Table I

α-keto acid	alcohol	product	reactn conditions[a]	solvent	yield range, %
α-ketobutyric accid	methanol	methyl propionate	light, heat	benzene	76-81
			dark, heat	benzene	68-73
			dark, ambient	acetonitrile	63-75
α-ketobutyric acid	ethanol	ethyl propionate	light, heat	benzene	81-86
			dark, heat	benzene	68-81
			dark, ambient	acetonitrile	53-59
pyruvic acid	methanol	methyl acetate	light, heat	benzene	60-64
			dark, heat	benzene	59-63
			dark, heat	acetonitrile	59-71
			dark, ambient	acetonitrile	57-64
pyruvic acid	ethanol	ethyl acetate	light, heat	benzene	63-72
			dark, heat	benzene	67-77
			dark, heat	acetonitrile	61-78
			dark, ambient	acetonitrile	73-78
benzoylformic acid	methanol	methyl benzoate	light, heat	benzene	71-78
			dark, heat	benzene	79-94
			dark, ambient	benzene	79-85
benzoylformic acid	ethanol	ethyl benzoate	light, heat	benzene	81-86
			dark, heat	benzene	78-81
			dark, ambient	benzene	73-88

[a] Heat indicates the reflux temperature of the solvent/alcohol mixtures.

an excess of alcohol (from 4 to 20 mol excess) was used. No alcohol oxidation products were found.

Experimental Section

Analyses were performed on Varian Models 3400 and 3700 VPC's and a Hewlett-Packard 5700A VPC. Liquid chemicals used in the reaction mixtures and the standard VPC mixtures all had greater than 99.5% purity as determined on a gas chromatograph. The benzene and the acetonitrile solvents were spectroscopically pure and were used as purchased. VPC analyses were done on 6 ft × 0.25 in. copper columns of 10% SE-30, 7% SE-30, 3% Carbowax 20M, and 10% Carbowax 20M. The *N*-iodosuccinimide was determined to have 98.0–99.5% active iodine and was used as purchased. Irradiation of reaction mixtures was effected with a GE Projector Spot 150-W, 130-V tungsten lamp.

Oxidative Decarboxylation of the Methyl Alcohol Hemiacetal of α-Ketobutyric Acid with *N*-Iodosuccinimide and Irradiation. A 5-mL solution of 0.113 g (1.30 mmol) of α-ketobutyric acid, 0.166 g (5.20 mmol) of methyl alcohol, and 0.124 (1.10 mmol) of chlorobenzene (internal standard) in benzene was added to 0.644 g (2.86 mmol) of NIS contained in a 10-mL flask. A condenser with a drying tube was attached to the flask. The mixture was stirred and irradiated. Reaction times and VPC percentage yields of methyl propionate were as follows: 12 min (49%), 37 min (75%), 2.5 h (81%), 3.5 h (81%). Elemental iodine determination gave 0.979 mmol (75%). Succinimide was recovered in 86% yield. No methyl formate, a possible oxidation product of the methyl alcohol hemiacetal of formaldehyde, was found.

Oxidative Decarboxylation of the Ethyl Alcohol Hemiacetal of α-Ketobutyric Acid with NIS in the Dark with Heat. A 5-mL solution of 0.104 g (1.02 mmol) of α-ketobutyric acid, 0.202 g (4.39 mmol) of ethyl alcohol, and 0.114 g (1.01 mmol) of chlorobenzene (internal standard) in benzene was added to 0.459 g (2.04 mmol) of NIS contained in a 10-mL flask. The condenser was protected with a $CaCl_2$ drying tube. The flask was wrapped in Al foil and the mixture heated at reflux. Reaction times and VPC percentage yields of ethyl propionate were as follows: 15 min (70%), 45 min (78%), 1.25 h (79%), 2 h (81%), 3 h (80%). Titration for elemental iodine gave 87% recovery. Succinimide was recovered in 67% yield. No ethyl acetate, a possible oxidation product of the ethyl alcohol hemiacetal of acetaldehyde, was found.

Oxidative Decarboxylation of the Methyl Alcohol Hemiacetal of Benzoylformic Acid with NIS in the Dark with Heat. A 5-mL solution of 0.153 g (1.02 mmol) of benzoylformic acid, 0.641 g (20.0 mmol) of methyl alcohol, and 0.120 g (1.06 mmol) of chlorobenzene (internal standard) in benzene was added to 0.466 g (2.07 mmol) of NIS in a 10-mL round-bottomed flask. The condenser was topped with a $CaCl_2$ drying tube. The flask was wrapped in Al foil. The mixture was stirred. Reaction times and VPC percentage yields of methyl benzoate are given: 1 h (49%), 3 h (67%), 4.75 h (71%), 6 h (75%), 7.5 h (79%). Iodine was found with a yield of 84%. Succinimide was recovered in 53% yield.

Oxidative Decarboxylation of the Methyl Alcohol Hemiacetal of Benzoylformic Acid with NIS in the Dark at Ambient Temperatures. A 5-mL solution of 0.157 g (1.05 mmol) of benzoylformic acid, 0.641 g (20.0 mmol) of methyl alcohol, and 0.120 g (1.06 mmol) of chlorobenzene (internal standard) in benzene was added to 0.490 g (2.18 mmol) of NIS contained in a 10-mL flask. The condenser was protected with a $CaCl_2$ drying tube. The flask was wrapped with Al foil and the mixture stirred. Reaction times and percentage yields of methyl benzoate are given: 2 h (17%), 21 h (37%), 84 h (80%), 122 h (85%), 144 h (85%). Titration for iodine gave 1.09 mmol (104%). Succinimide (1.74 mmol) was recovered in 84% yield.

Iodine Determination. The iodine produced in the oxidations was determined by adding the reaction mixtures to 25 mL of a 1:1 mixture of acetic acid and water. Several drops of concentrated HCl were added, and the iodine was titrated with a standardized solution of thiosulfate.

Succinimide Determination. Succinimide was recovered by cooling the reaction mixtures and filtering the precipitated solid.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. We also thank the Department of Chemistry of the University of Kentucky for mass spectrometry data.

Registry No. NIS, 516-12-1; α-ketobutyric acid, 600-18-0; pyruvic acid, 127-17-3; benzoylformic acid, 611-73-4; methyl propionate, 554-12-1; ethyl propionate, 105-37-3; methyl acetate, 79-20-9; ethyl acetate, 141-78-6; methyl benzoate, 93-58-3; ethyl benzoate, 93-89-0.

An Improved Method for the Decyanation of N,N-Disubstituted Cyanamides

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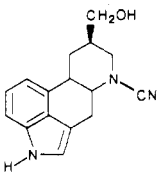
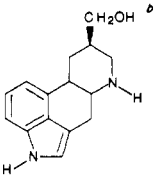
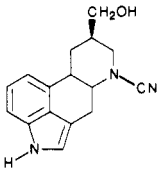
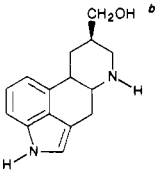
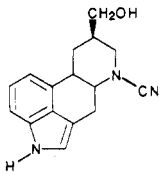
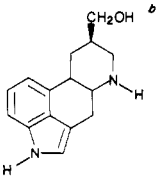
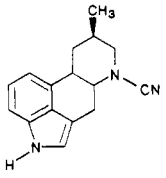
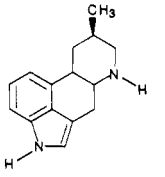
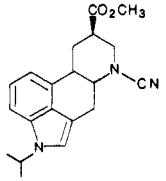
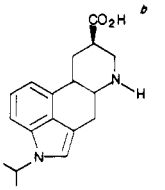
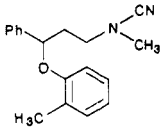
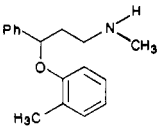
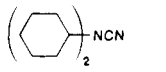
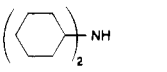
The decyanation of N,N-disubstituted cyanamides to secondary amines is a well-known method[1] that is used extensively, particularly in conjunction with the von Braun degradation for the N-dealkylation of alkaloids. Typically,

(1) Vliet, E. B. In *Organic Syntheses*, 2nd ed.; Gilman, H., Blatt, A. H., Eds.; Wiley: New York, 1941; Collect. Vol. I, pp 201-202.

0022-3263/87/1952-3166$01.50/0

Table I

substrate	product	solvent	time, h	yield,[a] %
		cyclohexanol	4	53
		propylene glycol	2	77
		ethylene glycol	2	83
		ethylene glycol	2	85
		ethylene glycol	2.75	88
		ethylene glycol	3	74
$(PhCH_2)_2NCN$	$(PhCH_2)_2NH$[c]	ethylene glycol	0.25	84
$PhN(CN)CH_3$	$PhNHCH_3$[c]	ethylene glycol	3	79
Ph_2NCN	Ph_2NH[c]	ethylene glycol	0.25	80
$(C_8H_{17})_2NCN$	$(C_8H_{17})_2NH$[c]	ethylene glycol	2	46
		ethylene glycol	2	0[d]

[a] All yields are based upon purified products which had satisfactory elemental analyses (±0.4%) except as noted. [b] Good elemental analyses could not be obtained for these compounds due to their hygroscopic nature (6.5% to 7.0% H_2O by Karl Fischer after drying). [c] Product isolated as the HCl salt. [d] 86.4% recovered starting cyanamide.

hydrolysis is effected with mineral acid in aqueous or mixed solvent systems,[1-4] but acid sensitivity can lead to extensive degradation.[5] Consequently, several alternative methods have been developed,[4-11] but these methods generally suffer from low yields, multiple steps, tedious processing, or reaction times measured in days.

Of these reported methods, basic hydrolysis would appear to have the greatest promise. Decyanation can be successful in aqueous sodium hydroxide,[1,12] but incomplete reactions have been observed.[13] The intermediates of these incomplete reactions, N-substituted ureas, have been converted to the desired secondary amines with nitrous acid,[14] but this reaction is capricious.[5] Similarly, alcoholic KOH may generate either the desired secondary amine[13] or the intermediate isourea.[14]

Recent investigations in this laboratory have shown that the difficulties with basic hydrolysis of disubstituted cyanamides can be overcome by the use of NaOH or KOH in ethylene glycol. At temperatures of greater than 120 °C, 2 equiv of sodium hydroxide pellets effect complete cleavage in 15 min to 3 h. Isolations are easy, and yields and purity are typically high. The reagents are inexpensive, and the reaction is readily adapted to any scale. The choice of solvent is critical to maximize yields and minimize degradation products. High boiling alcohols such as propylene glycol, glycerol, and cyclohexanol may be used, but ethylene glycol is preferred. The use of nonalcoholic high boiling solvents such as Me_2SO or DMF results in extensive degradation.

This method is not well-suited for disubstituted cyanamides that cleave to amines that are highly soluble in water or ethylene glycol. Also, the yields decrease markedly for *N,N*-dialkylcyanamides as the alkyl chain branches and lengthens.

In conclusion, a new method for the decyanation of N,N-disubstituted cyanamides has been developed that offers significant advantages over alternative procedures that have been reported in the literature.

Experimental Section

All of the nonsymmetrical N,N-disubstituted cyanamides were made by von Braun cleavages of their parent tertiary amines. *N,N*-Dibenzylcyanamide and *N,N*-dioctylcyanamide were synthesized via the alkylation of cyanamide with their respective alkyl halides. *N,N*-Dicyclohexylcyanamide and *N,N*-diphenylcyanamide were prepared from the reaction of their respective secondary amines with cyanogen bromide. Elemental analyses were performed by the physical chemistry department of the Lilly Research Laboratories.

The cleavage of *N,N*-dibenzylcyanamide is representative of the decyanation procedure: 2.22 g (10 mmol) of *N,N*-dibenzylcyanamide and 0.8 g (20 mmol) of sodium hydroxide pellets were combined in 22 mL of ethylene glycol and heated to 130 °C. A sample spotted for TLC (silica gel; 5:3 hexane/ethyl acetate) after only 15 min revealed that all of the starting material had reacted. Hence, the reddish brown solution was chilled to 20 °C. Water and diethyl ether (22 mL each) were added and stirred vigorously. The resulting layers were separated. The ether layer was dried over sodium sulfate and then concentrated in vacuo to 2.20 g of brown oil. The oil was redissolved in 30 mL of diethyl ether and then saturated with hydrogen chloride gas. The resulting precipitate was collected by suction filtration and dried to give dibenzylamine hydrochloride (1.96 g, 84%) as an off-white solid.

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(14) Nakahara, Y.; Niwaguchi, T. *Chem. Pharm. Bull.* **1971**, *19*, 2337.

Anal. Calcd for $C_{14}H_{16}ClN$: C, 71.94; H, 6.90; Cl, 15.17; N, 5.99. Found: C, 71.77; H, 6.62; Cl, 15.31; N, 6.12.

Acknowledgment. I am grateful to Mr. Gifford Marzoni for supplying the data on the cleavage of the dihydrolysergic ester derived cyanamide.

Synthesis of Optically Active *cis*-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic Acid via Intramolecular Alkylation of a Chiral Enolate

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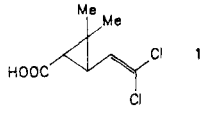
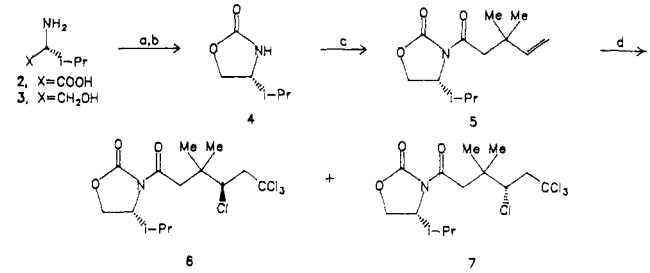
A large number of the agriculturally important synthetic pyrethroid insecticides are esters of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (1). The impact of stereochemistry about the cyclopropane ring on insecticidal activity necessitates the development of efficiednt methods for the stereoselective synthesis of the various enantiomers of 1.[2,3] We previously reported a new stereoselective synthesis of *cis*-1 using the intramolecular alkylation of an amide enolate to establish the relative stereochemistry.[4] We now report our observations in attempts to extend this methodology to the synthesis of optically active (1*R*,3*R*)-1 using a chiral enolate.[5]



1

The synthesis of the appropriate starting materials for cyclization is illustrated in Scheme I. Oxazolidinone **4** was prepared in two steps from (*R*)-valine (**2**) by reduction with BH_3–SMe_2[6] followed by treatment of the resultant amino alcohol **3**[7] with carbonyldiimidazole. Oxazolidinone **4** was treated with NaH followed by addition of 3,3-dimethyl-4-pentenoyl chloride[4a] to yield **5**, in 85% yield. Compound **5** was reacted with $Fe(CO)_5$ in CCl_4 to afford a 3:2 mixture of addition products **6** and **7**, respectively, in 86% yield. The isomeric products were separated by preparative HPLC to afford the pure major isomer **6** and the minor

Scheme I[a]



[a] (a) BH_3–SMe_2; (b) carbonyldiimidazole; (c) NaH, $ClCOCH_2C(Me)_2CH{=}CH_2$; (d) $Fe(CO)_5$, CCl_4.

isomer **7**. The spectroscopic properties of **6** and **7** were nearly identical with the exception of the ^1H NMR resonances attributed to the diastereotopic protons adjacent to the carbonyl group. In **7** one resonance was shifted upfield by 0.15 ppm and the other was shifted downfield by 0.16 ppm relative to the corresponding resonances in **6**. Consequently, the stereochemistry of **6** was determined by single-crystal X-ray analysis.[1b]

The ring closures of **6** and **7** initiated by enolate formation were studied separately. It should be expected that in one instance (i.e., **7**) cyclization should be highly stereoselective due to the combined facial differentiation of the enolate and normal (*Z*)-enolate preference to yield cis stereochemistry in the ring closure through a backside S_N2 reaction.[4a] In the case of **6**, where these factors oppose each other, much poorer stereoselection should be anticipated. Treatment of **6** with NaH produced a 70% yield of a 1:23:74:2 mixture of cyclized products **8a**:**8b**:**8c**:**8d**, respectively, as determined by HPLC and NMR spectral analysis (Scheme II). Under indentical reaction conditions, compound **7** produced an 84% yield of a 92:1:2:5 mixture of products **8a**:**8b**:**8c**:**8d**, respectively.

Final confirmation of the isomeric composition of the cyclization mixtures was accomplished by conversion to **1** by hydrolysis and dehydrohalogenation. Each mixture was treated with LiOMe followed by treatment of the crude methyl esters with KOH.[5d] The mixture of isomers **8** derived from **6** gave **1**, $[\alpha]^{25}_D$ −13.2°, in 77% yield. The mixture of isomers **8** obtained from **7** gave **1**, $[\alpha]^{25}_D$ +18.9°, in 77% yield. The ratios of cis to trans products in each case were easily confirmed by examination of the relative intensities of the resonance for the vinyl proton in the ^1H NMR spectrum of crude product.[3] These data, combined with the magnitude and sign of the optical rotation of samples of **1** in comparison with literature values,[3] verified the ratios of isomers in **8** as shown above.

Experimental Section[8]

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Anhydrous tetrahydrofuran (THF) was obtained by distillation from sodium–benzophenone immediately prior to use. Anhydrous *N*,*N*-dimethylformamide (DMF) was obtained by distillation from CaH_2 immediately prior to use. Anhydrous MeOH was obtained by distillation from $Mg(OMe)_2$ immediately prior to use. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(*R*)-(−)-2-Amino-3-methyl-1-butanol (3). Following a previously described procedure for reduction of racemic valine,[6] **3**

(1) (a) Dow Chemical U.S.A. (b) North Carolina State University. Address correspondance regarding the X-ray structure of **6** to this author at Central Research, Pfizer Inc., Groton, CT 06340.

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(7) The optical purity of **3** was determined to be >98% ee by examination of the ^{19}F NMR spectra and HPLC resolution of diastereomeric α-methoxy-α-(trifluoromethyl)phenylacetamide derivatives: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(8) All melting points and boiling points are uncorrected. NMR chemical shifts are expressed as δ values (ppm) relative to a Me_4Si internal standard. Significant NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant(s) in hertz.

0022-3263/87/1952-3168$01.50/0