

Reactivity of 3,3'-Methylenebis(5-phenyl)oxazolidine with Urea, Thiourea and Cyanamide. An Alternative Mechanism for the α -Ureidoalkylation of 2-Amino-1-phenylethanol

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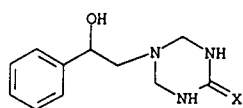
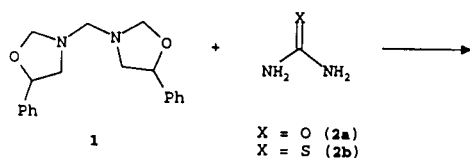
The title compound **1** reacts with urea, thiourea and cyanamide, yielding the corresponding 1,3,5-triazin-2-one **3a**, -2-thione **3b** and an *N,N*-dicyanobisaminal **4** derivative, respectively. An alternative mechanism for this class of α -ureidoalkylations is proposed.

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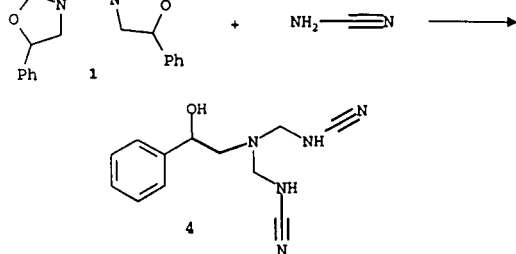
The propensity of the oxazolidine ring system to be opened by nucleophiles is well-documented in heterocyclic chemistry [1]. In particular, complex metal hydrides [2], Grignard reagents [3] and enamines [4], have been employed as nucleophilic partners. However, to our knowledge, few references can be found in the literature dealing with bisoxazolidines as electrophilic substrates [5].

We wish here to report on the ability of the title compound (**1**) to react with urea and thiourea to give, respectively, 5-(2-hydroxy-2-phenylethyl)-1,3,5-triazin-2-one **3a** and -2-thione **3b** (Scheme 1). The bisoxazolidine (**1**) also acts as a substrate for cyanamide, providing in this case a *N,N*-dicyanobisaminal **4** (Scheme 2).

Scheme 1



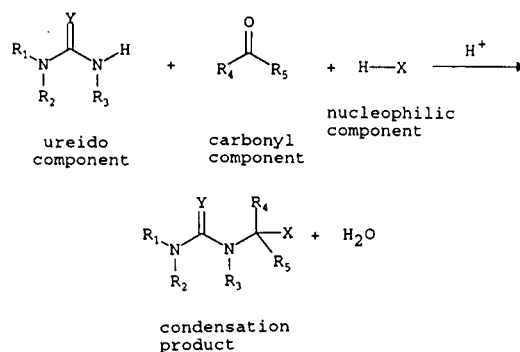
Scheme 2



Thiourea displays a higher reactivity, furnishing **3b** in good yields after heating in water at 80° for 2 hours. Urea gives the reaction only at higher temperature (100°/2-3 hours), whereas cyanamide reacts sluggishly with bisoxazolidine **1** giving a moderate yield of the corresponding

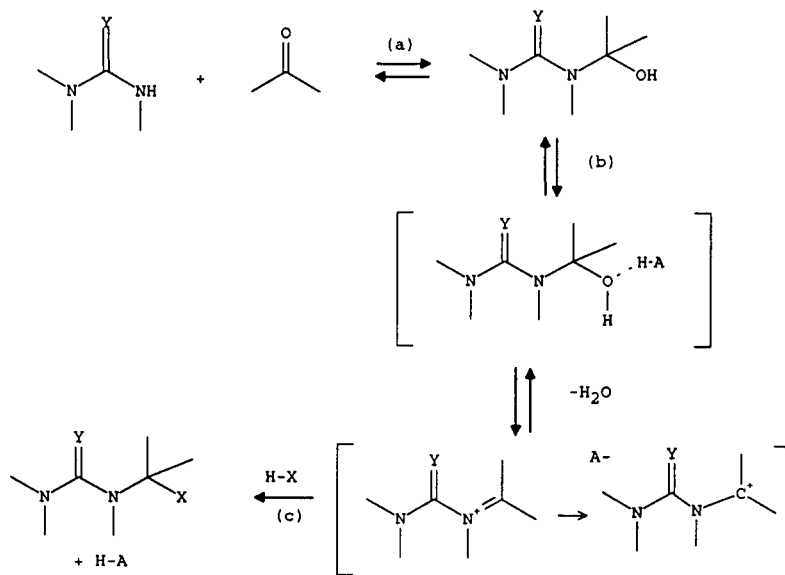
adduct. The reactions reported above can be considered as examples of α -ureidoalkylation, a very important class of reactions in the industrial synthesis of many chemical products, that is characterized by a wide scope [6] and has found interesting applications [7] (Scheme 3).

Scheme 3

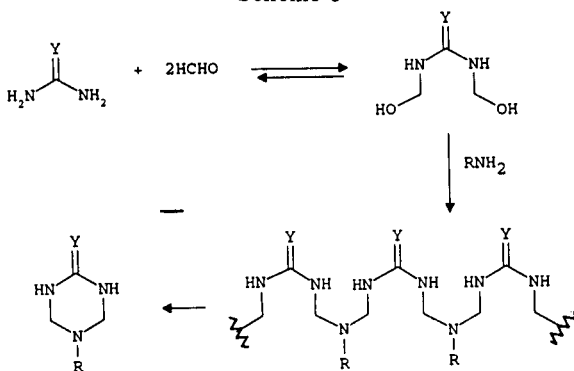


In the cases we report, a pre-formed condensation product (the bisoxazolidine) reacts with the ureido component to give the final products. The generally accepted mechanism [6] for α -ureidoalkylations (Scheme 4) entails: (a) nucleophilic attack of the ureido component onto the carbonyl compounds followed by (b) acid catalyzed iminium ion formation and (c) capture of the reactive iminium intermediate by the nucleophilic partner. In our case, if this mechanism were operating, the bisoxazolidine should act as a source of formaldehyde (the carbonyl compound) and 2-amino-1-phenylethanol (the nucleophilic partner). Apparently this mechanism cannot account for the reactions we observed. In the reactions of Schemes 1-3, in fact, no acid catalysis is operating and therefore an intermediate iminium ion (Scheme 4) can be reasonably ruled out. In addition, the bisoxazolidine (**1**) is stable *per se* under the reaction conditions (water, 60-100°, 1-6 hours). According to [5a], bisoxazolidines are indeed *formed* by heating a phenylethanolamine with a slight excess of aqueous formaldehyde in boiling water. These observations are in disagreement with another possible mechanism [6b] (Scheme 5) involving formation of a methylolurea followed by a

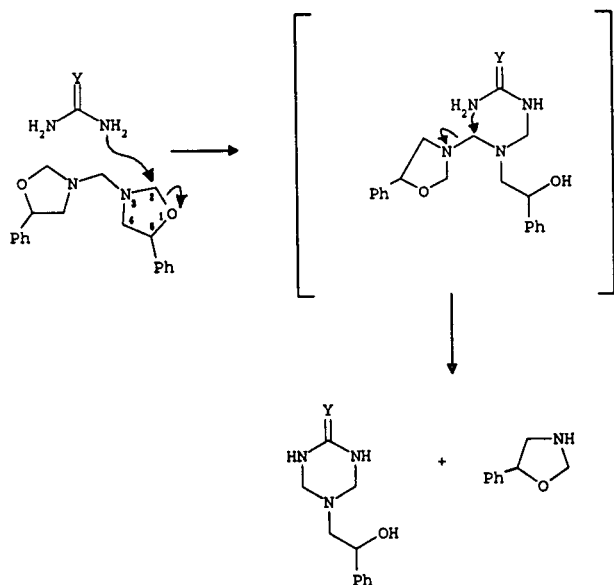
Scheme 4



Scheme 5



Scheme 6



polycondensation with a final thermally induced intramolecular transureidomethylation with cyclization. We therefore propose for our reactions a different mechanism based on a double nucleophilic attack of the carbamic nitrogens, to the C-2 of the oxazolidine part of **1** and, successively, to the aminal methylene as depicted in Scheme 6.

An initial attack to the aminal carbon of **1** followed by an oxazolidine ring opening would give rise to the same products but seems less probable for the lower electrophilicity of the C(N,N) compared to the C(O,N) as well for statistical reasons. A similar mechanism can be drawn when cyanamide is the nucleophilic partner and **4** is the product. 2-Amino-1-phenylethanol, a reaction by-product, is likely to come from 5-phenylisoxazolidine hydrolysis [1] under the reaction conditions.

In summary, we have reported the first description of reactivity of an easily accessible bisoxazolidine towards urea, thiourea and cyanamide. The mechanism proposed diverges from those usual for α -ureidoalkylations.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 257 Infrared spectrophotometer. The ¹H-nmr and ¹³C-nmr spectra were recorded on a Varian VXR-200 at 200 MHz (H) or 50 MHz (C). Mass spectra were recorded at 70 eV on a Varian MAT CH-7 mass spectrometer. All compounds had ir, nmr and ms spectra fully consistent with their structures.

3,3'-Methylenebis(5-phenyl)oxazolidine (**1**).

(\pm)-2-Amino-1-phenylethanol (47 g, 0.342 mole) was dissolved in 1N hydrochloric acid (350 ml). To this solution, 90 ml (1.53 moles, 4.5 equivalents) of 40% aqueous formaldehyde were

added dropwise and the mixture was stirred at room temperature for 48 hours. The solution was then kept to pH 4, evaporated, taken up with ethanol and filtered. The filtrates were evaporated and directly flash-chromatographed (eluent: ethyl acetate 80, methanol 20, triethylamine 2). The first elution product was **1** (45 g, 42%, mp 70-72° after recrystallization from diisopropyl ether); ¹H-nmr (DMSO-d₆): δ 7.1-7.4 (m, 10H, 2 Ph), 4.86 (dd, 2H, 2CH₂OH, J = 7.9 Hz, J = 6.7 Hz), 4.54 and 4.61 (2d, 4H, 2OCH₂N, J = 5.6 Hz), 3.57 (dd, 2H, 2CHCHH, J = 11.6 Hz), 3.47 (s, 2H, 2NCH₂N), 2.69 (dd, 2H, CHCH₂N, J = 7.9 Hz, J = 11.6 Hz); ¹³C-nmr (deuteriochloroform): δ 142.1 (C-1, Ph), 127.4 (C-4, Ph), 125.5 and 128.5 (C-2 and C-3, Ph), 86.1 (NCH₂O), 76.4 (CHCH₂N), 74.8 (NCH₂N), 58.9 (CHCH₂N); ms: (m/z, 70 eV) 246 (M + H)⁺, 204, 138, 107; ir (Nujol): ν 1400, 1310, 1290, 1210, 1050, 1040, 1020, 1015, 915, 860, 755, 695 cm⁻¹.

Anal. Calcd. for C₁₅H₂₂N₂O₂: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.28; H, 7.15; N, 8.86.

5-(2-Hydroxy-2-phenylethyl)-1,3,5-triazin-2-one (**3a**).

One g (3.22 mmoles) of **1** was suspended in water (10 ml) in the presence of 0.2 g (3.3 mmoles) of urea and the mixture refluxed for 3 hours. After evaporation the residue was directly flash-chromatographed (eluent: dichloromethane 90, methanol 10, 30% ammonium hydroxide 1) to give 0.51 g (72%) of a white hygroscopic solid, melting at 40-50° due to the presence of water; ¹H-nmr (DMSO-d₆): δ 7.1-7.4 (m, 5H, Ph), 6.26 (bs, 2H, 2CH₂NHCO), 5.24 (d, 1H, OH, J = 4.1 Hz), 4.65 (m, 1H, CHOH), 3.9-4.1 (m, 4H, 2CH₂NH), 2.6-2.9 (m, 2H, CHCH₂); ms: (m/z, 70 eV) 222 (M + H)⁺, 203, 162; ir (Nujol): ν 3500-3050 (broad), 1640, 1510, 1400, 1290, 1160, 1100, 1020 cm⁻¹.

Anal. Calcd. for C₁₁H₁₅N₃O₂·0.9H₂O: C, 55.64; H, 7.13; N, 17.69. Found: C, 55.71; H, 7.08; N, 17.42.

5-(2-Hydroxy-2-phenylethyl)-1,3,5-triazine-2-thione (**3b**).

The bisoxazolidine **1** (1 g, 3.22 mmoles) was heated in water (10 ml) with thiourea (0.245 g, 3.22 moles) for 1 hour at 80°. The product formed, having the same R_f (tlc: ethyl acetate 80, methanol 20, triethylamine 2) as thiourea was filtered and dried (0.62 g, 81%, mp 189-191°); ¹H-nmr (DMSO-d₆): δ 8.04 (bs, 2H, 2CH₂NHCS), 7.1-7.4 (m, 5H, Ph), 5.33 (d, 1H, CHOH, J = 4.1 Hz), 4.68 (m, 1H, CHOH), 3.95 and 4.03 (2d, 4H, 2CH₂NH, J = 13.0

Hz), 2.69 (dd, 1H, CHCH₂N, J = 7.5 Hz, J = 13.2 Hz), 2.58 (dd, 1H, CHCH₂N, J = 4.9 Hz, J = 13.2 Hz); ms: (m/z, 70 eV) 237 (M + H)⁺, 162, 107, 76; ir (Nujol): ν 3390, 3300, 3200, 1540, 1525, 1290, 1190, 1160, 1060, 995, 880 cm⁻¹.

Anal. Calcd. for C₁₁H₁₅N₃OS: C, 55.67; H, 6.37; N, 17.71; S, 13.51. Found: C, 55.35; H, 6.36; N, 17.47; S, 13.15.

2-[N,N-(Biscyanamidomethyl)]amino-1-phenylethanol (**4**).

The bisoxazolidine **1** (1 g, 3.22 mmoles) was refluxed in water (10 ml) with cyanamide (0.52 g, 13.4 mmoles) for 6 hours. After evaporation, the crude residue was flash-chromatographed on silica gel (eluent: chloroform 90, methanol 10, water 1) to give 0.32 g (40%) of a light brown solid (mp 181-184°); ¹H-nmr (DMSO-d₆): δ 7.61 (bs, 2H, 2CH₂NHCN), 7.1-7.4 (m, 5H, Ph), 5.34 (d, 1H, CHOH, J = 4.3 Hz), 4.71 (m, 1H, CHOH), 4.04 and 4.12 (2d, 4H, 2CH₂NHCN, J = 12.7 Hz), 2.5-2.8 (m, 2H, CHCH₂N); ms: (m/z, 70 eV) 246 (M + H)⁺, 204, 138, 107, ir (Nujol): ν 3500-3100 (broad), 2140, 1630, 1560, 1300, 1160, 1060, 1020, 905, 880, 820 cm⁻¹.

Anal. Calcd. for C₁₂H₁₅N₅O: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.76; H, 6.20; N, 28.64.

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