tained in $CDCl_3$ using a Bruker WM-300 spectrometer, and the chemical shifts are reported in δ units using Me_4Si as an internal standard. Mass spectra were obtained with a MAT-311A spectrometer. Flash chromatography was performed using 230-400 mesh silica gel 60 in a 5 cm × 25 cm column.

2-[(2,2-Dimethyl-7-methoxychromen-5-yl)amino]benzoic Acid (2). A 4.83-g (20.0-mmol) sample of 5-amino-2,2-dimethyl-7-methoxychromene hydrochloride (**1**) was combined with 4.42 g (22.0 mmol) of 2-bromobenzoic acid, 4.32 g (44.0 mmol) of KOAc, 0.12 g (0.60 mmol) of $Cu(OAc)_2 \cdot H_2O$, and 3.1 mL (22 mmol) of triethylamine in 100 mL of 2-propanol, and this mixture was refluxed for 24 h. The solvent was then removed on the rotary evaporator, and the residue was partitioned between 150 mL of CH_2Cl_2 and 100 mL of 1 N $HCl_{(aq)}$. The phases were separated, and the aqueous phase was washed twice with 10-mL portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$) and concentrated to give 6.28 g (97%) of a brown foam. This material was redissolved in CH_2Cl_2 and absorbed onto 60 g of SiO_2, which was placed at the top of a flash chromatography column. The column was eluted with hexane/acetone/acetic acid (80:20:0.5) to provide 5.05 g of material, which was crystallized from 100 mL of hexane to give 3.43 g of product, mp 131-133 °C. The mother liquor was concentrated, and the residue was dissolved in 15 mL of hot hexane. As the solution cooled, the hexane was decanted from an oily impurity which precipitated. The product that crystallized from the decanted solution was collected to give an additional 0.32 g, raising the overall yield to 58%: ^1H NMR δ 1.45 (s, 6 H), 3.77 (s, 3 H), 5.50 (d, 1 H, J = 10 Hz), 6.30 (d, 1 H, J = 2 Hz), 6.39 (d, 1 H, J = 10 Hz), 6.43 (d, 1 H, J = 2 Hz), 6.73 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 1 Hz), 6.92 (dd, 1 H, J = 8 Hz, J = 1 Hz), 7.33 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 2 Hz), 8.04 (dd, 1 H, J = 8 Hz, J = 2 Hz), 9.14 (bs, 1 H); IR 1662, 1615, 1568, 1240, 1150, 772 cm^{-1}; mass spectrum, m/e 325 (M^+). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.17; H, 6.10; N, 4.27.

Des-*N*-methylacronycine (3). A 1.63-g (5.0-mmol) sample of anthranilic acid **2**, mp 131-133 °C, was combined with 3.5 mL (25 mmol) of trifluoroacetic anhydride in 50 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 3 days. The mixture was then concentrated on the rotary evaporator. The residue was partitioned between CH_2Cl_2 and $NaHCO_{3(aq)}$, and the aqueous phase was washed with additional CH_2Cl_2. The combined CH_2Cl_2 solution was then shaken for 5 min with 10% aqueous NaOH since TLC indicated that this procedure simplified the product mixture, presumably through hydrolysis of the trifluoroacetic acid amides present. The aqueous phase was washed with additional CH_2Cl_2, and the combined organic phase was dried over $MgSO_4$ and filtered. The filtrate was added to 16 g of SiO_2, and the solvent was removed on the rotary evaporator. The SiO_2 with the product mixture absorbed onto it was placed at the top of a flash SiO_2 column which was eluted first with 80:20:0.5 hexane/acetone/acetic acid to remove acidic components. Among these was a fraction containing mostly starting material. This fraction was concentrated, redissolved in CH_2Cl_2, and washed with $NaHCO_{3(aq)}$ to remove residual acetic acid. Starting material remained in the CH_2Cl_2, which was dried and concentrated. The residue was recrystallized from hexane to provide a 50-mg sample of recovered **2**, mp 119-120 °C, identified on the basis of its ^1H NMR spectrum and elemental analysis. Subsequent elution of the column with 70:30 hexane/acetone provided product containing fractions which were concentrated to give 0.958 g (62%) of the desired product as an analytically pure, fluffy, yellow solid, mp 258-260 °C (lit.[2a] mp 268-270 °C). Recrystallization from acetone/hexane raised the mp to 273-275 °C.

A similar procedure using a 1.63-g sample of crude anthranilic acid **2**, which had been obtained in 96% yield from aminochromene **1**, provided 0.800 g (52%) of des-*N*-methylacronycine, mp 260-262 °C, and 90 mg of recovered starting material, mp 121-123 °C. Further purification of the product was necessary to obtain a correct elemental analysis: recrystallization from acetone/hexane with one reworking of the mother liquor gave a total of 0.647 g (42%). The analytically pure material had a mp of 263-265 °C: ^1H NMR δ 1.48 (s, 6 H), 3.92 (s, 3 H), 5.60 (d, 1 H, J = 10 Hz), 6.21 (s, 1 H), 6.66 (d, 1 H, J = 10 Hz), 7.21 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 1 Hz), 7.29 (dd, 1 H, J = 9 Hz, J = 1 Hz), 7.55 (ddd, 1 H, J = 9 Hz, J = 7 Hz, J = 1 Hz), 8.25 (bs, 1 H), 8.41 (dd, 1 H, J = 8 Hz, J = 1 Hz); IR 3441, 1632 cm^{-1}; mass spectrum, m/e 307 (M^+). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.20; H, 5.66; N, 4.53.

Acronycine (4). To a combination of 1.54 g (5.0 mmol) of des-*N*-methylacronycine, 0.341 g (1.5 mmol) of benzyltriethylammonium chloride, 25 mL of 50% $NaOH_{(aq)}$, and 25 mL of 2-butanone was added 0.47 mL (7.5 mmol) of methyl iodide, and this mixture was stirred at 60-70 °C for 3 h. The cooled reaction mixture was diluted with 100 mL of CH_2Cl_2 and a small amount of water. The aqueous phase was washed with additional CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_2Cl_2 and absorbed onto 15 g of SiO_2. This SiO_2 was placed at the top of a flash column, which was eluted with 75:25 hexane/acetone to provide 1.55 g (96%) of analytically pure acronycine as a light yellow solid: mp 173-175 °C (lit.[2a] mp 175-176 °C) (recrystallization from EtOAc/hexane did not raise the melting point); ^1H NMR δ 1.55 (s, 6 H), 3.83 (s, 3 H), 3.99 (s, 3 H), 5.51 (d, 1 H, J = 10 Hz), 6.32 (s, 1 H), 6.55 (d, 1 H, J = 10 Hz), 7.25 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 1 Hz), 7.36 (dd, 1 H, J = 9 Hz, J = 1 Hz), 7.63 (ddd, 1 H, J = 9 Hz, J = 7 Hz, J = 2 Hz), 8.39 (dd, 1 H, J = 8 Hz, J = 2 Hz); IR 1622 cm^{-1}; mass spectrum, m/e 321 (M^+). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.69; H, 5.90; N, 4.27.

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Registry No. 1·HCl, 66385-03-3; **2**, 125108-96-5; **3**, 13255-08-8; **4**, 7008-42-6; 2-$BrPhCO_2H$, 88-65-3.

A New Preparation of Difunctionalized Enamines from Thioamides Using Silver(I) Carbonate[1]

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Difunctionalized enamines are useful synthetic intermediates and have been obtained by a variety of condensation and extrusion reactions.[3] The basic reaction conditions employed in the condensation of active methylene compounds with electrophilic intermediates are often incompatible with other functional groups and can lead to racemization at sites adjacent to the electrophilic reaction center. In order to find milder conditions, we considered the use of silver carbonate. As a thiophilic reagent,[4] silver carbonate can complex with thioamide sulfur **1a** to generate thioiminium intermediate **3**, and as a base it can generate nucleophiles from active methylene compounds. In this paper, we report that the condensation of carbonucleophiles with thioiminium intermediates in the presence of silver carbonate at ambient temperature results in the formation of the corresponding enamines (Schemes I and II). This modification leads to the replacement of the amide bond by the corresponding enamine moiety, which is a useful modification of peptide backbones[5] with

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(2) Fellow of the NSERC-Canada, 1985-.

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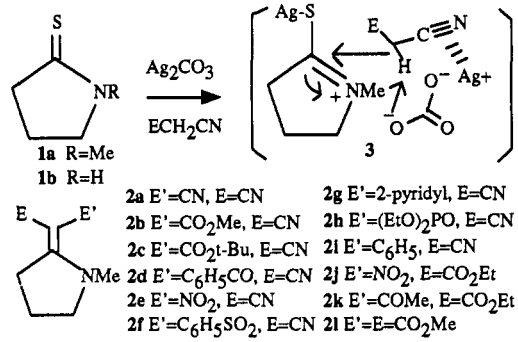
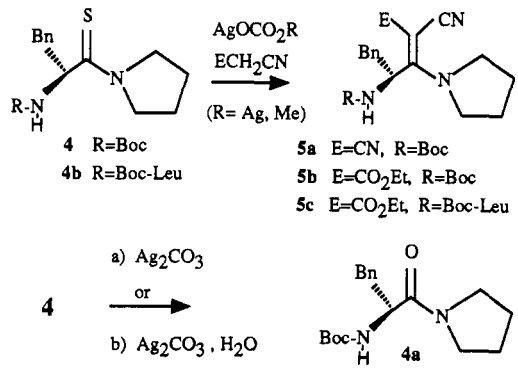
0022-3263/90/1955-2246$02.50/0

Scheme I



Scheme II



interesting biological implications.

The condensation of malononitrile with *N*-methyl thiolactam **1a** in presence of silver carbonate[6,7] in acetonitrile at 25 °C gave enamine **2a** (88%, Table I). No reaction was observed with monoprotic thiolactam **1b**, proving that neutral silver complexes are unreactive. These conditions are simpler[3] and the reactions are faster than those with silver tetrafluoroborate or mercury(II) trifluoroacetate followed by the addition of sodium hydride (24 h). The reaction was found to occur readily with nucleophiles bearing two strongly electron-withdrawing groups, if at least one of them is a cyano group (**2a–g**). This requirement is based on the observation that other active methylene compounds of similar acidities[8] such as ethyl acetoacetate or dimethyl malonate failed to react (**2k**, **2l**). As an exception, ethyl nitroacetate, which has exceptionally acidic methylene hydrogens gave enamine **2j** (26%). This increased acidity by the nitro group also explains the higher yield of **2e** compared to **2b** while less acidic phenylacetonitrile failed to react (0%, **2i**). The effect of steric hindrance of the *tert*-butyl ester in **2c** (15%) as compared to the methyl ester in **2b** (33%) is also significant. A substantial solvent effect was observed as tetrahydrofuran afforded better yields of enamines (**2b**) although minor side products were produced (**2d**, **2f**).

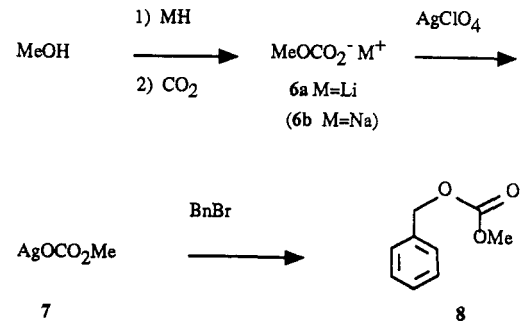
With use of silver carbonate, enamines **5a** and **5b** (Scheme II) were prepared from thioamide **4**. During the formation of **5b**, amide **4a** was also formed and isolated. The formation of **4a** with or without added water suggests that the carbonate anion can act as a nucleophile toward the thioiminium intermediate[9] (Scheme II). We reasoned that more soluble and less nucleophilic carbonate derivatives such as **6a**, **6b**, and **7** (Scheme III) might give better yields of enamines. Indeed, we found that the use of sodium methyl carbonate (**6b**)[10] as an additive (1 to 3 equiv) gave enamines with increased yields but with longer reaction times. In order to accelerate the reactions, the silver reagent **7** was prepared by reacting silver perchlorate with lithium methyl carbonate (**6a**)[11] (Scheme III). With the use of **7**,[12] the reaction was faster and the yield of **5a** (58%) was better as compared to freshly prepared silver carbonate (20%), and with silver carbonate used along with **6b**

Table I. Condensation Conditions for the Preparation of Enamines 2a–l and 5a–c

product	reagent	reaction time,[a] h	yield,[b] %
2a	Ag_2CO_3	1	88
	1. $AgBF_4$, 2. NaH	24	65
	1. $Hg(CO_2CF_3)_2$, 2. NaH	24	82[d]
2b	Ag_2CO_3	1	33
	Ag_2CO_3/**6b**	2	40, 66[c]
2c	Ag_2CO_3	5	15
2d	Ag_2CO_3	2	55
	Ag_2CO_3/**6b**	4	75[c,d]
2e	Ag_2CO_3	2	65
2f	Ag_2CO_3	3	38
	Ag_2CO_3/**6b**	5	55, 75[c,d]
	7	1	41
2g	Ag_2CO_3	3	15[c]
2h	Ag_2CO_3	10	0
2i	Ag_2CO_3	10	0
2j	Ag_2CO_3	2	26
2k	Ag_2CO_3	10	0
2l	Ag_2CO_3	10	0
5a	Ag_2CO_3	3	20 (0% **4a**)
	Ag_2CO_3/**6b**	3	56 (0% **4a**)
	7	1	58 (0% **4a**)
5b	Ag_2CO_3	3	21 (74% **4a**)
	Ag_2CO_3/**6b**	3	73 (21% **4a**)
	7	1	36 (20% **4a**)
5c	Ag_2CO_3/**6b**	5	55

[a] Monitored by TLC analysis [b] Isolated from flash chromatography. [c] Prepared in tetrahydrofuran. [d] Enamine[b] containing unidentified minor side products.

Scheme III



(5) Sauvê, G.; Le Berre, N.; Zacharie, B. *Tetrahedron Lett.* **1988**, *29*, 2299–2302.

(6) The yield is higher with freshly prepared silver carbonate: McCloskey, C. M.; Coleman, G. H. In Organic Syntheses; Horning, E. C., Ed.; John Wiley & Sons; New York, 1955; Collect. Vol. 3, pp 434–436.

(7) Pressure builds up as the reaction advances and the mixture turns black.

(8) Bernasconi, C. F.; Kanavarioti, A. *J. Am. Chem. Soc.* **1986**, *108*, 7744–7751.

(9) For an analogous hydrolysis of thioacetals with silver(I) oxide, see ref 4b.

(10) Replacement of **6b** by **6a** led to lower yields of enamines. (b) Kovalenko, V. I. *Zhur. Obshch. Khim.* **1952**, *22*, 1546–1550. (b) Boehm, Mehta, *Chem. Abstr.* **1952**, *32*, 9043.

(11) Reagent **7** is stored at −15 °C. Preparation of the lithium methyl carbonate: lithium hydride (2.0 g, 0.25 mol) is added to anhydrous methanol (600 mL) under a stream of carbon dioxide at 0 °C (10 min). The solvent is removed on rotatory evaporator to leave **6a** as a white solid (20.1 g, 98%).

(12) The chemical structure of **7** was proved by preparing the benzyl derivative **8** (91% from chromatography) from reacting **7** with benzyl bromide (1.3 equiv) in acetonitrile at 25 °C (10 h). ^1H NMR δ 3.80 (s, 3 H, CH_3O), 5.16 (s, 2 H, CH_2O), 8.91 (m, 5 H, Ar); IR 1750, 1275 cm^{-1}; exact mass calcd for $C_9H_{10}O_3$ 166.0630, found 166.0627.

the yield was similar (56%). The enamine **5b** was also obtained with the use of **7**, but in a lower yield (36%).

The requirement of the reaction for derivatives of acetonitrile may be rationalized by complexation of the nitrile group with silver(I) cation,[13] which in turn increases the acidity of the methylene hydrogens while bringing all three reacting species in close proximity. Complexation of the pyridyl nitrogen with silver(I) cation would also explain why **2g** (15%) is formed, whereas phenylacetonitrile failed to react.

Analysis of the ^{1}H NMR spectrum of the dipeptidic enamine **5c** (55% from **4b**) did not show the presence of the other diastereoisomer,[5] providing evidence that racemization did not occur under these experimental conditions.

In summary, the use of silver carbonate in conjunction with the base **6b** or the new silver salt **7** allows the preparation of difunctionalized enamines complementary to existing methods and compatible with other functionalities in the molecule while maintaining the chiral integrity.

Experimental Section

Methanol was distilled from magnesium and acetonitrile was distilled from calcium hydride prior to use. Nuclear magnetic resonance spectra were determined on a Bruker WH-400 (^{1}H 400 MHz) spectrometer in deuterated chloroform/tetramethylsilane. Mass spectra (HRMS) were recorded on a Kratos MS50TCTA spectrometer at the Université de Montréal. Melting points were measured on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were measured at 589 nm on a Rudolph Research Autopol III polarimeter. Infrared spectra were taken in chloroform on a Beckman Acculab 8 spectrophotometer. Merck silica gel 60 (230–400 mesh ASTM) was used for column chromatography.

Sodium Methyl Carbonate (6b). In a liter flask containing dry methanol (500 mL) at 0 °C are added both by portions hexane-washed sodium (10.0 g) and pellets of carbon dioxide (10–20 g) over a period of 30 min. The solution is stirred vigorously until disappearance of sodium. More carbon dioxide pellets are added so that the internal temperature does not exceed 10 °C and settles at −20 °C at the end of the reaction. The solid is filtered on fritted glass and washed with diethyl ether (50 mL) and dried under vacuum; 40.7 g of **6b** are obtained (93%).

Silver Methyl Carbonate (7). To dry methanol (10 mL) at 0 °C is added lithium hydride (37 mg, 4.62 mmol) followed by a stream of carbon dioxide (excess). Diethyl ether is added (10 mL) and this solution is added under dim light to a solution of anhydrous silver perchlorate (1 g, 4.8 mmol) in 1:1 methanol/diethyl ether (20 mL). The white solid is collected by filtration on fritted glass and dried under vacuum to give **7** (804 mg, 95%). The solid is stored under nitrogen at −15 °C and slightly darkens during filtration.

General Procedure 1: (1-Methyl-2-pyrrolidinylidene)-propanedinitrile (2a). To a solution of thiolactam **1a** (80 mg, 0.69 mmol) and malononitrile (125 mg, 1.9 mmol) in acetonitrile (2 mL) is added silver carbonate (204 mg, 0.96 mmol) under argon. The mixture is stirred vigorously at 25 °C for 1 h. The mixture is filtered on fritted glass and rinse with CH_2Cl_2, and the concentrated crude is purified by flash chromatography on silica gel (AcOEt/hex/CH_2Cl_2 1:1:1 then 1:0:0) to give **2a** (90 mg, 88%). The solid is recrystallized in hot CCl_4 followed by hexane: mp 100–101 °C; ^{1}H NMR δ 2.1 (q, J = 7.6 Hz, 2 H, CH_2), 3.0 (t, J = 7.9 Hz, 2 H, CH_2), 3.38 (s, 3 H, CH_3), 3.72 (t, J = 7.3 Hz, 2 H, CH_2N); IR 2200, 1605, 1310 cm^{-1}; exact mass calcd for $C_8H_9N_3$ 147.0798, found 147.0767.

General Procedure 2: Methyl Cyano(1-methyl-2-pyrrolidinylidene)acetate (2b). Enamine **2b** (38 mg, 40%) was obtained from **1a** (60 mg, 0.52 mmol), **6b** (100 mg, 1 mmol), methyl cyanoacetate (122 mg, 1.24 mmol), and silver carbonate (195 mg, 0.72 mmol) after chromatography (AcOEt/hex/CH_2Cl_2 1:2:1 then 1:0:0): mp 110–111 °C (AcOEt–hex); ^{1}H NMR δ 2.03 (q, J = 7.6 Hz, 2 H, CH_2), 3.30 (t, J = 7.9 Hz, 2 H, CH_2), 3.44 (s, 3 H, CH_3), 3.61 (t, J = 7.4 Hz, 2 H, CH_2N), 3.72 (s, 3 H, CH_3O); IR 2940, 2200, 1680, 1565, 1280 cm^{-1}; exact mass calcd for $C_9H_{12}N_2O_2$ 180.0899, found 180.0886.

***tert*-Butyl Cyano(1-methyl-2-pyrrolidinylidene)acetate (2c).** Following procedure 1, enamine **2c** was obtained after chromatography (AcOEt/hex 1:2 then 1:1): mp 95–96 °C (AcOEt–hex); ^{1}H NMR δ 1.49 (s, 9 H, CH_3), 1.97 (q, J = 7.7 Hz, 2 H, CH_2), 3.26 (t, J = 7.8 Hz, 2 H, CH_2), 3.41 (s, 3 H, CH_3N), 3.56 (t, J = 7.4 Hz, 2 H, CH_2N); IR 2900, 2200, 1680, 1585, 1290 cm^{-1}; exact mass calcd for $C_{12}H_{18}N_2O_2$ 222.1369, found 222.1359.

(1-Methyl-2-pyrrolidinylidene)benzoylacetonitrile (2d). Following procedure 1, enamine **2d** was obtained after chromatography (AcOEt/hex 1:1 then 2:1): mp 95–96 °C (AcOEt–hex); ^{1}H NMR δ 2.1 (m, 2 H, CH_2), 3.37 (m, 5 H, CH_3 and CH_2), 3.73 (m, 2 H, CH_2N), 7.41 (m, 3 H, Ar), 7.78 (m, 2 H, Ar); IR 2200, 1630, 1565, 1300 cm^{-1}; exact mass calcd for $C_{14}H_{14}N_2O$ 226.1107, found 226.1060.

(1-Methyl-2-pyrrolidinylidene)nitroacetonitrile (2e). Following procedure 1, enamine **2e** was obtained after chromatography (AcOEt): mp 87–88 °C ($CHCl_3$–hex): ^{1}H NMR δ 2.14 (m, 2 H, CH_2), 3.44 (br s, 3 H, CH_3), 3.58 (m, 2 H, CH_2), 3.82 (m, 2 H, CH_2N); IR 2200, 1695, 1610, 1310 cm^{-1}; exact mass calcd for $C_7H_9N_3O_2$ 167.0696, found 167.0693.

(1-Methyl-2-pyrrolidinylidene)(phenylsulfonyl)acetonitrile (2f). By following procedure 1, enamine **2f** was obtained after chromatography (AcOEt/hex/CH_2Cl_2 1:2:1 then 1:1:1): mp 124–125 °C (CH_2Cl_2–hex); ^{1}H NMR δ 1.98 (q, J = 7.5 Hz, 2 H, CH_2), 3.17 (t, J = 7.8 Hz, 2 H, CH_2), 3.36 (s, 3 H, CH_3), 3.60 (t, J = 7.3 Hz, 2 H, CH_2N), 7.51 (m, 3 H, Ar), 7.94 (d, J = 7.3 Hz, 2 H, Ar); IR 2200, 1580, 1315, 1155 cm^{-1}; exact mass calcd for $C_{13}H_{14}N_2O_2S$ 262.0777, found 262.0812.

α-(1-Methyl-2-pyrrolidinylidene)-2-pyridineacetonitrile (2g). By following procedure 1, enamine **2g** was obtained as an oil after chromatography (AcOEt/hex 3:2): ^{1}H NMR δ 1.96 (q, J = 7.3 Hz, 2 H, CH_2), 3.21 (t, J = 7.6 Hz, 2 H, CH_2), 3.41 (s, 3 H, CH_3), 3.54 (t, J = 7.0 Hz, 2 H, CH_2), 6.92, 7.45, 7.57 (3 m, 3 H, Ar), 8.41 (s, 1 H, Ar); IR 3000, 2180, 1590, 1310 cm^{-1}; exact mass calcd for $C_{12}H_{13}N_3$ 199.1111, found 199.1106.

Ethyl (1-Methyl-2-pyrrolidinylidene)nitroacetate (2j). Following procedure 1, enamine **2j** was obtained after chromatography (AcOEt/hex 1:1) as a yellowish oil: ^{1}H NMR δ 1.33 (t, J = 7.1 Hz, 3 H, CH_3), 2.1 (t, J = 7.4 Hz, 2 H, CH_2), 2.92 (s, 3 H, CH_3N), 3.32 (t, J = 7.7 Hz, 2 H, CH_2), 3.7 (t, J = 7.2 Hz, 2 H, CH_2N), 4.31 (q, J = 7.1 Hz, 2 H, CH_2O); IR 2980, 1710, 1590, 1300 cm^{-1}; exact mass calcd for $C_9H_{14}N_2O_4$ 214.0954, found 214.0957.

(2*S*)-[2-(*t*-Boc-amino)-3-phenyl-1-(1-pyrrolidinyl)-propylidene]propanedinitrile (5a). From procedure 2, using a 3.4:1.7:1 ratio of **6b**/Ag_2CO_3/**4**, enamine **5a** was obtained after chromatography (AcOEt/hex 7:12) as an oil: $[\alpha]^{25}_D$ = +310.4° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9 H, CH_3), 1.61, 1.69, 1.85 (3 m, 4 H, CH_2 cycl), 2.73 (m, 1 H of CH_2 cycl), 3.14, 3.32 (2 m, 2 H, β CH_2), 3.37 (m, 1 H of CH_2 cycl), 3.87 (m, 2 H, CH_2 cycl), 4.84 (m, 1 H, α CH), 5.60 (m, 1 H, NH), 7.31 (m, 5 H, Ar); IR 2960, 2200, 1700, 1550, 1500 cm^{-1}; exact mass calcd for $C_{21}H_{26}N_4O_2$ 366.2058, found 366.2115.

Ethyl (4*S*)-2-Cyano-4-(*t*-Boc-amino)-5-phenyl-3-(1-pyrrolidinyl)-2-pentenoate (5b) and Amide (4a). From procedure 2, using a 4.1:2.8:1 ratio of **6b**/Ag_2CO_3/**4**, enamine **5b** was obtained after chromatography (AcOEt/hex 1:3) as an oil: $[\alpha]^{25}_D$ = +207.3° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.37 (m, 3 H, CH_3), 1.39 (s, 9 H, CH_3), 1.80 (m, 4 H, CH_2 cycl), 3.16, 3.40 (2 m, 4 H, CH_2N, β CH_2), 3.86 (m, 2 H, CH_2), 4.25 (m, 2 H, CH_2O), 5.16 (m, 1 H, α CH), 6.63 (m, 1 H, NH), 7.28 (m, 5 H, Ar); IR 2980, 2200, 1715, 1530, 1285 cm^{-1}; exact mass calcd for $C_{23}H_{31}N_3O_4$ 413.2316, found 413.2322. **Amide 4a:** ^{1}H NMR δ 1.43 (s, 9 H, CH_3), 1.74 (m, 4 H, CH_2 cycl), 2.58 (m, 1 H, CH_2 cycl), 2.97 (m, 2 H, β CH_2), 3.34 (m, 3 H, CH_2 cycl), 4.59 (q, J = 5.4 Hz, 1 H, α CH), 5.33 (d, J = 8.6 Hz, 1 H, NH), 7.21 (m, 5 H, Ar).

Ethyl (4*S*)-2-Cyano-4-[(*t*-Boc-L-leucyl)amino]-5-phenyl-3-(1-pyrrolidinyl)-2-pentenoate (5c). From procedure 2, using a 4.1:2.8:1 ratio of **6b**/Ag_2CO_3/**4b**, enamine **5c** was obtained by chromatography (AcOEt): $[\alpha]^{25}_D$ = +39.0° (*c* 1, $CHCl_3$); ^{1}H NMR

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δ 0.91 (d, J = 6.1 Hz, 6 H, CH_3 Leu), 1.36 (br s, 3 H, CH_3CH_2O), 1.44 (s, 9 H, CH_3 Boc), 1.58, 1.79 (2 m, 7 H, CH, CH_2 Leu, $2CH_2$ cycl), 3.12, 3.41 (2 m, 4 H, β CH_2 Phe, CH_2 cycl), 3.74 (m, 1 H, α CH Leu), 4.09 (m, 2 H, CH_2N cycl), 4.24 (m, 2 H, CH_2O), 4.81 (m, 1 H, α CH Phe), 5.48 (m, 1 H, NH Boc), 7.28 (m, 5 H, Ar), 8.3 (m, 1 H, NH Phe); IR 2995, 2200, 1720, 1680, 1540, 1285 cm^{-1}; exact mass calcd for $C_{29}H_{42}N_4O_5$ 526.3158, found 256.3206.

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Registry No. **1a**, 10441-57-3; **2a**, 53583-60-1; **2b**, 26978-74-5; **2c**, 125138-99-0; **2d**, 125139-00-6; **2e**, 125139-01-7; **2f**, 125139-02-8; **2g**, 125139-03-9; **2j**, 125139-04-0; **4**, 118525-55-6; **4a**, 125139-05-1; **4b**, 118525-57-8; **5a**, 118525-58-9; **5b**, 125139-06-2; **5c**, 125139-07-3; **6a**, 41792-67-0; **6b**, 6482-39-9; **7**, 100477-67-6; **8**, 13326-10-8; $CH_2(CN)_2$, 109-77-3; $NCCH_2COOMe$, 105-34-0; $NCCH_2COOBu$-t, 1116-98-9; $PhCOCH_2CN$, 614-16-4; $NCCH_2NO_2$, 13218-13-8; $PhSO_2CH_2ICN$, 7605-28-9; O_2NCH_2COOEt, 626-35-7; $NCCH_2COOEt$, 105-56-6; $PhCH_2Br$, 100-39-0; Ag_2CO_3, 534-16-7; 2-pyridineacetonitrile, 2739-97-1.

Halogen Effect on the Ring Opening of Pulegone Hydrohalides

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The ring-opening reaction of pulegone hydrochloride (**2a**) with nucleophiles such as NaOH, $LiNMe_2$, and LAH, reported by Plesek[1] and Overberger,[2] serves as a convenient means for the synthesis of acyclic chiral compounds (see Scheme I). In conjunction with our continuing interest in the stereocontrolled synthesis of steroid side chains,[3] an application of this useful ring-opening reaction of α-(2-halo-2-methylethyl)cyclohexanones was envisioned. However, the yields reported by the above two groups were relatively low for synthetic applications, and it was our intent to improve the yields and expand the scope of this reaction through the understanding of the dynamics that control it. Of particular interest to us were the effect of halogens in these reactions and the possible use of carbon nucleophiles for such a ring-opening reaction.

Results and Discussion

The pulegone hydrohalides, hydrochloride **2a**,[1,2] hydrobromide **2b**,[4] and hydroiodide **2c**,[4] were prepared quantitatively by passing the corresponding dry hydrogen halide gas through neat (+)-(*R*)-pulegone (1) at 0–5 °C. These relatively unstable hydrohalides were obtained as a 4.9–5.6:1 mixture of stereoisomers, of which the trans isomer is predominant in all cases as judged from their ^1H NMR spectra, indicating the presence of the characteristic axial hydrogen at C-2 ($^3J_{2,3eq}$ = 3.8–4.6 Hz, $^3J_{2,3ax}$ = 12.1–12.9 Hz, and $^4J_{2,6ax}$ = 1.0–2.3 Hz). Treatment of pulegone hydrochloride (**2a**) with NaOH, $LiNMe_2$, and LAH resulted in the formation of (+)-(*R*)-citronellic acid (**5**), (−)-(*R*)-*N*,*N*-dimethylcitronellamide (**6**), and (+)-(*R*)-citronellol (**7**), respectively, with yields comparable to those reported by Overberger[2] (see Table I). In an attempt to improve the low yield of (+)-(*R*)-citronellol, hydrobromide **2b**[4] was treated with LAH under the same conditions employed with hydrochloride **2a**, which resulted in the improvement of the yield of **7** from 16% to 45%. In a belief that this may be an indication of a trend, hydroiodide **2c** was next treated with LAH as above, and the yield of **7** was further improved to 60%. Encouraged by these results, we then investigated the ring opening of the pulegone hydrohalides with NaOH and $LiNMe_2$ but found that as the atomic weight of the halogen increases the yield of these reactions decrease (Table I). It should be noted in this regard that the hydrofluoride derivative of pulegone was not successfully prepared when pulegone was exposed to dry HF gas.

In an effort to yet further improve the yield of citronellol (**7**), reduction of pulegone hydrohalides **2a–c** with non-lithium-based hydrides such as $NaB(OMe)_3H$ and DIBAL was examined. The reduction with the former reagent gave mixtures of stereoisomeric pulegols and some unidentifiable olefinic compounds in low yields from each of the three hydrohalides. In contrast, the use of the latter reagent resulted in the formation of **7** in 79, 59, and 0% yields for the hydrochloride, hydrobromide, and hydroiodide, respectively. It is interesting to note that the trend observed for LAH was opposite to that of all of the other nucleophiles studied. We next sought to directly obtain the ester or thioester of citronellic acid (**5**) from the pulegone hydrohalides with an alkoxide or thiolate anion as a nucleophile, respectively. However, treatment of the

Scheme I

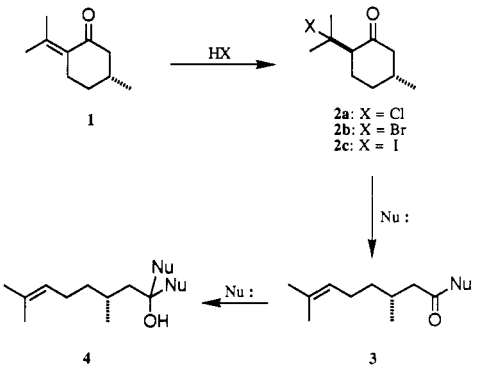

Table I. Nucleophilic Addition of Pulegone Hydrohalides

reagent	product R	yield (%)[a] from 2a (X = Cl)	2b (X = Br)	2c (X = I)
NaOH	COOH (**5**)	52[b,c]	28[c]	0[c]
$LiNMe_2$	$CONMe_2$ (**6**)	47[b]	30	0
LAH	CH_2OH (**7**)	16[b]	45	60
DIBAL	CH_2OH (**7**)	79	59	0
MeLi	$COCH_3$ (**8**)	78	44[d]	0[e]
n-BuLi	CO-*n*-Bu (**9**)	75	0[e]	0[e]
t-BuLi	CO-*t*-Bu (**10**)	63[c]	31[c]	0[c]
PhLi	COPh (**11**)	60	0	0

[a] Isolated yields except where indicated. [b] Yields reported by Oberverger,[2] confirmed in this study. [c] Recovered pulegone makes up the balance. [d] Isolated as a 1.4:1 inseparable mixture of **8** and bis-adduct **4** (Nu = Me). [e] Only bis-adducts and pulegone recovered.

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