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A FACILE AND PRACTICAL PROCEDURE FOR THE STEREOSELECTIVE SYNTHESIS OF (*Z*)-3-QUINUCLIDINYLIDENE-ACETIC ACID DERIVATIVE

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Abstract-A study of the isomerization of methyl (*E*)-3-quinuclidinylideneacetate derivative to the corresponding *Z*-isomer is reported. Theoretical calculations, performed using the MM3 molecular mechanics method, are in agreement with the experimental results. A facile and practical procedure for the stereoselective synthesis of methyl (*Z*)-3-quinuclidinylideneacetate derivative, *via* the Horner-Wadsworth-Emmons reaction with sodium methoxide in methanol, is also described.

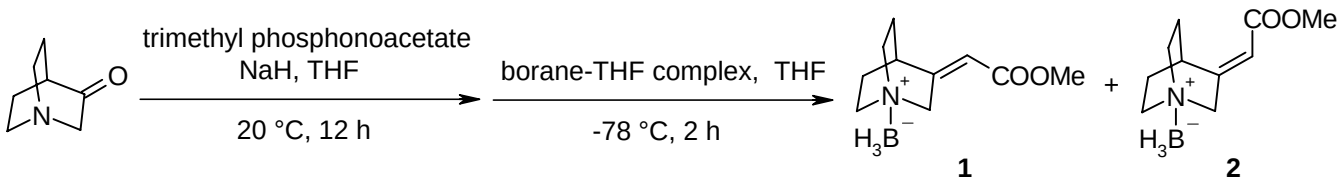
Substituted quinuclidines constitute an important group of biologically active compounds including muscarinic receptor agonists,[1] neurokinin-1 receptor antagonists[2] and squalene synthase inhibitors.[3] For the purposes of an ongoing study of squalene synthase inhibitors,[3c] we required an efficient method to prepare methyl (*Z*)-3-quinuclidinylideneacetate. Although the lack of chirality of (*Z*)-3-quinuclidinylideneacetic acid makes it an attractive scaffold for bioactive molecules, its stereoselective synthesis has never previously been reported.

Stotter *et al.* reported that (*E*)-3-ethylidenequinuclidine was less stable than the corresponding *Z*-isomer and isomerized to a mixture of the more stable *Z*-isomer and β,γ-deconjugated endocyclic alkene isomer in a ratio of 93:7 upon treatment with sodium in HMPA.[4] This study prompted us to investigate the isomerization reaction of the methyl 3-quinuclidinylideneacetate derivative which is easily prepared as a 1:1 mixture of the *Z*-isomer and *E*-isomer *via* the Horner-Wadsworth-Emmons reaction with 3-quinuclidinone in the presence of sodium hydride in tetrahydrofuran.

Here we describe the results of our studies on the isomerization reactions of the methyl 3-quinuclidinylideneacetate derivative, and also report the stereoselective synthesis of methyl (*Z*)-3-quinuclidinylideneacetate derivative *via* the Horner-Wadsworth-Emmons reaction.

RESULTS AND DISCUSSION

As in our previous study, [methyl (*Z*)-3-quinuclidinylideneacetate]-*N*-borane (**1**) and the corresponding *E*-isomer (**2**) were prepared as a 1:1 mixture in good yield *via* the Horner-Wadsworth-Emmons methodology, followed by protection of the bridgehead nitrogen atoms as borane complexes, without competitive hydroboration of the double bonds (Scheme 1).[3c, 5] The complexes were separated by silica gel column chromatography. Quinuclidine-*N*-borane complexes, which are useful intermediates to avoid N-alkylation in alkylation reactions, liberate the parent amines on exposure to acidic solution.[4] Efforts were thus focused on isomerization reactions under non-acidic conditions. α,β-Unsaturated esters are, however, known to be easily converted into the corresponding β,γ-deconjugated esters under basic conditions. [6]



Scheme 1. Preparation of methyl 3-quinuclidinylideneacetate derivatives (**1**) and (**2**)

It is well recognized that molecular mechanics calculations can be used to predict the outcome of organic reactions that take place under thermodynamic control. Thus, we first performed theoretical studies in order to predict the most thermodynamically stable isomers. Estimation of the global minimum total energy of the compounds was performed with the MM3 molecular mechanics method included in a Tektronix Computer Aided Chemistry Worksystem (version 5.02).[7]

Figure 1 shows the three possible isomers of methyl 3-quinuclidinylideneacetate. The computation indicates that the desired *Z*-α,β-unsaturated ester (**A**) is the most thermodynamically stable of these three isomers. The MM calculation of the total energy leads to an energy difference between the *Z*-α,β-unsaturated ester (**A**) and the corresponding *E*-isomer (**B**) of 1.3 kcal/mol, in favor of **A**. The corresponding β,γ-deconjugated ester (**C**) appears to be highly unfavorable compared to the *Z*-α,β-unsaturated ester (**A**), by 26 kcal/mol. We therefore expect that the undesirable isomerization of the *Z*- and/or *E*-α,β-unsaturated ester to the corresponding β,γ-deconjugated endocyclic alkene

isomer would not occur if the isomerization reaction were carried out under basic conditions, and also anticipate that the desired *Z*-α,β-unsaturated ester (**1**) should significantly predominate in thermodynamic equilibrium.

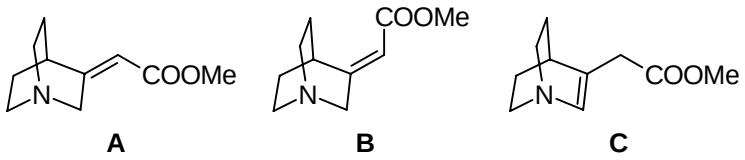


Figure 1. Three possible isomers of methyl 3-quinuclidinylideneacetate

The experimental results of the isomerization reactions under several different conditions are summarized in Table 1. Our investigations of the reaction were conducted with a 1:1 mixture of the *Z*-α,β-unsaturated ester (**1**) and the corresponding *E*-isomer (**2**) as a substrate. The *Z*/*E* ratios of the reaction products were determined by integration of the vinyl proton signals in the 300 MHz ^{1}H NMR spectrum.

Treatment of the 1:1 mixture of the *Z*-isomer (**1**) and the *E*-isomer (**2**) with a catalytic amount (0.1 equiv.) of iodine[8] did not affect the ratio of the two isomers (Entry 1). The isomerization of the *E*-isomer (**2**) to the desired *Z*-isomer (**1**) was achieved by treatment with a catalytic amount (0.1 equiv.) of potassium carbonate in methanol[9] (12 h at 50 °C) without hydrolysis of the ester function, producing quantitative amounts of a mixture of the desired *Z*-isomer (**1**) and the corresponding *E*-isomer (**2**) in a ratio of 10:1 in favor of **1** (Entry 2). As expected, the corresponding β,γ-deconjugated endocyclic alkene was not detected in the reaction mixture (analyzed by ^{1}H NMR spectrometry). Treatment with 0.1 equiv. of sodium methoxide in methanol[6a, b] also gave a 10:1 mixture of **1** and **2**, in near quantitative combined yield, without accompanying deconjugation, and without hydrolysis of the α,β-unsaturated ester (Entry 3). However, using triethylamine[6c] instead of potassium carbonate or sodium methoxide resulted in no isomerization (Entry 4). An attempt to isomerize the *E*-isomer (**2**) to the desired *Z*-isomer (**1**) failed when the reaction was performed in tetrahydrofuran in the presence of potassium carbonate (Entry 5). It is likely that the isomerization of the *E*-isomer (**2**) to the *Z*-isomer (**1**) proceeds through a pathway involving a sequence of deprotonation and reprotonation steps. The isomerization reaction with potassium carbonate in methanol did not proceed at 20 °C (Entry 6).

The equilibrium *Z*/*E* ratio and the time required to reach thermodynamic equilibrium are also shown in Table 1 (Entries 7 and 8). Brief exposure (3 h) to potassium carbonate resulted in a *Z*/*E* ratio of 3:1 (Entry 7). Treatment with potassium carbonate for 48 h produced a mixture of the *Z*-isomer (**1**) and the

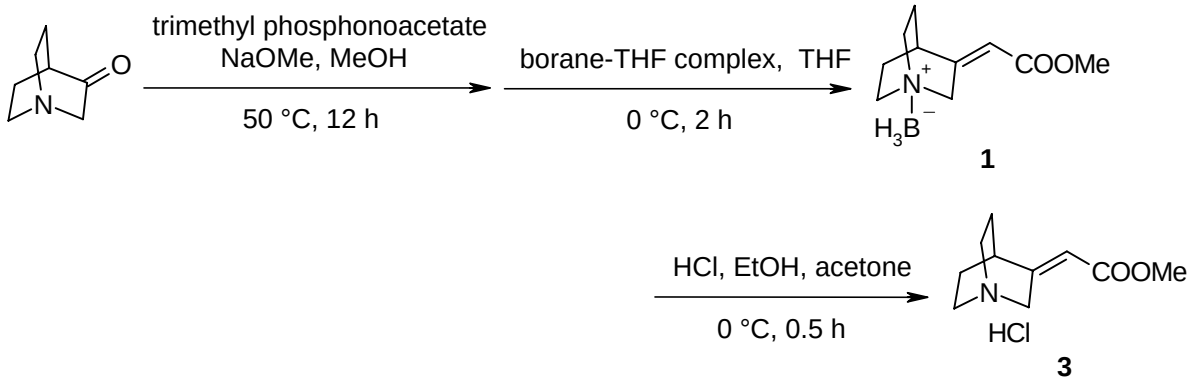
E-isomer (**2**) in a ratio of 10:1 in favor of **1** (Entry 8). These results indicate that the final *Z*/*E* ratio of the isomerization reaction is governed by the thermodynamics of the system, and it can be concluded that the *Z*/*E* ratio at thermodynamic equilibrium is 10:1.

Table 1. Isomerization of methyl 3-quinuclidinylideneacetate derivatives[a]

Entry	Reagent[b]	Solvent	Condition		Obtained **1**/**2** ratio[c]	Yield (%)[d]
1	I_2	benzene	50 °C,	12 h	1:1	-
2	K_2CO_3	MeOH	50 °C,	12 h	10:1	100
3	NaOMe	MeOH	50 °C,	12 h	10:1	95
4	Et_3N	MeOH	50 °C,	12 h	1:1	-
5	K_2CO_3	THF	50 °C,	12 h	1:1	-
6	K_2CO_3	MeOH	20 °C,	12 h	1:1	-
7	K_2CO_3	MeOH	50 °C,	3 h	3:1	100
8	K_2CO_3	MeOH	50 °C,	48 h	10:1	97

[a] A 1:1 mixture of the *Z*-isomer (**1**) and the *E*-isomer (**2**) was used as a substrate for the isomerization reaction. [b] 0.1 Equiv. of reagent was used. [c] The *Z*/*E* ratios of the reaction products were determined by integration of the vinyl proton signals in the 300 MHz ^{1}H NMR spectrum. [d] Combined yield of the *Z*-isomer (**1**) and the *E*-isomer (**2**). When no significant change in a ratio of the isomers occurred, the yield was not obtained.

The isomerization of the *E*-isomer into the desired *Z*-isomer was accomplished in the presence of a catalytic amount of sodium methoxide in methanol. A few research groups have reported that Horner-Wadsworth-Emmons reactions of triethyl phosphonoacetate derivatives with several types of carbonyl compounds proceed in the presence of sodium ethoxide in ethanol.[10] Thus, we attempted the stereoselective construction of the methyl (*Z*)-3-quinuclidinylideneacetate derivative *via* a sequence of the Horner-Wadsworth-Emmons reaction and the isomerization reaction with sodium methoxide in methanol. Treatment of 3-quinuclidinone with trimethyl phosphonoacetate in the presence of sodium methoxide in methanol, followed by protection of the bridgehead nitrogen atom as a borane complex, provided a mixture of (methyl 3-quinuclidinylideneacetate)-*N*-borane in a ratio of *Z*/*E* of 10:1, as a crystalline solid (Scheme 2). Recrystallization of this mixture gave a facile method for purification, removing the *E*-isomer (**2**), providing a highly *Z*-enriched mixture of (methyl 3-quinuclidinylideneacetate)-*N*-borane in a Z/*E* ratio of 22:1 in 65% combined yield from 3-quinuclidinone.



Scheme 2. Preparation of methyl (*Z*)-3-quinuclidinylideneacetate derivative (**1**) and (**3**)

Methyl (*Z*)-3-quinuclidinylideneacetate hydrochloride was obtained as a crystalline solid from **1** in 96% yield using the deprotection procedure reported by Stotter *et al*.,[4] without accompanying isomerization of the double bond (Scheme 2).

In conclusion, we have established a facile and practical route to the stereoselective synthesis of methyl (*Z*)-3-quinuclidinylideneacetate derivative. Isomerization of [methyl (*E*)-3-quinuclidinylideneacetate]-*N*-borane (**2**) to the corresponding *Z*-isomer (**1**) was achieved by treatment with a catalytic amount of weak base, such as potassium carbonate or sodium methoxide, in methanol, establishing a thermodynamic equilibrium between the *Z*-isomer (**1**) and the corresponding *E*-isomer (**2**) in a ratio of 10:1 in favor of **1**. Results of molecular mechanics MM3 calculations, showed methyl (*Z*)-3-quinuclidinylideneacetate to be the most thermodynamically stable of the three possible isomers, in agreement with the experimental results. This isomerization procedure was developed into a convenient method for the stereoselective synthesis of the methyl (*Z*)-3-quinuclidinylideneacetate derivative *via* the Horner-Wadsworth-Emmons reaction with sodium methoxide in methanol. This simple procedure can offer a non-chiral quinuclidine moiety as a useful intermediate for various bioactive molecules.

EXPERIMENTAL

Melting points were measured with a Yanaco MP-500D melting point apparatus without correction. ^{1}H NMR spectra were measured with a JEOL LA300 spectrometer and ^{13}C NMR spectra were measured with a JEOL EX400 spectrometer. The chemical shifts are expressed in δ units using tetramethylsilane as the internal standard. IR spectra were recorded on a Horiba FT-720 spectrometer. MS spectra were taken at FAB method with a JEOL JMS-700T spectrometer. The elemental analysis was performed with a Yanaco MT-5 microanalyzer (C, H and N) and a Yokogawa IC-7000S ion chromatographic analyzer (halogen). Starting materials, reagents and solvents were purchased from commercial sources

(Aldrich Chem. Co., Kanto Chemical Co., Ltd. or Tokyo Kasei Kogyo Co., Ltd.) and used without further purification. The progress of reactions was followed by TLC using Merck Silica gel $60F_{254}$. Chromatographic purification was performed on Merck Kieselgel 60 (0.040-0.063 mesh).

Preparation of [methyl (*Z*)-3-quinuclidinylideneacetate]-*N*-borane (1) and [methyl (*E*)-3-quinuclidinylideneacetate]-*N*-borane (2) using sodium hydride/trimethyl phosphonoacetate in tetrahydrofuran: To a stirred solution of trimethyl phosphonoacetate (9.09 g, 49.9 mmol) in tetrahydrofuran (38 mL) was added sodium hydride (2.00 g, 49.9 mmol, 60% dispersion in mineral oil) at 0 °C and the whole was stirred for 0.5 h. The reaction mixture was allowed to warm to ambient temperature and stirred for a further 0.5 h. 3-Quinuclidinone[11] (4.81 g, 38.4 mmol) was added at 0 °C and stirred for 0.5 h. The reaction mixture was allowed to warm to ambient temperature and stirred for a further 12 h. After addition of H_2O (20 mL), the reaction mixture was extracted with chloroform (100 mL × 2). The extract was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give a colorless oil. The resulting oil was dissolved in tetrahydrofuran (100 mL) and cooled to -78 °C. To this solution was added a solution of borane-tetrahydrofuran complex in tetrahydrofuran (50.0 mL, 1.0 M, 50.0 mmol) dropwise and stirred for 2 h. After addition of H_2O (5.0 mL), the reaction mixture was allowed to warm to ambient temperature and stirred for 0.5 h. The reaction mixture was extracted with ethyl acetate (100 mL × 2). The extract was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with a 4:1 mixture of *n*-hexane and ethyl acetate to give **2** as a colorless crystalline solid (4.41 g, 48%) from the first fraction and **1** as a colorless crystalline solid (4.34 g, 47%) from the second fraction.

1: mp 116-117 °C (from diisopropyl ether); TLC R_f = 0.29 (ethyl acetate/*n*-hexane = 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78-2.02 (4H, m, H-5 and H-8 of quinuclidine), 2.63-2.67 (1H, m, H-4 of quinuclidine), 2.99-3.20 (4H, m, H-6 and H-7 of quinuclidine), 3.73 (3H, s, OC*H*$_3$), 4.13-4.16 (2H, m, H-2 of quinuclidine), 5.76 (1H, t, *J* = 2.6 Hz, C=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.31 (C-5 and C-8 of quinuclidine), 32.37 (C-4 of quinuclidine), 51.39 (O*C*H$_3$), 53.51 (C-6 and C-7 of quinuclidine), 61.41 (C-2 of quinuclidine), 112.83 (C=*C*H), 158.46 (C-3 of quinuclidine), 166.07 (*C*=O); IR (KBr, cm^{-1}) ν 2360, 1706, 1253, 1170, 1155; HRMS (FAB, *m/z*) calcd for $C_{10}H_{17}NO_2B$ (M - H^+) 194.1352. Found 194.1362. Anal. Calcd for $C_{10}H_{18}NO_2B$: C, 61.57; H, 9.30; N, 7.18. Found: C, 61.57; H, 9.54; N, 7.20.

2: mp 171-173 °C (from diisopropyl ether); TLC R_f = 0.42 (ethyl acetate/*n*-hexane = 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79-2.01 (4H, m, H-5 and H-8 of quinuclidine), 2.97-3.18 (4H, m, H-6 and H-7 of quinuclidine), 3.66-3.68 (2H, m, H-2 of quinuclidine), 3.72 (3H, s, OC*H*$_3$), 4.16-4.20 (1H, m, H-4 of quinuclidine), 5.68 (1H, t, *J* = 2.0 Hz, C=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.69 (C-5 and C-8 of

quinuclidine), 25.31 (C-4 of quinuclidine), 51.30 (O*C*H_3), 53.70 (C-6 and C-7 of quinuclidine), 61.10 (C-2 of quinuclidine), 112.81 (C=*C*H), 157.82 (C-3 of quinuclidine), 165.94 (*C*=O); IR (KBr, cm^{-1}) ν 2375, 1706, 1234, 1166, 1153; HRMS (FAB, *m/z*) calcd for $C_{10}H_{17}NO_2B$ (M - H^+) 194.1352. Found 194.1340. Anal. Calcd for $C_{10}H_{18}NO_2B$: C, 61.57; H, 9.30; N, 7.18. Found: C, 61.42; H, 9.44; N, 7.18.

Isomerizaion of *E*-α,β-unsaturated ester (2) into the corresponding *Z*-isomer (1): To a stirred solution of a 1:1 mixture of **1** and **2** (300 mg, 1.54 mmol) in methanol (15 mL) was added potassium carbonate (20 mg, 0.15 mmol) at ambient temperature. The mixture was stirred for 12 h at 50 °C and cooled to ambient temperature. The reaction mixture was poured into 150 mL of water and extracted with ethyl acetate (100 mL). The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated *in vacuo* to afford **1** as a colorless crystalline solid (300 mg, 100 %), which contained small amount of the corresponding *E*-isomer (**2**) (10:1, determined by integration of the vinyl proton signals in the 300 MHz ^{1}H NMR spectrum).

Preparation of [methyl (*Z*)-3-quinuclidinylideneacetate]-*N*-borane (1) using sodium methoxide/trimethyl phosphonoacetate in methanol: Sodium (27.6 g, 1.20 mol) was added to methanol (800 mL) at 0 °C in portion and the mixture was stirred for 1 h. Trimethyl phosphonoacetate (200 g, 1.10 mol) was added at 0 °C dropwise and stirred for 1 h. A solution of 3-quinuclidinone (125 g, 1.00 mol) in methanol (200 mL) was added at 0 °C dropwise to the reaction mixture and the whole was stirred for 0.5 h. The reaction mixture was allowed to warm to 50 °C and stirred for a further 18 h. After concentration *in vacuo*, the residue was diluted with chloroform (1.0 L). The mixture was washed with H_2O and brine, dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The resulting oil was dissolved in tetrahydrofuran (600 mL) and cooled to 0 °C. To this solution was added a solution of borane-tetrahydrofuran complex in tetrahydrofuran (917 mL, 1.0 M, 917 mmol) dropwise and the mixture was stirred for 2 h. After addition of H_2O (600 mL), the reaction mixture was allowed to warm to ambient temperature and stirred for 0.5 h. The reaction mixture was extracted with ethyl acetate (600 mL). The extract was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residual solid was recrystallized from diisopropyl ether to give **1** as a colorless crystalline solid (110 g, 65%), which was contaminated by small amount of the corresponding *E*-isomer (**2**) (22:1, determined by integration of the vinyl proton signals in the 300 MHz ^{1}H NMR spectrum).

Preparation of methyl (*Z*)-(3-quinuclidinylidene)acetate hydrochloride (3): A solution of **1** (630 mg, 3.01 mmol) in acetone (6.3 mL) was treated with hydrogen chloride in methanol (10 %, 3.0 mL) at

0 °C for 0.5 h. Ether (20 mL) was added and the resulting precipitate was filtered to give **3** as a colorless crystalline solid (630 mg, 96%): mp 218-219 °C (from acetone-diisopropyl ether); TLC R_f = 0.21 ($CHCl_3$/methanol/*c.* NH_3 = 100/10/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75-1.86 (2H, m, H-5 and H-8 of quinuclidine), 1.96-2.07 (2H, m, H-5 and H-8 of quinuclidine), 2.49-2.52 (1H, m, H-4 of quinuclidine), 3.24-3.33 (4H, m, H-6 and H-7 of quinuclidine), 3.66 (3H, s, OCH_3), 4.34-4.37 (2H, m, H-2 of quinuclidine), 5.97 (1H, t, *J* = 2.6 Hz, C=C*H*), 11.95 (1H, br s, *H*Cl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.29 (C-5 and C-8 of quinuclidine), 30.06 (C-4 of quinuclidine), 45.19 (C-6 and C-7 of quinuclidine), 51.15 (C-2 of quinuclidine), 53.41 (O*C*H_3), 113.03 (C=*C*H), 155.73 (C-3 of quinuclidine), 165.60 (*C*=O); IR (KBr, cm^{-1}) ν 1699, 1242, 1151; HRMS (FAB, *m/z*) calcd for $C_{10}H_{16}NO_2$ (M + H^+) 182.1181. Found 182.1179; Anal. Calcd for $C_{10}H_{15}NO_2$•HCl: C, 55.17; H, 7.41; N, 6.43; Cl, 16.29. Found: C, 54.80; H, 7.35; N, 6.42; Cl, 16.37.

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7. Theoretical studies were performed using the MM3 molecular mechanics method included in a Tektronix Computer Aided Chemistry Worksystem (version 5.02) package. The program was compiled on a Pentium III 600 MHz system and used for all computations. Structures were pre-optimized using MM3 method. Each molecule was subjected to an extensive conformational search by systematically rotating each free rotatable bond by 10° increments. The generated conformers were optimized and the most stable conformation was obtained by molecular mechanics using Augmented MM3.
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11. 3-Quinuclidinone was prepared from commercially available 3-quinuclidinone hydrochloride as follows. To a stirred solution of potassium carbonate (270 g, 1.95 mmol) in H_2O (800 mL) was added 3-quinuclidinone hydrochloride (192 g, 1.19 mol) at ambient temperature in portion and the mixture was stirred for 1 h. The reaction mixture was extracted with chloroform (600 mL ×

2). The extract was dried over potassium carbonate and concentrated in vacuo. Benzene (150 mL) was added to the resulting residue and the mixture was concentrated *in vacuo* to give 3-quinuclidinone (140 g, 94%) as a colorless solid.