Base catalysed methanolation of 4-anilinomethylene-2-phenyl-2-oxazolin-5-one: Unexpected formation of N-benzylozaminoacetanilide

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The reaction of 4-anilinomethylene-2-phenyl-2-oxazolin-5-one 1 with 3.0 equivalents of sodium methoxide in methanol affords N-benzylozaminoacetanilide 3. Further, methyl 3-anilino-2-benzylozaminopropenoate 2 also affords product 3, when treated with sodium methoxide in methanol at reflux temperature. A plausible mechanism for this conversion has been proposed.

In continuation of our studies on 4-heteromethylene oxazolones with various O- and N-nucleophiles, we report herein a base catalysed methanolation of 4-anilinomethylene-2-phenyl-2-oxazolin-5-one 1 with sodium methoxide in methanol at reflux temperature. However, the base catalysed methanolation of oxazolone 1 was known in the literature to afford methyl 3-anilino-2-benzylozaminopropenoate 2.

The 4-anilinomethylene-2-phenyl-2-oxazolin-5-one 1 was treated with 3.0 equivalents of sodium methoxide in methanol at reflux temperature to prepare methyl 3-anilino-2-benzylozaminopropenoate 2. In contrast, it completed in three hours and gave a solid product with melting-point 210-12°C and molecular formula C15H20N2O5, which is characterised as N-benzylozaminoacetanilide 3 from its spectral and chemical data (Scheme 1). Its IR spectrum showed absorption bands at 3377 and 3315 cm$^{-1}$ for two NH groups and bands at 1684 and 1639 cm$^{-1}$ for two amide carbonyls. The $^1$H NMR spectrum of 3 exhibited D$_2$O exchangeable signals at δ 10.08 as singlet and at δ 8.86 as broad singlet for PhNH and methylene NH protons respectively, and a doublet at δ 4.08 for methylene protons which becomes singlet after D$_2$O shaking. The mass spectrum of 3 showed molecular ion (M$^+$) peak at 254 and base peak at 93.

When the ester 2 was treated with sodium methoxide in methanol at reflux temperature, the isolated product was characterised as anilide 3 from its mp, mixed mp and spectral data. This supported the formation of anilide 3 from oxazolone 1 via intermediate 2.

Further, to study the reaction mechanism, p-toluidine and p-anisidine were introduced as a co-substrate in the separate reactions of oxazolone 1 and ester 2 with sodium methoxide in methanol under similar reaction conditions. The isolation of only product 3, in both the cases, suggested that the anilino group was not free in the conversion of ester into anilide.

When, 4-(p-toluidinomethylene)-2-phenyl-2-oxazolin-5-one was treated with sodium methoxide in methanol with co-substrate (aniline) and without co-substrate at reflux temperature for a longer period, a mixture of two products, methyl 3-(p-toluidino)-2-benzylozaminopropenoate and N-substituted amide were obtained in major (58%) and minor (11%) yields respectively in both the cases. Formation of N-substituted amide further evidenced that p-toluidino group was not liberated in these conversions. The plausible mechanism for this conversion is shown in Scheme 1.

Experimental Section

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Elemental analysis were obtained using Perkin-Elmer 240C CHN analyzer. IR spectra were recorded on JASCO FT/IR-5300 infrared spectrophotometer, $^1$H NMR spectra on JEOL FX-90Q and 250 MHz Bruker instrument (chemical shifts in δ, ppm) using TMS as an internal standard and mass spectra on a Shimadzu GCMS-QP-1000A spectrometer. Reactions were monitored on TLC using silica gel PF 254 + 366 (Merck). 4-Arylaminozamethylene-2-phenyl-2-oxazolin-5-one 1 was prepared according to literature procedure.

**Scheme 1.**

**Methyl 3-anilino-2-benzylozaminopropenoate 2.** Oxazolone 1 (1.0 m mole) was treated with sodium methoxide, [prepared from sodium (3m mole) and methanol (8 mL)], and the reaction mixture was stirred at room temperature for 2 hr. Solvent was evaporated in vacuo and water was added. The solid obtained was filtered, dried, and recrystallised from ethanol to give an ester 2, yield 81%, mp 175°C (lit.6)
mp 175 °C); IR(KBr): 3339, 3246, 1693, 1660, 1631, cm⁻¹; ¹H NMR (CDCl₃, 90 MHz): δ 3.86 (s, 3H, OCH₃), 6.86-7.11 (m, 3H, ArH), 7.20-7.60 (m, 5H, ArH), 7.74 (d, 1H, J=12Hz, =CH), 7.77-7.59 (m, 2H, ArH), 8.24 (br s, NH, exchangeable with D₂O), 8.92 (br, d, 1H, J = 12Hz, exchangeable with D₂O); ¹³C NMR (CDCl₃, 90 MHz): δ 52.17 (OCH₃), 102.77 (C), 115.77, 122.43, 127.31, 128.83, 129.59, 130.24, 132.02, 133.87, (2 x C₆H₅), 141.18 (=CH), 165.56 (PhCO), 166.48 (C=O).

**Scheme I**

Methanolation of 4-anilinomethylene-2-phenyl-2-oxazolin-5-one with sodium methoxide in methanol: Formation of N-benzoylaminooctanilide. Oxazolone I (1.0 mmole) was added to a solution of sodium methoxide, [prepared from sodium (3 mmole) and methanol (8 mL)] and the reaction mixture was heated at reflux temperature for 3 hr. Solvent was evaporated in vacuo and water was added to the reaction mixture. It was neutralised with dil. HCl (keeping cool) upto pH 7 and the precipitate obtained was filtered, washed with water, dried and recrystallised from ethanol to give a product 3 in 79% yield, mp 210-12 °C (lit., mp 213 °C, lit. 212 °C), IR (KBr): 3377, 3315, 1684, 1639, 1602 cm⁻¹; ¹H NMR (DMSO-d₆, 250 MHz, Bruker): δ 4.08 (d, 2H, J = 5.7 Hz, CH₂), 7.05 (m, 1H, PhH), 7.32 (m, 2H, PhH), 7.46-7.55 (m, 5H, PhH), 7.92 (m, 2H, PhH), 8.86 (br s, NH, exchangeable with D₂O), 10.08 (s, 1H, PhNH, exchangeable with D₂O); ¹³C NMR (DMSO-d₆, 62.89 MHz): δ 43.29 (CH₂), 119.15, 123.23, 127.34, 128.75, 128.88, 131.38, 133.98, 138.98 (2 x C₆H₅), 166.63 (PhNHCO), 167.83 (PhCO); MS: (m/z) (%)
Reaction of ester 2 with sodium methoxide. A mixture of 2 (1.0 mmole) and sodium methoxide (2 mmoles, sodium in 8 mL methanol) was heated at reflux temperature for 2 hr. The solvent was evaporated in vacuo and water was added. It was neutralised with dil. HCl and the precipitate obtained was filtered, washed with water, dried and recrystallised from ethanol to afford product 3 in 72% yield.

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References