Efficient Method for the Synthesis of 1,4-Disubstituted 5-Carbomethoxypyrimidin-6-ones

Chris A. Veale,*,† Gary B. Steelman,† and Margaret M. Chow‡

Medicinal Chemistry Department, Zeneca Pharmaceuticals Group, A Business Unit of ZENECA Inc., Wilmington, Delaware 19897

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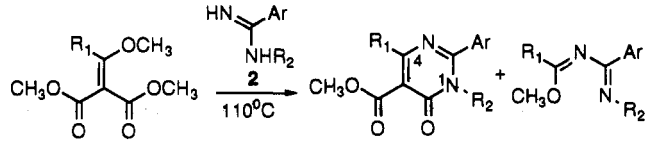
As part of a project aimed at finding nonpeptidic inhibitors of the enzyme human leukocyte elastase, we have explored the biological activity of a series of pyrimidinone-based inhibitors. The pyrimidinone **3** was a key intermediate in the synthesis of these compounds, where the pyrimidinone ring had been prepared via a cyclization reaction between dimethyl (methoxymethylene)malonate (**1a**) and a substituted amidine such as **2a** (entry 1, Table I).[1] This procedure afforded good yields of pyrimidinones with complete regiochemical control. However, attempts to extend this procedure to the synthesis of the 4-alkyl-substituted pyrimidinone (R_1 = CH_3, entry 2) using the methyl-substituted (methoxymethylene)malonate **1b** with amidine **2a** were less successful, affording the desired pyrimidinone as the minor product of the reaction. Instead, the major product of this reaction was found to be the acyclic compound **4**, which was formed in 82% yield.

A survey of the literature did not reveal any related examples of this approach for the synthesis of 1,4-disubstituted 5-carbomethoxypyrimidinones.[2] However, 3-substituted 2-(alkoxycarbonyl)-2-propenoates which lack the methoxy leaving group in the 3-position of **1b** are reported to react with unsubstituted amidines, such as benzamidine, to provide the corresponding dihydropyrimidinones in good yield.[3] We reasoned that if an N-substituted amidine (e.g., **2a**) could be used in place of benzamidine, coupling this reaction with a subsequent oxidation step would provide a method for the synthesis of the desired 1,4-disubstituted pyrimidinones.

In contrast to the problem encountered with (methoxymethylene)malonate **1b**, amidine **2a** and dimethyl ethylidenemalonate **5a** underwent Michael addition followed by ring closure to provide dihydropyrimidinone **6b** in high yield as an inseparable 4:1 mixture of diastereoisomers (Scheme I). Attempts at oxidizing dihydropyrimidinone **6b** to the pyrimidinone **3b** by a variety of dehydrogenation procedures including DDQ, palladium on carbon at elevated temperatures, and nickel peroxide[4] were unsuccessful, resulting in recovered starting material. MnO_2 has been reported[5] to effect oxidation of a series

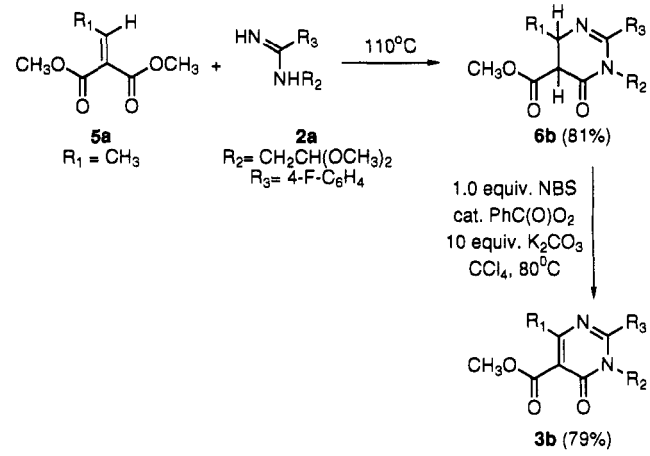
Table I. Reactions of Amidines with Substituted (Methoxymethylene)malonates



1 3 4

entry	1 R_1 =	2 R_2 =	2 Ar =	ratio 3:4	yield (%) 3 + 4
1	**1a** H	$CH_2CH(OCH_3)_2$	**2a** 4-F-Ph	100:0	85
2	**1b** CH_3	$CH_2CH(OCH_3)_2$	**2a** 4-F-Ph	1:6	95
3	**1b** CH_3	CH_3	**2b** 4-F-Ph	1.6:1	68
4	**1b** CH_3	H	**2d** Ph	100:0	77

Scheme I



5a R_1 = CH_3 **2a** R_2= $CH_2CH(OCH_3)_2$, R_3= 4-F-C_6H_4 **6b** (81%) **3b** (79%)

dihydropyrimidinones, although none of the examples contained substitution at the N-1 position. Application of this reagent in the oxidation of **6b** was found to be inefficient, resulting in prolonged reaction times and difficulty in driving the reaction to completion.[6] However, successful oxidation was achieved by employing a one-pot bromination–dehydrobromination sequence using *N*-bromosuccinimide in the presence of finely ground potassium carbonate and catalytic amounts of benzoyl peroxide, which afforded pyrimidinone **3b** in 79% yield. We presume that the oxidation proceeds via a radical-initiated allylic bromination of the 4-position followed by facile elimination of HBr due to the acidity of the C-5 proton. Both diastereoisomers of **6b** were oxidized in this reaction, as is shown by both the absence of starting materials and the high yields obtained.

We have found this two-step procedure to be generally useful for the preparation of a variety of 1,4-disubstituted pyrimidinones (Table II). Entries 1–5 show that the procedure is tolerant of sensitive functional groups, which further increases its utility. Particularly noteworthy is the success of this method in the placement of sterically demanding groups simultaneously at the 1 and 4 positions of the pyrimidinone ring (e.g., entries 4 and 5), which would be expected to be problematic in light of the results obtained with the substituted methoxymethylene malonate **1b** (*vide infra*).

The alkylidine malonates **5** used in Table II were readily available via a Knoevenagel condensation of dimethyl malonate and the requisite aldehyde (R_1CHO) or obtained

† Pulmonary Chemistry Section.
‡ Structural Chemistry Section.

(1) Gupta, K. A.; Saxena, A. K.; Jain, P. C. *Ind. J. Chem.* **1982**, *21B*, 228.
(2) In contrast to the reaction of **1b** and **2a**, *N*-propylbenzamidine has been reported to react with methyl acetoacetate to give the corresponding pyrimidinone in moderate yield. Sitte, A.; Paul, H. *Chem. Ber.* **1969**, *102*, 615.
(3) Cho, H.; Ueda, M.; Ohnaka, Y.; Hayashimatsu, M. *Heterocycles* **1984**, *22*, 1959.
(4) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.
(5) Atwal, K. S.; Ahmed, S. Z.; Bird, J. E.; Delaney, C. L.; Dickinson, E. J.; Ferrara, F. N.; Hedberg, A.; Miller, A. V.; Moreland, S.; O'Reilly, B. C.; Schaeffer, T. R.; Waldron, T. L.; Weller, H. N. *J. Med. Chem.* **1992**, *35*, 4751.

(6) Treatment of compound **6b** with 6 equiv of MnO_2 gave only 20% of the dihydropyrimidone **3b** after 88 h in refluxing benzene.

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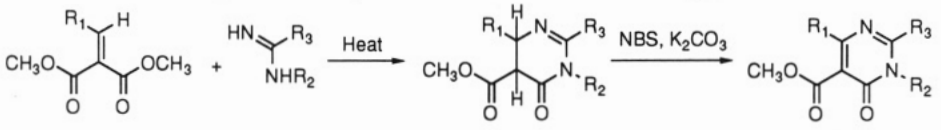
Table II. Synthesis of 1,4-Disubstituted 5-Carbomethoxypyrimidinones



5 2 6 3

entry	alkylidene malonate 5	R1 =	amidine 2	R2 =	R3 =	dihydropyrimidinone 6[a] (%)	pyrimidinone 3[a] (%)
1	5a	methyl	$CH_2CH(OCH_3)_2$	2a	$4\text{-}FC_6H_4$	6b (81)	3b (79)
2	5b	iPr	$CH_2CH(OCH_3)_2$	2a	$4\text{-}FC_6H_4$	6c (79)	3c (89)
3	5c	$-(CH_2)_3OSi^tBuPh_2$	$CH_2CH(OCH_3)_2$	2a	$4\text{-}FC_6H_4$	6d (74)	3d (70)
4	5d	$4\text{-}IC_6H_4$	$CH_2CH(OCH_3)_2$	2a	$4\text{-}FC_6H_4$	6e (73)	3e (90)
5	5e	*tert*-butyl	$CH_2CH(OCH_3)_2$	2a	$4\text{-}FC_6H_4$	6f (69)	3f (85)
6	5a	methyl	methyl	2b	$4\text{-}FC_6H_4$	6g (65)	3g (76)
7	5a	methyl	benzyl	2c	C_6H_5	6h (77)	3h (45)
8	5a	methyl	H	2d	C_6H_5	6i (74)	3i (78)
9	5a	methyl	n-propyl	2e	$4\text{-}FC_6H_4$	6j (93)	3j (74)
10	5b	iPr	H	2f	CH_3O	6k (55)[b]	3k (62)

[a] Yield of isolated purified material. [b] 2 equiv of sodium methoxide was used to generate the amidine free base from the H_2SO_4 salt.

commercially. The substituted amidines **2** were made by a Pinner synthesis from the appropriate nitrile (R_3CN) via the intermediate imidate hydrochlorides, which were then reacted with the desired amine (R_2NH_2) to give the amidines in high overall yield. This route is very flexible, allowing control of the substitution pattern of the pyrimidinone ring by appropriate choice of the aldehyde, nitrile, and amine starting materials.

Proof that the cyclization reaction proceeds with the indicated regiochemistry was obtained from an X-ray crystal structure of **3e** (Figure 1). Interestingly, this crystal structure shows that the C-4 iodophenyl group forces the neighboring carbomethoxy substituent out of planarity with the pyrimidinone ring by 67°.

We believe that the formation of the acyclic compound **4** in the reaction of **1b** and **2a** is the result of a severe steric interaction which develops in the cyclization transition state between an axially disposed 4-position substituent (methoxyl or R_1) and the substituent on nitrogen (R_2) in the intermediate Michael adduct **7** (eq 1).[7] This steric interaction disfavors ring closure. The 4-position methoxyl group in **7** is appropriately positioned to effect a Grob type fragmentation, via oxonium ion **8**. In cases where ring closure is difficult, this becomes the favored pathway resulting in acyclic compound **4** as the major product.

The results in Table I provide further support for the hypothesis that an interaction between one of the 4-position substituents and R_2 impedes ring closure. Independent removal of either R_1 or R_2 (entries 1 and 4) results in the formation of only the desired pyrimidinones. Additionally, as shown by entries 2 and 3, an increase in the size of R_2 results in a corresponding increase in the amount acyclic compound **4** that is obtained.

Thus, in reactions between an alkylidene malonate (**5**) and a substituted amidine (**2**), the lack of the 4-position methoxyl in Michael adduct **9** (eq 1) removes the frag-

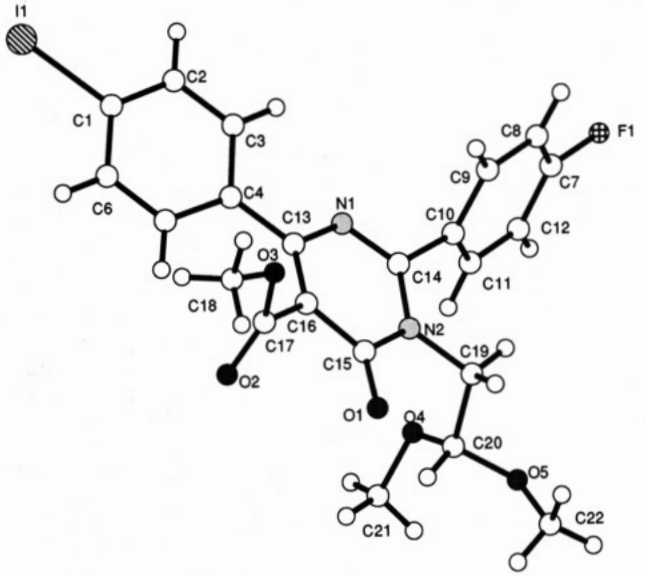
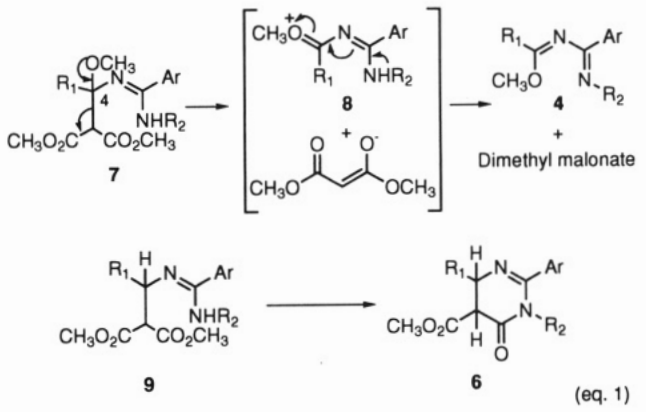
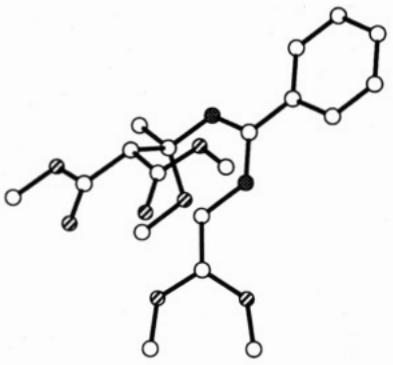


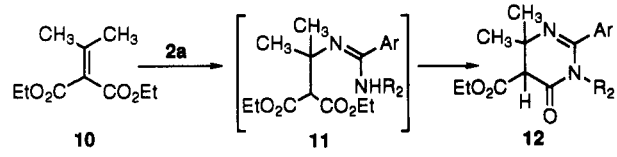
Figure 1. X-ray crystal structure of **3e**.



(7) While the precise details of the transition-state are unknown, inspection of molecular models suggests that a severe steric clash would occur between an axial 4-position substituent (arbitrarily depicted here as methoxyl) and the N-1 substituent making ring closure a high-energy process. The fragmentation reaction relieves the steric congestion and becomes the dominate reaction.



mentation pathway resulting in cyclic products.[8] Consistent with this proposal, the reaction between diethyl alkylidenemalonate **10** and amidine **2a** provides only the cyclized product **12** in 69% yield (eq 2). The steric



(eq.2)

environment in the cyclization transition state of **11** is presumably similar to that encountered in **7**, but the lack of a methoxyl group to effect fragmentation directs the course of the reaction to the formation of the cyclic product.

In summary, we have developed an efficient method for the synthesis of 1,4-disubstituted 5-carbomethoxypyrimidinones which is both high yielding and avoids the formation of the fragmentation product **4**, which results when one of the traditional methods of pyrimidinone synthesis is employed.

Experimental Section

General Methods. Analytical samples were homogeneous by TLC and afforded spectroscopic results consistent with the assigned structures. Proton NMR spectra were obtained in DMSO-d_6, unless otherwise noted, using a Varian AM-300 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. Mass spectra (MS) were recorded on a Kratos MS-80 instrument operating in the chemical ionization (CI) mode. High-resolution mass spectra were obtained on a VG70V-SE instrument. Elemental analyses for carbon, hydrogen, and nitrogen were determined by the Zeneca Pharmaceuticals Group Analytical Chemistry Department on a CEC 240XA elemental analyzer. Chromatography refers to flash chromatography conducted on Kieselgel 60, 230–400 mesh (E. Merck, Darmstadt), using the indicated solvents. Solvents used for reactions or chromatography were either reagent grade or HPLC grade. Reactions were run under an argon atmosphere at ambient temperature unless otherwise noted. Solutions were evaporated under reduced pressure on a rotary evaporator. The following compounds were prepared by the referenced procedures: methyl 4-methyl-2-(methoxycarbonyl)-2-pentenoate (**5a**),[9] methyl 3-(4-iodophenyl)-2-(methoxycarbonyl)-2-propenoate (**5d**),[10] and methyl 4,4-dimethyl-2-(methoxycarbonyl)-2-pentenoate (**5b**).[11]

Method A. Synthesis of 4-Substituted 5-Carbomethoxy-4,5-dihydropyrimidinones: 1-*N*-Propyl-2-(4-fluorophenyl)-4-methyl-1,4,5,6-tetrahydro-6-oxo-5-pyrimidinecarboxylic Acid, Methyl Ester (6j). A solution of dimethyl ethylidenemalonate (**5a**) (2 mL, 14 mmol) and *N*-(2,2-dimethoxyethyl)-4-(fluorophenyl)carboxamidine (**2a**) (2.54 g, 14 mmol) in methanol (15 mL) was heated at 110 °C for 3 h (distilling the solvent as the reaction proceeded). The mixture was cooled and diluted with ethyl acetate (200 mL), and the solution was washed with H_2O (2 × 50 mL) and brine (1 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, the solution was filtered, and the solvent was evaporated. The residual oil was purified by flash column chromatography (eluting with Et_2O/hexanes (70:30) v/v) to provide 3.9 g (93%) of **6j** as an oil containing an inseparable mixture of cis and trans isomers. Major isomer: ^{1}H NMR (300 MHz) δ 7.56–7.51 (m, 2H), 7.34–7.27 (m, 2H), 3.96–3.90 (m, 1H), 3.69 (s, 3H), 3.52 (d, 1H, *J* = 11 Hz), 3.33–3.24 (m, 2H), 1.35–1.28 (m, 2H), 1.24 (d, 3H, *J* = 6.7 Hz), 0.64 (t, 3H, *J* = 7.3 Hz); MS (CI) 307 (100, M + H), 287 (10); HRMS calcd for $C_{16}H_{19}N_2O_3F$ 306.1379, found 306.1363.

Method B. Oxidation of 4-Substituted 5-Carbomethoxy-4,5-dihydropyrimidin-6-ones: 1-*N*-Propyl-2-(4-fluorophenyl)-4-methyl-1,6-dihydro-6-oxo-5-pyrimidinecarboxylic Acid, Methyl Ester (3j). A mixture of **6j** (2.2 g, 7.2 mmol), *N*-bromosuccinimide (1.28 g, 7.2 mmol), benzoyl peroxide (100 mg, 0.4 mmol), and *finely ground* potassium carbonate (9 g, 72 mmol) in carbon tetrachloride (70 mL) was vigorously stirred and heated at reflux for 0.5 h. The mixture was cooled to room temperature and poured into H_2O (100 mL), and the product was extracted into CH_2Cl_2 (3 × 100 mL). The organic layers were dried over anhydrous $MgSO_4$, the solution was filtered, and the solvent was removed to give an oil. The crude material was purified by flash column chromatography (eluting with Et_2O/hexanes, gradient elution, (60:40–100:0) v/v) to give 1.62 g (74%) of **3j** as a white solid: mp 101.5–103 °C; ^{1}H NMR (300 MHz) δ 7.68 (dd, 2H, *J* = 5.5, 8.7 Hz), 7.38 (t, 2H, *J* = 8.7 Hz), 3.83 (s, 3H), 3.73 (t, 2H, *J* = 5.8 Hz), 2.24 (s, 3H), 1.46 (m, 2H), 0.65 (t, 3H, *J* = 7.4 Hz); MS (CI) 305 (100, M + H), 273 (40). Anal. Calcd for $C_{16}H_{17}N_2O_3F$: C, 63.14; H, 5.63; N, 9.20. Found: C, 62.81; H, 5.59; N, 9.09.

2-Phenyl-4-methyl-1,6-dihydro-6-oxo-5-pyrimidinecarboxylic Acid, Methyl Ester (3i). Method B: white solid; mp 207–210 °C; ^{1}H NMR (300 MHz) δ 13.12 (s, 1H), 8.13 (d, 2H, *J* = 7.3 Hz), 7.56 (m, 3H), 3.81 (s, 3H), 2.32 (s, 3H); MS (CI) 245 (100, M + H), 213 (40). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.46. Found: C, 63.53; H, 5.01; N, 11.29. **3i** was also prepared as follows: A solution of methyl 2-(methoxycarbonyl)-3-methoxy-2-butenoate (**1b**, 500 mg, 2.65 mmol) and benzamidine (**2d**, 350 mg, 2.91 mmol) in methanol (10 mL) was heated at reflux for 3 h. The resulting oil was crystallized from Et_2O to give 550 mg (77%) of **3i**.

Reaction of Methyl 2-(Methoxycarbonyl)-3-methoxy-2-butenoate (1b) with *N*-(2,2-Dimethoxyethyl)-4-(fluorophenyl)carboxamidine (2a). A solution of **1b**[12] (0.94 g, 5 mmol) and amidine **2a** in methanol (5 mL) was heated at 110 °C (distilling solvent) for 1 h. The resulting oil was purified by flash column chromatography (gradient elution, EtOAc/CH_2Cl_2 (10:90–100:0)) to provide 150 mg of recovered **1b**, 975 mg (82%) of **4**, and 195 mg (13%) of **3b**. Data for **4**: oil; ^{1}H NMR (300 MHz) δ 7.83–7.78 (dd, 2H, *J* = 5.7, 8.8 Hz), 7.26–7.20 (t, 2H, *J* = 8.9 Hz), 4.63 (t, 1H, *J* = 5.4 Hz), 3.80 (s, 3H), 3.31 (s, 6H), 3.27 (d, 2H, *J* = 5.4 Hz), 1.74 (s, 3H); ^{13}C NMR (75 MHz) δ 165.39 (d, *J* = 249 Hz), 163.22, 160.03, 133.75, 130.75 (d, *J* = 8.9 Hz), 116.52 (d, *J* = 21.6 Hz), 105.65, 54.21, 54.00, 52.07, 17.66; HRMS calcd for $C_{14}H_{19}FN_2O_3$ 282.1379, found 282.1381. Data for **3b**: white solid; mp 116–117 °C; ^{1}H NMR (300 MHz) δ 7.69–7.65 (dd, 2H, *J* = 5.4, 8.8 Hz), 7.40–7.35 (t, 2H, *J* = 8.9 Hz), 4.53 (t, 1H, *J* = 5.4 Hz), 4.03 (d, 2H, 5.4 Hz), 3.83 (s, 3H), 3.15 (s, 6H), 2.26 (s, 3H); ^{13}C NMR (75 MHz) δ 167.00, 164.17 (d, *J* = 252 Hz), 161.87, 161.21, 159.99, 132.13 (d, *J* = 9 Hz), 131.84 (d, *J* = 3.2 Hz), 117.52, 116.15 (d, *J* = 22 Hz), 101.28, 54.61, 52.26, 47.31, 21.36. Anal. Calcd for $C_{17}H_{19}FN_2O_5$: C, 58.28; H, 5.47; N, 8.00. Found: C, 58.29; H, 5.49; N, 7.90.

Methyl 6-[(*tert*-Butyldiphenylsilyl)oxy]-2-(methoxycarbonyl)-2-hexenoate (5c). A solution of 4-[(*tert*-butyldiphenylsilyl)oxy]butanal[13] (0.832 g, 2.5 mmol), dimethyl malonate (0.33 g, 2.5 mmol), piperidine (0.01 g, 0.1 mmol), and benzoic acid (0.01 g, 0.08 mmol) in benzene (10 mL) was refluxed (4 h) using a Dean-Stark trap to remove H_2O. The resulting solution was diluted with EtOAc (100 mL) and washed sequentially with 0.1 N HCl (2×, 25 mL), H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic extract was dried over anhydrous $MgSO_4$, and the solvent was removed. The resulting oil was chromatographed (Et_2O/hexane (35:65)) to provide 0.8 g (73%) of **5c** as an oil: ^{1}H NMR (300 MHz) δ 7.62–7.59 (m, 4H), 7.48–7.40 (m, 6H), 7.03 (t, 1H, *J* = 7.8 Hz), 3.72 (s, 3H), 3.70 (s, 3H), 3.64 (t, 2H, *J* = 6.0 Hz), 2.36 (m, 2H), 1.67 (m, 2H), 0.98 (s, 9H); HRMS calcd for $C_{25}H_{33}O_5Si$ (M + H) 441.2097, found 441.2094.

(8) The transition state in this reaction is presumably also less sterically congested.

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(12) Vonltter, F. A.; Steffen, K. D. U.S. patent 5,041,619, July 16, 1990.
(13) Rowley, M.; Leeson, P. D.; Williams, B. J.; Moore, K. W.; Baker, R. *Tetrahedron* **1992**, *48*, 3557.

N-(2,2-Dimethoxyethyl)-4-(fluorophenyl)carboxamidine Hydrochloride (2a). To a solution of ethyl 4-(fluorophenyl)carboximidate hydrochloride[14] (101.6 g, 0.499 mol) in methanol (1 L) was added aminoacetaldehyde dimethyl acetal (60 mL, 0.549 mol) at 0 °C, and the resulting solution was allowed to stand for 24 h. The solvent was removed, and the resulting oil was crystallized from Et_2O/CH_2Cl_2 to provide 91.5 g (70%) of **2a** as a white solid: mp 152–155 °C; ^1H NMR (300 MHz) δ 9.97 (bs, 1H), 9.73 (bs, 1H), 9.37 (bs, 1H), 7.88–7.83 (m, 2H), 7.52–7.46 (m, 2H), 4.71 (t, 1H, J = 5.4 Hz), 3.60 (d, 2H, J = 5.4 Hz), 3.36 (s, 6H); MS (CI) 227 (90, M + H), 195 (100). Anal. Calcd for $C_{11}H_{16}ClFN_2O_2 \cdot 0.25H_2O$: C, 49.44; H, 6.22; N, 10.48. Found: C, 49.39; H, 6.12; N, 10.64. A 20-g portion of this material was then converted to the free base by dissolution in 1 N NaOH (300 mL) and extraction into CH_2Cl_2 (3 × 300 mL). The organic layers were dried ($MgSO_4$) and the solvent removed to provide the free base (14 g), as an oil, which was used in the cyclizations in Table I.

X-ray Structural Analysis of 3e.[15] $C_{22}H_{20}FlN_2O_5$ crystallized in the monoclinic space group $P2_1/c$ with a = 10.653(2) Å, b = 8.455(2) Å, c = 24.532(8) Å, β = 102.46(2)°, V = 2157.6(10) Å^3, M = 538.3, Z = 4, D_x = 1.657 g cm^{-3}, $F(000)$ = 1072. Intensity data with index ranges of $0 \le h \le 11$, $0 \le k \le 8$, $-25 \le l \le 25$ were collected at room temperature on a Siemens P4/RA diffractometer with graphite-monochromated CuKa radiation (λ = 1.541 78 Å), using a 2θ–θ scan for the 2θ range of 3.0–110°. A total of 2640 independent reflections were collected, of which 2415 reflections with $F_o^2 > 2.0\sigma(F_o^2)$ were then used for refinement. A semiempirical absorption correction based on ψ-scan data was applied to the reflections; transmission factors ranged from 0.0111 to 0.0773 for μ = 12.06 mm^{-1}. The structure was solved using Patterson methods and refined by least-squares analysis to R = 0.0478, $wR = [\sum w(F_o - F_c)^2/\sum wF_o^2] = 0.0626$ with weights given by $w^{-1} = \sigma^2(F_o) + 0.0008F_o^2$ and S = 1.83. Anisotropic temperature factors were introduced for all non-hydrogen atoms, while hydrogen atoms were assigned ideal geometries and refined using the Riding model. In the final difference Fourier map, the largest remaining residual density peak was 1.14 eÅ^{-3}, while the largest density hole left was −0.53 eÅ^{-3}; both are found near the iodine atom (within 1.2 Å). Structure solution and refinement were performed with the SHELXTL IRIS system of programs (Siemens Analytical X-Ray Instruments, 1991).

Acknowledgment. We thank Ms. Bobbie Scott for help in preparation of this manuscript and Dr. Fred Brown for helpful suggestions.

Supplementary Material Available: ^1H NMR and mass spectral data for the compounds described in Table II (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Sarett, L.; Hoff, D. R.; Herry, D. W. Belg. patent 660,836, Sept 9, 1965.

(15) The authors have deposited atomic coordinates for **3** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.