

SHORT
COMMUNICATIONS

Synthesis of New Heterocyclic System, Pyrido[3,2-*e*][1,3]thiazine by Mannich Reaction

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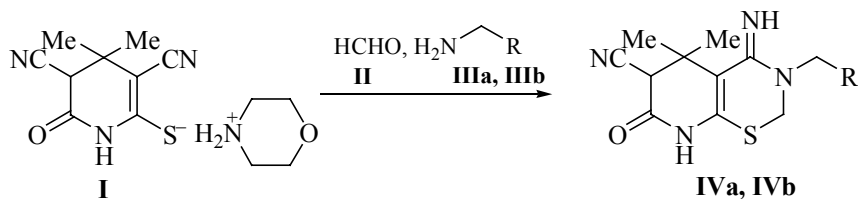
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Mannich reaction is successfully used in the syntheses of substituted triazolo[3,4-*b*]-1,3,5-thiadiazines [1], pyrido[1,2-*a*]-1,3,5-triazines [2], and 3,7-diazabicyclo[3.3.1]-nonanes [3]. To the aminomethylation in [1] substituted 1,3,5-triazole-2-thiols were subjected, and in [2, 3], substituted 2(1*H*)-thioxopyridine-3-carbonitriles. In the latter compounds the cyano group was not involved in chemical transformation in the course of aminomethylation.

The aminomethylation of morpholinium 4,4-dimethyl-6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-2-thiolate (**I**) with formaldehyde (**II**) and primary amines **IIIa**, **IIIb** under the conditions of Mannich reaction [4] resulted in the formation of a new heterocyclic system, 4-imino-5,5-dimethyl-7-oxo-3-benzyl- [or 3-(furan-2-ylmethyl)]-3,4,5,6,7,8-hexahydro-2*H*-pyrido-[3,2-*e*][1,3]thiazine-6-carbonitriles (**IVa**, **IVb**).

The mechanism of the discovered reaction, the range



of its applicability, and the chemical and biological characteristics of compounds **IVa**, **IVb** are under study and will be published elsewhere.

Morpholinium 4,4-dimethyl-6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-2-thiolate (I) was obtained by procedure [5]. Yield 2.7 g (91%), mp 213–215°C. IR spectrum, ν , cm^{-1} : 3353 (NH), 2257, 2188 ($\text{C}\equiv\text{N}$), 1674 (CONH). ^1H NMR spectrum, δ , ppm: 1.00 (3H, Me), 1.22 (3H, Me), 3.27 m (4H, CH_2NCH_2), 3.84 m (4H, CH_2OCH_2), 4.18 s (1H, C^5H), 7.51 br.s (2H, $^+\text{NH}_2$), 10.47 br.s (1H, NH). Found, %: C 52.91; H 6.05; N 18.94. $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$. Calculated, %: C 53.04; H 6.16; N 19.03.

3-Benzyl-4-imino-5,5-dimethyl-7-oxo-3,4,5,6,7,8-

hexahydro-2*H*-pyrido[3,2-*e*][1,3]-thiazine-6-carbonitrile (IVa). A mixture of 1.1 ml (10 mmol) of benzylamine (**IIIa**) and 3.6 ml (40 mmol) of 37% formaldehyde water solution in 15 ml of ethanol was heated to boiling, and then 2.94 g (10 mmol) of salt **I** was added, and the mixture was boiled for 40 min. From the boiling reaction mixture crystalline product **IVa** precipitated, which was filtered off on cooling, washed with ethanol and hexane. Yield 1.73 g (53%), yellow powder, mp 290–293°C. IR spectrum, ν , cm^{-1} : 3422, 3330 (NH), 2246 ($\text{C}\equiv\text{N}$), 1664 (CONH). ^1H NMR spectrum, δ , ppm: 1.09 (3H, Me), 1.14 (3H, Me), 3.78 d, 3.94 d (1H each, NCH_2 , 2J 15.0 Hz), 4.09 s (1H, H^6), 4.97 d, 5.53 d (1H each, SCH_2N , 2J 15.0 Hz),

7.15–7.25 m (2H, Ph), 7.27–7.48 m (3H, Ph), 8.91 br.s (1H, NH), 9.10 br.s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 21.90, 23.50, 36.42, 50.95, 54.08, 55.86, 60.48, 117.15, 127.88, 128.32, 129.20, 135.05, 171.95, 173.27, 192.95. Mass spectrum, m/z (I_{rel} , %): 328(4) [$M + 2$] $^+$, 327(11) [$M + 1$] $^+$, 326(48) [M] $^+$, 284(14), 235(9) [$M - \text{PhCH}_2$] $^+$, 178(8), 148(6), 127(34), 106(41), 91(100) [PhCH_2] $^+$, 82(11), 65(16), 45(4). Found, %: C 62.45; H 5.44; N 17.05. $\text{C}_{17}\text{H}_{18}\text{N}_4\text{OS}$. Calculated, %: C 62.55; H 5.56; N 17.16. M 326.423.

4-Imino-5,5-dimethyl-7-oxo-3-(furan-2-yl-methyl)-3,4,5,6,7,8-hexahydro-2H-pyrido[3,2-*e*]-[1,3]thiazine-6-carbonitrile (IVb) was obtained similarly to compound **IVa** using 0.92 ml (10 mmol) of furan-2-ylmethylamine (**IIIb**). Yield 1.8 g (57%), yellow powder, mp 310–312°C. IR spectrum, ν , cm^{-1} : 3429, 3308 (NH), 2248 ($\text{C}\equiv\text{N}$), 1661 (CONH). ^1H NMR spectrum, δ , ppm: 1.07 (3H, Me), 1.09 (3H, Me), 3.92 d, 3.95 d (no 1H, NCH_2 , 2J 15.0 Hz), 4.02 s (1H, H^6), 5.15 d, 5.27 d (1H each, SCH_2N , 2J 15.0 Hz), 6.35 s (1H, H^3 of furan), 6.44 s (1H, H^4 of furan), 7.63 s (1H, H^5 of furan), 8.83 br.s (1H, NH), 9.01 br.s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 21.61, 23.43, 36.18, 49.30, 50.90, 54.32, 60.42, 101.91, 110.01, 111.06, 117.23, 143.75, 148.26, 171.75, 173.23, 192.47. Mass spectrum, m/z (I_{rel} , %): 318(4) [$M + 2$] $^+$, 317(11) [$M + 1$] $^+$, 316(58) [M] $^+$, 287(26), 235(6) [$M - \text{furan-2-ylmethylene}$], 222(10), 127(29), 96(26), 81(100) [$\text{furan-2-ylmethylene}$] $^+$, 67(9), 53(27). Found, %: C 56.91;

H 5.05; N 17.54. $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$. Calculated, %: C 56.95; H 5.10; N 17.71. M 316.385.

IR spectra were recorded on an instrument FIR-spectrometer Spectrum One (Perkin Elmer) from pellets with KBr, ^1H NMR spectra were registered on a spectrometer Bruker DR-500 (500.13 MHz) in $\text{DMSO}-d_6$, internal reference TMS. ^{13}C NMR spectra were obtained on a spectrometer Varian VXR-300 (125.74 MHz) from solutions in $\text{DMSO}-d_6$, internal reference TMS. Mass spectra were taken on an instrument MKh-1321 (70 eV) with a direct admission of the sample into the ion source. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent acetone–hexane, 3:5, development in iodine vapor and under UV irradiation. Melting point were determined on a Koeffler heating block.

REFERENCES

- Haijian, S., Zhongyi, W., and Haoxin, S., *Chimia.*, 1997, vol. 51, p. 529; *Ref. Zh. Khim.*, 1998, 13Zh272.
- Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P., *Khim. Geteritsikl. Soedin.*, 2007, p. 621.
- Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P. *Monatsh. Chem.*, 2007, vol. 138, p. 489.
- Vatsuro, K.V. and Mishchenko, G.L., *Imennye reaktsii v organicheskoi khimii* (Personal Reaction in Organic Chemistry), Moscow: Khimiya, 1976, p. 268.
- Dyachenko, V.D., Nikishin, A.A., and Litvinov, V.P., *Khim. Geteritsikl. Soedin.*, 1997, p. 996.