1,4-Dichloro-1,4-dimethoxybutane as a Mild Reagent for the Conversion of Primary Amines to Pyrroles. Synthesis of a Pyrrole Compound from Tobacco

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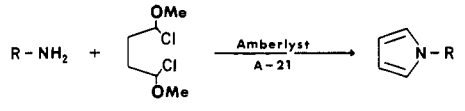
Received December 9, 1982

1,4-Dichloro-1,4-dimethoxybutane (**2**) reacts with primary amines, amino esters, and amino acids to give the corresponding N-substituted pyrroles. The synthesis of compound **9**, a compound found in flue-cured tobacco, is described.

The conversion of primary amines to pyrroles has previously been achieved by reaction with 2,5-dimethoxytetrahydrofuran (**1**) under refluxing acetic acid.[1] The reaction is useful for the synthesis of a number of N-substituted pyrroles. It is obviously not applicable to compounds that are acid or heat sensitive.

Recently, we have prepared 1,4-dichloro-1,4-dimethoxybutane (**2**) by the reaction of 2,5-dimethoxytetrahydrofuran with trimethylchlorosilane.[2] Compound **2** can be considered as a more reactive functional equivalent of **1** and should be capable of converting primary amines to pyrroles. We found that when benzylamine (**3a**) reacted with **2** in the presence of a tertiary base such as triethylamine or *N,N*-diisopropylethylamine, 1-benzylpyrrole (**4a**) can indeed be obtained but in poor yield (5–30%). When NaOMe in methanol was used as the neutralizing agent, the predominant product was 1,1,4,4-tetramethoxybutane with 1-benzylpyrrole again in about 30% yield.



3 **2** **4**

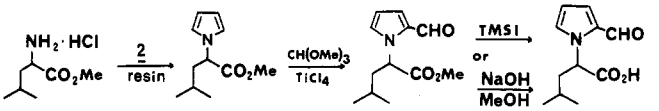
3a, R = CH_2Ph
3b, $CH_2CO_2Et \cdot HCl$
3c, $CH(CH_2Ph)CO_2Et \cdot HCl$
3d, CH_2CO_2H

4a, R = CH_2Ph
4b, CH_2CO_2Et
4c, $CH(CH_2Ph)CO_2Et$
4d, CH_2CO_2H

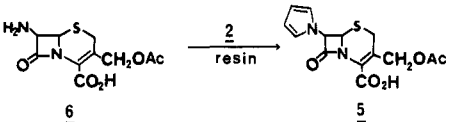
We were thus pleased to find that when the weakly basic ion-exchange resin Amberlyst A-21[3] was used for neutralization, the reaction gave 1-benzylpyrrole in nearly quantitative yield. The reaction conditions were very mild (see Experimental Section) and can be applied to the conversion of α-amino esters (e.g., **3b** and **3c**) to the corresponding pyrrole compounds. By using a more polar solvent, even amino acids (e.g., **3d**) can be converted directly to the pyrrole derivatives.

The utility of the present reaction can be illustrated by the following example. Nudelman et al. prepared 6-(1-pyrrolyl)cephalosporanic acid (**5**) in two steps by reacting *tert*-butyl 6-aminocephalosporanate with **1** in refluxing acid followed by hydrolysis in an overall yield of 7–8%.[4] We were able to prepare **5** directly from 6-aminocephalosporanic acid (**6**) and **2** in 65% isolated yield. Furthermore, with use of our conditions, the much more labile 6-(1-pyrrolyl)penicillanic acid (**7**) can also be prepared directly from 6-aminopenicillanic acid (**8**) in 67% isolated yield.

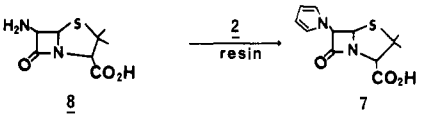
Scheme I



10 **11** **9**



6 **5**



8 **7**

Finally, we have applied the reaction to the synthesis of the 2-formylpyrrole derivative **9**, a compound that is found in flue-cured tobacco and may have desirable flavoring properties.[5] The synthesis is outlined in Scheme I. Leucine methyl ester hydrochloride was converted to the pyrrole compound **10**. Formylation of **10** with dichloromethyl methyl ether and titanium tetrachloride at room temperature gave a mixture of 2- and 3-formyl derivatives **11** and **12**, which could be separated by column chromatography but with the 3-isomer predominating.[6] Formylation at lower temperature gave exclusive 2-formylation with, however, considerable amount of unreacted **10**. We were able to overcome this problem effectively by using trimethyl orthoformate/titanium tetrachloride as the formylating agent. Under this condition, the 2-isomer was obtained in high yield to the near exclusion of the 3-isomer. Hydrolysis of **11** with sodium hydroxide in methanol gave **9**. When excess hydroxide was used, the compound **9** was devoid of optical activity, indicating that racemization at the chiral center had occurred. The problem can be overcome by hydrolysis with 1.2 equiv of sodium hydroxide. Alternatively, cleavage of the methyl ester moiety with trimethyliodosilane proved equally satisfactory, giving **9** with optical rotation of $[\alpha]_D$ −16.4° ($CDCl_3$).

Experimental Section

Melting points (mp) were determined on a Gallenkamp block and are uncorrected. Mass spectra (MS) were obtained on DuPont

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21-094B mass spectrometer, in the direct inlet mode. Infrared (IR) spectra were obtained on a Perkin-Elmer 297 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian T-60, T-60A, and XL-200 spectrometers, using tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts are given in the δ scale in parts per million (ppm). Doublets (d), triplets (t), quartets (q), and multiplets (m) were recorded at the center of the peaks; other abbreviations used are singlets (s) and broad (b). ^{13}C NMR spectra were recorded on XL-200 or WH-90 spectrometers.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} aluminum-backed plates and was visualized by dipping into a solution of ammonium molybdate (2.5 g) and ceric sulfate (1 g) in concentrated H_2SO_4/H_2O (10 mL/90 mL) and heating on a hot plate. Woelm silica (32–63 μm) was used for flash chromatography.[8]

Solvents were reagent grade unless otherwise specified. THF was dried from Na, CH_3CN from CaH_2, and CH_2Cl_2 from P_2O_5, Me_2SO from NaOH, and the solvents were distilled prior to use. All evaporations were carried out under reduced pressure (water aspirator) with a bath temperature of 25–40 °C. Optical rotation was measured on Perkin-Elmer 141 polarimeter.

Elemental analyses were performed by Guelph Chemical Lab. Ltd., Guelph, Ontario, Canada.

1,4-Dichloro-1,4-dimethoxybutane (2). To 2,5-dimethoxytetrahydrofuran (1; 1.32 g, 10 mmol) in $CHCl_3$ (20 mL) in an ice bath was added trimethylchlorosilane (0.1 mol, 12.6 mL) dropwise under N_2 atmosphere. The reaction mixture was allowed to warm to room temperature. After 2 days, solvent was evaporated in vacuo. The product was purified by distillation to give a colorless liquid: bp 71–74 °C (0.8 mmHg), yield 1.6 g (86%); ^{1}H NMR ($CDCl_3$) δ 5.50 (m, 2 H), 3.45 (s, 6 H), 2.25 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 99.87, 57.47 (OMe), 34.54.

A Typical Procedure for the Conversion of Primary Amines to N-Substituted Pyrroles. To 5 mmol of primary amine in dry CH_2Cl_2 (30 mL) was added the dichloro compound **2** (1.13 g, 6 mmol) dropwise at 0 °C under N_2. To the mixture was added 3 g of Amberlyst A-21 resin. The reaction mixture was allowed to warm to room temperature. After overnight, the mixture was filtered on a fine-sintered glass filter and the filtrate evaporated in vacuo. The product was purified by flash chromatography, using hexane–ethyl acetate as eluent.

Compound **4a** (90% yield):[7] ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 5 H), 6.9 (t, 2 H), 6.3 (t, 2 H), 5.3 (s, 2 H); MS, *m/z* (relative intensity) 157 (M^+, 50.8), 91 (100).

Compound **4b** (92% yield): ^{1}H NMR ($CDCl_3$) δ 6.65 (t, 2 H), 6.2 (t, 2 H), 4.6 (s, 2 H), 4.2 (q, 2 H), 1.25 (t, 3 H); MS, *m/z* (relative intensity) 153 (M^+, 88.5), 80 (100). Anal. Calcd: C, 62.8; H, 7.2; N, 9.2. Found: C, 62.8; H, 7.3; N, 9.2.

Compound **4c** (94% yield): ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H), 6.95 (t, 2 H), 6.3 (t, 2 H), 4.82 (dd, 1 H), 4.22 (m, 2 H), 3.4 (m, 2 H), 1.2 (t, 3 H); MS, *m/z* (relative intensity) 243 (M^+, 93.2), 170 (100), 152 (99.3), 91 (70). Anal. Calcd: C, 74.1; H, 7.0; N, 5.8. Found: C, 74.0; H, 7.1; N, 5.7.

Preparation of 1-Pyrrolylacetic Acid (4d). One millimole of glycine (75 mg) and 0.5 g of resin were stirred in Me_2SO for 1 day. Under N_2 atmosphere, the dichloro compound **2** (0.236 g, 1.2 mmol) was added dropwise and followed by another 0.5 g of resin. The reaction mixture was stirred overnight and then filtered and concentrated under reduced pressure (0.5 mm) to remove Me_2SO. The residue was purified by flash chromatography, using methanol–ethyl acetate (3:2) as eluent, to give **4d** (60%): ^{1}H NMR (Me_2SO + $CDCl_3$) δ 6.65 (t, 2 H), 6.1 (t, 2 H), 4.55 (s, 2 H), 8.9 (br, 1 H). The same compound was obtained by hydrolysis of **4b**.

Preparation of 7-(1-Pyrrolyl)cephalosporanic Acid[4] (5). A quantity of 0.27 g (1 mmol) of 7-aminocephalosporanic acid was stirred in 10 mL of Me_2SO for 20 min and then 1 g of resin was added. After 1 day, the dichloro compound **2** (0.236 g, 1.2 mmol) was added dropwise. The reaction mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure (0.5 mm) to remove Me_2SO. The residue was purified by flash chromatography, using methanol–ethyl acetate (1:1) as eluent, to give **5** (65%): ^{1}H NMR (Me_2SO) δ 6.72 (t, 2 H), 6.23 (d, 1 H), 6.07 (t, 2 H), 5.2 (d, 1 H), 4.9 (q, 2 H), 3.5 (q, 2 H), 2.0 (s, 3 H); IR (KBr) 1760 cm^{-1} (β-lactam).

Preparation of 6-(1-Pyrrolyl)penicillanic Acid (7). A quantity of 0.216 g (1 mmol) of 6-aminopenicillanic acid was stirred overnight in 10 mL of dimethyl sulfoxide and then 0.5 g of Amberlyst A-21 resin was added. After 1 day, the dichloro compound **2** (0.236 g, 1.2 mmol) was added dropwise and followed by another 0.5 g of resin. The reaction mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure (0.5 mm) to remove Me_2SO. The residue was purified by flash chromatography, using methanol–ethylacetate (2:3) as eluent, to give **7** (67%): ^{1}H NMR (CD_3OD) δ 6.78 (t, 2 H), 6.03 (t, 2 H), 5.21 (d, 1 H), 4.69 (d, 1 H), 3.44 (s, 1 H), 1.58 (s, 3 H), 1.23 (s, 3 H); IR (KBr) 1735 cm^{-1} (β-lactam).

Preparation of Compound 10. L-Leucine methyl ester hydrochloride (1.82 g, 10 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 10 min. Amberlyst A-21 resin (2.5 g) was introduced and then the dichloro compound **2** (2.26 g, 12 mmol) was added dropwise at 0 °C under N_2. After 30 min, to the mixture was added 5 g of the resin again. The reaction mixture was allowed to warm to room temperature. After overnight, the mixture was filtered on a fine-sintered glass filter and the filtrate evaporated in vacuo. The crude product was purified by TLC–mesh column chromatography,[9] using hexane–ethyl acetate (7:3) as eluent: R_f 0.48; $[\alpha]_D$ −3.8° ($CDCl_3$); 71% (yield); ^{1}H NMR ($CDCl_3$) δ 6.75 (t, 2 H), 6.17 (t, 2 H), 4.65 (t, 1 H), 3.70 (s, 3 H), 1.95 (m, 2 H), 1.40 (m, 1 H), 0.95 (d, 3 H), 0.83 (d, 3 H); MS, *m/z* (relative intensity) 195 (M^+, 50.9), 139 (100). Anal. Calcd: C, 67.7; H, 8.7; N, 7.2. Found: C, 67.7; H, 8.7; N, 7.3.

Formylation of Compound 10 To Give Compounds 11 and 12. (a) With Dichloromethyl Methyl Ether. To dichloromethyl methyl ether[10] (0.125 g, 1.1 mmol) in dry CH_2Cl_2 (5 mL) was added $TiCl_4$ (0.21 g, 1.1 mmol) dropwise at −20 °C under N_2. After 10 min, pyrrole **10** (0.195 g, 1 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise over 5 min. The reaction mixture was stirred for 5 h at −20 °C and allowed to warm to room temperature. After overnight, the mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with 10% aqueous sodium bicarbonate solution and then with water. After drying over anhydrous $MgSO_4$, the solvent was removed. The residue was separated by TLC–mesh column chromatography,[9] using hexane–ethyl acetate (7:3) as eluent, to give compound **11** (10%) and compound **12** (50%).

When the reaction was carried out for 6 h at −40 °C, it gave compound **11** in 10% yield together with the unreacted starting material **10**.

(b) With Trimethyl Orthoformate. To trimethyl orthoformate (0.127 g, 1.2 mmol) in dry CH_2Cl_2 (5 mL) was added $TiCl_4$ (0.21 g, 1.2 mmol) dropwise at −40 °C under N_2. Pyrrole **10** (0.195 g, 1 mmol) in dry CH_2Cl_2 (2 mL) was then added dropwise over 5 min. After the reaction mixture was stirred at −40 °C for 1.5 h, the mixture was allowed to warm to room temperature. The solution was quenched with 1 mL of water and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was separated by TLC–mesh column chromatography,[9] using hexane–ethyl acetate (7:3) as eluent, to give compound **11** (80%) and compound **12** (10%).

For compound **11**: ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1 H), 7.2 (br, 1 H), 6.97 (d, d, 1 H), 6.33 (d, d, 1 H), 6.1 (t, 1 H), 3.72 (s, 3 H), 1.98 (m, 2 H), 1.4 (m, 1 H), 0.92 (d, 3 H), 0.89 (d, 3 H); mass spectrum, *m/z* (relative intensity) 223 (M^+, 68.5), 194 (69.9), 164 (69), 152 (75.6), 122 (67.6), 108 (100), 94 (97.2), 80 (72.7); IR ($CDCl_3$) 1745, 1668 cm^{-1}; $[\alpha]_D$ −6.5° ($CDCl_3$). Anal. Calcd: C, 64.5; H, 7.7. Found: C, 64.6; H, 7.7.

For compound **12**: ^{1}H NMR ($CDCl_3$) δ 9.8 (s, 1 H), 7.37 (t, 1 H), 6.73 (t, 1 H), 6.56 (m, 1 H), 4.65 (t, 1 H), 3.7 (s, 3 H), 1.92

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(m, 2 H), 1.4 (m, 1 H), 0.91 (d, 3 H); mass spectrum, m/z (relative intensity) 223 (M^+, 63.4), 167 (100), 164 (49.3), 122 (44.2), 108 (55), 94 (82), 80 (60.9).

Hydrolysis of 11 To Give Compound 9. (a) With Sodium Hydroxide. To compound 11 (0.112 g, 0.5 mmol) in methanol (5 mL) was added aqueous sodium hydroxide solution (1.2 equiv, 24 mg of NaOH in 1 mL of water). After the reaction mixture was refluxed overnight, the mixture was cooled to room temperature and then poured to 10 mL of water. This solution was washed with ether and the aqueous layer was then acidified with diluted HCl to pH 3 and extracted with ether. The combined ethereal layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to give quantitatively a pale yellowish solid: mp 74–77 °C; $[\alpha]_D$ −16.4° ($CDCl_3$); ^1H NMR ($CDCl_3$) δ 11 (br, 1 H), 9.48 (s, 1 H), 7.17 (br, 1 H), 6.98 (d,d, 1 H), 6.32 (dd, 1 H), 6.05 (t, 1 H), 2.0 (m, 2 H), 1.4 (m, 1 H), 0.91 (d, 3 H), 0.88 (d, 3 H); mass spectrum, m/z (relative intensity) 209 (M^+, 52.7), 180 (75.4), 138 (63.6), 122 (66), 108 (71.3), 94 (78.1), 80 (62.2), 41 (100); IR (KBr) 3250–2400, 1740, 1610 cm^{-1}; $[\alpha]_D$ −16.4° ($CDCl_3$). Anal. Calcd: C, 63.1; H, 7.2. Found: C, 63.2; H, 7.3.

When quite excess aqueous sodium hydroxide solution was used, compound 9 showed no optical activity.

(b) With Trimethyliodosilane. This reaction was carried out according to Jung's method.[11] To compound 11 (0.112 g, 0.5 mmol) in dry $CHCl_3$ (5 mL) was added trimethyliodosilane (0.143 mL, 1 mmol). The solution was stirred overnight at room temperture while protected from light. The mixture was then poured into 5% aqueous $NaHCO_3$. The aqueous layer was washed with ether, acidified with diluted HCl to pH 3, and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give yellowish solid 9 (55%). The physical data was identical with that of method a.

Acknowledgment. We thank NSERC and FCAC for financial support of this research.

Registry No. 1, 696-59-3; 2, 86428-38-8; 3a, 100-46-9; 3b, 623-33-6; 3c, 3182-93-2; 3d, 56-40-6; 4a, 2051-97-0; 4b, 5145-67-5; 4c, 86436-62-6; 4d, 19167-98-7; 5, 66967-05-3; 6, 957-68-6; 7, 86436-63-7; 8, 551-16-6; 9, 86436-64-8; 10, 86436-65-9; 11, 86436-66-0; 12, 86436-67-1; Amberlyst A-21, 9049-93-8; L-leucine methyl ester hydrochloride, 7517-19-3.

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Intramolecular Addition of Enolates to Pyridinium Ions: Formation of Spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines]

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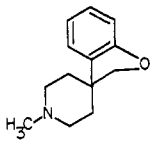
Received October 13, 1982

Intramolecular addition of ketone and ester enolates to *N*-alkylpyridinium species produced spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines] in 82–93% yields. When the ketone adducts were treated with hydriodic acid in ethanol at room temperature and the ester adducts treated with triethylammonium iodide in refluxing ethanol, the original pyridinium salts were produced in excellent yields. An attempt to extend the intramolecular pyridinium enolate addition to the synthesis of the 4a-phenylisoquinoline system failed but produced instead the 4-phenylquinoline system. The addition of enolates to *N*-acylpyridinium salts was moderately successful when the ketone enolates were generated with the hindered base 2,6-dimethyl-4-(1-piperidyl)pyridine.

The spiro[benzofuran-3(2*H*),4′-piperidines] **1**, represent an interesting substructure of the morphine molecule (**2**).



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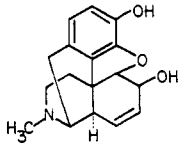
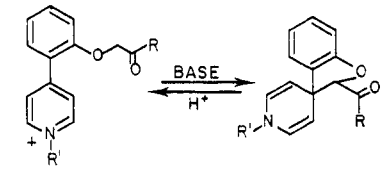


2

Although known for some time, this fragment has not been extensively explored since no exceptionally active analgesics have been found in this series.[1] Recently, it has reappeared as an early intermediate in a general route to the morphine system.[2] It is well suited to this role in that it is a relatively simple fragment which contains the important quaternary carbon of the morphine skeleton. Thus, the question of stereochemistry can be addressed early in the synthesis. We wished to explore the applicability of the derivative fragment, the spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines], **4**, toward the total synthesis of the morphine alkaloids.[3] We expected that these derivatives would be available by the intramolecular addition of enolates to pyridinium ions of type **3** (eq 1). This



3 R = OEt, CH_3

3 R′ = Alkyl, Acyl

4

(1)

addition reaction is well documented for both the intra- and intermolecular modes[4] and has found utility in the synthesis of several alkaloid systems such as ajmalicine,[5] yohimbine,[6] and sesbanine.[7]

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