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Articles

Unnatural Amino Acids. 1. A Facile Synthesis of the Methyl Ester of Aziridine-2-carboxylic Acid

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Abstract:

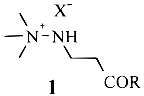
The methodology of aziridine-2-carboxylic acid methyl ester (4) synthesis by aziridine ring formation from methyl 3-(2,2,2-trimethylhydrazinio)propionate bromide (1a) has been developed by N−N bond cleavage. The process gives the title compound in 75% theoretical yield (>99% purity). We found important factors for a successful key reaction, including the optimal temperature range between 140 and 160 °C, a 4−6-fold excess of K_2CO_3 as the base of choice, drying and smoothing of starting materials, an increase in the surface of reactants by rotation, and a lack of water and other solvents in the reaction mixture. The influence of other basic cyclization materials and other reaction conditions in the formation of side products 8−16 is discussed.

Introduction

Aziridine-2-carboxylic acid is an important building block for the synthesis of unnatural amino acids and peptides in peptide chemistry.[1] The significant role of the title compound as a potential starting material becomes more evident with the usage of aziridines as C_2 chiral auxiliaries.[2] The stability of free aziridine-2-carboxylic acid and its esters differs from that of natural amino acids and their esters. Usually, stable cyclic amino acids (for example, proline) give unstable esters, which are protected as hydrochlorides, whereas the opposite pattern of activity (that is, that the ester is more stable than the carboxylic acid) is observed in the case of aziridine-2-carboxylic acid. Thus, aziridine-2-carboxylic acid methyl ester is stable for more than 50 h at 100 °C in dry atmospheric conditions.

We have studied the properties of aziridinecarboxylic acids during the last decade. As a result we have found that hydraziniopropionates **1** (for example, R = OMe) are convenient starting materials for the synthesis of the cardiovascular drug mildronate (**2**)[3] and the anticancer immunomodulator leakadine (**3**).[4]

In an early paper Harvey[5] used the hydraziniopropionamides **1** (R = N(Me)Ph, yield 35%, and R = N(*i*-Pr)Ph, yield 57%) for closure to form the aziridine ring. We have developed this method[6] for the corresponding esters **1** (R = OMe, yield 30%, and R = OEt, yield 5%). The yields in this process were fairly low, because of the high nucleophilicity of the base (NaOMe) used in the transformation. When we changed from the methoxide to the less nucleophilic hydride, the yields increased. However, the process remained unsatisfactory for industrial use,[7] because the solvent of choice, DMSO, forms azeotropic mixtures with ester **4**.



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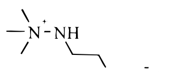

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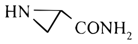
Mildronate



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Leakadine

1a R =OMe, X = Br; **1b** R =OMe, X = I; **1c** R =OMe, X =Cl; **1d** R = NEt_2, X = I; **1e** R = NBu_2, X = I; **1f** R = NHEt, X = I; **1g** R = NH_2, X = I

Results and Discussion

The goal of the recent investigation is to understand and optimize the process of aziridine ring closure. In preliminary experiments we assessed the heterogeneous process of cyclization in the presence of K_2CO_3 as a base. These investigations[6,7] indicated which parameters are more important for the transformation outlined in Scheme 1.

On the basis of our initial observations we investigated several important parameters: the nature of the basic cyclization agent; the nature of the solvent; the nature of the counterion (X^-) in substrate **1**; the presence of the diluent material (when reaction is carried out without solvent); the surface properties of heterogeneous reactants; the temperature of the process; the stoichiometry of the reactants. We will discuss the main results obtained by changing all the parameters mentioned above.

The Nature of the Basic Cyclization Agent. Experiments with different inorganic and organic bases were examined. Potassium, sodium, and calcium carbonates, CaO, potassium and sodium hydroxides, and potassium and calcium hydrides were used as inorganic materials. Different organic solvents were used: diglyme, monoethanolamine, diethanolamine, triethanolamine, and organic bases such as

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(1) (a) Tanaka, T.; Nakajima, K.; Maeda, T.; Nakamura, A.; Hayashi, N.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3579. (b) Nakajima, K.; Tanaka, T.; Neya, M.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3237. (c) Okawa, K.; Nakajima, K.; Tanaka, T.; Neya, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 174. (d) Okawa, K.; Yuki, M.; Tanaka, T. *Chem. Lett.* **1979**, 1085. (e) Okawa, K.; Nakajima, K. *Biopolymers* **1981**, *20*, 1811. (f) Tanaka, T.; Nakajima, K.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1352.

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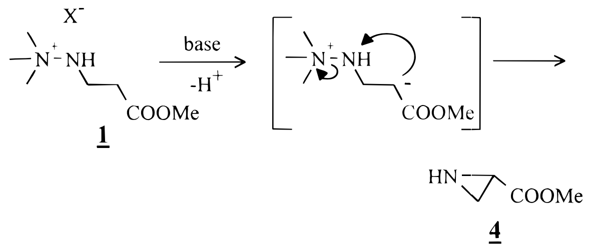
Table 1. **The role of cyclization agents, solvents, and temperature in the cyclization of ester 1a**

entry	base (equiv)	solvent or filling (% to bromide **1a**)	bath temp, °C	yield of ester **4**, %
1	K_2CO_3 (3)	PEG-400 (25)	170	20
2	NaOMe (2)	PEG-400 (30)	170	24
3	Na_2CO_3 (3)	PEG-1500 (25)	200	traces
4	Na_2CO_3 (3)	diglyme (25)	180	traces
5		quinoline (35)	160	traces
6	Na_2CO_3 (2)	quinoline (25)	160	traces
7		$KF{\cdot}2H_2O$	200	
8	K_2CO_3 (1.5)	monoethanolamine (40)	160	traces
9		monoethanolamine (40)	100	
10	K_2CO_3 (2)	diethanolamine (35)	220	
11		diethanolamine (15)	200	
12	NaOH (2)	triethanolamine (35)	150	
13		triethanolamine (35)	220	
14	NaOH (1.5)	silicone oil (30)	200	
15	NaOMe (2)	silicone oil (30)	110	
16	Na_2CO_3 (1)	NaOAc	200	26[a,b]
17	Na_2CO_3 (1.5)	sulfolane (30)	180	3[a,c]
18	K_2CO_3 (1.5)	sulfolane (30)	180	63[a,d]
19	NaH (1.5)	DMSO (25)	100	20
20	NaH (1.5)	MeCN	80	traces
21	NaH (1.5)	THF	60	traces
22	CaH_2 (4)	DMSO	100	traces
23	NaOH (1.5)	ethylene glycol	170	

[a] Footnotes *b*−*d* give the measured amounts of volatile by-products (calculated from GC analyses). [b] 8%. [c] 19%. [d] 18%.

Scheme 1



NaOMe and NaOAc. Reactions were examined both in homogeneous media (solvents, entries 17−23, Table 1) and in heterogeneous media (without solvents or partially dissolved; entries 1−16, Table 1). In general, low-boiling products were distilled from the reaction mixture (except entries 20 and 21, Table 1, when low-boiling solvents were evaporated at room temperature before distillation). Products were analyzed by GC analysis, and results are summarized in Table 1. The amount of by-products was calculated from GC data. We did not measure remaining nonvolatile aziridine products in the reaction mixture, because they are only water soluble.

No ester **4** formation was registered in the absence of base (entries 7, 9, 11, and 13, Table 1). K_2CO_3 is the only base which gave satisfactory results in homogeneous media (entry 18, Table 1). Sodium hydroxide and potassium hydroxide increase the ester hydrolysis relative to K_2CO_3 (eqs 1 and 2.

Table 2. **The effect of cyclization conditions in heterogeneous media without rotation (K_2CO_3 was used as a base)[a]**

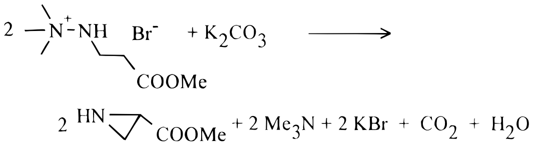
entry	base,[b] equiv	solvent or filling	yield of ester **4**, %	by-products,[d] %
1	1.5	MeOH[c]	24	55
2	5	MeOH[c]	29	9
3	5	Fe	61	5
4	1.5	Al_2O_3	28	25
5	2		56	11
6	3		67	5
7	4		74	2
8	5		82	3
9	6		87	5
10	10		90	6
11	2	SiO_2	22	34

[a] All reactions except entries 1 and 2 were performed at bath temperature 160−180 °C. [b] Equivalents of K_2CO_3 per 1 equiv of ester **1a**. [c] Reactions performed in boiling methanol. [d] By-products were determined by GC.

Table 3. **The effect of cyclization conditions in heterogeneous media with rotation[a]**

entry	base (equiv to bromide **1a**)	filling (equiv to bromide **1a**)	yield of ester **4**, %	volatile by-products,[c] %
1	CaO[b] (3)		14	16
2	Na_2CO_3[b] (10)		36	11
3	K_2CO_3 (10)	KOH (1)	6	*d*
4	K_2CO_3 (10)		92	2
5	K_2CO_3 (10)	KBr (2)	58	2
6	K_2CO_3 (10)	KBr (4)	63	6
7	K_2CO_3 (3)	SiO_2	81	6

[a] All reactions (entries 3−7) were performed at bath temperature 140−160 °C. [b] Reaction was performed at bath temperature 160−180 °C. [c] By-products were determined by GC. [d] Volatile by-products were not formed.



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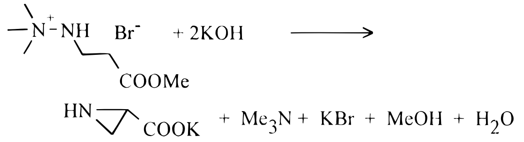
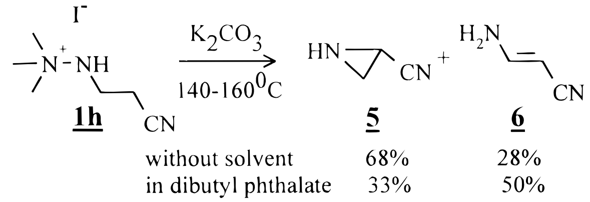


(2)

In the KOH case (eq 2) twice as much water per mole of substrate is produced. In the case of K_2CO_3, the presence of water is not dramatic (entry 4 in Table 3) and yields are high (92%). The addition of 1 equiv of KOH to the same reaction conditions (entry 3 in Table 3) probably hydrolyses the ester group, and cleavage of the aziridine ring takes place. As a consequence, the yield is decreased to 6%. It seems that organic bases like triethanolamine, diethanolamine, and monoethanolamine are too weak for α-deprotonation. The same result is observed with CaO and $CaCO_3$. In the case of Na_2CO_3, side reactions are favored. The yield of ester **4** is only 36% while the side products are formed in 11% yield (entry 2, Table 3). NaH employed in the cyclization of **1a** in DMSO (entry 19, Table 1) gave only 20% of ester **4**; the low yield is explained by formation of nonvolatile by-products. Distillation of the reaction mixture gave an azeotropic mixture (1:1) of ester **4** and DMSO. Dramatic differences in yields (accordingly 3% and 63%) were observed between the Na_2CO_3 and K_2CO_3 in the sulfolane solution (entries 17 and 18, Table 1). Therefore in our approach K_2CO_3 is the cyclization agent of choice. We are sure that the aziridine formation process is remarkably stabilized by the absence of water and hydroxide impurities (compare entries 3 and 4, Table 3) in K_2CO_3.

Scheme 2



The Nature of the Solvent. At the beginning we used low-boiling solvents: THF, methanol, and acetonitrile. Better results were expected from high-boiling ones, such as DMSO, ethylene glycol, diglyme, sulfolane, and dibutyl phthalate or liquid filling materials, such as polyethylene glycols (PEG-400, PEG-1500) and silicon oil. The best results are summarized in Table 1. Our observations indicate that low-boiling solvents are useless (entries 20 and 21, Table 1), because deprotonation and N−N bond cleavage are not completed. Methanol as a solvent stands in a very special position. We have used it as the solvent and for an increase of the contact surface of both reactants, ester **1a** and K_2CO_3 in the heterogeneous media. For this purpose we mixed a saturated solution of ester **1a** with K_2CO_3 and removed the solvent at 30 °C at reduced pressure. After that we used such an activated reaction mixture in the subsequent reactions. The only difference observed at room temperature was the slight evolution of trimethylamine in the latter case. Some interesting results were obtained with PEG-400 as the solvent. Although the yields are low, 20−24% (entries 1 and 2, Table 1), NaOMe gives pure aziridine **4**. This is the only case when NaOMe gave better yields than K_2CO_3. Compared with other solvents used, sulfur-containing solvents (sulfolane and DMSO[7]) gave the best yields. Unfortunately, distillation failed, because ester **4** and DMSO gave an azeotropic mixture (1:1). After that we tried to separate DMSO from ester **4** by freezing it out, but could not do it completely. We failed at a similar separation of sulfolane from ester **4** by distillation and freezing out technology.

The Nature of Counterion (X^-) in Substrate 1a. When the reactions are carried out in solvents, the nature of the anion (X^-) is significant. In general, the increase of nucleophilicity in the order Cl < Br < I is followed by the decrease of the yields of aziridine. The reason for that is the cleavage of the aziridine ring by halide ions as nucleophiles. Hydrazinium iodides[7] derived from hydrazinosuccinates form only enamines instead of aziridines. Further, we checked the cyclization reaction of nitrile **1h** under the optimized reaction conditions. Thus, in the case of nitrile iodide **1h** (Scheme 2), the ring−chain tautomer, enamine **6**, is formed in good yield together with aziridine **5**. Generally we have observed that the reaction without solvent succeeds better in the experiments with ester **1a** and nitrile **1h**. Moreover, with dibutyl phthalate the main product is not aziridine **5**, but enamine **6** (product ratios are given in Scheme 2).

The Presence of the Diluent Material. Additives (when reaction is done without any solvent) play an important role. We have examined the influence of the widely used inert materials Al_2O_3 and SiO_2. The third material chosen is KBr, because it is formed in the reaction as a side product. Different amounts of KBr (2−4-fold excess) do not change the yields significantly, but they "baked" thoroughly the reaction mixture. **WARNING**: Be careful, when reactions are realized in large (10 L) rotating glass flasks. As another filling material we have used aluminum oxide (activated, neutral, Brockman). The yield of ester **4** was decreased, but impurities increased (entry 4, Table 2). SiO_2 (sand) gave worse results in the reactions without rotation (entries 11 and 5, Table 2). The disadvantage of the method with SiO_2 additive is adherence of reactants to the flask. Therefore no filling material improves results compared to K_2CO_3 alone.

The Increase of the Surface of Reactants. One of the ways to increase the surface of reactants is the rotation of the reaction mixture. From Table 3, entry 7, it is obvious that rotation improves the process. All results could be compared from Tables 2 and 3.

The Temperature of the Process. Temperature plays the main role in all chemical reactions. In this particular case, the success of the process depends on the efficacy of α-deprotonation and the thermal cleavage of the N−N bond in hydrazinium species **1a**−**g**. It is not clear yet what the driving force of the reaction is: is it the thermal cleavage of the N−N bond or α-deprotonation of the hydrazinium compounds **1**? Our earlier investigations showed[5,7] that deprotonation occurs also at lower temperatures (60−100 °C). Low-boiling solvents do not work well, because at temperatures below 100 °C the N−N bond in species **1a**−**g** is comparatively stable. To remove doubts regarding this issue, we examined the reaction of inorganic bases ($CaCO_3$, Na_2CO_3, K_2CO_3) in the melt of ester **1a**.

Temperatures of 140−160 °C are high enough for the K_2CO_3 cyclization experiments. With weaker bases (CaO and $CaCO_3$) only trace amounts of ester **4** are formed at the same temperatures. When the temperature is raised to 170−180 °C, the title compound is formed in low yield (20%). A further increase to 200−210 °C caused cleavage of the C−N bond in the starting hydrazinium ester **1a**.

We found that the solubility of $CaCO_3$ at the melt (temperature, 135 °C) is approximately 1%. Na_2CO_3 under these conditions does not dissolve at all, but K_2CO_3 reacts vigorously with the melt. We elevated the temperature and found that a vigorous reaction with Na_2CO_3 started at 155 °C. However, the process with Na_2CO_3 does not go cleanly (entry 2, Table 3), and remarkable amounts of by-products were obtained. When the reaction mixture was put in the rotary evaporator (K_2CO_3 used as a base), reaction started at 120−130 °C and the major part of volatile products was distilled off at the oil bath temperature of 140−160 °C. The same reaction without rotation started only when the oil bath temperature reached 140−150 °C. The main part of the desired ester **4** was distilled off at 160−180 °C. We attempted to increase the yield by elevation of the temperature to 200−210 °C. However, the yield of the main product was unchanged, and the amount of by-products increased from 3% to 15%. We assumed that the problems decreased from the presence of a thick layer of reactants.

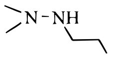
To achieve more regular heating we added Fe dust. Unfortunately, yields were decreased from 82% to 61% (in experiments with a 5-fold excess of K_2CO_3; compare entries

3 and 8 in Table 2) and by-products increased from 3% to 5%.

There are three advantages for additional rotation of the reaction solid materials: (1) higher purity of products due to a reaction temperature decrease of 20 °C (compare entries 4 in Table 3 and 10 in Table 2); (2) homogeneous mixing and controlled heat flow; (3) maintenance of mobility due to the evolution of Me_3N and distillation of products.

The Ratio of the Reactants. An excess of K_2CO_3 results in an obvious increase of product, but the by-product slightly increases, too (Table 2). The best yields (67−92%) were obtained with a 3−10-fold excess of K_2CO_3. Therefore the optimal ratio of hydrazinium bromide **1a** to K_2CO_3 is from 1:3 to 1:10. Large-scale processes require more delicate attention to the environment, and the preferred ratio of reactants would be 1:3 to 1:5.

The Analysis of Reaction By-Products. Tables 1−3 summarize quantitative results of the by-products formed in the reaction of aziridine ring formation. Now we are going to characterize the main by-products in this transformation. The direct correlation that the decrease of the yields of ester **4** is connected with the increase of by-products is not surprising. The main by-products formed are esters **7**−**15**. From the GC results we realized that all carbonates used for the cyclization gave the same by-products. The difference between them (K_2CO_3, $CaCO_3$, Na_2CO_3) is only in the quantities and ratios. Thus, K_2CO_3 gives the smallest amount of by-products, these increase in the case of Na_2CO_3, and they reach a maximum with $CaCO_3$ as the base. The impurities were measured by the GC−MS method. Reaction by-products were formed by the general procedure in the reaction of ester **1a** with a 5-fold excess of $CaCO_3$ in an oil bath at 170−180 °C. Under these conditions only 1% of ester **4** was formed.



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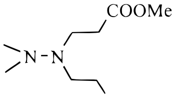

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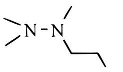

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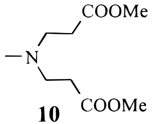

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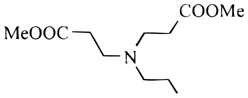

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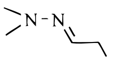

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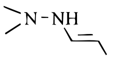

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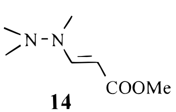

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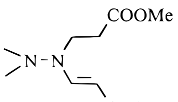

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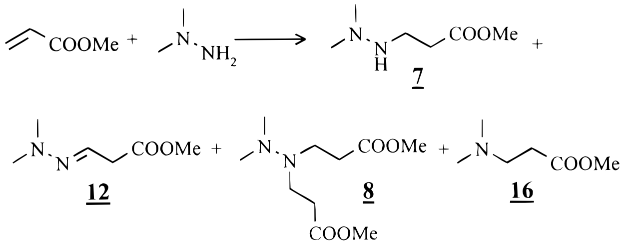
In the case of $CaCO_3$, 78% of reaction products are hydrazines **7** and **8** and oxidized products **12** or **13**. The reason for the formation of esters **7**−**15** is the thermal cleavage of C−N or N−N bonds. The fragments formed may react themselves to give hydrazines **8** and **9** and amines **10** and **11**. Among the products one could find partially oxidized hydrazines **13**−**15**. GC−MS data confirmed formation of methyl group migration products **9** and **14** together with partially oxidized esters **12**−**15**. In the case of Na_2CO_3 the major by-product (11%) isolated by distillation is hydrazine **7**, but with K_2CO_3 the amounts of the same impurities usually are not higher than 1−2%.

Scheme 3



Ester **12** was prepared (Scheme 3) and characterized as the side product in the reaction of methyl acrylate and 1,1-dimethylhydrazine in 7% yield. Other impurities in this reaction, ester **8** and methyl 3-(dimethylamino)propionate (**16**), were obtained in smaller (<1%) yields. The latter compound could be avoided with careful fractional distillation of the starting 1,1-dimethylhydrazine. The amount of ester **8** in the reaction mixture usually is minimized with a small excess (∼10%) of 1,1-dimethylhydrazine.

Conclusions

We have improved the methodology of aziridine-2-carboxylic acid methyl ester synthesis to close the aziridine ring by N−N bond cleavage. This process works well in heterogeneous media with K_2CO_3 as the base of choice. Previous similar methods exploited hydrazinium salts in reaction with alkoxides or strongly basic anion exchange resins (Amberlites) and gave low yields (<50%) of aziridines. The yield by our method is 75% of theory after purification (two distillations), and the purity of ester **4** is 99%. We have determined important factors for a successful reaction. Among them are the optimal temperature range between 140 and 160 °C, a 4−6-fold excess of K_2CO_3, drying and fine grinding of starting materials, an increase in the surface of reactants by rotation, simultaneous distillation of product from reaction mixture, and lack of water and other solvents in the reaction mixture. All attempts to find effective solvents for the reaction were unsuccessful. The absence of solvent eventually might be a serious problem in scaling up the procedure to multikilogram quantities, but the process works reasonably well in the 1−10 mol range. Unexpectedly, the better results were obtained in heterogeneous media. This means that small changes in the physical quality of starting materials and in the experimental conditions may influence the yields more than in the homogeneous process.

Experimental Section

^1H NMR spectra were recorded on a Bruker WH-90/DS spectrometer at 90 MHz. GC−MS analyses were recorded with a Kratos MS-25 GC−MS chromato-mass spectrometer (70 eV). Gas chromatographic analyses were performed with glass columns (3% KOH + 25% dinonyl phthalate on Chromosorb WHP 80/100; column size 2.5 m × 2.1 mm; column temperatures, 80 °C for 2 min, then 80−110 °C at 5 deg/min; injector temperature, 170 °C; detector 200 °C; He gas carrier at 15 psi).

Starting Materials. Methyl 3-(2,2,2-trimethylhydrazinio)propionate bromide (1a) is prepared according to the known general procedure[6,8] starting from methyl acrylate and 1,1-dimethylhydrazine in a Michael addition. Alkylation of Michael adduct methyl 3-(2,2-dimethylhydrazino)propionate (**7**) with methyl bromide in boiling polar protic (preferably ethanol) solvent gives ester **1a**. Crystallization from ethanol gives colorless crystals with mp 132−133 °C. Product was dried at temperatures not higher than 50−60 °C. ^{1}H-NMR ($CDCl_3$, TMS): δ 2.67 (t, $J = 6$ Hz, CH_2CO, 2H), 3.39 (t, $J = 6$ Hz, CH_2N, 2H), 3.40 (s, $(CH_3)_3N^+$, 9H), 3.77 (s, OCH_3, 3H).

Besides the main ester, methyl 3-(2,2-dimethylhydrazino)-propionate (**7**) (Scheme 3), other esters **8**, **12**, and **16** obtained as by-products were purified by distillation and characterized. **3,3′-(2,2-Dimethylhydrazinediyl)bis(propionic acid) dimethyl ester (8**) (less than 1% in the reaction mixture) was distilled as a colorless liquid with bp 121−123 °C at 6 Torr; $n^{20}_D = 1.450$. ^{1}H NMR ($CDCl_3$, TMS): δ 2.23 (s, $(CH_3)_2N$, 6H), 2.42 (t, $J = 6.2$ Hz, CH_2CO, 4H), 2.71 (t, $J = 6.2$Hz, CH_2N, 4H), 3.62 (s, OCH_3, 6H). Anal. Calcd for $C_{10}H_{20}N_2O_4$: C, 51.7; H, 8.7; N, 12.1. Found: C, 51.5; H, 8.6; N, 11.8. Ester **8** was alkylated with methyl bromide in ethanol solution, and the product **3,3′-(2,2,2-trimethylhydraziniumdiyl)bis(propionic acid) dimethyl ester bromide (18)** was characterized by ^{1}H NMR ($CDCl_3$): δ 2.67 (t, $J =$ 6.3Hz, CH_2CO, 4H), 3.49 (t, $J = 6.3$ Hz, CH_2N, 4H), 3.70 (s, $(CH_3)_3N^+$ and OCH_3, 15H). Anal. Calcd for $C_{11}H_{23}BrN_2O_2$: C, 44.8; H, 7.9; N, 9.5. Found: C, 45.0; H, 8.0; N, 9.5. **Methyl 3-(2,2-dimethylhydrazono)propionate (12)** (∼7% in the reaction mixture) was distilled as a colorless liquid with bp 56 °C at 3 Torr; $n^{21}_D = 1.467$. ^{1}H NMR ($CDCl_3$, TMS): δ 2.72 (s, $(CH_3)_2N$, 6H), 3.16 (t, CH_2CO, 2H), 3.63 (s, OCH_3, 3H), 6.49 (d, $CH{=}N$, 1H). Anal. Calcd for $C_6H_{12}N_2O_2$: C, 50.0; H, 8.3; N, 19.4. Found: C, 50.2; H, 8.4; N, 19.1. **Methyl 3-(dimethylamino)propionate (16**) was distilled as a colorless liquid. ^{1}H NMR ($CDCl_3$, TMS): δ 2.21 (s, $(CH_3)_2N$, 6H), 2.52 (m, CH_2CH_2, 4H), 3.65 (s, OCH_3, 3H). Ester **16** was alkylated by methyl bromide in ethanol solution, and the product **methyl 3-(trimethylammonio)propionate bromide (17)** was characterized by ^{1}H NMR (D_2O, DSS): δ 3.00 (t, CH_2CO, 2H), 3.13 (s, $(CH_3)_3N^+$, 9H), 3.69 (t, CH_2N^+, 2H), 3.71 (s, OCH_3, 3H). Anal. Calcd for $C_7H_{16}BrNO_2$: C, 37.2; H, 7.1; N, 6.2. Found: C, 37.0; H, 7.1; N, 6.3.

General Procedure. Methyl Ester of Aziridine-2-carboxylic Acid (4). In a 2 L round-bottom flask were mixed 241.0 g (1.0 mol) of dry, finely ground methyl 3-(2,2,2-trimethylhydrazinio)propionate bromide (**1a**) and 690.0 g (5.0 mol) of K_2CO_3. K_2CO_3 has to be dried carefully and the content of hydroxides checked (direct test of carbonates). The flask was connected to a rotary evaporator (vertical condenser; H_2O stream; receiving flask was cooled with dry ice) and heated in an oil bath at 140 °C. When the vigorous reaction was over, the temperature of the bath was increased to 160 °C; 107.6 g of raw material by distillation (contains 78.6% of ester **4** by GC) was obtained. The calculated yield of ester **4** is 83.7%. The crude product was dried by Na_2SO_4 (if H_2O was more than 5%) or CaH_2. Distillation (small amount of hydroquinone in receiving flask is added) gave 75.4 g (74.7% of theory) of the ester **4** as a colorless liquid with bp 67−68 °C at 11 Torr; $n^{17}_D = 1.4430$; $d^{17} = 1.124$. Purity (GC data): >99% (stabilized by hydroquinone). ^{1}H NMR ($CDCl_3$, TMS): δ 1.1 (s, NH, 1H), 1.73 (dd, $J = 5.2$ and 1.8 Hz, C_3H, 1H), 1.89 (dd, $J = 3.0$ and 1.8 Hz, C_3H, 1H), 2.47 (dd, $J = 5.2$ and 3.0 Hz, C_2H, 1H), 3.77 (s, OCH_3, 3H).

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