and reversibly in ketonic solutions of secondary amines[12] and readily react with nitro olefins.[13] In addition, careful hydrolysis of isolated **3a** yields **2a**.

Experimental Section

Pmr spectra were determined on a Varian A-60 instrument. Chemical shifts are relative to internal TMS. Visible and infrared spectra were measured on Cary-14 and Perkin-Elmer 21 spectrophotometers, respectively. Elemental analyses were performed by G. I. Robertson, Jr., Florham Park, N. J. 07932. All melting points are uncorrected.

Enamine of Diethylamine and Diethyl Ketone (5).—This enamine was prepared by the method of White and Weingarten[14] and was purified by distillation on a spinning-band column at reduced pressure: bp 64° (10 mm); ir 1636 cm^{-1} (NC=C); pmr ($CDCl_3$) δ 4.20 (q, 1, J = 7 Hz, NC=CH, cis). The pmr spectrum of the crude oil prior to distillation showed an additional quartet at δ 5.06 (J = 7 Hz) assigned to NC=CH, trans.

Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.80; H, 13.50; N, 10.20.

Enamine of Piperidine and Diethyl Ketone (6).—The enamine was prepared by the method of Stork and coworkers[12] and was purified as described for **8**: bp 80° (10 mm); ir 1640 cm^{-1} (NC=C); pmr ($CDCl_3$) δ 4.39 (q, 1, J = 7 Hz, NC=CH, cis). The pmr spectrum of the crude oil prior to distillation showed an additional quartet at δ 4.70 (J = 7 Hz) assigned to NC=CH, trans.

Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.51; H, 12.60; N, 9.16.

Diethylammonium and Piperidinium Anions (2a and 2b).—TNB (5.45 g), diethylamine (5.56 g), and diethyl ketone (6.55 g) were dissolved in dry DMSO (5 ml). The resulting dark oil was stirred for 24 hr at room temperature. Dry ether (500 ml) was then added and the mixture was stirred for 2 hr. The brown precipitate which formed was filtered and washed with copious amounts of dry ether. Recrystallization of this crude product from an 80:20 mixture of ether–methanol yielded red crystals of pure **2a** (0.5 g): mp 175°; vis max (CH_3OH) 508 nm (ϵ 29,500); ir (KBr) 1715 cm^{-1} (C=O); pmr (DMSO-d_6) δ 8.5 (s, H^{δ}), 5.7 (t, J = 3 Hz, H^{α}), 4.6 (broad, 2 H^{γ}), 3.0 (q, 4, J = 7 Hz, $(CH_3CH_2)_2NH_2^+$), ~2.9 (2 H^{β}, under $Et_2NH_2^+$), 1.2 (t, 6, J = 7 Hz, $(CH_3CH_2)_2NH_2^+$), 0.9 (d, 6, J = 7 Hz, R′ = R″ = CH_3).

Anal. Calcd for $C_{15}H_{24}N_4O_7$: C, 48.38; H, 6.50; N, 15.05. Found: C, 48.10; H, 6.49; N, 14.88.

Red crystals of **2b** (0.6 g) were prepared with piperidine in a similar manner: mp 161–163°; vis max (CH_3OH) 508 nm (ϵ 26,200); ir (KBr) 1710 cm^{-1} (C=O); pmr (DMSO-d_6) δ 8.4 (s, H^{δ}), 5.8 (t, J = 3 Hz, H^{α}), 4.5 (broad, 2 H^{γ}), 1.6–3.0 (m, 10, $(CH_2)_5NH^+$), ~2.8 (2 H^{β}, under $(CH_2)_5NH^+$), 0.9 (d, 6, J = 7 Hz, R′ = R″ = CH_3).

Anal. Calcd for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 49.37; H, 6.38; N, 13.86.

Diethylimmonium and Piperidinium Zwitterions (3a and 3b).—The enamine (**5** or **6**) was added to a solution of TNB (1.0 g) in anhydrous ether (50 ml) under a dry nitrogen atmosphere. An immediate red coloration was observed which intensified with time. After 24 hr at 35°, a dark red oil separated from the solution. This was transferred to 100 ml of an 80:20 ether–methanol solution. The mixture was stirred for 1 hr during which time the oil was transformed into a finely divided red solid. Recrystallization of this material from ether–methanol solution yielded red needles of **3**.

For **3a** (0.3 g): mp 195° dec; vis max (CH_3OH) 505 nm (ϵ 26,700); ir (KBr) 1637 cm^{-1} ($C=N^+$); pmr (DMSO-d_6) δ 8.3 (s, H^{δ}), 6.1 (t, J = 3 Hz, H^{α}), 4.2 (broad, 2 H^{γ}), 3.9 (q, 4, J = 7 Hz, $(CH_3CH_2)\overset{+}{N}_2{=}C$), ~2.6 (2 H^{β}, under DMSO-d_5), 1.6 (d, 6, R′ = R″ = CH_3), 1.2 (t, 6, J = 7 Hz, $(CH_3CH_2)_2\overset{+}{N}{=}C$).

Anal. Calcd for $C_{15}H_{22}N_4O_6$: C, 50.84; H, 6.26; N, 15.81. Found: C, 50.86; H, 6.27; N, 15.62.

For **3b** (0.5 g): mp 210° dec; vis max (CH_3OH) 505 nm (ϵ 23,800); ir (KBr) 1623 cm^{-1} ($C=N^+$); pmr (DMSO-d_6) δ 8.3 (s, H^{δ}), 6.0 (t, J = 3 Hz, H^{α}), 4.1 (broad, 2 H^{γ}), 1.7–3.2 (m, 10, $(CH_2)_5\overset{+}{N}{=}C$), ~2.6 (2 H^{β}, under DMSO-d_5), 1.3 (d, 6, R′ = R″ = CH_3).

Anal. Calcd for $C_{16}H_{22}N_4O_6$: C, 52.45; H, 6.05; N, 15.29. Found: C, 52.70; H, 6.26; N, 15.01.

Hydrolysis of 3a.—A solution of **3a** (0.1 g), H_2O (~0.25 ml), and DMSO (5 ml) was stirred at room temperature. Aliquots (1 ml) were taken at intervals of several hours and quenched in 5 ml of ether. Quenching yielded an orange powder which was filtered and dried to remove traces of moisture and diethyl ketone. Infrared spectra of these samples showed them to be a mixture of **2a** and **3a**, the amount of the former increasing as the hydrolysis time increased. After 12 hr at 45°, conversion to **2a** was complete.

Registry No.—**2a**, 27331-99-3; **2b**, 27332-00-9; **3a**, 27332-01-0; **3b**, 27332-02-1; *cis*-**5**, 27332-03-2; *trans*-**5**, 27332-04-3; *cis*-**6**, 27332-05-4; *trans*-**6**, 27384-95-8.

Acknowledgments.—This research was supported by the Army Research Office at Durham, Grant No. DAHCO4 69 C 0064, and the Research Corporation.

(12) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrill, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(13) M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).
(14) W. A. White and H. Weingarten, *ibid.*, **32**, 213 (1967).

Carbamoyl Chloride Formation from Chloramine and Carbon Monoxide

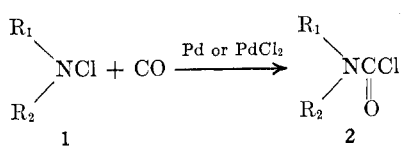
TAKEO SAEGUSA,* TETSUO TSUDA, AND YO ISEGAWA

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

Received March 13, 1970

The formation of acid halide from alkyl halide and carbon monoxide in the presence of a group VIII metal compound is well known.[1] The product is described as being derived by the insertion of carbon monoxide into the carbon–halogen bond. As to the insertion of carbon monoxide into the heteroatom–halogen bond, the reaction of sulfenyl chloride with carbon monoxide has been reported recently[2] in which the carbonyl group is inserted into the sulfur–chlorine bond in the absence of any added catalyst. The present report is concerned with the insertion of carbon monoxide into the nitrogen–chlorine bond.

The reaction of chloramine (**1**) with carbon monoxide is effectively catalyzed by palladium metal or palladium chloride to produce carbamoyl chloride (**2**). The reaction proceeds fairly smoothly under milder reaction conditions. Table I summarizes the results of the carbonylation of *N*-chlorodimethylamine. The yield of **2a** (R_1 = R_2 = CH_3) depends on the reaction temperature, the nature of solvent, the amount of catalyst, and the carbon monoxide pressure. Here a trace amount of tetramethylurea was detected as the sole by-product. When the reaction temperature was higher than 50°, the yield of dimethylcarbamoyl chloride decreased and



1 2

(1) C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Logos Press and Academic Press, New York, N. Y., 1967, p 149.
(2) W. A. Thaler, *Chem. Commun.*, 527 (1968).

TABLE I

CARBONYLATION OF *N*-CHLORODIMETHYLAMINE[a]

$(CH_3)_2NCl$, mmol	Catalyst, g-atom	Solvent, ml	CO, kg/cm²	$(CH_3)_2NCOCl$, %[b]
10	Pd, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	70[c]	85
10	Pd, 0.1	$CH_3OCH_2CH_2OCH_3$, 5	65[c]	36
10	Pd, 0.1	$CH_3OCH_2CH_2OCH_3$, 5	70	99
5	Pd, 0.5	$CH_3OCH_2CH_2OCH_3$, 2.5	5	8
10	Pd, 0.1	C_6H_6, 5	60	71
10	Pd, 0.1	CH_3CN, 5	60	44
10	Pd, 0.1	*n*-C_6H_{14}, 5	60	19
10	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	70[c]	42

[a] The reaction was carried out in a stainless steel pressure tube at 50° for 20 hr without stirring and shaking. [b] The yield of *N*,*N*-dimethylcarbamoyl chloride was based on the chloramine added. [c] The reaction was carried out at room temperature.

TABLE II

CARBONYLATION OF OTHER DIALKYLCHLORAMINES[a]

R_2NCl, 10 mmol	Catalyst, mmol	Solvent, ml	R_2NCOCl, %[b]
$(C_2H_5)_2NCl$	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	$(C_2H_5)_2NCOCl$, 66
$(C_2H_5)_2NCl$	$RhCl_3$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	$(C_2H_5)_2NCOCl$, 21
	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	 53
 [c]	$PdCl_2$, 0.5	C_6H_6, 4	 80
	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	 45
$C_6H_5CH_2N(CH_3)Cl$	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	$C_6H_5CH_2N(CH_3)COCl$, 15
$C_6H_5CH_2N(CH_3)Cl$[c]	$PdCl_2$, 0.5	$CH_3C_6H_5$, 7	$C_6H_5CH_2N(CH_3)COCl$, 35

[a] The reactions except where noted were carried out for 20 hr at room temperature under the carbon monoxide pressure of 50 kg/cm². [b] The yield of carbamoyl chloride is based on the chloramine added. [c] The reaction was carried out in a glass tube which was put in a stainless steel tube.

the yield of the tetramethylurea by-product increased to several per cents. Using 1,2-dimethoxyethane as solvent at 150°, product **2a** reacted with the solvent to yield β-methoxyethyl-*N*,*N*-dimethylcarbamate. When pyridine was used as a solvent instead of 1,2-dimethoxyethane, the reaction did not take place and *N*-chloramine was recovered nearly quantitatively.

The carbonylation of other dialkylchloramines also proceeded using palladium chloride or rhodium trichloride as catalysts (Table II). The yields of the carbonylation products of *N*-chloropiperidine, *N*-chloromorphine, and *N*-chloro-*N*-methylbenzylamine were estimated from the amount of the corresponding urethanes derived from the carbamoyl chloride products by treatment with ethanol in the presence of triethylamine. In all cases of Table II, the ir spectra of the reaction mixtures displayed an absorption at 1735 cm^{-1} characteristic of a carbonyl group, indicating that carbonylation took place. The occurrance of carbonylation was thus indicated. The carbamoyl chloride resulting from the carbonylation of *N*-chloropiperidine could be isolated by distillation. When the reaction was carried out in a glass tube surrounded by a stainless steel tube (as indicated by footnote *c* in Table II), the yields of the carbamoyl chlorides were improved. Otherwise, the stainless steel wall of the reaction tube may catalyze the decomposition of the chloramine or the carbamoyl chloride product.

The carbonylation reaction can also be applied to monoalkylchloramine. Since *N*-methylcarbamoyl chloride and *N*-ethylcarbamoyl chloride which are formed in the reaction are unstable when subjected to glpc analysis (*e.g.*, *N*-methylcarbamoyl chloride decomposes to methyl isocyanate and hydrogen chloride at 90°), the carbonylated products were converted to methyl *N*-methylcarbamate and methyl *N*-ethylcarbamate, respectively, by treatment of the reaction mixture with methanol (Table III).

TABLE III

CARBONYLATION OF MONOALKYLCHLORAMINES

RNHCl, mmol	Catalyst, mmol	Solvent	Carbonylated product, % yield[a]
CH_3NHCl,[b] 5	Pd, 0.05	$(n\text{-}C_4H_9)_2O$	30
C_2H_5NHCl,[c] 10	$PdCl_2$, 1.0	$(C_2H_5)_2O$	22

[a] The yield of product was based on the chloramine added. [b] The reaction proceeded at 50° for 20 hr under the carbon monoxide pressure of 60 kg/cm². [c] The reaction proceeded at room temperature for 20 hr under the carbon monoxide pressure of 50 kg/cm².

The carbamoyl chloride formation from chloramine and carbon monoxide does not proceed in the absence of palladium metal, palladium chloride, or rhodium trichloride catalyst. Metallic copper, silver, and nickel as well as potassium chloroplatinate were not effective at least under reaction conditions of the present study.

Experimental Section

Materials.—Unless otherwise indicated, the reagents and authentic samples were obtained commercially. 1,2-Dimethoxyethane, benzene, *n*-hexane, di-*n*-butyl ether, and diethyl ether were dried by refluxing over sodium wire and distilled. Pyridine was dried over calcium hydride and distilled. Acetonitrile was dried over phosphorus pentoxide and distilled. The carbon monoxide cylinder was a commercial one.

Preparation of *N*-Haloalkylamines.—*N*-Chloramines were prepared according to the procedures given by Coleman.[3] *N*-Chlorodimethylamine (bp 46°), *N*-chlorodiethylamine [bp 41°

(3) G. H. Coleman and C. R. Hauser, *J. Amer. Chem. Soc.*, **50**, 1193 (1928); G. H. Coleman, *ibid.*, **55**, 3001 (1933).

(95 mm)], *N*-chloropiperidine [bp 54.5–55° (35 mm)], and *N*-chloromorphorine [bp 47° (17 mm)] were isolated by fractional distillation. *N*-Chloro-*N*-methylbenzylamine was prepared from *N*-methylbenzylamine–HCl and sodium hypochlorite in an aqueous medium. The oily layer which was separated from the reaction mixture was dried over calcium chloride and subjected to the carbonylation reaction without purification by distillation. *N*-Chloromonoalkylamines were prepared from the monoalkylamine–HCl and sodium hypochlorite in the presence of ether. The ether layer was dried over calcium chloride and was subjected directly to the carbonylation reaction.

Carbonylations of Dialkylchloramines (Tables I and II).—A typical procedure is as follows. In a 50-ml stainless steel tube, palladium metal (commercial palladium metal was used directly), 0.0106 g (0.1 g-atom), *N*-chlorodimethylamine (10 mmol), and solvent (1,2-dimethoxyethane was usually employed) (5 ml) were placed and then carbon monoxide was compressed. The tube was closed and was heated at a desired temperature for about 20 hr. Then carbon monoxide was purged off and the reaction mixture was subjected to glpc analysis (a column packed with silicon on Celite was used). The products were identified by comparison of the glpc retention time and ir spectrum with the authentic *N*,*N*-dimethylcarbamoyl chloride. In the cases of *N*-chloropiperidine, *N*-chloromorphorine, and *N*-chloro-*N*-methylbenzylamine, the yields of the products were determined by the glpc analysis of the corresponding urethanes which were formed by treatment of the reaction mixture with excess ethanol in the presence of triethylamine.

Carbonylations of Monoalkylchloramines (Table III).—The following example illustrates the procedure used in the carbonylations of monoalkylchloramines. In a 50-ml stainless steel tube, palladium metal, 0.0053 g (0.05 g-atom), and *N*-chloromethylamine ether solution (5 mmol) were placed, and then carbon monoxide was compressed up to 60 kg/cm² at −78°. The tube was closed and was heated at 50° for 20 hr. The carbon monoxide was purged off, and excess methanol and triethylamine were added to the reaction mixture. The product was identified and its yield was estimated by the form of methyl *N*-methylcarbamate by glpc.

Registry No.—**1** ($R_1 = R_2 = H$), 10599-90-3; **1** ($R_1 = R_2 = CH_3$), 1585-74-6; **2** ($R_1 = R_2 = H$), 463-72-9; carbon monoxide, 630-08-0.

A Convenient Synthesis of Pteroic Acid[1]

LAURENCE T. PLANTE

Department of Biology, University of California at San Diego, La Jolla, California 92037

Received August 5, 1970

Previous syntheses of pteroic acid[2-10] result in preparations that are contaminated with simple pteridines, presenting a formidable problem of purification. The reductive condensation of 2-acetylamino-4-hydroxy-6-formylpteridine with *p*-aminobenzoic acid or with ethyl *p*-aminobenzoate by formic acid or aryl thiols[11] was found to be unsatisfactory, giving variable yields of pteroic acid containing large amounts of pteridine impurities. The present note describes an improved version of the latter synthesis in which pteroic acid is obtained free of contaminating pteridines, thus avoiding the problem of purification.

Ethyl *p*-aminobenzoate and 2-acetylamino-4-hydroxy-6-formylpteridine in glacial acetic acid afforded the corresponding Schiff's base, which without isolation was reduced to ethyl N^2-acetylpteroate by dimethylamine borane, a procedure introduced by Billman and McDowell[12] for the reduction of aromatic Schiff's bases. Saponification of the ethyl ester of N^2-acetylpteroic acid so obtained gave pure pteroic acid which traveled as a single spot on paper chromatography and was free of all fluorescent pteridines. Conversion of this pteroic acid to dihydrofolic and tetrahydrofolic acids gave compounds that showed full enzymatic activity with dihydrofolate reductase of the L 1210 murine leukemia and with thymidylate synthetase of *E Coli*.

Dimethylamine borane appears to be the reagent of choice for the reduction of this Schiff's base. The complete reduction of the 9,10 double bond before reaction at the 5,6 or 7,8 positions is noteworthy. Continued reduction with more amine borane gives dihydro- and tetrahydropteroates. Under these conditions, the acetylpteridine aldehyde alone is reduced in the pyrazine ring before reaction at the carbonyl group takes place.

Experimental Section[13]

Glacial acetic acid (5 ml) was added to a mixture of 330 mg (2 mmol) of ethyl *p*-aminobenzoate and 307 mg (1 mmol) of 2-acetylamino-4-hydroxy-6-formylpteridine dimethylformamide monosolvate.[14] The mixture was stirred briefly. Then a solution of 100 mg of dimethylamine borane in 1.5 ml of glacial acetic acid was added. The suspension turned bright yellow. Stirring was continued at ambient temperature for 20 min. The suspension was warmed to 60° for 10 min and cooled to 25°. The solid was filtered and washed with 5 ml of glacial acetic acid, then with 10 ml of anhydrous ether. The solid was dried at ambient temperature in the dark to give 384 mg (100%) of pale yellow ethyl N^2-acetylpteroate. The solid was dissolved in 5 ml of hot (100°) dimethylformamide and cooled to 30°. Then 2 ml of anhydrous ether was added with stirring to give a homogeneous solution. After standing at ambient temperature, ethyl N^2-acetylpteroate began to crystallize. The flask was stored in a freezer (−35°) overnight. The solid was filtered, washed with anhydrous ether, and dried. This procedure gave 322 mg (84%) of the ethyl ester. The nmr spectrum in deuterated trifluoroacetic acid showed a triplet at δ 0.97 (3 H, J = 7 cps, ester CH_3), singlet at 2.0 (3 H, acetyl CH_3), quartet at 4.07 (2 H, J = 7 cps, ester CH_2), singlet at 4.84 (2 H, bridge CH_2), doublet at 7.35 (2 H, J = 9 cps, benzene CH), doublet at 7.88 (2 H, J = 9 cps, benzene CH), and a singlet at 8.67 (1 H, pteridine CH).

Anal. Calcd for $C_{18}H_{18}N_6O_4$: C, 56.53; H, 4.74; N, 21.98. Found: C, 56.5; H, 5.0; N, 21.8.

The solid ester was saponified with 50 ml of 0.10 *N* sodium hydroxide solution at 100° (under N_2) for 0.5 hr while protected

(1) This work was supported by U. S. Public Health Serivce Grant No. CA 11449.

(2) C. W. Waller, B. L. Hutchings, J. H. Mowat, E. L. R. Stokstad, J. H. Boothe, R. B. Angier, J. Semb, Y. SubbaRow, D. S. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, J. P. Sickels, and J. M. Smith, Jr., *J. Amer. Chem. Soc.*, **70**, 19 (1948).

(3) M. E. Hultquist, E. Kuh, D. B. Cosulich, M. J. Fahrenbach, E. H. Northey, D. R. Seeger, J. P. Sickels, J. M. Smith, Jr., R. B. Angier, J. H. Boothe, B. L. Hutchings, J. H. Mowat, J. Semb, E. L. R. Stokstad, Y. SubbaRow, and C. W. Waller, *ibid.*, **70**, 23 (1948).

(4) F. E. King and P. C. Spensley, *Nature*, **164**, 574 (1949).

(5) H. S. Forrest and J. Walker, *J. Chem. Soc.*, 2002 (1949).

(6) F. Weygand and V. Schmied-Kowarzik, *Chem. Ber.*, **82**, 333 (1949).

(7) F. E. King and P. C. Spensley, *J. Chem. Soc.*, **2**, 144 (1952).

(8) D. I. Weisblat, B. J. Magerlein, A. R. Hanze, D. R. Myers, and S. T. Rolfson, *J. Amer. Chem. Soc.*, **75**, 3625 (1953).

(9) D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. J. Fairburn, and S. T. Rolfson, *ibid.*, **75**, 5893 (1953).

(10) F. Weygand and H. Bestman, *Chem. Ber.*, **88**, 1992 (1955).

(11) M. Sletzinger and M. Tishler, U. S. Patent 2816109 (1957).

(12) J. H. Billman and J. W. McDowell, *J. Org. Chem.*, **26**, 1437 (1961).

(13) Microanalyses were performed by Dr. C. K. Fitz, Needham Heights, Mass. Paper chromatography was on Whatman No. 1 paper, ascending. Pteroic acid was observed as a spot that quenches ultraviolet light. Nmr spectra were taken on the Varian T-60 with tetramethylsilane as external standard.

(14) M. Sletzinger, D. Reinhold, J. Grier, M. Beachem, and M. Tishler, *J. Amer. Chem. Soc.*, **77**, 6365 (1955). The nmr spectrum of the acetylpteridine aldehyde revealed that it crystallized as a monosolvate from dimethylformamide.