_2CH_2{-}SC_6H_5$$

R	M.P.	Formula	Nitrogen, %	
			Calcd.	Found
Ethyl	41–42.5	$C_{11}H_{15}NO_2S$	6.22	6.45
n-Butyl	49–50	$C_{13}H_{19}NO_2S$	5.61	5.68
Cyclohexyl	58–59	$C_{15}H_{21}NO_2S$	5.01	5.25
Phenyl	56–58	$C_{15}H_{15}NO_2S$	5.12	5.18
p-Tolyl	66–68	$C_{16}H_{17}NO_2S$	4.88	5.07
p-Ethoxyphenyl	83.5–84.5	$C_{17}H_{19}NO_3S$	4.41	4.18
p-Chlorophenyl	83–84	$C_{15}H_{14}ClNO_2S$	4.55	4.72
p-Acetophenyl	80–81	$C_{17}H_{17}NO_3S$	4.44	4.60
p-Nitrophenyl	85–87	$C_{15}H_{14}N_2O_4S$	8.80	8.68

TABLE II

O-ALKYL- AND ARYL-*N*-(β-BENZOYLOXYETHYL)URETHANS


$$R{-}O{-}\underset{\underset{O}{\|}}{C}{-}\underset{H}{N}{-}CH_2CH_2{-}O{-}\underset{\underset{O}{\|}}{C}{-}C_6H_5$$

R	M.P.	Yield, %	Formula	Nitrogen, %	
				Calcd.	Found
Ethyl	83–85	46[a]	$C_{12}H_{15}NO_4$	5.90	6.20
n-Butyl	50–51	50[a]	$C_{14}H_{19}NO_4$	5.28	5.40
Cyclohexyl	117–119	70[a]	$C_{16}H_{21}NO_4$	4.81	4.97
Phenyl	116–117	30[b]	$C_{16}H_{15}NO_4$	4.91	5.13

[a] After standing for about a year at room temperature and without a solvent. [b] After standing for 5 days at room temperature and without a solvent.

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[1] G. Meguerian and L. B. Clapp, *J. Am. Chem. Soc.*, 73, 2121 (1951).

[2] L. B. Clapp, *J. Am. Chem. Soc.*, 73, 2584 (1951).

[3] S. Gabriel and R. Stelzner, *Ber.*, 21, 1053 (1888).