An Efficient Synthesis of 2-Acylpyrroles

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Received December 6, 1984

Pyrrolylmagnesium bromide reacted with thiol- and selenolesters in the presence of cuprous iodide to afford 2-acylpyrroles regioselectively.

It has been proposed that the 2-pyrrolylcarbonyl group in the molecule of polyether antibiotic A23187 (calcimycin) **1**¹⁾ might participate in forming a complex with the calcium cation.²⁾ In the course of our synthetic studies³⁾ aimed at the unique ionophore **1**, we required an efficient method for the preparation of 2-acylpyrroles. Interestingly, the 2-acylpyrrole system is also the significant part of another calcium ionophore X-14547A molecule **2**.⁴⁾ The recent communications⁵⁾ discussing the preparative procedure for such substances prompted us to detail our independent results regarding the synthesis of

2-acylpyrroles.^{3c)}

RESULTS AND DISCUSSION

A number of acylations of pyrroles have been accomplished through Friedel-Crafts or pyrrole Grignard reactions.⁶⁾ However, the courses of those reactions have often been unpredictable because the acylations can take place not only at the carbon atom but also at the nitrogen atom on the pyrrole ring. Loader and Anderson reported that ethyl thioacetate reacted with pyrrolylmagnesium bromide giving 2-acetylpyrrole selectively.⁷⁾ In order to

FIG. 1.

FIG. 2.

extend the methodology, we examined the use of a phenylthiol ester derivative of carboxylic acid to acylate pyrrole. As a prototype with the appropriate functionalities, a carboxylic acid **5** was prepared from commercially available 5-hydroxypentanal **3** through a Wittig reaction, base-catalyzed cyclization and saponification.

Conversion of the acid **5** to the corresponding phenylthiol ester **6** was achieved by treatment with *N,N'*-carbonyldiimidazole and thiophenol in DMF (79% yield).⁸⁾ The ester consisted of two diastereomers (**6a** and **6b**) which were separable by column chromatography. An attempt at direct reaction of **6** with pyrrolylmagnesium bromide was unsuccessful and only a complicated mixture was produced. However, the addition of cuprous iodide into the media was effective to define the course of the reaction. When **6** was allowed to react with a mixture of the Grignard reagent (3 eq) and the copper salt (1.5 eq) in THF-ether at room temperature for 3 hr, the 2-acylpyrrole derivative **9** was obtained in a moderate (~40%) yield together with some minor products of indefinite structure. It was revealed that no isomerization of the methyl group in the major product took place under the reaction conditions, although a compound of an α,β -unsaturated 2-ketopyrrole type, probably formed by β -elimination from **9**, was detected in the minor products. The separated diastereomers **6a** and **6b** afforded the respective products **9a** and **9b**.

The problems of facilitating the conversion and reducing the by-product formation were solved by employing the more reactive phenylselenenol ester **7** or pyridinethiol ester **8**. The preparation of **7** was carried out by treating **5** with phenylselenocyanate and tri-*n*-butylphosphine in dichloromethane⁹⁾ in a 70% yield. The selenol ester **7** gave the 2-acylpyrrole **9** in a 77~84% yield with no significant by-product when subjected to reaction with a mixture of pyrrolylmagnesium bromide and cuprous iodide. The reaction was completed smoothly within 30 min~1 hr at room temperature. The pyridinethiol ester **8**, prepared from **5** and dipyridyldisulfide with triphenyl-

phosphine¹⁰⁾ (94%), was also converted to **9** in a 74~81% yield under the same conditions. Analogously to the case of the phenylthiol ester **6**, the respective diastereomers of the phenylselenenol esters **7a** and **7b**, as well as those of the pyridinethiol esters **8a** and **8b**, were separable from each other by column chromatography. Although the stereochemical relationship between the α - and β -positions (*erythro* or *threo*) of those esters was not elucidated, each separated substance was transformed to the corresponding 2-acylpyrrole with retention of its stereochemistry. The high efficiency and general applicability of this facile procedure are further illustrated by the conversions depicted in Table I.

The pyrrolyl copper complex seems to be the effective species in this reaction, although little is known with respect to the exact mechanism. The following evidence suggests the presence of the complex: The yield of the desired product was markedly diminished when the conversions were carried out in the absence of

TABLE I.

Substrate	Product	Isolated yield (%)
ref. 9 10	ref. 5c 16	91.0
refs. 10, 11a 11	16	93.4
ref. 9 12	17	71.3
ref. 11 13	17	92.7
ref. 9 14	18	76.7
15	18	94.4

FIG. 3.

cuprous iodide. The reactant solution, alternatively prepared by the addition of pyrrole to a mixture of ethylmagnesium bromide and cuprous iodide, also resulted in sufficient conversion of the esters to the 2-acylpyrroles. Finally, it is noteworthy that this procedure was successfully adopted for the key transformation (**19**→**20**, 80% yield) in the total synthesis of antibiotic A23187 **1**.^{3b)}

EXPERIMENTAL

All melting points are uncorrected. ¹H-NMR and ¹³C-NMR spectra were measured with Varian EM 360, JEOL JNM FX 90Q and JNM FX400 spectrometers. IR spectra were recorded on a Shimadzu IR-430 spectrophotometer. Mass spectra were obtained with a Hitachi RMU-6MG mass spectrometer. The recorded *R_f* value was observed on Kieselgel 60 F₂₅₄ plate (thickness, 0.25 mm). GLC analyses were carried out on a Shimadzu GC-6AM instrument with a glass column (2 m × 3 mm) packed with 5% OV-1 on Chromosorb W.

2-(2-Tetrahydropyranyl)propionic acid 5. A mixture of commercially available 5-hydroxypentanal **3** (3.0 g, ~50% purity) and (carboethoxyethylidene)triphenylphosphorane (12 g) was heated overnight under reflux in 150 ml of dry toluene. After removal of the solvent *in vacuo*, the residue was extracted with *n*-hexane and the insoluble material was removed by filtration. The *n*-hexane extract was concentrated and the residue was submitted to a bulb-to-bulb distillation (140~150°C/15 mmHg) to remove the volatile impurities. The non-volatile material was chromatographed on 300 g of silica gel (Merck, Kieselgel 60, 70~230 mesh). Elution with *n*-hexane-ethyl acetate (3:2) gave 2.0 g of the α,β-unsaturated water **4**. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 3400, 1710, 1645; ¹H-NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.30 (3H, t, *J* = 8 Hz), 1.84 (3H, brs), 3.65 (2H, m), 4.18 (2H, q, *J* = 8 Hz), 6.75 (1H, t, q, *J* = 7 Hz, 1.5 Hz). The above ester **4** (2.0 g) was dissolved in 40 ml of dry DMF and stirred overnight with 40% Triton B-MeOH (1 ml) at room temperature. The mixture was diluted with water (150 ml) and extracted with *n*-hexane. The extract was washed with water and brine, and

dried over anhydrous MgSO₄. Evaporation of the solvent left 1.3 g of a cyclized product which was a mixture of methyl and ethyl esters. The mixture of esters (611 mg), without purification, was saponified by heating in 0.2 M KOH-95% MeOH aq. (50 ml) for 6 hr. After cooling, the mixture was neutralized by stirring with the cation exchange resin, Amberlist A15. Removal of the resin by filtration was followed by concentration to give a crude acid **5**, which was purified by column chromatography on 70 g of silica gel. Elution with ethyl acetate-acetic acid (9:1) afforded 544 mg of a diastereomeric mixture of the carboxylic acid **5** (25% from crude **3**). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: ~3000, 1710; ¹H-NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.18 and 1.20 (3H, d × 2, *J* = 7 Hz), 11.7 (1H, s); ¹³C-NMR (CDCl₃): 12.2, 13.0, 23.2, 25.8, 28.5, 28.8, 44.9, 45.6, 68.9, 69.0, 78.5, 79.2, 178.9, 179.7.

Phenyl 2-(2-tetrahydropyranyl)propanethioate 6 (diastereomers **6a** and **6b**). According to the reported procedure,⁸⁾ the carboxylic acid **5** (286 mg) was treated with *N,N'*-carbonyldiimidazole (319 mg) in 8 ml of DMF at -10°C under a nitrogen atmosphere for 2 hr, and then with thiophenol (203 μl) for 1 hr. The reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with water and brine, and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude product mainly consisting of two diastereomeric phenylthioesters (**6a**, *R_f* 0.38; **6b**, *R_f* 0.31; *n*-hexane-ethyl acetate, 9:1). Column chromatographic separation on 75 g of silica gel (*n*-hexane-ethyl acetate, 95:5) afforded 117 mg of the less polar fraction (**6a**, 97% of isomeric purity by GLC) and 151 mg of the more polar fraction, a mixture of **6a** (23%) and **6b** (77%). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1700; MS *m/z*: 250 (2, M⁺), 142 (7), 141 (40), 110 (3), 109 (5.5), 86 (11), 95 (100); ¹H-NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: **6a**, 1.27 (3H, d, *J* = 7 Hz), 7.27 (5H, s); **6b**, 1.14 (3H, d, *J* = 7 Hz), 7.27 (5H, s).

Phenyl 1-(2-tetrahydropyranyl)ethanecarboselenoate 7 (diastereomers **7a** and **7b**). According to the reported procedure,⁹⁾ the carboxylic acid **5** (120 mg) was treated with phenyl selenocyanate (130 mg) and tri-*n*-butylphosphine (0.34 ml) in 6 ml of dichloromethane at room temperature under a nitrogen atmosphere for 2.5 hr. After removal of the solvent *in vacuo*, the residue was chromatographed on 50 g of silica gel. Elution with *n*-hexane-ethyl acetate (95:5) gave 75 mg of the less polar

isomer-rich fraction (**7a**:**7b**=89:11 by GLC) and 74 mg of the more polar isomer-rich fraction (**7a**:**7b**=1:4). **7a** *Rf* 0.43 (*n*-hexane-ethylacetate, 9:1); $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.28 (3H, d, $J=7$ Hz), 1.4~1.9 (6H, m), 2.84 (1H, m), 3.44 (1H, m), 3.52 (1H, m), 4.00 (1H, m), 7.39 (3H, m), 7.50 (2H, m); $^{13}\text{C-NMR}$ (CDCl_3): 13.4, 23.4, 25.9, 57.3, 68.9, 78.3, 126.6, 128.8, 129.2, 135.8, 203.0. **7b** *Rf* 0.35; $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.12 (3H, d, $J=7$ Hz), 1.4~1.9 (6H, m), 2.88 (1H, m), 3.42 (1H, m), 3.58 (1H, m), 3.98 (1H, m), 7.39 (3H, m), 7.50 (2H, m); $^{13}\text{C-NMR}$ (CDCl_3): 13.2, 23.3, 25.8, 28.5, 57.2, 68.7, 79.0, 128.6, 129.2, 135.7, 204.0.

2-(2-Tetrahydropyranyl)propanethioic acid *S*-2-pyridyl ester **8** (diastereomers **8a** and **8b**). According to the reported procedure,¹⁰ the carboxylic acid **5** (53 mg) was treated with 2,2'-dipyridyl disulfide (128 mg) and triphenylphosphine (150 mg) in 10 ml of dichloromethane at room temperature for 6 hr. After removal of the solvent *in vacuo*, the residue was chromatographed on 25 g of silica gel. Elution with *n*-hexane-ethyl acetate (3:2) afforded 21.5 mg of the less polar isomer-rich fraction and 58 mg of the more polar isomer-rich fraction. **8a** *Rf* 0.51 (*n*-hexane-ethylacetate, 1:1); $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.32 (3H, d, $J=7$ Hz), 1.50 (4H, m), 1.70 (1H, m), 1.86 (1H, m), 2.84 (1H, m), 3.44 (1H, m), 3.54 (1H, m), 4.02 (1H, m), 7.30 (1H, m), 7.63 (1H, d, m, $J=8$ Hz), 7.75 (1H, d, t, $J=2$ Hz, 8 Hz), 8.64 (1H, m). **8b** *Rf* 0.45; $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.21 (3H, d, $J=7$ Hz), 1.50 (4H, m), 1.70 (1H, d, $J=3$ Hz), 1.87 (1H, m), 2.85 (1H, m), 3.43 (1H, m), 3.60 (1H, m), 3.98 (1H, m), 7.30 (1H, m), 7.63 (1H, m), 7.75 (1H, m), 8.63 (1H, m).

Selenolesters (**10**, **12** and **14**) and 2-pyridinethiol esters (**11**, **13** and **15**) were prepared in accordance with Grieco's procedure⁹) and that of Mukaiyama,¹⁰) respectively.

Cyclohexylmethanethioic acid *S*-2-pyridyl ester **15**. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.8~2.0 (11H, br m), 2.57 (2H, d, $J=6.8$ Hz), 7.26 (1H, m), 7.65 (1H, m), 7.73 (1H, m), 8.62 (1H, m). *Anal.* Found: C, 66.13; H, 7.32; N, 5.81. Calcd. for $\text{C}_{13}\text{H}_{17}\text{ONS}$: C, 66.35; H, 7.28; N, 5.95%.

General procedure for the formation of 2-acylpyrroles. To a suspension of cuprous iodide (0.57 mmol, 108.6 mg) in dry THF (0.8 ml) was added a solution of 0.5 *N* pyrrolylmagnesium bromide (1.15 mmol, 2.3 ml, freshly prepared from 1 *N* ethereal ethylmagnesium bromide and excess pyrrole in THF), with stirring on an ice-cooled water bath under a nitrogen atmosphere. After stirring for 30 min, a solution of the selenolester or 2-pyridinethiol ester (0.38 mmol) in dry THF (3 ml) was added to the mixture. The bath was then removed and stirring was continued at room temperature for 1~3 hr. After checking the completion of the reaction by TLC, a saturated NH_4Cl solution (2 ml) was added and the mixture was stirred for 15 min. The mixture was filtered through celite to remove the precipitate, and the filtrate was extracted with ether.

The ethereal extract was washed with water and brine, and dried over anhydrous Na_2SO_4 . Removal of the solvent *in vacuo* afforded a crude 2-acylpyrrole which was purified by column chromatography on silica gel.

2-(2-Tetrahydropyranyl)propionylpyrrole **9**. **9a** (the less polar isomer). *Rf* 0.38 (*n*-hexane-ethyl acetate, 7:3); mp 80°C (recrystallized from *n*-hexane); IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3250, 1620, 1540; $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.27 (3H, d, $J=7$ Hz), 3.24 (1H, d, q, $J=9$ Hz, 7 Hz), ~3.49 (2H, m), 4.03 (1H, m), 6.29 (1H, m), 6.96 (1H, m), 7.06 (1H, m); $^{13}\text{C-NMR}$ (CDCl_3): 14.9, 23.3, 26.1, 30.2, 47.2, 68.9, 79.6, 110.7, 116.6, 125.1, 192.9. *Anal.* Found: C, 69.49; H, 8.28; N, 6.74. Calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_2\text{N}$: C, 69.54; H, 8.27; N, 6.76%. **9b** (the more polar isomer). *Rf* 0.31 (ditto); mp 93°C (recrystallized from *n*-hexane); IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3250, 1625, 1540; $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.12 (3H, d, $J=7$ Hz), 3.24 (1H, d, q, $J=9$ Hz), 3.39 (1H, m), 3.67 (1H, d, d, $J=2$ Hz, 9 Hz, 11 Hz), 3.88 (1H, m), 6.27 (1H, m), 6.96 (1H, m), 7.03 (1H, m), 9.30 (1H, br); $^{13}\text{C-NMR}$ (CDCl_3): 13.7, 23.5, 26.0, 28.8, 46.8, 68.7, 79.5, 110.6, 116.5, 124.7, 193.4. *Anal.* Found: C, 69.06; H, 8.23; N, 6.75. Calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_2\text{N}$: C, 69.54; H, 8.27; N, 6.76%.

Phenyl 2-pyridyl ketone **16**. mp 77~78°C (recrystallized from *n*-hexane), *Rf* 0.53 (*n*-hexane-ethyl acetate 9:1); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3280, 1620, 1570, 1540; $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 6.30 (1H, m), 6.88 (1H, m), 7.14 (1H, m), 7.50 (3H, m), 7.88 (2H, m), 10.15 (1H, br). *Anal.* Found: C, 77.17; H, 5.25; N, 8.16. Calcd. for $\text{C}_{11}\text{H}_9\text{ON}$: C, 77.17; H, 5.30; N, 8.18%.

Cyclohexyl 2-pyridyl ketone **17**. mp 85~86°C (recrystallized from cold *n*-hexane), *Rf* 0.62 (*n*-hexane-ethyl acetate 9:1); IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3275, 1615, 1540; $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.0~2.0 (10H, m), 3.00 (1H, m), 6.24 (1H, m), 6.90 (1H, m), 7.00 (1H, m), 9.85 (1H, br). *Anal.* Found: C, 74.04; H, 8.47; N, 7.79. Calcd. for $\text{C}_{11}\text{H}_{15}\text{ON}$: C, 74.54; H, 8.53; N, 7.90%.

Cyclohexylmethyl 2-pyridyl ketone **18**. mp 95~96°C (recrystallized from *n*-hexane), *Rf* 0.63 (*n*-hexane-ethyl acetate, 9:1); IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3250, 1610, 1540; $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.8~2.0 (11H, m), 2.62 (2H, d, $J=7$ Hz), 6.25 (1H, m), 6.88 (1H, m), 7.00 (1H, m), 9.90 (1H, br). *Anal.* Found: C, 75.16; H, 8.85; N, 7.27. Calcd. for $\text{C}_{12}\text{H}_{17}\text{ON}$: C, 75.35; H, 8.96; N, 7.32%.

Acknowledgments. We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the NMR spectra, and Dr. H. Honma and his staff for the elemental analyses. We also thank Ms. A. Takahashi for her technical assistance.

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