A Short Synthesis of the Triazolopyrimidine Antibiotic Essramycin

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A short synthesis of the 1,2,4-triazolo[1,5-*a*]pyrimidine antibiotic essramycin is described involving condensation of aminoguanidine with ethyl benzoylacetate to give an amino-1,2,4-triazole, followed by condensation with ethyl acetoacetate to form the pyrimidone ring.

Compounds containing the N−N bond are relatively rare among natural products. Examples include the hydrazine peptide negamycin,[1] the pyrazolopyridazine nigellicine,[2] pyridazinomycin,[3] and the piperazic acid-containing cyclodepsipeptides.[4] In addition there are a number of naturally occurring diazo compounds such as cremeomycin.[5] Recently a new antibiotic substance was isolated from the fermentation broth of a marine organism (*Streptomyces* sp. Isolate Merv8102) collected from sediments in the Mediterranean Sea off the Egyptian coast.[6] The compound named essramycin was assigned as the 1,2,4-triazolo[1,5-*a*]pyrimidine **1**, an extremely unusual structure for a naturally occurring substance. We now report a short synthesis of essramycin, the first (and only) triazolopyrimidine natural product.

Although not isolated as natural products previously, 1,2,4-triazolo[1,5-a]pyrimidines are nevertheless quite well-known compounds, being previously investigated, for example, as vasodilators and herbicides.[7] In planning a synthesis of essramycin (**1**) we considered routes based on the known triazolopyrimidine acetic acid derivative **2**[8] or on the amino-1,2,4-triazole **3**[9] (Scheme 1). In the event, we elected to use the latter precursor, and therefore our synthesis started with the condensation of aminoguanidine bicarbonate with ethyl benzoylacetate in *n*-butanol to give the amino-1,2,4-triazole **3** in 32% yield. Although this compound has been described previously,[9] few data were reported, and therefore we fully characterized the compound. With amino-1,2,4-triazole **3** available, it remained to construct the pyrimidone ring by condensation with ethyl acetoacetate. Although in principle this condensation could result in the formation of isomers of the desired structure **1**, according to which carbonyl of the acetoacetic ester reacts first, and which nitrogen of the triazole ring participates in the subsequent cyclization, we were confident that under acidic reaction conditions the desired isomer **1** would result. Thus it has been reported that the condensation of 5-substituted 3-amino-1,2,4-triazoles proceeds through reaction at the acetoacetate ketone with formation of an aminocrotonate intermediate that cyclizes at N-2 of the triazole ring.[10,11] In the event this proved correct, and condensation of the 3-amino-1,2,4-triazole **3** with ethyl acetoacetate in acetic acid gave essramycin (**1**) in excellent yield (Scheme 2). The ^{1}H and ^{13}C NMR spectroscopic data closely matched those of the natural product, and therefore we conclude that essramycin does indeed have the unusual triazolopyrimidine structure **1**.

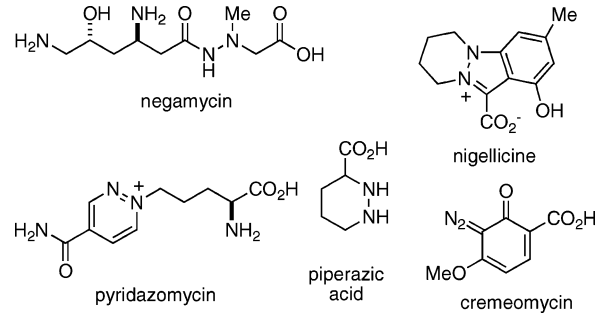
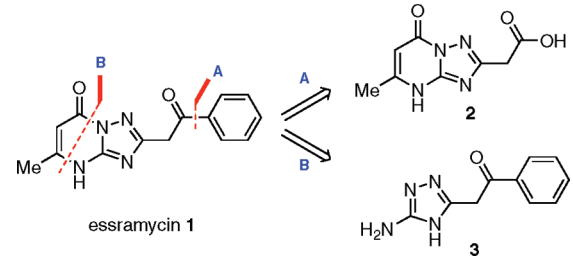


Figure 1. Some natural products with N−N bonds.

Scheme 1. Structure of Essramycin (**1**) and Its Retrosynthetic Analysis



Experimental Section

Commercially available reagents were used throughout without purification unless otherwise stated. Analytical thin-layer chromatography was carried out on aluminum-backed plates coated with silica gel 60 GF_{254} and visualized under UV light at 254 and/or 360 nm and/or by chemical staining. Flash chromatography was carried out using silica 60A, with the eluent specified. Infrared spectra were recorded in the range 4000−600 cm^{-1} in solution in the solvent specified or as solids in attenuated total reflectance (ATR) mode. NMR spectra were recorded at 400 MHz (100 MHz ^{13}C frequency). Chemical shifts are quoted in parts per million (ppm) and are referenced to residual H in the deuterated solvent as the internal standard. Coupling constants, *J*, are quoted in Hz. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI).

2-(5-Amino-4*H*-1,2,4-triazol-3-yl)-1-phenylethanone, 3. A suspension of aminoguanidine bicarbonate (4.73 g, 35 mmol) and ethyl benzoylacetate (6.72 g, 35 mmol) in *n*-butanol (20 mL) was heated under reflux at 125 °C for 6 h. During this time all solids went into solution. The mixture was cooled and kept in a refrigerator overnight. The suspension was filtered and the solid was washed with *n*-butanol (10 mL) and water (10 mL). The colorless solid thus obtained was resuspended in DMF (25 mL) and stirred for 30 min. The suspension was finally filtrated and washed with DMF (10 mL) to give the title compound **3** as a colorless solid (2.26 g, 11.2 mmol, 32%): mp 208−209 °C (lit.[9] mp 195−198 °C); (found: M + H^{+}, 203.0930; $C_{10}H_{10}N_4O$+H^{+} requires 203.0927); ν_{max} ($CHCl_3$)/cm^{-1} 3391, 3328, 2985, 1731, 1375, 1251, 1046; δ_H (400 MHz; DMSO-d_6) 11.79 (1H, br s, NH), 7.98 (2H, m, ArH), 7.59 (3H, m, ArH), 5.81 (2H, br s,

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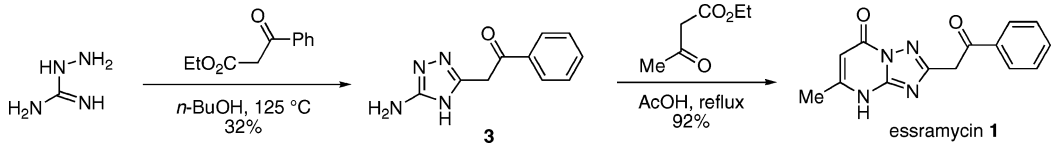
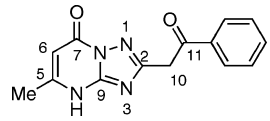
Scheme 2. Synthesis of Essramycin



NH_2), 4.11 (2H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 195.7 (C═O), 156.7 (C), 136.2 (C), 135.0 (C), 133.2 (CH), 128.6 (CH), 124.7 (CH), 39.7 (CH_2); *m*/*z* (ESI) 225 (M + Na^+), 203 (M + H^+).



Essramycin, 1. 2-(5-Amino-4*H*-1,2,4-triazol-3-yl)-1-phenylethanone (**3**) (90 mg, 0.5 mmol) was suspended in acetic acid (2 mL). Ethyl acetoacetate (102 mg, 0.8 mmol) was added, and the resulting mixture was stirred and heated under reflux for 17 h. Evaporation of the solvent *in vacuo* and purification of the residue by chromatography (eluting with MeOH/CH_2Cl_2, 10:90 v/v) gave the title compound **1** as a colorless solid (108 mg, 0.4 mmol, 92%): mp 220−223 °C (lit.[6] mp 219−221 °C); (found: M + H^+, 269.1036; $C_{14}H_{12}N_4O_2$+H^+ requires 269.1033); λ_{max} (CH_3OH)/nm 244 (log ε 4.20), 272 (4.01); ν_{max} (ATR))/cm^{-1} 3011, 1649, 1601, 1464, 1406, 1019; δ_H (400 MHz; DMSO-d_6) 8.04 (2 H, dd, *J* 8.2, 1.0, ArH), 7.66 (1 H, *J* 7.3, 1.3, ArH), 7.54 (2 H, tt, *J* 7.8, 1.4, ArH), 5.80 (1 H, s, H-6), 4.53 (2 H, s, 10-CH_2), 2.29 (3 H, s, 5-CH_3); δ_C (100 MHz; DMSO-d_6) 195.1 (C-11), 159.2 (C-2), 155.5 (C-7), 150.9 (C-9), 136.0 (ArC), 133.6 (ArCH), 128.8 (ArCH), 128.5 (ArCH), 98.3 (C-6), 39.5 (C-10), 18.6 (5-CH_3); *m*/*z* (ESI) 291 (M + Na^+), 286 (M + NH_4^+), 269 (M + H^+).

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all compounds. This can be accessed free of charge via the Internet at http://pubs.acs.org.

References and Notes

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