

Unexpected Formation of 4,4,6-Trimethyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile via Tandem Knoevenagel Condensation–Michael Addition–Intramolecular Cyclization

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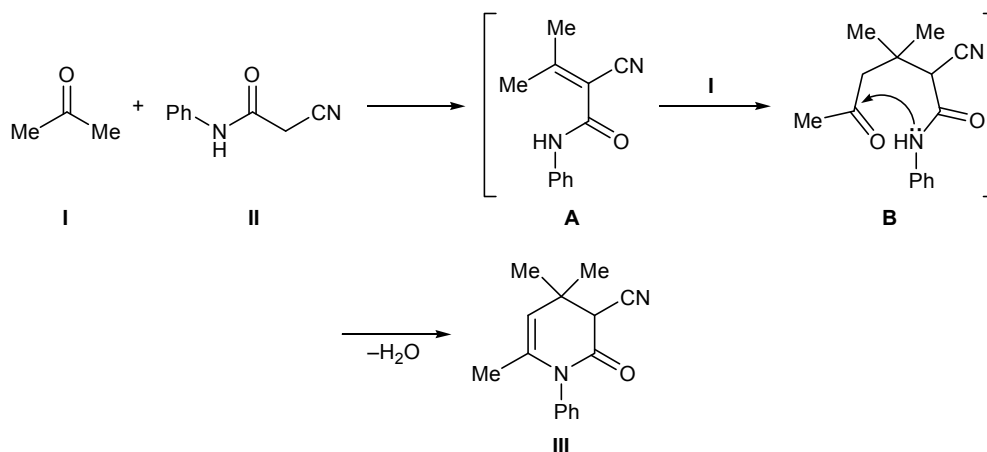
Abstract—Knoevenagel condensation (Cope version) of acetone with cyanoacetanilide resulted in the formation of 4,4,6-trimethyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile whose structure was determined by X-ray analysis.

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Prospects in the design of pharmacologically active compounds on the basis of 4,4-disubstituted tetrahydropyridines stimulated studies on new accessible methods for their synthesis [1]. Such structures are generally obtained by condensation of aliphatic ketones with cyanoacetamides [2] or of cinnamic acid chloride with substituted 3-aminoacrylonitriles [3]. We previously proposed a new synthesis of 4,4-disubstituted tetrahydropyridines by reaction of substituted ethyl crotonates with cyanothioacetamide and *N*-methylmorpholine [4].

In the present work we examined the condensation of acetone (**I**) with cyanoacetanilide (**II**) according to Knoevenagel (Cope version) [5]. However, we failed to isolate the corresponding alkene **A**, for the latter underwent further transformations. Presumably, Michael addition of acetone **I** to alkene **A** gave adduct **B**, and its subsequent intramolecular condensation resulted in the formation of previously unknown 4,4,6-trimethyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile (**III**) (Scheme 1). The structure of compound **III** was unambiguously proved by X-ray anal-

Scheme 1.

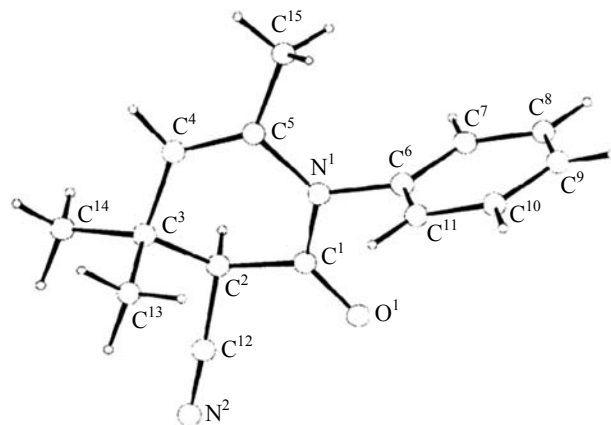


ysis. The general view of molecule **III** is shown in figure; principal bond angles and bond angles are also given. The $N^1C^1C^2C^3C^4C^5$ six-membered ring is not planar (deviations of atoms from the mean-square plane reach 0.31 Å); it has a half-boat conformation with the following modified Cramer–Pople parameters [6]: $S = 0.65$, $\psi = 26.0^\circ$, $\theta = 49.0^\circ$. Owing to steric hindrances, the benzene ring (C^6-C^{11}) is almost orthogonal to the $N^1C^1-C^5$ ring: the corresponding dihedral angle is 83.9° . The N^1 atom is characterized by planar-trigonal bond configuration with the sum of the bond angles $359.9(6)^\circ$. Effective conjugation between the lone electron pair on the N^1 atom and π -system of the double $C^1=O^1$ bond is responsible for shortening of the N^1-C^1 bond to 1.363(3) Å relative to purely single $N(sp^2)-C(sp^2)$ bond (1.43–1.45 Å [7]). The molecular conformation is quite favorable for such interaction: the torsion angle $O^1C^1N^1C^6$ is as small as 1.5° .

EXPERIMENTAL

The IR spectrum of **III** was recorded in mineral oil on an IKS-40 spectrometer. The 1H NMR spectrum was measured on a Bruker DR-500 instrument (500.13 MHz) using tetramethylsilane as internal reference. The mass spectrum (electron impact, 70 eV) was obtained on a Chrommas HP 5890/5972 GC–MS system (HP-5 MS column; sample was injected as a solution in methylene chloride). The melting point was determined on a Kofler hot stage. The progress of the reaction was monitored by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; development with iodine vapor.

The X-ray diffraction data for a single crystal of compound **III**, $0.08 \times 0.15 \times 0.55$ mm, were acquired at room temperature on a Bruker Apex II automatic CCD diffractometer (Mo K_α irradiation, $\lambda = 0.71069$ Å, $\theta_{max} = 29^\circ$, $-15 \leq h \leq 7$, $-9 \leq k \leq 9$, $-17 \leq l \leq 20$). Total of 6512 reflection intensities were measured (3346 independent reflections with $R_{int} = 0.035$). Monoclinic crystals with the following unit cell parameters: $a = 11.715(3)$, $b = 7.433(2)$, $c = 15.251(4)$ Å; $\beta = 90.933(7)^\circ$; $V = 1327.9(6)$ Å 3 ; M 240.3; $Z = 4$; $d_{calc} = 1.20$ g/cm 3 ; $\mu = 0.77$ cm $^{-1}$; $F(000) = 512$; space group $P1/2n$ (no. 14). The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using CRYSTALS software package [8]. The refinement was performed with 1243 reflections characterized by $I > 3\sigma(I)$ (163 refined parameters, 7.6 reflections per parameter). All hydrogen atoms were localized by difference syntheses of electron density and were refined



Structure of the molecule of 4,4,6-trimethyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile (**III**) according to the X-ray diffraction data. Principal bond lengths and bond angle: N^1-C^1 1.363(3), N^1-C^5 1.435(3), N^1-C^6 1.454(3), C^1-C^2 1.521(4), C^2-C^3 1.540(4), C^3-C^4 1.506(4), C^4-C^5 1.324(4) Å; $C^1N^1C^5$ 122.4(2) $^\circ$.

with fixed positional and thermal parameters. Chebyshev's weight scheme [9] with four parameters (0.56, -0.91 , 0.14 , and -0.57) was applied. The final divergence factors were $R = 0.045$, $R_w = 0.047$; goodness of fit 1.109. The residual electron density from the Fourier difference series was -0.22 and 0.16 e/Å 3 .

4,4,6-Trimethyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile (III). A mixture of 0.18 ml (2.5 mmol) of acetone (**I**), 1.6 g (1 mmol) of cyanoacetanilide (**II**), and a catalytic amount of piperidinium acetate in 25 ml of benzene was heated for 6 h under reflux in a flask equipped with a Dean–Stark trap. After separation of the calculated amount of water, the solvent was distilled off, and the light yellow precipitate was filtered off and washed with ethanol. Yield 1.95 g (81%), mp 175 – $178^\circ C$ (from MeOH). IR spectrum, ν , cm $^{-1}$: 1670 (C=O), 2248 (C \equiv N). 1H NMR spectrum, δ , ppm: 1.23 s (3H, CH $_3$), 1.30 s (3H, CH $_3$), 1.55 s (3H, CH $_3$), 4.05 s (1H, 3-H), 5.04 s (1H, 5-H), 7.12 d (2H, H_{arom} , $J = 7.04$ Hz), 7.36 t (1H, H_{arom} , $J = 7.51$ Hz), 7.43 t (2H, H_{arom} , $J = 7.51$ Hz). Mass spectrum: m/z 241 (base peak) [$M + 1$] $^+$. Found, %: C 74.88; H 6.67; N 11.59. C $_{15}$ H $_{16}$ N $_2$ O. Calculated, %: C 74.97; H 6.71; N 11.66.

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