Notes

Alternative Syntheses of N-[4'-(Alkoxycarbonyl)phenyl]-3-pyrrolidinones[1]

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N-[4'-(Alkoxycarbonyl)phenyl]-3-pyrrolidinone (1, Scheme I) is a key starting material for the synthesis of a number of fused heterocycles,[4,5] among them certain analogues of the anticancer drug Methotrexate. For example, alkylation of the pyrrolidine enamine of 1 with (ethoxymethylene)malononitrile, followed by cyclization with ammonia and further annulation and functionalization reactions, leads to the fused pyrroline 3, which is of interest as a precursor to a "tied-back" deaza analogue of Methotrexate.[6] Similarly, Knoevenagel condensation of 1 with cyanoacetamide gives 4, which, followed by further functionalization and annulation reactions, leads to 5, a precursor of a novel deaza analogue of the natural folate cofactor for thymidylate synthase[7] (Scheme I). The title compound (1) has previously been prepared by reacting *tert*-butyl 4-fluorobenzoate and 3-pyrrolidinol in DMSO/K_2CO_3 at 120 °C for 7 h followed by oxidation (48% overall yield),[6] by Diels-Alder cycloaddition of 2-methoxy-1,3-butadiene with methyl *p*-nitrosobenzoate followed by acid hydrolysis of the resulting enol ether, hydrogenolysis of the N-O bond, and final intramolecular dehydrative cyclization (14% overall yield),[8] and by decarbomethoxylation[6] of *N*-[4'-(methoxycarbonyl)-phenyl]-4-(methoxycarbonyl)-3-pyrrolidinone, prepared by way of a Dieckmann cyclization (23% overall yield).[9] In this paper we report two additional syntheses of 1.

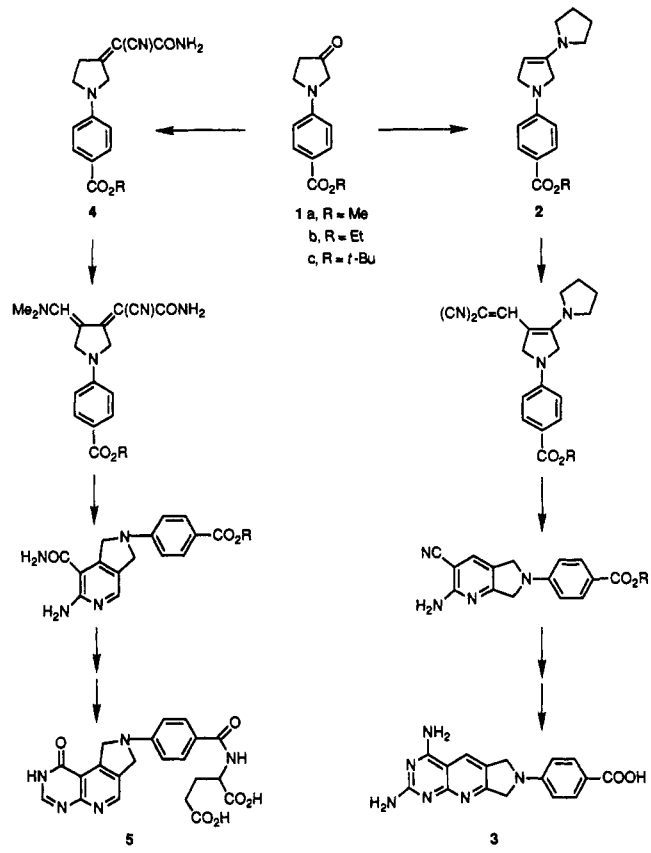
Discussion

We have found that the condensation of 4-bromo-1,2-epoxybutane (6) with a slight excess of an alkyl 4-aminobenzoate (7) under argon in a sealed reaction flask at 120 °C for 2-4 h gives the desired *N*-[4'-(alkoxycarbonyl)-phenyl]-3-pyrrolidinol (8) in satisfactory yields (Scheme II). Trituration of the dark, viscous reaction mixture with methylene chloride afforded a white crystalline product, identified as the HBr salt of 7, which could be easily removed by filtration. Column chromatography of the remaining material gave 8. The *tert*-butyl analogue 8c was obtained by refluxing 6 and 7c in xylene for 8 h. The infrared spectra of all three analogues of 8 exhibited strong hydroxyl and carbonyl stretching absorption at ca. 3480 and 1670 cm^{-1}, respectively.

The starting epoxide (6) was prepared from 4-bromo-1-butene (Aldrich) and *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 for 24 h.[10] Gas chromatographic analysis of the reaction mixture typically indicated yields above 97% before workup. Isolated yields of 6, which was used without purification, were in the range 85-88%. Overall yields of pyrrolidinol 8 from 4-bromo-1-butene were 45-55%.

The second approach to 1 was based on recent work by Joullié.[11] Alkylation of 7a with *cis*-1,4-dichloro-2-butene in methanol containing 2 equiv of sodium acetate and a catalytic amount of potassium iodide (Finkelstein condi-

Scheme I



(1) Presented in part at the Eleventh International Congress of Heterocyclic Chemistry, Heidelberg, Federal Republic of Germany, August 16-21, 1987 (Abstract LMP 41).
(2) Present address: American Cyanamid Co., Princeton, NJ 08540.
(3) Present address: Merrell-Dow Pharmaceutical, Cincinnati, OH 45215.
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(5) For a review of the preparation of 3-pyrrolidinols (from which pyrrolidinones are readily prepared), see: Flanagan, D. M.; Joullié, M. M. *Heterocycles* **1987**, *26*, 2247.
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tions) gave an excellent yield of the 3-pyrroline **9a**.[12] Hydroboration–oxidation of **9a** afforded a 63% yield of **8a**.

Attempts to oxidize 8 to 1 using Jones' oxidation conditions were unsuccessful. However, 1 was obtained in moderate yields (50–60%) using Moffatt oxidation conditions (with either trifluoroacetic acid or 99% phosphoric acid as the acid catalyst),[13] Ag_2CO_3 on Celite in refluxing benzene,[14] or the recently introduced catalytic tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide procedure.[15]

In the oxidation of 8 with both Ag_2CO_3 on Celite and tetrapropylammonium perruthenate (TPAP) a significant amount of starting material remained in all reactions despite several attempts to drive the reactions to completion.[16] In the case of TPAP, others have overcome this problem by using acetonitrile as a cosolvent with methylene chloride.[17] In our case, treatment of 8 with 2 equiv of *N*-methylmorpholine *N*-oxide and 5 mol % of TPAP in 10% acetonitrile in methylene chloride gave both product 1 and recovered starting material in yields that were nearly identical with those obtained when using methylene chloride alone.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover instrument and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1720 FT spectrophotometer. Proton NMR spectra were recorded on a Varian EM 360 instrument. All analytical thin-layer chromatograms were performed using Baker-flex silica gel 1B2-F sheets. Column chromatography was carried out using 70–230-mesh silica gel.

***N*-[4′-(Methoxycarbonyl)phenyl]-3-pyrrolidinol (8a). From 4-Bromo-1-butene. Method A.** 4-Bromo-1,2-epoxybutane (**6**) (2.45 g, 16.2 mmol)[10] was placed in a pressure reaction bottle with methyl 4-aminobenzoate (**7a**) (4.09 g, 18.5 mmol). The flask was purged with argon, sealed, and placed in an oil bath preheated to 120 °C for 2 h. The reaction flask was removed from the oil bath, and the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2, and allowed to stand overnight. The hydrogen bromide salt of methyl 4-aminobenzoate was removed by filtration, and the concentrated filtrate was placed on a silica gel column (3.5 × 10 cm) and eluted with $CHCl_3$/hexanes (4:1). The mobile phase was gradually increased to 100% $CHCl_3$ and the product (**8a**) was collected (R_f = 0.30 in chloroform) and concentrated to give 2.23 g (54.4% based on 4-bromo-1-butene) of **8a** as tan crystals: mp 138–141 °C; IR (KBr) 3450, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47–1.81 (broad, OH), 2.07 (m, 2 H), 3.22–3.53 (m, 4 H), 3.77 (s, 3 H, OCH_3), 4.56 (m, 1 H), 6.50 and 7.91 (AB q, 4 H, J = 9 Hz). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.83; N, 6.33. Found: C, 64.73; H, 6.83; N, 6.22.

***N*-[4′-(Ethoxycarbonyl)phenyl]-3-pyrrolidinol (8b).** The epoxide **6** (2.45 g, 16.2 mmol) was placed in a pressure reaction bottle with ethyl 4-aminobenzoate (**7b**) (3.06 g, 18.5 mmol). The flask was purged with argon, sealed, and placed in an oil bath preheated to 120 °C for 6 h. The reaction bottle was removed from the oil bath and allowed to cool to room temperature, and the contents were diluted with CH_2Cl_2/hexanes (2:1) and allowed to stand overnight. The hydrogen bromide salt of ethyl 4-aminobenzoate (1.27 g) was removed by filtration, and the concentrated filtrate was placed on a silica gel column (3.5 × 10 cm) and eluted with $CHCl_3$/hexanes (4:1). The mobile phase was gradually increased to 100% $CHCl_3$, and the product was collected (R_f = 0.25 in 4% methanol/$HCCl_3$) and concentrated. The product was purified further by recrystallization from benzene/hexanes to give 2.18 g (50.2% based on 4-bromo-1-butene) of **8b** as tan crystals: mp 102–104 °C; IR (KBr) 3477, 1668, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, 3 H, J = 7.5 Hz), 2.12 (m, 3 H, CH_2 and OH), 3.29–3.60 (m, 4 H), 4.29 (q, 2 H, J = 7.5 Hz), 4.61 (m, 1 H), 6.50 and 7.91 (AB q, 4 H, J = 9 Hz). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.19; H, 7.10; N, 5.96.

***N*-[4′-(*tert*-Butoxycarbonyl)phenyl]-3-pyrrolidinol (8c).** A mixture of *tert*-butyl 4-aminobenzoate **7c** (1.28 g, 6.62 mmol) and epoxide **6** (0.75 g, 4.97 mmol) in xylene (15 mL) was refluxed under argon for 8 h. After cooling, the reaction was diluted with CH_2Cl_2 and the solid that formed was removed by filtration. The filtrate was concentrated and applied to a silica gel column. Elution with $CHCl_3$ (50 mL), followed by 2% MeOH in $CHCl_3$, afforded **8c** as white crystals. An analytical sample was obtained by recrystallizing the product twice from benzene: yield 0.42 g (32%); mp 165–167 °C (lit.[6] mp 166–168 °C); IR (Nujol) 3491, 1673, 1611 cm^{-1}; MS m/z 263 (M^+), 207 ($M^+ - C_4H_8$), 190, 163, 150, 135, 91, 77, 65, 57; ^1H NMR [$(CD_3)_2CO$] δ 1.54 (s, 9 H), 2.12 (m, 2 H), 3.28–3.59 (m, 4 H), 4.61 (m, 1 H), 4.78 (d, 1 H, OH), 6.46 and 7.83 (AB q, 4 H, J = 9 Hz, Ar).

***N*-[4′-(Methoxycarbonyl)phenyl)]-3-pyrroline (9a).** A suspension of methyl 4-aminobenzoate (**7a**) (20.00 g, 0.132 mol), *cis*-1,4-dichloro-2-butene (21.3 g, 0.162 mol), anhydrous sodium acetate (21.7 g, 0.265 mol), and potassium iodide (1.00 g) in anhydrous methanol (60 mL) was refluxed for 5 h, during which time the mixture turned pale yellow and there was considerable precipitation. After cooling to room temperature, the contents of the flask were poured into ice–water (500 mL). The insoluble residue was removed by filtration, and the filtrate was treated at 5 °C with 10% NaOH (50 mL) and allowed to stand at room temperature overnight (16 h). The solid residue that formed was collected by filtration and dissolved in CH_2Cl_2 (50 mL). The aqueous filtrate was extracted with CH_2Cl_2 (2 × 100 mL), and the combined CH_2Cl_2 solutions were washed with water (2 × 100 mL) and brine and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo afforded a yellow, flaky solid, which was recrystallized from glacial acetic acid to yield 22.20 g (83%) of pure **9a**: mp 140–142.5 °C; IR (KBr) 3070, 2940, 2870–2820, 1695, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H, OCH_3), 4.1 (s, 4 H, CH_2NCH_2), 5.95 (s, 2 H, vinyl H), 6.45 and 7.95 (AB q, 4 H, ArH, J = 9 Hz); MS M^+ = 203. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.34; N, 7.02.

***N*-[4′-(Methoxycarbonyl)phenyl]-3-pyrrolidinol (8a). From 1,4-Dichloro-2-butene. Method B.** A solution of BH_3·THF (60 mL of a 1 M solution, 0.060 mol) was added dropwise with stirring to an ice-cooled solution of **9a** (9.9 g, 49 mmol) in dry THF (80 mL). The reaction mixture was stirred at rt for 1 h and then quenched carefully with water (10 mL). After treatment with 3 N NaOH (60 mL), the reaction was cooled to 0 °C, treated with 10 mL of 30% H_2O_2, allowed to warm to rt, and stirred for an additional h. The reaction mixture was then treated with water (200 mL) and aqueous 5% Na_2SO_3 (200 mL), and the product was extracted with ethyl acetate (3 × 100 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to yield a pale yellow solid. Recrystallization from benzene/hexanes afforded the analytical sample as an off-white solid, 6.8 g (63%), mp 138–141 °C. This material was identical in all respect with a sample of **8a** prepared as described above from 4-bromo-1-butene (method A).

***N*-[4′-(Methoxycarbonyl)phenyl]-3-pyrrolidinone (1a).** Trifluoroacetic acid (0.65 mL) was added dropwise to a solution of **8a** (2.0 g, 9.0 mmol), dicyclohexylcarbodiimide (6.33 g, 31.0 mmol), and dry pyridine (1.2 mL) in a mixture of dry DMSO (35 mL) and dry benzene (35 mL) at 0 °C. A thick white precipitate formed immediately, and the reaction was allowed to warm to

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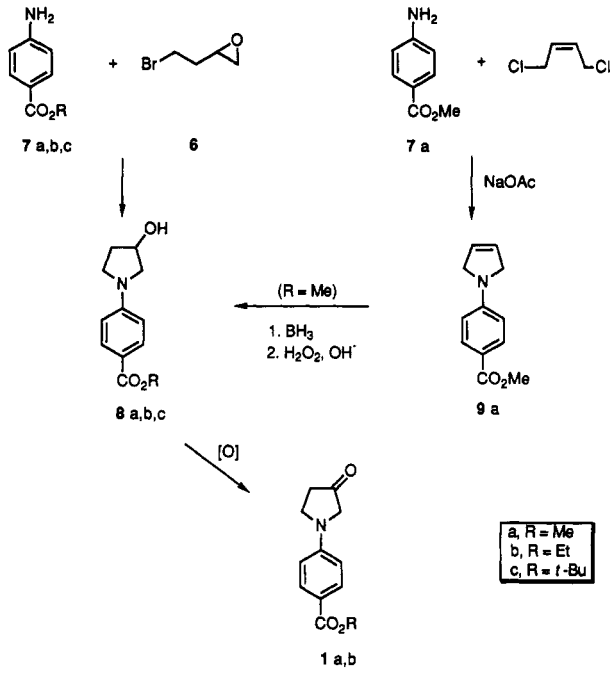
Scheme II



rt. The reaction was stirred at rt for 48.5 h and then quenched by addition of ethyl acetate (125 mL). Dicyclohexylurea was removed by filtration, and the filtrate was washed with water (3 × 250 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated to afford an orange gum. Trituration with ether/hexanes afforded 1.22 g (61%) of a tan solid: mp 162–165 °C (lit.[8] mp 162–164 °C); ^1H NMR ($CDCl_3$) δ 2.72 (t, 2 H, CH_2CO, J = 7 Hz), 3.7–3.9 (superimposed t and s, 4 H, 2 CH_2N), 3.93 (s, 3 H, OCH_3), 6.22 and 7.94 (AB q, 4 H, ArH, J = 9 Hz).

***N*-[4′-(Ethoxycarbonyl)phenyl]-3-pyrrolidinone (1b). Method A.** The pyrrolidinol **8b** (100 mg, 0.42 mmol) and *N*-methylmorpholine *N*-oxide (148 g, 1.26 mmol) were dissolved in CH_2Cl_2 (5 mL) containing ca. 250 mg of powdered 4-Å molecular sieves and stirred for 10 min. Tetrapropylammonium perruthenate (TPAP, 7 mg, 0.02 mmol) was added, and the reaction mixture, which had turned black, was stirred for 4 h. The mixture was concentrated by rotary evaporation and applied directly to a silica gel column. Elution with CH_2Cl_2 followed by 1% MeOH in CH_2Cl_2 afforded recovered starting material (26 mg) and 53 mg (52%) of **1b** as colorless flakes: mp 143–144.5 °C; IR (Nujol) 1758, 1687, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, 3 H), 2.68 (t, J = 7.5 Hz, 2 H), 3.68 (t, J = 7.5, superimposed on a singlet at δ 3.68, 4 H), 4.22 (q, J = 7 Hz, 2 H), 6.43 and 7.78 (AB q, J = 9 Hz, 4 H). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.96; H, 6.52; N, 6.07.

Method B. The pyrrolidinol **8b** (500 mg, 2.12 mmol) and dicyclohexyl carbodiimide (1.43 g, 6.94 mmol) were dissolved in dry DMSO (13 mL). Crystalline phosphoric acid (99%, 100 mg, 1.06 mmol) was added, and the reaction mixture stirred for 22 h, diluted with ethyl acetate, chilled and made slightly basic by the addition of 1 N NaOH. Precipitated dicyclohexyl urea was removed by filtration, and the filtrate was dried ($MgSO_4$) and concentrated. Purification by the procedure described above in method A afforded 200 mg (40%) of **1b**, identical in all respects (NMR, IR, mp) with material prepared by method A.

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Registry No. **1a**, 90030-20-9; **1b**, 117098-11-0; **6**, 13287-42-8; **7a**, 619-45-4; **7b**, 94-09-7; **7c**, 18144-47-3; **8a**, 134031-02-0; **8b**, 134054-95-8; **8c**, 94930-28-6; **9a**, 134031-03-1; (*Z*)-1,4-dichloro-2-butene, 1476-11-5.

Highly Crowded Perchloropolyphenyl-*p*-xylylenes with Exceptional Thermal Stability

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Introduction

As a continuation of our work on overcrowded aromatic chlorocarbons, we synthesized the perchloro-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-*p*-xylylene (**5**; perchlorinated Thiele's hydrocarbon[1]) and studied its properties. Only four reports[2-5] dealing with this chlorocarbon have appeared to date. Ballester et al.[2-4] described products whose IR and UV spectra corresponded to mixtures of **5** and as much as 50 mol % of its αH, $\alpha' H$ precursor **3**. Veciana et al.[5] claimed that a synthesis of **5** was performed, but neither physical nor chemical properties of the product were given. Because the bulky chlorine substituents would force the twisting of the exocyclic carbon–carbon double bonds of the perchlorinated *p*-xylylenes, thus favoring the formation of a triplet state, perchloro-1,4-bis(9-fluorenylidene)cyclohexadiene (**6**) was also synthesized and its multiplicity ascertained.

Results and Discussion

Perchloro-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-*p*-xylylene (5). The $AlCl_3$-catalyzed Friedel–Crafts alkylation of pentachlorobenzene by $\alpha H,\alpha' H$-octachloro-*p*-xylene (**2**; prepared by Friedel–Crafts alkylation of 1,2,4,5-tetrachlorobenzene (**1**) by $CHCl_3$)[6] gave $\alpha H,\alpha' H$-tetraicosachloro-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-*p*-xylene (**3**). Reaction of **3** with tetrabutylammonium hydroxide in THF DMSO afforded a dark reddish violet solution of the corresponding dianion **4**. This dianion was oxidized with chloranil to yield a virtually insoluble brick red compound, which was identified as chlorocarbon **5**. The UV–vis (λ 508 nm, ϵ 23 150) and IR spectra of **5** showed that the compounds reported by Ballester et al. (λ 502, ϵ 20 662)[2,4] and (λ 497 nm, ϵ 12 130)[3,4] were in fact mixtures of xylylene **5** and 11–50 mol % of its immediate precursor, the $\alpha H,\alpha' H$ derivative **3**. Upon crystallization, xylylene **5** incorporates 1 mol of $CHCl_3$. The chloroform is lost at 215 °C, and **5** decomposes at 395 °C. The compound's magnetic susceptibility (specific magnetic susceptibility = -0.510×10^{-6} emu) and the fact that a solution of **5** gives no ESR spectrum at room temperature clearly show that xylylene **5** is neither a triplet nor a double doublet, but a singlet. In contrast, it should be mentioned that the high degree of twisting about the

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