Syntheses of Antibacterial 2,4-Diamino-5-benzylpyrimidines. Ormetoprim and Trimethoprim

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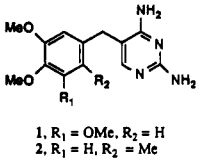
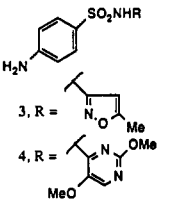
A general and mild method for the synthesis of 2,4-diamino-5-benzylpyrimidines was achieved by the Friedel–Crafts reaction between 2-(methoxymethylene)-3-methoxypropanenitrile (**10**) and an activated aromatic substrate followed by treatment with guanidine. The method is illustrated by a synthesis of ormetoprim (**2**) in 75% overall yield from 3,4-dimethoxytoluene (**12**). Efficient syntheses of trimethoprim (**1**) and **2** were also accomplished via prior base-catalyzed 1,3-prototropic isomerization of cinnamonitriles **19** and **20**, respectively, followed by condensation with guanidine. **12** was prepared from 3-bromo-4-methoxytoluene by a Cu(I)-catalyzed displacement of bromine by methoxide and 4,5-dimethoxy-2-methylbenzaldehyde was obtained from **12** in 87% yield by a pyridine-catalyzed Vilsmeier reaction using DMF–$POCl_3$.

Certain benzylpyrimidines, such as trimethoprim (**1**) and ormetoprim (**2**), are potent and selective inhibitors of bacterial dihydrofolate reductase, the enzyme responsible for the NADPH-dependent reduction of 7,8-dihydrofolate to 5,6,7,8-tetrahydrofolate. The latter is essential for various biosynthetic reactions that require the transfer of one carbon atom, such as in the biosynthesis of nucleic acids and certain amino acids (e.g., serine and methionine).[1] Trimethoprim is used solely, or in combination with sulfamethoxazole (**3**), to treat a wide range of bacterial infections in humans, and ormetoprim is used in combination with sulfadimethoxine (**4**) to control bacterial infections and coccidiosis in poultry.[2c] When used in combination, **1** and **2** act as potentiators of **3** and **4**, respectively.[2]

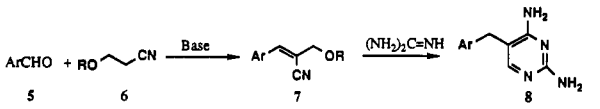


1, R_1 = OMe, R_2 = H
2, R_1 = H, R_2 = Me

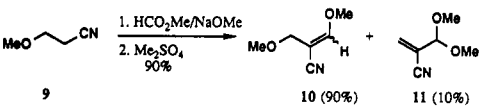


Previous syntheses of 2,4-diaminobenzylpyrimidines **8** frequently employed the condensation of an aromatic aldehyde **5** with a 3-alkoxypropanenitrile **6** followed by treatment of the resulting cinnamonitrile **7** with guanidine (Scheme I).[3] Although there have been some improvements[4] in this approach, the low yields of pyrimidines obtained and the relatively high cost of certain of the starting aromatic aldehydes[5] necessitated further work to find efficient and practical syntheses of these important benzylpyrimidines. In the present report we describe syntheses of **2** by applications of the Friedel–Crafts reaction (Schemes II and III) and of **1** and **2** by base-catalyzed 1,3-prototropic isomerization of the cinnamonitriles, **19** and **20**, respectively, followed by condensation of the derived products with guanidine (Scheme IV).

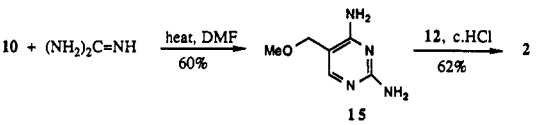
Scheme I



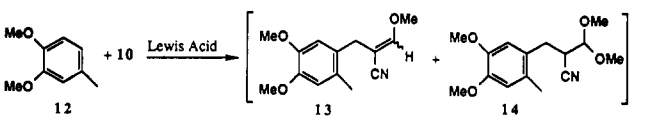
Scheme II

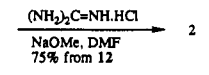


Scheme III



2-(Methoxymethylene)-3-methoxypropanenitrile (**10**),[6] readily available from the condensation of 3-methoxypropanenitrile with methyl formate followed by methylation with dimethyl sulfate, was found to be a powerful electrophile in the Friedel–Crafts reaction. Thus, when **10**, neat or in solution (e.g., CH_2Cl_2 or toluene) was treated with an alkoxy-substituted benzene (e.g., **12** for a synthesis of ormetoprim **2**) in the presence of a Lewis acid (e.g., BF_3·OEt_2, *p*-TSA, $AlCl_3$, $SnCl_4$) a facile reaction occurred to give the *E*/*Z* enol ether mixture **13**, accompanied by the acetal **14** as a minor component. Addition of guanidine to this mixture gave **2** in 75–85% yield. Although partial conversion of **10** into the acetal **11** occurred under the reaction conditions, **11** was found to be effective as **10** in the Friedel–Crafts reaction.





In an alternative synthesis of ormetoprim using the Friedel–Crafts reaction (Scheme III), **10** was condensed with guanidine that had been thermally generated from it carbonate to give the pyrimidine **15** in 60% yield. A Friedel–Crafts reaction between **15** and 3,4-dimethoxy-

(1) Hitchings, G. H. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 879, and references cited therein.

(2) (a) Sirotnak, F. M., Burchall, J. J., Ensminger, W. W., Montgomery, J. A., Eds. *Folate Antagonists as Therapeutic Agents*; Academic Press: New York, 1984; Vol. 1. (b) Rubin, R. H.; Swartz, M. N. *New Engl. J. Med.* **1980**, *303*, 426. (c) *Feed Additive Compendium*; Miller: Minnesota, 1992; p 325.

(3) Stenbuck, P.; Baltzly, R.; Hood, H. M. *J. Org. Chem.* **1963**, *28*, 1983.

(4) Brossi, A.; Hoffer, M.; Grunberg, E.; Mitrovic, M. *J. Med. Chem.* **1971**, *14*, 462.

(5) $374/kg from Aldrich Chemical Co. Inc., Milwaukee, WI 53201. Manchand, P. S.; Belica, P. S.; Wong, H. S. *Synth. Commun.* **1990**, *20*, 2659.

(6) Nishino, T.; Kiyokawa, M.; Miichi, Y.; Tokuyama, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1127.

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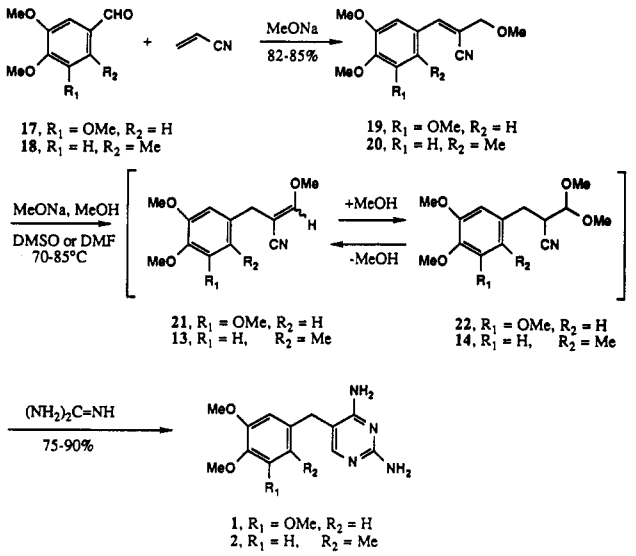
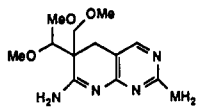
Scheme IV



toluene in the presence of hydrochloric acid or phosphoric acid gave ormetoprim in 62% yield.

Curiously, if guanidine is generated from its hydrochloride with sodium methoxide and the resulting mixture is then treated with **10**, none of the desired product **15** is obtained. Instead, the main product isolated, in 27% yield, was **16**, the structure of which is assigned on the basis of spectral data. An analogous reaction between **11** and acetamidine has been reported.[6]



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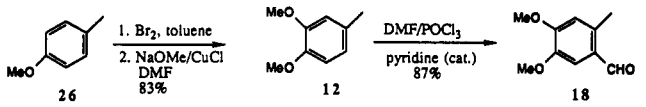
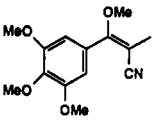
Not unexpectedly, the nature of the product obtained from the Friedel–Crafts reaction was determined by the substituents on the benzene ring. This precluded a practical synthesis of the most important member of the benzylpyrimidines, namely, trimethoprim (**1**), since the Friedel–Crafts reaction between **10** and 1,2,3-trimethoxybenzene invariably gave a mixture of regioisomeric products. Related results were reported by Roth et al.[7] in their attempt to prepare trimethoprim by the Brossner condensation of 2,4-diamino-5-(hydroxymethyl)pyrimidine with 2,6-dimethoxyphenol.

Because of limitations of the Friedel–Crafts and Brossner reactions with respect to the synthesis of trimethoprim (**1**), we reexamined the synthesis of **1** from the cinnamonitrile **19** (Scheme IV). The latter is easily prepared in high yield by the condensation of 3,4,5-trimethoxybenzaldehyde with 3-methoxypropanenitrile, which may be generated in situ from acrylonitrile with methanolic sodium methoxide. In order to form the pyrimidine ring with guanidine, prior conversion of **19** into the enol ether **21** is necessary, a transformation that would result in deconjugation from the benzene ring. A base-catalyzed 1,3-prototropic isomerization was examined to effect this transformation. Our initial choice of base was guanidine since this would also lead to pyrimidine formation. However, treatment of **19** with guanidine under a variety of conditions led to the formation of a considerable amount of resinous material with only modest yields of **1**, a result in accord with that reported by other workers.[3] A facile

Scheme V



isomerization of **19** into **21** was eventually found when alkoxide bases were employed, particularly when the reaction was carried out in aprotic dipolar solvents such as DMSO and DMF. Thus, heating a solution of cinnamonitrile **19** in DMSO to ca. 80 °C with anhydrous methanolic sodium methoxide produced a mixture, which, from GC–MS and isolation experiments, was found to consist of the enol ether *E*/*Z* mixture **21** (20%, 1:1 *E*/*Z* mixture), acetal **22** (76.5%), and **23** (3.5%) of undefined stereochemistry. Treatment of this mixture with guanidine, which had been liberated from its carbonate with sodium methoxide, gave **1** in 75% yield. A similar process was used to prepare ormetoprim (**2**) in 85% yield from the cinnamonitrile **20**.



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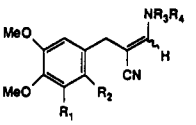

24, R1 = H, R2 = R3 = R4 = Me
25, R1 = OMe, R2 = R3 = H, R4 = Ph

A number of factors influenced the yields of pyrimidines **1** and **2** obtained from the cinnamonitriles **19** and **20**, respectively. Water had a most detrimental effect on the alkoxide-catalyzed isomerization of the cinnamonitriles, thus curtailing the possibility of carrying out a "one-pot" synthesis of **1** and **2** directly from the aldehydes **17** and **18**, respectively. Also, the combination of solvent and guanidine salt used affected the yields significantly. The combination of DMSO–guanidine carbonate resulted in the highest yields (75–90%) of pyrimidines, whereas DMSO–guanidine hydrochloride led to the lowest yields (20–30%). In DMF the carbonate and hydrochloride salts of guanidine gave **1** and **2** in yields of 60–80%. When the isomerization was carried out in DMF, the dimethylamine derivative **24** was isolated in 10% yield. In contrast to the relatively mild conditions (reflux in ethanol) required to effect condensation of the related aniline derivative **25**[8] with guanidine, **24** reacted extremely sluggishly with guanidine (DMSO, 170 °C, 3.5 h) to give **2** in 15% yield.

Ancillary to the synthesis of ormetoprim (**2**), efficient syntheses of 3,4-dimethoxytoluene (**12**) and of 4,5-dimethoxy-2-methylbenzaldehyde (**18**) were achieved from 4-methoxytoluene (**26**) by the following series of reactions (Scheme V). Bromination of **26** with bromine in toluene followed by Cu(I)-catalyzed exchange of bromine by methoxide gave **12** in 83% yield, which on Vilsmeier formylation with DMF–$POCl_3$ afforded **18** in 87% yield. Yields in the Vilsmeier formylation were increased when the reaction was carried out in the presence of a small quantity of pyridine.

In conclusion, the Friedel–Crafts reaction was found to be an excellent method for preparing certain benzylpyrimidines. In cases where this is inappropriate because of the substitution pattern on the aromatic ring, an efficient alternative involves isomerization of a cinnamonitrile (e.g., **19**) to give an enol ether (e.g., **21**), which on condensation with guanidine furnishes the pyrimidine.

(7) Stuart, A.; Paterson, T.; Roth, B.; Aig, E. *J. Med. Chem.* **1983**, *26*, 667.

(8) Cresswell, R. M.; Mentha, J. W.; Seaman, R. L.; Yeowell, D. A. *Third Int. Congr. Het. Chem.*, Tohoku Univ. Sendai, Jpn, Aug 23–27, 1971; Abst. C-26-1 (U. S. Patent 3697512, Oct 10, 1972).

Experimental Section

General Methods. Melting points were determined in capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise indicated, infrared (IR) and nuclear magnetic resonance spectra (NMR) were determined in $CHCl_3$ and $CDCl_3$, respectively; ^1H and ^{13}C NMR spectra were recorded at 200 and 50.4 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane, and coupling constants (J) are expressed in hertz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). ^{13}C NMR assignments are based on chemical shifts and off-resonance and DEPT spectra and are tentative. Mass spectra (MS) were determined with a direct inlet system with ionization energy of 70 eV; m/z values are given with relative intensities in parentheses. Thin-layer chromatograms (TLC, silica gel G) were purchased from Merck (Darmstadt); spots were visible under short-wavelength UV light or made visible by spraying with 10% phosphomolybdic acid in ethanol and heating the plates to 100 °C.

2-(Methoxymethylene)-3-methoxypropanenitrile (10). A 600-mL Parr reactor was charged with 63.4 g (1.17 mol) of freshly prepared NaOMe and 350 mL of anhydrous toluene. The mixture was cooled to ca. 10 °C and was treated with 94.5 g (1.11 mol) of 3-methoxypropanenitrile followed by 67.0 g (1.11 mol) of methyl formate. The mixture was heated to 50 °C under 50 atm of carbon monoxide for 19 h, cooled to room temperature, and flushed with Ar. The solid was collected by filtration, washed with some toluene, and transferred to a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, condenser, and thermometer. Toluene (400 mL) was added followed by 110 mL (146.5 g, 1.16 mol) of dimethyl sulfate. The mixture was stirred at 50 °C for 15 h, cooled to room temperature, and treated with 20.8 mL of Et_3N. Stirring was continued for 30 min, and the mixture was diluted with 200 mL of brine. The organic phase was collected, and the aqueous phase was reextracted with 150 mL of toluene. The combined extracts were dried ($CaCl_2$) and evaporated to give 152.8 g of crude **10** as a pale yellow oil, which was distilled through a 1-ft × 1-in. Vigreux column to give 112.7 g (80%) of **10** (3:2 mixture of E/Z isomers) as a colorless oil, bp 78–81 °C (0.15 Torr): UV (EtOH) 230 nm (ϵ = 13750); IR 2220, 1648, 1450 cm^{-1}; ^1H NMR δ 3.05/3.06 (3 H, s), 3.70/3.71 (3 H, s), 3.82 (2 H, s), 6.75/6.85 (1 H, s); ^{13}C NMR δ 56.98/57.46 (OCH_3), 61.78/62.0 (OCH_3), 64.22/68.61 (CH_2), 87.02/89.58 (s, sp^2C), 116.10/118.20 (CN); MS m/z 127 (18, M^+), 96 (100). ^1H NMR of the crude product indicated the presence of ca. 10% of **11**, which was removed by distillation, bp 40–42 °C (0.15 Torr): ^1H NMR δ 3.35 (6 H, s), 4.90 (1 H, br s), 6.18 (2 H, s).

3,4-Dimethoxytoluene (12). A stirred solution of 122.0 g (1.0 mol) of 4-methoxytoluene in 300 mL of toluene cooled to −10 °C was treated with 168.8 g (1.05 mol) of Br_2 at a rate such that the temperature was kept between −10 and 0 °C. Stirring was continued at −5 to 0 °C for 1.0 h, and the mixture was concentrated in vacuo at 50 °C to give 208.2 g of crude 3-bromo-4-methoxytoluene. This was dissolved in 120 mL of DMF and added to a stirred mixture of 325.0 g (6.02 mol) of freshly prepared NaOMe in 1.0 L of MeOH. Freshly prepared cuprous chloride[9] (9.9 g, 0.1 mol) was added, and the mixture was stirred at reflux for 4.5 h. It was cooled to room temperature, poured into 1.2 L of brine, and filtered. The filter cake was washed with four 500-mL portions of warm toluene, each wash being used to reextract the brine filtrate. The combined extracts were washed with 1.2 L of H_2O, dried ($MgSO_4$), and evaporated to give 153.0 g of crude **12** (93% purity by GC). Distillation through a 1-ft × 1-in. Vigreux column gave 126.2 g (83%) of **12**, bp 53–54 °C (0.15 Torr): UV (EtOH) 277–280 (ϵ = 2700), 227 (ϵ = 7400) nm; ^1H NMR δ 2.21 (3 H, s), 3.71 (6 H, s), 6.63 (3 H, s); ^{13}C NMR δ 20.86 (CH_3), 55.60 (OCH_3), 55.80 (OCH_3), 111.24 (CH), 112.40 (CH), 120.76 (CH), 130.25 (s, ArC), 146.84 (s, ArC), 148.70 (s, ArC); MS m/z 152 (100, M^+), 137 (33), 121 (33), 109 (25), 91 (13). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.14; H, 7.86.

Enol Ether 13. A stirred solution of 15.2 g (0.1 mol) of **12** and 13.97 g (0.11 mol) of **10** under argon was treated with 3.0 mL of $BF_3{\cdot}OEt_2$. The mixture was stirred at 60 °C for 17 h, cooled to room temperature, and diluted with 100 mL of EtOAc and 100 mL of brine. The organic phase was collected, and the aqueous phase was reextracted with 100 mL of EtOAc. The combined extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$), and evaporated to give 25.1 g of a gum, which was dissolved in 25 mL of Et_2O and stirred at room temperature overnight. After being stirred at 0 °C for 1 h, the product was collected by filtration and washed with cold (0 °C) Et_2O (2 × 10 mL) to give 8.52 g (34%) of **13**, from which 5.71 g of one isomer was obtained by crystallization from MeOH, mp 89–90 °C: UV (EtOH) 201 (ϵ = 39850), 231 (ϵ = 18800), 284 (ϵ = 3670) nm; IR 2210, 1645, 1570 cm^{-1}; ^1H NMR δ 2.22 (3 H, s), 3.30 (2 H, s), 3.75 (3 H, s), 3.84 (6 H, s), 6.38 (1 H, s), 6.60 (2 H, s); ^{13}C NMR δ 18.65 (CH_3), 31.68 (CH_2), 55.78 (OCH_3), 55.97 (OCH_3), 61.33 (OCH_3), 89.01 (s, vinyl C), 112.97 (d, Ar CH), 113.8 (d, Ar CH), 117.03 (CN), 126.81 (s, ArC), 128.23 (s, ArC), 147.03 (s, ArC), 147.68 (s, ArC), 160.45 (d, vinyl CH); MS m/z 247 (100, M^+), 232 (23), 216 (20), 200 (22), 184 (20), 165 (45). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.60; H, 6.91; N, 5.57.

Pyrimidine 15. A stirred mixture of 101.6 g (0.8 mol) of 2-(methoxymethylene)-3-methoxypropanenitrile (**10**) and 72.2 g (0.40 mol) of guanidine carbonate in 200 mL of DMF under argon was boiled at reflux for 4 h and then evaporated in vacuo at 50 °C. MeOH (150 mL) was added, and the crude product was collected by filtration. It was stirred at reflux with a solution of 40 g (1.0 mol) of NaOH in 300 mL of H_2O for 1.5 h and then treated with 160 g of NaCl. The mixture was cooled to 5 °C, and the product was collected by filtration. It was washed with cold H_2O (6 × 80 mL) and dried in vacuo to give 74.0 g (60%) of **15** as a pale yellow solid. A 10-g portion was subjected to short-path distillation (Kugelrohr, 140 °C (0.1 Torr)) to give 9.94 g of **15** as colorless crystals: mp 174–175 °C; UV (EtOH) 284 (ϵ = 7120), 235 (ϵ = 11820) nm; IR (KBr) 3475, 3425, 1620, 1060 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.16 (3 H, s), 4.10 (2 H, s), 6.22 (2 H, s, NH_2), 6.46 (2 H, s, NH_2), 7.53 (1 H, s); ^{13}C NMR ($(CD_3)_2SO$) δ 56.3 (OCH_3), 68.4 (t, CH_2), 102.8 (s, ArC), 156.6 (d, CH), 163.2 (s, 2x ArC); MS m/z 154 (60, M^+), 123 (100). Anal. Calcd for $C_6H_{10}N_4O$: C, 46.70; H, 6.53; N, 36.34. Found: C, 46.71; H, 6.58; N, 36.48.

4,5-Dimethoxy-2-methylbenzaldehyde (18). Phosphorus oxychloride (806.28 g, 490.1 mL, 5.25 mol) was added to 200 g (1.31 mol) of 3,4-dimethoxytoluene under argon with stirring. The mixture was heated to 80 °C, and 383.6 g (5.25 mol) of DMF was added at a rate such that the temperature was kept within the range 90–95 °C. The mixture was stirred at 95 °C for 1.25 h, 416 mg (5.26 mM) of pyridine was added, and stirring was continued at 95 °C for 2.25 h. The dark brown syrup was cooled to 40 °C, poured cautiously onto 2.4 kg of crushed ice, and extracted with toluene (4 × 750 mL). The extract was washed successively with H_2O (2 × 1.0 L), saturated $NaHCO_3$ (1.0 L), and H_2O (2.0 L), dried ($MgSO_4$), and evaporated to give 219 g (95.5%) of crude **18** as a light brown oil, which crystallized on standing overnight. GC analysis indicated a purity of 95%. Kugelrohr distillation of a 1.0-g sample gave 865 mg of pure **18**, mp 74–75 °C, with a purity estimated by GC to be >99.6%: UV (EtOH) 318 (ϵ = 7650), 281 (ϵ = 11600), 233 (ϵ = 19250), 205 (ϵ = 14100) nm; ^1H NMR δ 2.60 (3 H, s), 3.90 (3 H, s), 3.92 (3 H, s), 6.66 (1 H, s), 7.32 (1 H, s), 10.20 (1 H, s); ^{13}C NMR δ 17.88 (CH_3) 55.75 (2 × OCH_3), 111.02 (d, Ar CH), 113.40 (d, Ar CH), 126.75 (s, ArC), 135.61 (s, ArC), 147.20 (s, ArC), 153.33 (s, ArC), 189.86 (CHO); MS m/z 180. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.66; H, 6.71. Found: C, 66.62; H, 6.53.

4,5-Dimethoxy-2-methyl-2′-(methoxymethyl)-cinnamonitrile (20). A solution of 90.0 g (0.5 mol) of **18** in 66 mL of acrylonitrile and 135 mL of MeOH was added during 1.0 h to a stirred, cooled (ca. 10 °C) solution of 81.0 g (1.5 mol) of freshly prepared NaOMe in 200 mL of MeOH. The mixture was stirred under argon at room temperature for 18 h and cooled to −15 °C, and the product was collected by filtration. It was washed with cold H_2O (3 × 200 mL) and cold (−15 °C) 75% aqueous MeOH (2 × 100 mL) to give 105.8 g (85.6%) of **20**, mp 70–71 °C (lit.[4] mp 68–69 °C): UV (EtOH) 220 (sh, ϵ = 10420), 237 (ϵ = 9520), 250 (sh, ϵ = 7700), 295 (ϵ = 9980), 334 (ϵ = 11900) nm; IR 2230, 1605, 1100 cm^{-1}; ^1H NMR δ 2.30 (3 H, s), 3.40 (3 H, s), 3.88 (3 H, s), 3.91 (3 H, s), 4.15 (2 H, s), 6.68 (1 H, s), 7.33 (1 H, s), 7.61 (1 H, s); ^{13}C NMR δ 19.01 (CH_3), 55.72 (OCH_3), 55.97 (OCH_3), 58.12 (OCH_3), 73.70 (CH_2), 106.23 (s, vinyl C), 110.22 (d, Ar CH), 113.15 (CH), 115.93 (s, ArC), 118.30 (CN), 123.81 (s, ArC), 131.20

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(s, ArC), 142.85 (d, vinyl CH), 146.84 (s, ArC), 150.43 (s, ArC); MS m/z 247 (100, M^+), 232 (16), 216 (70). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.98; H, 6.82; N, 5.61.

Acetal 14. A solution of 12.35 g (0.05 mol) of cinnamonitrile **20** in 14 mL of anhydrous DMSO was added to a solution of freshly prepared NaOMe (from 2.325 g of Na in 38 mL of anhyd MeOH). The solution was stirred at 85 °C for 3.5 h, cooled to room temperature, poured into 200 mL of brine, and extracted with 150 mL of Et_2O. The extract was washed with brine (2 × 100 mL), dried ($MgSO_4$), and evaporated to give 13.1 g of an oil. TLC (40% EtOAc in hexane, phosphomolybdic acid spray) showed **14** at R_f 0.40 and **13** at R_f 0.19; **20** had R_f at 0.48. Chromatography of a 4-g portion over silica gel 60 (70–230 mesh) with 20% EtOAc in hexane gave 2.1 g of a gum, which was crystallized from MeOH at 0 °C to give 1.9 g (44%) of **14**, mp 71–73 °C (lit.[4] mp 60–61 °C): UV (EtOH) 230 (ϵ = 8200), 282 (ϵ = 3050) nm; IR 2240, 1608, 1518 cm^{-1}; ^1H NMR δ 2.30 (3 H, s), 2.85–3.05 (3 H, m), 3.47 (3 H, s), 3.50 (3 H, s), 3.86 (3 H, s), 3.87 (3 H, s), 4.45 (1 H, d, J = 6), 6.68 (1 H, s), 6.77 (1 H, s); ^{13}C NMR δ 18.7 (CH_3), 30.6 (CH_2), 38.0 (CH), 55.2 (OCH_3), 55.4 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 102.9 (d, CH), 113.2 (d, Ar CH), 113.8 (d, Ar CH), 118.9 (CN), 126.9 (s, ArC), 128.2 (s, ArC), 147.0 (s, ArC), 147.8 (s, ArC); MS m/z 279 (15), 165 (65), 75 (100). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.27; H, 7.91; N, 5.00. Found: C, 64.43; H, 7.52; N, 5.08.

Ormetoprim (2). A. From the Friedel–Crafts Reaction between 10 and 12. A mixture of 152.0 g (1.0 mol) of 3,4-dimethoxytoluene (**12**), 140.0 g (1.1 mol) of freshly distilled 2-(methoxymethylene)-3-methoxypropanenitrile (**10**), and 5.70 g (30 mM) of *p*-toluenesulfonic acid in 400 mL of anhyd toluene was boiled under reflux for 20 h and then evaporated in vacuo to give a partially crystalline mass (consisting of a 7:3 mixture of **13** and **14**) to which 700 mL of DMF was added. To the stirred solution, under argon, was added a freshly prepared solution of NaOMe in MeOH (from 57.5 g of clean Na and 700 mL of MeOH). The mixture was stirred at 65 °C for 30 min and treated with 239.0 g (2.5 mol) of guanidine hydrochloride. The temperature of the reaction was increased to 110 °C during 3 h with the removal of MeOH via a Dean–Stark trap. The mixture was stirred at 110 °C for 1 h, allowed to reach room temperature, and cooled to −10 °C. The product was collected by filtration and washed with four 1-L portions of H_2O followed by two 300-mL portions of cold (−15 °C) acetone to give 204.4 g (75%) of **2**. Recrystallization from 600 mL of hot DMF gave, after washing with 600 mL of H_2O followed by 200 mL of cold acetone and drying in vacuo at 75 °C, 190 g (69.5% from **12**) of **2**, mp 231–232 °C (lit.[4] mp 230 °C): UV ($CHCl_3$) 287 (ϵ = 10740) and 230 (ϵ = 22000) nm; IR (KBr) 3500, 3375, 3300, 1620, 1080 cm^{-1}; ^1H NMR ($(CD_3)_2SO$–CF_3CO_2H) δ 2.15 (3 H, s), 3.58 (2 H, s), 3.73 (3 H, s), 3.76 (3 H, s), 6.75 (1 H, s), 6.83 (1 H, s), 6.86 (1 H, s), 7.80 (2 H, br s, NH_2), 8.20 (2 H, br s, NH_2); MS m/z 274 (M^+ 73), 259 (22, M − 15), 243 (16), 164 (100). Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.26; H, 6.45; N, 20.59.

B. From Pyrimidine 15. A stirred mixture of 9.24 g (0.06 mol) of **15**, 9.12 g (0.06 mol) of **12**, 20 mL of MeOH, and 30 mL of concd HCl was stirred at reflux for 7.5 h, at room temperature overnight, and at 0 °C for 15 min. The product was collected by filtration, washed with H_2O (2 × 20 mL) and cold (0 °C) acetone, and crystallized from 20 mL of hot DMF to give 10.16 g (62%) of **2**, mp 230–232 °C, identical with the sample prepared above.

C. From Isomerization of Cinnamonitrile 20. A solution of 98.8 g (0.40 mol) of **20** in 120 mL of anhyd DMSO (some warming necessary) was added to a freshly prepared solution of NaOMe (from 18.52 g of Na in 300 mL of anhyd MeOH). The solution was stirred under argon at 85 °C for 3.5 h and treated with 72.0 g (0.40 mol) of guanidine carbonate, and the temperature was raised to 125 °C during 1.25 h with the removal of MeOH via a Dean–Stark trap. After being stirred at 115 °C for a further 1.5 h, the mixture was cooled to 5 °C, diluted with 500 mL of H_2O, and stirred at 25 °C for a further 1.0 h. The product was collected by filtration and was crystallized from 230 mL of hot DMF to give, after washing with H_2O and drying in vacuo at 80 °C, 93.1 g (85%) of **2**, mp 232 °C, with TLC (silica gel plates; 95:7.5:1 $CHCl_3$–CH_3OH–NH_4OH) and spectral (UV, IR, NMR, MS) properties identical to those obtained previously.

Compound 16. A solution of 6.35 g (0.05 mol) of **10** in 15 mL of anhyd DMSO was added to a solution of NaOMe (from 2.29 g of Na and 30 mL of MeOH). The mixture was stirred at 40 °C for 45 min, treated with 9.0 g of guanidine hydrochloride, and stirred at 110 °C for 1.5 h with the removal of MeOH (Dean–Stark). It was cooled to room temperature and diluted with 60 mL of cold H_2O, and the product was collected by filtration. It was washed with 200 mL of H_2O followed by 100 mL of acetone to give 3.9 g (27%) of **16**, mp 252–254 °C. Crystallization from hot DMF gave an analytical sample, mp 254–256 °C: UV (EtOH) 220 (ϵ = 13600), 242 (ϵ = 22900), 263 (ϵ = 8420), 319 (ϵ = 10390) cm^{-1}; IR (KBr) 3400, 3350, 3150, 1645, 1090 cm^{-1}; ^1H NMR ($(CD_3)_2SO$–CF_3CO_2H) δ 2.92 (2 H, s), 3.32 (3 H, s), 3.44 (6 H, s), 3.51 (1 H, d, J = 12), 3.83 (1 H, d, J = 12), 4.72 (1 H, s), 8.15 (1 H, s), 8.81 (1 H, br s); ^{13}C NMR ($(CD_3)_2SO$–CF_3CO_2H) δ 24.36 (t, CH_2), 47.30 (s, sp^3C), 57.99 (OCH_3), 58.18 (OCH_3), 58.56 (OCH_3), 71.82 (t, CH_2), 103.98 (s, sp^2C), 106.57 (d, CH), 110.75 (s, sp^2C), 153.66 (s, sp^2C), 163.13 (s, sp^2C); MS m/z 281 (50, M^+), 266 (12), 249 (8), 234 (18), 218 (42), 204 (100), 190 (40), 75 (90). Anal. Calcd for $C_{12}H_{19}N_5O$: C, 51.24; H, 6.81; N, 24.90. Found: C, 51.25; H, 6.89; N, 25.12.

3,4,5-Trimethoxy-2′-(methoxymethyl)cinnamonitrile (19). This was prepared from 3,4,5-trimethoxybenzaldehyde[5] in 82% yield according to the procedure given for **20** or by condensation with isolated 3-methoxypropanenitrile, mp 79–81 °C (lit.[4] mp 78–79 °C): UV (EtOH) 233 (ϵ = 15320), 307 (ϵ = 15250) nm; IR 2225, 1590, 1130 cm^{-1}; ^1H NMR δ 3.43 (3 H, s), 3.88 (9 H, s), 4.15 (2 H, s), 7.05 (2 H, s); ^{13}C NMR δ 56.10 (OCH_3), 56.20 (OCH_3), 58.04 (OCH_3), 60.70 (OCH_3), 73.47 (CH_2), 106.30 (2 × ArCH), 106.81 (s, vinyl C), 117.9 (CN), 128.4 (s, ArC), 140.3 (s, ArC), 144.9 (d, vinyl CH), 153.2 (s, ArC); MS m/z 263 (100, M^+), 248 (28), 332 (51), 216 (14), 201 (42). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.82; H, 6.64; N, 5.30.

The (*Z*) stereochemistry indicated for **19** was confirmed by a single-crystal X-ray analysis.[10]

***E*/*Z* Enol Ether Mixture 21 and Acetal 22.** A solution of 6.6 g (0.025 mol) of cinnamonitrile **19** in 5.0 mL of anhyd DMSO was added to a solution of freshly prepared NaOMe (from 0.63 g of Na and 8.5 mL of MeOH), and the mixture was stirred under argon at 70–75 °C for 1.5 h. It was cooled to room temperature, diluted with 100 mL of brine, and extracted with 200 mL of Et_2O. The extract was washed with 100 mL of brine, dried ($MgSO_4$), and evaporated to give 6.3 g of a gum. TLC (silica, 80% Et_2O in hexane) analysis gave the following results: **23**, R_f 0.70; acetal **22**, R_f 0.45, and enol ether mixture **21**, R_f 0.33. Chromatography on 50 g of neutral alumina (Grade II) with 20% EtOAc in hexane gave: (1) 5.8 g (79%) of **22**, which was crystallized from CH_2Cl_2–Et_2O, mp 69–71 °C: UV (EtOH) 230 (ϵ = 11000), 269 (ϵ = 760) nm; IR 2250, 1130 cm^{-1}; ^1H NMR δ 2.93 (2 H, s), 2.94 (1 H, m), 3.43 (3 H, s), 3.47 (3 H, s), 3.80 (3 H, s), 3.83 (6 H, s), 4.40 (1 H, d, J = 6), 6.50 (2 H, s); MS m/z 295 (90, M^+), 280 (10), 181 (100). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.26; H, 7.28; N, 4.72.

(2) 400 mg of **21** (6%) as a 1:1 *E*/*Z* mixture mp 117–121 °C (from CH_2Cl_2–Et_2O); UV (EtOH) 205 (ϵ = 43100), 230 (ϵ = 21250) nm; IR 2220, 1650, 1130 cm^{-1}; ^1H NMR δ 3.32 (2 H, s), 3.80 (3 H, s), 3.85 (9 H, s), 6.45 (2 H, s), 6.65 (1 H, s); MS m/z 263 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.98; H, 6.62; N, 5.30.

(3) 35 mg (0.05%) of compound **23**, mp 68–73 °C (from Et_2O–hexane), as a mixture of *E*/*Z* isomers: UV (EtOH) 206 (ϵ = 32600), 225 (inflection, ϵ = 19000), 274 (ϵ = 11300) nm; IR 2210, 1630, 1130 cm^{-1}; ^1H NMR δ 1.96 (3 H, s), 3.56 (3 H, s), 3.88 (9 H, s), 6.60 (2 H, s); MS m/z 263 (100, M^+), 248 (77), 232 (9). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.18; H, 6.61; N, 5.32.

Trimethoprim (1). A solution of 99.0 g (0.376 mol) of cinnamonitrile **19** in 63 mL of anhyd DMSO was added to a solution of freshly prepared NaOMe (from 9.45 g of clean Na and 175 mL of MeOH). The mixture was stirred under argon at 70–75 °C for 1.0 h and was then treated with 36.99 g (0.20 mol) of powdered guanidine carbonate. The mixture was heated to 110 °C during 1.0 h with the removal of MeOH via a Dean–Stark trap, stirred

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at this temperature for an additional 1.0 h, cooled to 5 °C, and diluted with 150 mL of H_2O. Stirring was continued at 5 °C for 1.0 h, and the product was collected by filtration. It was washed with 300 mL of H_2O followed by cold (5 °C) acetone (3 × 100 mL) to give 81.9 g (75.2%) of 1, mp 198–199 °C, homogeneous by TLC (silica gel; 95:1:7:1 $CHCl_3$–CH_3OH–NH_4OH): UV (EtOH) 230 (sh, ϵ = 19 200), 289 (ϵ = 6780) nm; IR 3525, 3425, 1620, 1130 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.54 (2 H, s), 3.65 (3 H, s), 3.73 (6 H, s), 5.83 (2 H, s), 6.16 (2 H, s), 6.53 (2 H, s), 7.55 (1 H, s); MS m/z 290 (100, M^+), 275 (20), 259 (20), 243 (7). Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.23; N, 19.30. Found: C, 57.66; H, 6.30; N, 19.58. Trimethoprim prepared above may be recrystallized from aqueous EtOH, 95% return, mp 199–200 °C.

Enamine 24. A stirred solution of NaOMe in MeOH (from 4.6 g of Na and 62.0 mL of MeOH) was treated under Ar with 24.7 g (0.1 mol) of cinnamonitrile **20** and 50.0 mL of DMF. The mixture was stirred at 98 °C for 18 h, cooled to room temperature, poured into 200 mL of brine, and extracted with Et_2O (2 × 200 mL). The extract was washed with 250 mL of brine, dried ($MgSO_4$), and evaporated to give 26 g of a brown semisolid, which gave 10 g of a solid on trituration with 50 mL of ether. Repeated crystallizations from MeOH/Et_2O, and finally MeOH, gave 5.0 g (19%) of **24**, mp 85–86 °C: UV (EtOH) 230 (ϵ = 9850), 285 (ϵ = 21 400) nm; IR 2170, 1625, 1090 cm^{-1}; NMR δ 1.98 (6 H, s), 2.23 (3 H, s), 3.26 (2 H, s), 3.83 (6 H, s), 6.11 (1 H, s), 6.65 (1 H, s), 6.71 (1 H, s); MS m/z 260 (100, M^+), 245 (57), 229 (20), 164 (70). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.19; H, 7.80; N, 10.83.

The sample of **24** prepared above was identical (mmp, mixed TLC, UV, IR, NMR) with a substance isolated from a preparation of **2** when DMF was used as a solvent and with the product derived from the NaOEt-catalyzed condensation of **18** with 3-(dimethylamino)propanenitrile[11] in DMSO.

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Registry No. **1**, 738-70-5; **2**, 6981-18-6; **9**, 110-67-8; (*Z*)-**10**, 50744-71-3; (*E*)-**10**, 39800-76-5; **11**, 7515-08-4; **12**, 494-99-5; (*Z*)-**13**, 68640-16-4; (*E*)-**13**, 141292-60-6; **14**, 7520-76-5; **15**, 54236-98-5; **16**, 141292-61-7; **17**, 86-81-7; **18**, 7721-62-2; **19**, 141292-62-8; **20**, 7520-75-4; (*E*)-**21**, 141292-63-9; (*Z*)-**21**, 141292-66-2; **22**, 7520-70-9; (*E*)-**23**, 141292-64-0; (*Z*)-**23**, 141292-67-3; **24**, 141292-65-1; **26**, 104-93-8; HCO_2Me, 107-31-3; $(NH_2)_2C{=}NH{\cdot}H_2CO_3$, 100224-74-6; $(NH_2)_2C{=}NH{\cdot}HCl$, 50-01-1; $H_2C{=}CHCN$, 107-13-1; 3-bromo-4-methoxytoluene, 22002-45-5.

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Asymmetric Synthesis of Pyrrolo[1,2-*b*][1,2]diazepine Derivatives as Potential Antihypertensive Drugs

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The asymmetric synthesis of compound **1**, with potential angiotensin-converting enzyme inhibitory activity, is reported. From the chiral precursor **5**, readily available from L-glutamic acid, two strategies to the key heterocyclic system pyrrolo[1,2-*b*][1,2]diazepine have been developed. The first one is based on the formation of the pyrrole nucleus in the early stages of the synthesis. The second strategy is based on the formation of the pyrrole in the final stages and can be regarded as a two-step Paal–Knorr *N*-aminopyrrole synthesis, in which intermediate N-protection is unnecessary.

Introduction

Angiotensin-converting enzyme (ACE; EC 3.4.15.1) is a peptidase which removes the carboxy-terminal dipeptide from several peptidic substrates.[1] ACE plays important physiological actions. The most relevant are the formation of the potent vasoconstrictor angiotensin II from the decapeptide angiotensin I[2] and the degradation of the vasodilating peptide bradykinin.[3] Compounds with inhibitory activity on ACE have application against hypertension[4] and congestive heart failure[5] in man, and several of them have been marketed. Captopril,[6] a thiol-containing compound, was the first orally effective ACE inhibitor; however, the incidence of some side effects was attributed to the mercapto function.[7] This led to the introduction of a new class of ACE inhibitors, the carboxyalkyl dipeptides, such as enalapril,[8] and more recently its conformationally restricted derivatives, the bicyclic lactams, such as benazepril[9] and cilazapril.[10]

Among the conformationally restricted derivatives, a seven-membered lactam is the common feature for the most active compounds. Furthermore, a benzo fusion

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