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SYNTHESIS OF AMIDINOFORMIC ACIDS USING BENZYL CYANOFORMATE AS A SYNTHON

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An efficient synthesis of a variety of N-substituted or N-unsubstituted amidinoformic acids was developed starting with benzyl cyanoformate.

There are some biologically interesting compounds originated either from nature or synthesis containing a partial structure derived from unsaturated α-amino acids or cyanoformates. For instance, kasugamycin[1], cephalosporin[2], thienamycin[3], virazole[4], and α-acetylenic α-aminoacids[5] contain such a structural moiety. The objective of the investigation described in this and the following papers was to develop methodology through the conversion of cyanoformate or its equivalents to the partial structures of biological interest described above.

Our approach is to start with cyanoformates and center on the two key operations: (1) selective activation of cyano group and (2) nucleophilic substitution with amino groups at the carbon of the cyano group equivalent. Cyanoformates are interesting synthetically, but the chemistry of them has not been extensively explored. The reason was considered to be due to difficulty in their synthesis[6]. Weber and Childs developed recently a simple preparation of cyanoformates using crown ether phase transfer catalyst. We have found that an inexpensive phase transfer catalyst tetra-n-butyl ammonium bromide (1 mol %) is satisfactory and more conveniently applied for the reaction of chloroformates and sodium cyanide in organic solvents-water system affording cyanoformates as shown in Table I.

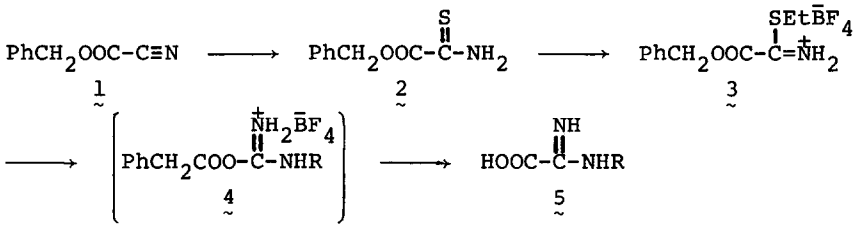
Table I. Preparation of Cyanoformates (1) by Phase Transfer Catalyst n-$Bu_4N^+Br^-$

R	Solvent	Temperature[7] (°C)	Time (min)	Yield (%)
Me	CH_2Cl_2-H_2O	0∿40	5	31
Et	CH_2Cl_2-H_2O	0∿10	30	73
CH_2CCl_3	C_6H_6-H_2O	0∿20	5	73
CH_2Ph	Toluene-H_2O	0∿40	5	87
Bu^t	CH_2Cl_2-H_2O	0∿5	15	trace

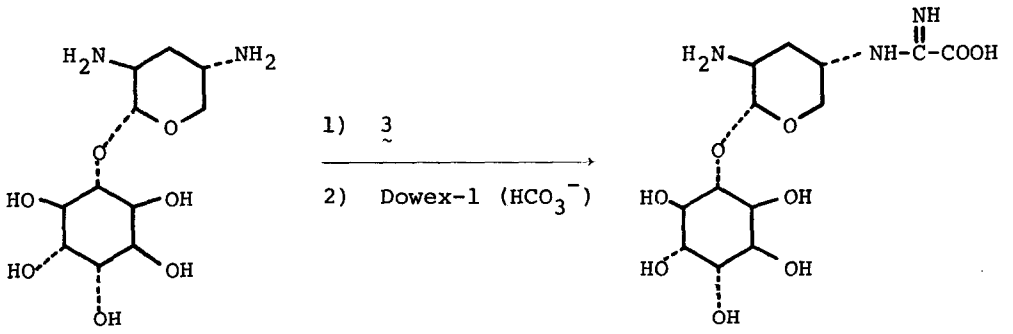
Our target functional group of the present study is N-substituted amidinoformic acid, which is unique and interesting moiety biologically, because it was

first found as a partial structure of kasugamycin in 1966[8]. The antibiotic is widely used for the prevention of rice blast and confirmed to be effective for Pseudomonas infection in humans[8].

Yoshimura and his co-workers first disclosed a synthesis of such functional groups either by the reaction of potassium thiooxamidate with alkylamines in water or by treatment of alkyl- and aryl-ammonium N-unsubstituted or substituted-thiooxamidate in methanol with mercuric oxide or lead oxide[9]. The Yoshimura's method is much superior to Nef's method[10] which was originally applied to the synthesis of kasugamycin[11], but still there are some problems in solubility, equilibrium and operation.



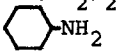
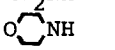
Thus, benzyl cyanoformate (1) was chosen as our starting material because of availability and consideration of the facile generation of carboxylic acid at the final stage. It was easily converted into thioamide 2 either by addition of hydrogen sulfide (>95%) or by treatment of benzyl alcohol-HCl followed by phosphorus pentasulfide (90%). Benzyl thiooxamidate (2) was activated by alkylation with triethyloxonium tetrafluoroborate to afford thiooxamimidate 3 in 94% yield. The reaction of 3 with one mole equivalent of an amine in methylene chloride at room temperature afforded the corresponding N-substituted or N-unsubstituted amidinoformic acid esters 4 almost instantaneously and was followed by hydrolysis with Dowex-1 (X 1, HCO_3^- form) to give the free acids 5 almost quantitatively as shown in Table II. Hydrogenolysis of 4 with Pd-C was generally unsucessful, affording 5 only in 40% yield. The selective substitution of ethylthio group with various amino groups proceeds very rapidly and the formation of amide group ($PhCH_2O_2C$- ⟶ RHNCO-) was observed with excess amount of amine and after much longer reaction time. Neutralization of 4 (R=CH_2Ph) with $NaHCO_3$ and allowing it to stand at room temperature for a long period gave an insoluble material which might be formed by cyclic dimerization. The overall yields for the formation of 5 are excellent and this methodology can be applied for most of the usual amino compounds, demonstrating highly effective routes for a variety of N-substituted amidinoformic acids. For instance, kasugamycin was obtained in 95% yield by reaction of kasuganobiosamine (6) with 3 followed by treatment with the ion exchange resin, showing that the equatorial amino group selectively reacted with 3 as expected[11].



6

Kasugamycin

Table II. Conversion of Thiooxamimidate 3 to Amidinoformic acid 5

Amine	Temperature (°C)	Time (min)	Yield (%)
NH_3	0	5	94
$MeNH_2$	r. t.	5	95
$EtNH_2$	r. t.	5	95
$HO(CH_2)_2NH_2$	r. t.	5	95
	r. t.	5	95
$PhCH_2NH_2$	r. t.	5	95
Me_2NH	r. t.	5	92
	r. t.	5	95
$PhNH_2$	r. t.	5	93

N-Benzyl amidinoformic acid 5 (R=CH_2Ph): To a solution of benzyl thioxamidate (2, 1.54 g, 7.90 mmol) dissolved in 40 ml of CH_2Cl_2 was added triethyloxonium tetrafluoroborate (1.51 g, 7.94 mmol) dissolved in 10 ml of CH_2Cl_2 in 5 min from a dropping funnel and the mixture was stirred at room temperature for 1 hr. After removal of the solvent, colorless crystals (3) were obtained and recrystallized from a mixed solvent of CH_2Cl_2 and n-hexane, showing mp 75-83° (dec.) and very hygroscopic (2.355 g, 7.58 mmol, 96%)[12]. Thiooxamimidate (500 mg, 1.61 mmol) dissolved in 3 ml of CH_2Cl_2 was added to a solution of benzylamine (173 mg, 1.61 mmol) in 7 ml of CH_2Cl_2 and the solution was stirred for 5 min. Removal of the solvent afforded a colorless solid (579 mg). It was dissolved in CH_3OH-H_2O (7:1, 8 ml) and treated with Dowex-1 (X 1, HCO_3^-) until the pH became ~8, and stirred at room temperature for 20 min. After removal of the resin the filtrate was condensed under a reduced pressure, depositing crystalline material. The crystals were washed with 5 ml of CH_2Cl_2 affording colorless N-benzyl amidinoformic acid (279 mg, 1.56 mmol, 97%), showing mp 176-178° after recrystallization from MeOH-CH_3COCH_3[12].

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References and Notes

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7. The reaction was carried out at 0°C at the beginning, but found to be exothermic and the temperature raised during the addition of sodium cyanide, as shown here.
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11. Y. Suhara, K. Maeda, H. Umezawa, and M. Ohno, Advances in Chemistry Series No. 72 "Deoxy Sugars", p. 15 (1968).
12. It is impractical and unnecessary to purify the hygroscopic ammonium salt of tetrafluoroboric acid, and the salt is directly used for the next substitution. Satisfactory spectral and analytical data were obtained for all the compounds described in Table I and II.

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