SCHMIDT REACTION OF USNIC ACID

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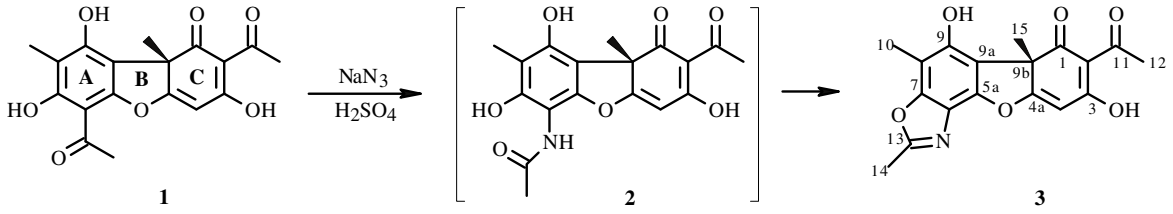
Many natural compounds are interesting platforms for creating drugs. Therefore, synthetic transformations of isolated secondary metabolites continue to play an important role in medicinal chemistry. A promising starting material is the yellow lichen pigment (+)-usnic acid (**1**). It is known to possess a broad spectrum of biological activity including antiviral, antibiotic, antituberculosis, analgesic, and insecticidal activity [1]. Considering the biological activity of usninic acid and the relatively simple methods for isolating it from plant raw material [2], it seemed advisable to develop synthetic transformations that introduce new functional groups into its structure.

Attempts were made previously to introduce an amide into ring A of usninic acid using a Schmidt reaction [3]. However, only starting (+)-usnic acid (**1**) was isolated in 93% yield from the reaction mixture containing an equimolar amount of sodium azide. We chose more forcing conditions for carrying out the Schmidt reaction that included **1** (1 mmol), $CHCl_3$ (10 mL), and conc. H_2SO_4 (3 mL) with heating at 50-60°C for 2 h with a four-fold excess of sodium azide. The expected amide derivative **2** did not form. Further rearrangement occurred with involvement of the phenol hydroxyl in the *o*-position to the reacting acyl group to form oxazole **3**. The reaction mixture was neutralized with aqueous KOH (5%) and extracted twice with $CHCl_3$ (30 mL each). The combined $CHCl_3$ extract was dried over calcined $MgSO_4$. Compound **3** was purified by chromatography over silica gel (100-160 μ, Merck) with elution by $CHCl_3$. The yield after chromatography was 70%. Cyclic oxazole-type products were observed previously from the Schmidt reaction of β-diketones [4].



Compound **3** was prepared previously [3] in two steps from **1** by treatment first with monochloroamine in aqueous NaOH (0.6%) to form amide **2** followed by reaction with thionylchloride at 55°C to isolate oxazole derivative **3** in 27% overall yield.

PMR and ^{13}C NMR spectra (AV-300 spectrometer, Bruker, operating frequency 300.13 MHz for ^1H, 100.61 MHz for ^{13}C) in $CDCl_3$ were recorded for the sample obtained by us.

The PMR spectrum agreed with the one published [3].

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 201.2 (s, C-11), 197.9 (s, C-1), 191.2 (s, C-3), 180.4 (s, C-4a), 163.1 (s, C-13), 153.2 (s, C-7), 148.3 (s, C-9), 141.6 (s, C-5a), 118.9 (s, C-6), 108.7 (s, C-8), 104.8 (s, C-2), 104.1 (s, C-9a), 97.5 (d, C-4), 59.7 (s, C-9b), 31.7 (q, C-15), 27.6 (q, C-12), 14.0 (q, C-14), 8.4 (q, C-10).

IR spectrum (ν, cm^{-1}): 3662, 3050, 2932, 1689, 1644, 1594, 1536, 1461, 1357, 1303, 1200, 1113, 1094, 1065, 958.

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