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AMINOMETHYLATION OF 1,2,3,4-TETRAHYDROPYRIDINE-6-THIOLATES: A NOVEL APPROACH TO SYNTHESIS OF 3,7-DIAZABICYCLO[3.3.1]NONANE DERIVATIVES

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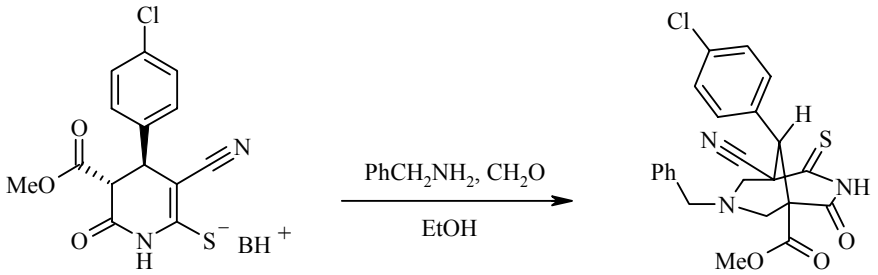
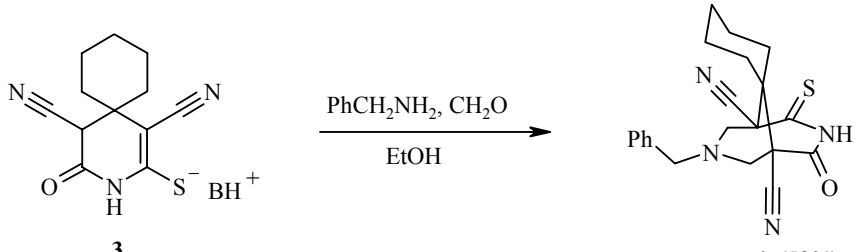
We showed earlier that condensation of formaldehyde and primary amines with N-methylmorpholinium 4-aryl-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates leads to formation of pyrido[2,1-*b*][1.3.5]-thiadiazine derivatives [1]. It seemed logical to study the behavior of structural analogs of the above-indicated thiolates under Mannich reaction conditions. We have established that treatment of N-methylmorpholinium 5-cyano-3-methoxycarbonyl-2-oxo-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-thiolate (**1**) with benzylamine and CH_2O under mild conditions leads to formation of the bicyclic product **2** instead of the expected 1,3,5-thiadiazine derivative. Aminomethylation of the spiro-linked pyridine thiolate **3** also leads to formation of the 3,7-diazabicyclo[3.3.1]nonane derivative **4**. Thus introducing an acceptor substituent in the 3 position of the



1 **2** (41%)



3 **4** (52%)

1 B = N-methylmorpholine; **3** = B = piperidine

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tetrahydropyridine ring of the original thiolate radically changes the regioselectivity of the aminomethylation process: in this case, the C(3) and C(5) atoms rather than the heteroatoms act as the active nucleophilic centers. The structure of compounds **2, 4** has been confirmed by spectral data. Thus in the IR spectra we observe absorption bands for stretching vibrations in the intervals ν 3180-3175 cm^{-1} (NH), 2265-2250 cm^{-1} (unconjugated C≡N group), 1720 cm^{-1} (C(O)NH), 1480-1470 cm^{-1} (C(S)NH, "thioamide II" band), and the absorption bands for a conjugated nitrile functional group are missing. Among the most characteristic signals that can be observed in the ^1H NMR spectrum for 3,7-diazabicyclo[3.3.1]nonanes, we must note the broadened peak for the NH proton at δ 13.66-13.45 ppm and the signal from the C(9)H proton (for compound **2**) at δ 3.99 ppm. The $C(6)H_2$ and $C(8)H_2$ protons are observed in the δ 3.37-2.94 ppm region as a pair of doublets of doublets. We must note that the protons of the methylene groups of the 1,3,5-thiadiazine ring resonate at δ 5.14-4.50 ppm [1]. The stereoselectivity of the reaction and the spatial structure of the synthesized diazabicyclo[3.3.1]nonanes will be considered in a later paper.

The ^1H NMR spectra were taken on a Varian Gemini 200 (200 MHz) in DMSO-d_6, internal standard Me_4Si. The IR spectra were obtained on an IKS-29 (nujol). Thiolates **1** [2] and **3** [3, 4] were obtained by familiar methods.

Diazabicyclo[3.3.1]nonanes 2, 4. A mixture of the corresponding thiolate (**1, 3**) (2.5 mmol), benzylamine (0.27 ml, 2.5 mmol), and excess (2.5 ml) 37% CH_2O in EtOH (15 ml) was boiled for 3 min. The solution was filtered through a paper filter and allowed to stand for 48 h at ~20°C. The product was separated and recrystallized from an appropriate solvent.

7-Benzyl-9-(4-chlorophenyl)-5-cyano-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylic Acid Methyl Ester (2). Bright yellow crystals, yield 41%; mp 213-215°C (Me_2CO–*i*-PrOH, 1:1). IR spectrum, ν, cm^{-1}: 1470 (C=S), 1720 ($C=O_{amide}$), 1740 ($C=O_{ether}$), 2265 (C≡N), 3180 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 13.49 (1H, br. s, NH); 7.38-7.18 (9H, m, 2 Ar); 3.99 (1H, br. s, C(9)H); 3.72 (2H, br. s, NCH_2Ph); 3.33 (3H, s, CO_2CH_3); 3.37 and 3.07 (1H each, both d, ^2J = 10.9, $C(6)H_2$); 3.25 and 2.97 (1H each, both d, ^2J = 11.1, $C(8)H_2$). Found, %: C 59.60; H 4.48; N 9.10. $C_{23}H_{20}ClN_3O_3S$. Calculated, %: C 60.86; H 4.44; N 9.26.

7-Benzyl-2-oxo-4-thioxo-3,7-diazaspiro(bicyclo[3.3.1]nonane-9,1'-cyclohexane)-1,5-dicarbonitrile (4). Yellow crystals, yield 52%; mp 218-220°C (aq. EtOH). IR spectrum, ν, cm^{-1}: 1480 (C=S), 1720 (C=O), 2250 (2 C≡N), 3175 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 13.66 (1H, br. s, NH); 7.20 (5H, m, C_6H_5); 3.67 (2H, br. s, NCH_2Ph); 3.23 and 3.02 (2H, both d, ^2J = 11.4, $C(6)H_2$ or $C(8)H_2$); 3.20 and 2.94 (2H, both d, ^2J = 11.4, $C(8)H_2$ or $C(6)H_2$); 2.12-1.54 (10H, m, $(CH_2)_5$). Found, %: C 65.97; H 5.90; N 14.71. $C_{21}H_{22}N_4OS$. Calculated, %: C 66.64; H 5.86; N 14.80.

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