Acid-Catalyzed Reactions of Ethyl Cyanoformate with Aromatic Amines in Acetic Acid: Facile Synthesis of N-Substituted Amidinoformic Acids and Ethyl 4-Quinazolone-2-carboxylate

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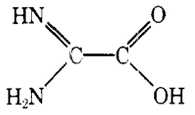
N-Substituted amidinoformic acids were synthesized by three different methods (via thiooxamic acid, ethyl 1-carbethoxyformimidate, and 1-carbethoxyformimidoyl chloride, respectively). The last one was found to be the simplest. 1-Carbethoxyformimidoyl chloride was formed in situ in the presence of amines, but could not be isolated due to its instability. Thus, ethyl cyanoformate was treated with arylamines in the presence of hydrogen chloride to give N-substituted ethyl amidinoformates in acetic acid. The effect of the amount of hydrogen chloride was striking and only a catalytically excess amount of hydrogen chloride was necessary. N-Substituted ethyl amidinoformate was not isolated and was directly hydrolyzed to give N-substituted amidinoformic acid. Sterically crowded amines (2,6-dialkylanilines) reacted with ethyl 1-carbethoxyformimidate to give N-substituted amidinoformic acids, but did not react with the imidoyl chloride. When the N-monosubstituted derivatives contained a carbethoxy group on the ortho position of the arylamino moiety, intramolecular cyclization occurred to give ethyl 4-quinazolone-2-carboxylate.

Amidinoformic acid (**1**) has a unique structure with three different functional groups (amino, imino, and carboxyl) on the same carbon atom and was firstly recognized in 1965 as a partial structure of antibiotic, Kasugamycin,[1] which has been used as a fungicide against Rice Blast. Amidinoformic acid (**1**) is a kind of α-amino acid, and N-substituted derivatives[2] of **1** show interesting biological activities.[3] With all this potential usefulness, synthesis of these derivatives was rather difficult. Well-known Pinner amidine synthesis[4] does not work very well on ethyl cyanoformate.[5] Thus far at least two preparative methods were reported (via diethyl oxalimidate[6] (**2**) and thiooxamic acid[2,7] (**3**)). These methods, however, do not always afford N-substituted derivatives of **1** in useful yields.

From the viewpoint that as well as **2** and **3**, ethyl 1-carbethoxyformimidate (**4**) and 1-carbethoxyformimidoyl chloride (**5**) are the same sp^2 carbon analogues which can be derived readily from ethyl cyanoformate, we intended to use the formate for the synthesis of N-substituted derivatives of **1**. We have found that reactions of **5** are the most useful ones,



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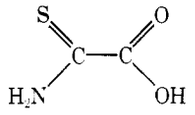

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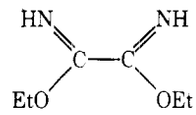

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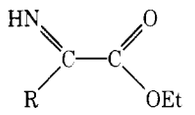

4, R = OEt
5, R = Cl

and show that this synthesis opens a general route to a series of ethyl 4-quinazolone-2-carboxylates (**7**).

Imidoyl chloride (**5**) derived from ethyl cyanoformate could not be isolated in our hands because of its instability.[8] However, we found that N-substituted derivatives of **1** could be obtained in reasonable yield in anhydrous acetic acid at 90 °C by the reaction of amines with ethyl cyanoformate in the presence of hydrogen chloride (Table I, method C). Method B via **4** gave N,N′-disubstituted oxamides as byproducts, because **4** has two reactive carbon atoms which cannot be differentially attacked by arylamines.

The yield of N-substituted derivatives of **1** was strikingly influenced by the amounts of hydrogen chloride added. N-Substituted amidinoformic acid was only poorly detected when the amount of hydrogen chloride used was equal to or less than that of the amine. However, addition of a small excess of hydrogen chloride to this reaction mixture gave N-substituted derivatives of **1** in reasonable yield. The presence of a large excess of hydrogen chloride (more than ca. 20% excess to that of amine) retarded the reaction.

From the product analysis, side reactions such as the reaction between imidoyl chloride and acetic acid and the oligomerization of ethyl cyanoformate were not significant. Thus, ethyl oxamidate and acetyl chloride (accordingly, acetanilide derivatives in the presence of arylamines) were not obtained (Former case). Amidinoformic acid was obtained in method C in a small amount (latter case: triazine (**6**) gave **1** by alkaline hydrolysis followed by acidification). Therefore, the low concentration of ethyl cyanoformate was very important in this reaction to avoid its trimerization to 2,4,6-tricarbethoxy-1,3,5-triazine (**6**).[9] A possible reaction pathway can be summarized as shown in Scheme I.

This simple procedure to prepare N-substituted amidinoformic acid makes it possible to get quinazoline derivatives by intramolecular cyclization. Thus, when a mixture of ethyl cyanoformate and ethyl *o*-aminobenzoate was heated in the presence of hydrogen chloride, we obtained ethyl 4-quinazolone-2-carboxylate (**7**).[10] However, when a mixture of ethyl cyanoformate and *o*-isopropenylaniline was heated under the same conditions as in method C, neither 2-carbethoxy-3,4-dihydro-4,4-dimethylquinazoline (**8**) nor *N*-(*o*-isopropenylphenyl)amidinoformic acid was obtained (Scheme II).

This method could not be applied to several amines such

Scheme I

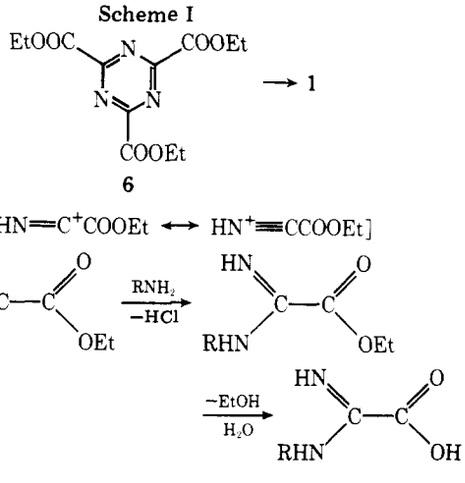

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Table I. Preparation of N-Substituted Amidinoformic Acids by Three Different Methods

R	registry no.	yield, % method A[b]	yield, % method B[c]	yield, % method C[d]	mp, °C[a]
m-chloro-phenyl	67662-58-2	15.1		40.8	*e* (145)
6-chloro-*o*-tolyl	67662-59-3	15.1		55.0	146 (161)
2,3-xylyl	67662-60-6	13.6		40.6	132 (151)
3,4-xylyl	67662-61-7	27.0		68.0	131 (153)
4-chloro-*o*-tolyl	67662-62-8	32.2	0[f]	53.7	141 (154)
2,4-xylyl	39894-65-0	34.4	0[f]		131 (150)
2,5-xylyl	67662-63-9	22.1	0.8[f]		135 (149)
2,6-diethyl-phenyl	67662-64-0		5.5	0	139 (153)
p-tolyl	34669-89-1		8.0	43.0	*e* (151)
2,6-xylyl	67662-65-1		12.5	0	149 (166)
o-bi-phenylyl	67662-66-2			56.0	141 (155)
4-diethyl-amino-2-methyl-phenyl	67662-67-3			62.6	134 (153)
o-methoxy-phenyl	67662-68-4			41.7	129 (150)

[a] Melting points were observed at ca. 1 °C/30 min warming rate in the temperature range within ca. 5 °C from melting points, and mp at ca. 1 °C/15 s warming rate were in parentheses. [b] Via arylammonium thiooxamate. [c] Via 1-carbethoxyformimidoyl chloride. [d] Via ethyl cyanoformate. [e] Observation of mp was difficult due to decarboxylation. [f] N,N'-Disubstituted oxamides were isolated as byproducts. The yields based on ethyl cyanoformate and mp were: R = 2,5-xylyl, 13.2%, 227–228 °C (lit.[13] 228–229 °C); R = 2,4-xylyl, 3.54%, 210–211 °C (lit.[13] 215–216 °C); R = 4-chloro-*o*-tolyl, 0.04%, 255–256 °C, respectively.

as alkylamines[11] and o,o'-disubstituted anilines (Table I). These o,o'-disubstituted aniline derivatives of amidinoformic acid were obtained in higher yield than the other derivatives in method B.

We found that addition of sodium perchlorate (or sodium borofluoride) increased the yield of N-substituted derivatives of 1 and that the reaction was retarded in the presence of sodium chloride (see Experimental Section). The detailed discussion of the reaction mechanism, however, is beyond our present work and must await further study.

Experimental Section

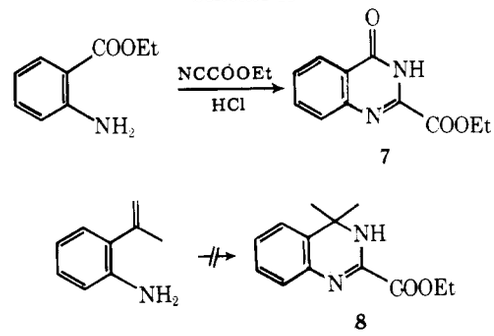
Potassium thiooxamate and ethyl 1-carbethoxyformimidate were prepared according to the methods reported in the literatures.[4b,12] All aromatic amines were commercially available and were used without further purification. Acetic acid was obtained from Wako Pure Chemical Industries (Water Content: Max. 0.3%, Super Special Grade). Infrared spectra were recorded as KBr tablets on a Hitachi 295 infrared spectrophotometer. Elemental analysis was performed by Mr. Hosogane and his associates of Showa Denko Co., Ltd. Melting points were not corrected.

General Procedure for the Preparation of N-Substituted Amidinoformic Acids. Yields, mp, IR, and elemental analyses of *N*-arylamidinoformic acids obtained in methods A, B, and C are shown in Table I.

***N*-(2,4-Xylyl)amidinoformic Acid (Method A: via Arylammonium Thiooxamate).** 2,4-Xylidinium thiooxamate (11.3 g; 0.05 mol; mp 122 °C; 2400–3400, 1480–1680, 1365, 800 cm^{-1}) and basic lead carbonate (39 g, 0.05 mol) were suspended in methanol (200 mL) and the mixture was stirred for 16 h at room temperature. The black precipitates thus obtained were filtered off and the filtrate was concentrated under reduced pressure to give white crystals. The crystals were recrystallized from ethanol. The white fine crystals obtained were 3.3 g (34.4%).

***N*-(2,5-Xylyl)amidinoformic Acid (Method B: via Ethyl 1-Carbethoxyformimidate).** A mixture of ethyl 1-carbethoxyformimidate (4.8 g, 0.033 mol) and 2,5-xylidine (4.0 g, 0.033 mol) was heated for 5 h at 100 °C in an oil bath. The reaction mixture was treated with 6 N hydrochloric acid at 100 °C for 2 h and was allowed to stand at room temperature to give yellowish crystals. The crystals were washed with acetone to give white fine crystals (1.3 g). The crystals were identified as *N,N'*-di(2,5-xylyl)oxamide by elemental analysis, mp, and IR. The aqueous layer was concentrated by evaporation and neutralized with potassium carbonate. After washing with hexane, the solution was evaporated to dryness. Then the powder was extracted with hot ethanol. From ethanol extracts, *N*-(2,5-xylyl)amidinoformic acid was crystallized. The white crystalline powder obtained was 0.05 g (0.8%).

Scheme II



***N*-(*p*-Tolyl)amidinoformic Acid (Method C: via Ethyl Cyanoformate).** Ethyl cyanoformate (3.96 g, 0.04 mol), *p*-toluidine hydrochloride (5.74 g, 0.04 mol), and 1.1 mL of acetic acid solution containing hydrogen chloride (0.0025 mol) were added to acetic acid (40 mL). The mixture was heated on an oil bath and allowed to stand at 90 °C for 2 h with occasional shaking until *p*-toluidine hydrochloride was dissolved. After addition of 6 N hydrochloric acid (40 mL), the reaction mixture was heated at 90 °C for 1.5 h. The solution was evaporated and the solid obtained was dissolved into a mixture of water (70 mL) and benzene (20 mL). The mixture was neutralized with potassium carbonate to give white powder (3.07 g, 43.0%). White cubic crystals were obtained by recrystallization from methanol: IR 3330, 3170, 1660, 1370 cm^{-1}.

2,4,6-Tricarbethoxy-1,3,5-triazine (6). A catalytic amount of dried hydrogen chloride was passed into ethyl cyanoformate (99.1 g, 1 mol) at an ice-cold temperature. This solution was allowed to stand for 4 days at room temperature to give white cyrstals. The crystals were filtered and washed with ethyl acetate (2 × 10 mL, white needle crystals, 52 g, 52.5%): mp 170–171 °C (lit.[9] mp 168–169 °C); IR 2850–3050, 1750, 1530, 1380, 1240, 1010 cm^{-1}.

Ethyl 4-Quinazolone-2-carboxylate (7). A mixture of ethyl *o*-aminobenzoate (3.3 g, 0.02 mol), ethyl cyanoformate (1.98 g, 0.02 mol), and hydrogen chloride (0.021 mol) in acetic acid (28 mL) was heated for 2.5 h at 120 °C. The precipitates obtained by evaporation were triturated with water to give white powder. Recrystallization from benzene (150 mL) gave white needle crystals (2.13 g, 48.9%): mp 192 °C (lit.[10] mp 179–180 °C); IR 2700–3250, 1740, 1685, 1600, 1310, 1170, 760 cm^{-1}.

***N*-(*p*-Tolyl)amidinoformic Acid. (Effects of Added Salts). $NaClO_4$.** A mixture of toluidine hydrochloride (3.608 g, 25.12 mmol), ethyl cyanoformate (2.70 g, 27.2 mmol), sodium perchlorate (1.556 g, 12.71 mmol), and hydrogen chloride (0.126 g, 3.46 mmol) in acetic acid (22.81 g) was heated at 90 °C for 2 h with occasional stirring. Solids were filtered out and 6 N hydrochloric acid (20 mL) was added to the filtrate. The acidic mixture was heated at 90 °C for 2 h. After evaporation of this mixture to near dryness under reduced pressure, water (30 mL) and benzene (20 mL) were added. The resulting mixture was made to be basic by the addition of sodium carbonate to give a solid. The solid obtained by filtration was washed with water (50 mL) and then with acetone (20 mL) and was again added to water (50 mL). This heterogeneous solution was stirred for 3 h. Filtration followed by washing with acetone (10 mL) and by drying at 50 °C under vacuum gave pure *N*-(*p*-tolyl)amidinoformic acid (1.806 g, 37.2% based on ethyl cyanoformate; 32% yield in a control run in the absence of sodium perchlorate).

In the presence of a stoichiometric amount of hydrogen chloride (to the amount of the amine) (i.e., a mixture of toluidine hydrochloride, sodium perchlorate, ethyl cyanoformate, and acetic acid) only free amidinoformic acid was obtained. In the presence of 5.14 mmol of excess hydrogen chloride (sodium perchlorate was added), *N*-(*p*-tolyl)amidinoformic acid was not obtained.

The reaction in the presence of sodium borofluoride gave similar results.

NaCl. A mixture of toluidine hydrochloride (3.602 g, 25.07 mmol), sodium chloride (0.571 g, 9.76 mmol), ethyl cyanoformate (2.50 g, 25.2 mmmol), and hydrogen chloride (0.0722 g, 1.98 mmol) in acetic acid (22.93 g) was heated at 90 °C for 2 h with occasional stirring. After filtration 6 N hydrochloride acid (20 mL) was added to the filtrate and the resulting solution was heated at 90 °C for 2 h. Then the reaction mixture was evaporated to near dryness under reduced pressure. The mixture of the solid, water (20 mL), and ethyl acetate (15 mL) was made basic by the addition of sodium carbonate. The white solid formed was separated by filtration, washed with water (200 mL) and with acetone (30 mL), and dried at 80 °C under vacuum. The solid (0.286 g) was free amidinoformic acid and *N*-(*p*-tolyl)amidinoformic acid was not obtained in any significant amount. A control experiment in the absence of sodium chloride gave *N*-(*p*-tolyl)amidinoformic acid (1.495 g, 33% yield based on ethyl cyanoformate).

Registry No.—**6,** 898-22-6; **7,** 29113-33-5; 2,4-xylidinium thiooxamate, 67662-69-5; 2-chloro-*o*-tolylammonium thiooxamate, 67662-70-8; 2,3-xylidinium thiooxamate, 67662-71-9; 3,4-xylidinium thiooxamate, 67662-72-0; 4-chloro-*o*-tolylammonium thiooxamate, 67662-73-1; 2,5-xylidinium thiooxamate, 67662-74-2; *m*-chloroanilinium thiooxamate, 67662-75-3; ethyl 1-carbethoxyformimidate, 816-27-3; 2,5-xylidine, 95-78-3; 2,6-diethylaniline, 579-66-8; *p*-toluidine, 106-49-0; 2,6-xylidine, 87-62-7; ethyl cyanoformate, 623-49-4; *p*-toluidine hydrochloride, 540-23-8; ethyl *o*-aminobenzoate, 87-25-2; *N,N'*-bis(2,5-xylyl)oxamide, 21022-14-0; *N,N'*-bis(2,4-xylyl)oxamide, 21022-26-4; *N,N'*-bis(4-chloro-*o*-tolyl)oxamide, 67662-76-4.

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Ring-Opening Reactions of 1*H*-Pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (3,7-Dideazaxanthine) and Two of Its Derivatives

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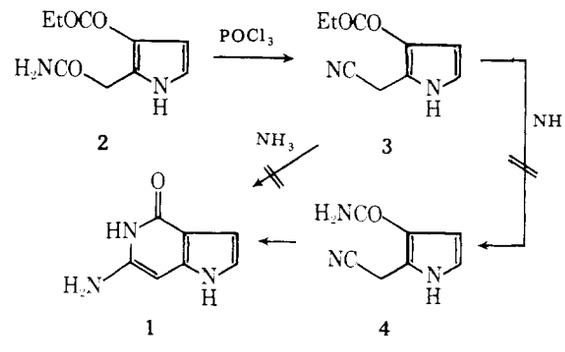
Failure to prepare 6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (i.e., 3,7-dideazaguanine, **1**) by an anticipated route led to reconsideration of the mechanism of a reaction in which ethyl 3-(ethoxycarbonyl)pyrrole-2-acetate (**5**) was reacted with aqueous methylamine. This subsequently revealed that 1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (i.e., 3,7-dideazaxanthine, **12**) and its 5-methyl (**8**) and 5-oxa (**13**) analogues undergo nucleophilic ring opening at their C-6 carbonyl leading to a number of 2,3-disubstituted pyrrole derivatives not readily obtainable otherwise. On the other hand, reaction of the 5-oxa analogue (**13**) with diazomethane proceeded via formation of a spirooxirane at its C-4 carbonyl which was also susceptible to ring opening in water and methanol to provide additional 2,3-disubstituted pyrroles.

An approach to 6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (3,7-dideazaguanine) (**1**) under recent scrutiny in this laboratory commenced with 3-(ethoxycarbonyl)pyrrole-2-acetamide (**2**)[1] as shown in Scheme I. The anticipated dehydration of **2** to 3-(ethoxycarbonyl)pyrrole-2-acetonitrile (**3**) occurred with no problems; however, attempts to convert **3** into **4**,[2] or directly into **1**,[2] with anhydrous ammonia consistently led to recovery of unreacted **3.**

The inability to transform **3** into **4** led to reconsideration of a reaction in which ethyl 3-(ethoxycarbonyl)pyrrole-2-acetate (**5**)[1,3] was treated with aqueous methylamine to produce **6** and **7** (Scheme II). Based on the results above with ammonia (see Scheme I) which indicated the 3-ethoxycarbonyl group of **3** to be unreactive toward nucleophilic substitution, simple amidation and amidation/partial hydrolysis of **5** by aqueous methylamine would not account for the formation of **6** and **7.** However, the formation of **6** and **7** can be rationalized if 5-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (1-methyl-3,7-dideazaxanthine) (**8**)[1] arises from **5** and undergoes attack by methylamine and water at its C-6 carbonyl with ring opening to **6** and **7.** This pathway is confirmed by the short-term (5 min rather than 5 h) reaction

Scheme I



of **5** with aqueous methylamine to form **8** and the amide **9** (the precursor to **8**)[1] and the subsequent reaction of **8** with aqueous methylamine to give **6** and **7.**

The alternative attack of methylamine/water at the C-4 carbonyl of **8** to form **6** and **10** was ruled out by the decarboxylation of **7** to 3-(*N*-methyl)carboxamido-2-methylpyrrole (**11**).

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