Chemistry of Heterocyclic Compounds, Vol. 31, No. 4, 1995

FORMYLATION OF 1,2,3,4-TETRAHYDRO-2,4,5-TRIMETHYLPYRROLO-1-2,*c*]PYRIMIDINE. ITS CONVERSIONS TO THE 7-FORMYL DERIVATIVE WITH OPENING OF THE TETRAHYDROPYRIMIDINE RING

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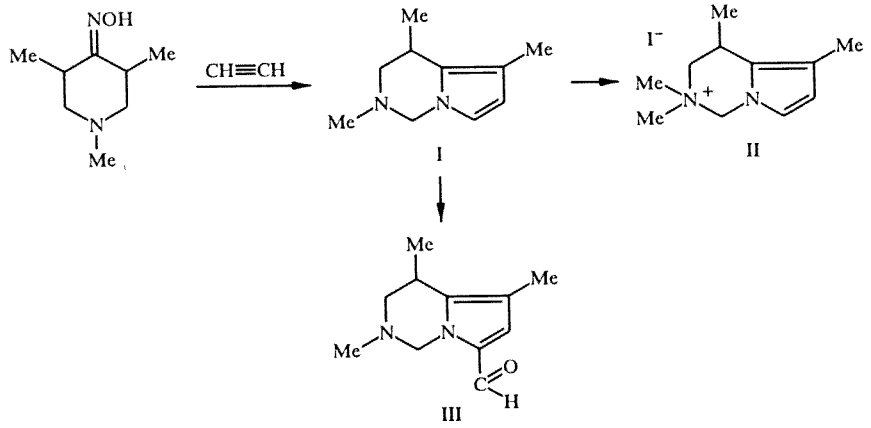
We have optimized the method for obtaining 1,2,3,4-tetrahydro-2,4,5-trimethylpyrrolo[1,2-c]pyrimidine. We carried out the reactions of quaternization, formylation, and opening of the tetrahydropyrimidine ring of its 7-formyl derivative and the oxime of this carbonyl compound.

Tetrahydropyrrolo[1,2-*c*]pyrimidines are compounds which have been practically unstudied. Suitable methods for their synthesis are lacking. This condensed heterocyclic system, combining pyrrole and cyclic aminal moieties, is of interest in the search for biologically active compounds and also as the starting compound for obtaining 2,5-disubstituted pyrroles.

In this paper, we describe the quaternization and formylation of tetrahydropyrimidine I and the reaction of its formyl derivative with nitrogen-containing nucleophiles.

We obtained 1,2,3,4-tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidine (I) for the first time in 16% yield by heterocyclization of the oxime of 1,3,5-trimethylpiperidin-4-one with acetylene under the conditions of the Trofimov reaction in the presence of potassium hydroxide [1]. Considering that rubidium hydroxide is more effective in reactions of heterocyclization of piperidin-4-one oximes [2], we converted the above-indicated oxime to compound I in the presence of 100 mole percent rubidium hydroxide. Under these conditions, the yield of compound I was 45%.

We know that aminals of the aliphatic series form unstable quaternary salts with alkyl halides [3]. The iodomethylate II obtained from tetrahydropyrrolopyrimidine I proved to be stable. A sample of this compound was stored without any change for more than seven months.



Russian University of International Friendship, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 534-539, April, 1995. Original article submitted March 14, 1995.

 0009-3122/95/3104-0468$12.50

TABLE 1. Parameters of PMR Spectra of Tetrahydropyrrolopyrimidines I-IV, VII, and Pyrroles V, VI

Compound	Proton chemical shifts, δ, ppm (spin–spin coupling constants, Hz)												
	protons of tetrahydropyrimidine ring							protons of pyrrole ring					
	1-H_a	1-H_e	3-H_a	3-H_e	4-H	2-CH_3	4-CH_3	6-H	7-H	5-CH_3	CHO	CH=N	N—OH
I	4,56 (−9,5)	4,27 (−9,5, 1,1)	2,56 (−12,1, 6,7)	2,82 (−12,1, 5,5, 1,1)	3,10	2,42	1,28 (6,9)	5,96 (2,5)	6,49	2,08	—	—	—
II	5,90 (−10,5)	5,47 (−10,5, 2,1)	3,56 (−11,9, 10,7)	2,14 (−11,9, 7,0, 2,1)	3,48	3,35 (3,79)	1,45 (6,7)	6,06 (2,8)	6,63	2,10	—	—	—
III	5,04 (−11,1)	4,70 (−11,1, 0,9)	2,60 (−12,1, 5,7)	2,80 (−12,1, 5,3, 0,9)	3,13	2,45	1,32 (6,9)	6,69	—	2,07	9,38	—	—
IV	5,04 (−11,9)	4,98 (−11,9)	2,75 (−12,8, 8,5)	2,99 (−12,8, 6,1)	3,20	2,48	1,28 (6,7)	6,15	—	2,07	—	7,92	10,3
VII	5,07 (−11,2)	4,78 (−11,2)	2,60 (−12,2, 6,1)	2,83 (−12,2, 5,5)	3,14	2,48	1,30 (7,0)	6,36	—	2,07	—	8,32	—
			2'-H		1'-H	N—CH_3	1'-CH_3	3-H	—	4-CH_3	—	CH=N	N—OH
V	—	—	2,84, 2,72	—	3,23, 3,16	2,45, 2,38	1,33, 1,32	6,20, 6,14	—	2,09	—	7,14, 7,91	10,25, 10,54
VI*	—	—	—	3,28, 3,37	3,88	2,92, 2,81	1,20, 1,36	6,57, 6,59	—	2,03, 1,83	—	—	—

*$COCH_3$ 2.09 (2.01).

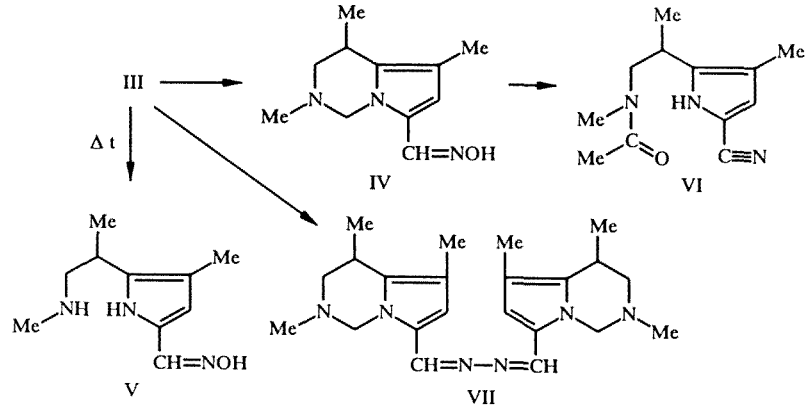
Vilsmeier—Haack formylation of tetrahydropyrrolopyrimidine I occurs at the α position of the pyrrole ring with formation of 7-formyl-1,2,3,4-tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]-pyrimidine (III).

Formation of oxime IV from the formyl derivative of III proceeds in quantitative yield when the reaction of compound III with hydroxylamine hydrochloride is carried out at room temperature in ethanol in the presence of sodium acetate. If the same reaction is carried out with prolonged boiling, then oximation of the carbonyl group is accompanied by hydrolysis of the cyclic amyl group. In this case, 2-hydroxyiminomethyl-4-methyl-5-(α-methyl-β-methylaminoethyl)pyrrole (V) is formed.

Opening of the tetrahydropyrrolopyrimidine ring also occurs when the oxime IV reacts with acetic anhydride. As a result of dehydration of the oxime group and acetylation of the β-methylaminoethyl group, 2-cyano-4-methyl-5-(α-methyl-β-N-methyl-N-acetylaminoethyl)pyrrole (VI) is formed.

These conversions of compounds III and IV to the pyrroles V and VI respectively represent a synthesis method for substituted pyrroles which are not easily available. If we consider that the starting compound in these syntheses is 1,3,5-trimethylpiperidin-4-one oxime, then this method is a feasible method for going from substituted γ-piperidones to pyrroles.

Condensation of compound III with hydrazine hydrate in the presence of acetic acid occurs easily. The azine VII is obtained in high yield.



In the mass spectra of compounds II-VII, we observe molecular ion peaks corresponding to their empirical formulas. The mass spectrum of azine VII is characterized by the presence of a maximum intensity fragmentary ion with *m/z* 190, due to cleavage of the molecule at the N—N bond. In the IR spectrum of the formyl-substituted compound III, a band at 1650 cm^{-1} corresponds to stretching vibrations of the C=O group. The stretching vibration band of the imine bond C=N in the spectra of compounds IV, V, and VII is located in the 1625-1640 cm^{-1} region. Furthermore, the spectra of compound V and VI are characterized by the presence of vibrational bands for the NH in the 3167-3450 cm^{-1} region, which supports cleavage of the aminal ring. The nitrile group in compound VI is responsible for the absorption band at 2210 cm^{-1}.

In the PMR spectra of compounds I-VII (Table 1), we observe signals from protons of the pyrrole moiety. For compounds I and II, these are signals from the 6-H and 7-H protons with a spin—spin coupling constant characteristic for pyrrole rings. In the spectra of compounds I-IV and VII, the CH_2 group in the 1 position is observed in the form of a characteristic spectrum of the AB type. Upon quaternization or upon introduction of an electron-acceptor group into the 7 position, these signals are shifted downfield. In the PMR spectra of compounds I-III, we observe a long-range spin—spin coupling constant $4J_{1e3e}$ of 0.9-2.1 Hz.

For compounds V and VI, the characteristic signals for the CH_2 group in the 4.27-5.07 ppm region are missing, which suggests cleavage of the aminal moiety. This is also indicated by the change in the multiplicity of the signal from the protons of the 2′-CH_2 group. The signals from protons of the pyrrole ring are found in the same region as for tetrahydropyrrolopyrimidines I-IV and VII. The presence in the PMR spectra of compounds V and VI of two signals from each proton indicates that they exist in the form of two isomers. For oxime V these are probably geometric isomers relative to the azomethine group, and for nitrile VI this is connected with the presence of two diastereoisomers.

The ^{13}C NMR spectra of compounds I, III, IV and pyrrole V are similar with respect to the position of the signals from like protons and the spin—spin coupling constant J_{CH}. In the spectrum of compound V, there is no signal from the $C_{(1)}$ carbon, which supports cleavage of the aminal moiety. The presence in the spectrum of oxime V of two signals from each carbon atom is connected with the existence of geometric isomers.

TABLE 2 Parameters of ^{13}C NMR Spectra of Tetrahydropyrrolopyrimidines I, III, IV, and Pyrrole V

C atoms in I, III, IV	Chemical shifts of carbon atoms, ppm, J_{CH}, Hz, in compounds				C atoms in V
	I	III	IV	V	
$C_{(1)}$	68,5	68,54 (151,9)	68,23 (155,65)	—	—
2-CH_3	41,7	41,97 (133,2)	39,84 (131,78)	35,96 and 35,60 (134,55)	N''—CH_3
$C_{(3)}$	59,2	57,51 (134,6)	56,33 (140,1)	56,60 and 56,81 (135,55)	$C_{(2'')}$
$C_{(4)}$	26,4	27,26 (129,0)	24,49 (127,62)	32,39 and 33,16 (127,62)	$C_{(1')}$
4-CH_3	11,5	11,29 (126,2)	11,84 (126,23)	11,24 and 11,72 (126,23)	1-CH_3
$C_{(4a)}$	127,1	139,45	131,54	133,80 and 133,6	$C_{(5)}$
$C_{(5)}$	109,5	117,12	115	115,8 and 115,27	$C_{(4)}$
$C_{(6)}$	113,4	125 (169,2)	116,04 (166,46)	116,32 and 116,61 (167,85)	$C_{(3)}$
$C_{(7)}$	115,1	128,52 (29,1)	122,1	122,72 and 22,43	$C_{(2)}$
5-CH_3	19,2	18,53 (127,6)	18,48 (126,23)	17,50 and 17,03 (127,62)	4-CH_3
CHO	—	177,84 (172,0)	—	—	—
CH=N	—	—	142,57 (163,69)	142,54 (163,69), 137,72 (169,28)	CH=N

The presence in the PMR spectra of compounds I-IV and VII of two spin—spin coupling constants J_{34} which are close (Table 2) shows that the tetrahydropyrimidine moiety exists in the form of an equilibrium mixture of two conformers with a pseudoaxial and a pseudoequatorial 4-CH_3 group.

Taking $^3J_{3a4a}$ = 10.1 Hz and $^3J_{3e4e}$ = 1.8 Hz (which we used in studying the conformational equilibrium of tetrahydropyrrolopyridines in [4]) as the limiting spin—spin coupling constants, using the average parameter method we estimated the conformer populations (Table 3).

EXPERIMENTAL

The PMR spectra were recorded on a Bruker M-400 spectrometer in $CDCl_3$, internal standard TMS. The mass spectra were obtained on an MKh-1303 instrument with a system for direct injection of the sample into the ion source with an ionizing potential of 70 eV. The IR spectra were taken on a UR-20 spectrometer in KBr pellets. Column chromatography was performed on Al_2O_3 (Brockmann activity II). For the thin-layer chromatography, we used plates with an adherent layer of Al_2O_3 and silica gel (Alufol and Silufol UV-254).

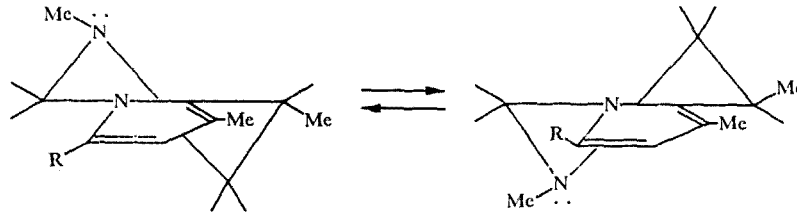
The elemental analysis data for C, H, and N correspond to the calculated values.

1,2,3,4-Tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidine (I, $C_{10}H_{16}N_2$). Acetylene was passed through a solution of 5 g (32 mmoles) of 1,3,5-trimethylpiperidin-4-one oxime and 3.3 g (32 mmoles) RbOH in 50 ml DMSO at 90°C until the oxime disappeared according to TLC. The mixture was poured over ice and extracted with ether, then dried with magnesium sulfate. The residue of 4.7 g after driving off the solvent was fractionated under vacuum. Obtained: 2.36 g (45%) compound I in the form of a yellow oil; T_{bp} 70-72°C (1 mm), R_f 0.6 (Silufol, ethyl acetate—ethanol, 2:1). Mass spectrum*: M^+ 164. Iodomethylate (II, $C_{11}H_{19}IN_2$); T_{mp} 210-212°C (from an alcohol—acetone mixture). Mass spectrum: M^+ 306.

*Here and in the following, we give the *m/z* values for the ion peaks in the mass spectra.

TABLE 3 Ratio of Conformers (%) in Solutions of Tetrahydropyrrolopyrimidines I, III, IV, VII

Compound	4-Me axial	4-Me equatorial
I	41	59
III	57	43
IV	48	52
VII	55	45



1,2,3,4-Tetrahydro-7-formyl-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidine (III, $C_{11}H_{16}N_2O$). Freshly distilled phosphorus oxychloride (4.3 g, 28 mmoles) was added dropwise at −5°C to 8.17 g (0.11 mmoles) DMF. This was stirred for 40 min at 20°C and then cooled down to −5°C. A solution of 2.3 g (14 mmoles) compound I in 7 ml DMF was added dropwise. The reaction mixture was heated up to 20°C. After 1.5 h, it was poured over ice, made alkaline with a 10% aqueous solution of sodium hydroxide up to pH 9. This was extracted with ether (6 × 150 ml) and dried with magnesium sulfate. The residue of 1.8 g after driving off the ether was chromatographed on a column (h = 16 cm, d = 1.5 cm), ethylacetate as the eluent. Obtained: 1.3 g (48%) compound II, a colorless oil which crystallized upon standing, T_{mp} 38-40°C, R_f 0.67 (Alufol, ethylacetate). IR spectrum: 1650 cm^{-1} C=O. Mass spectrum: M^+ 192.

1,2,3,4-Tetrahydro-7-hydroxyiminomethyl-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidine (IV, $C_{11}H_{17}N_3O$). A mixture of 0.5 g (2.6 mmoles) compound III, 0.36 g (5 mmoles) hydroxylamine hydrochloride, 1.04 g (7.7 mmoles) sodium acetate in 20 ml ethanol was stirred for 5 h at 20°C. The alcohol was driven off under vacuum. The residue was made alkaline with a 10% aqueous solution of sodium hydroxide up to pH 8. 0.24 compound IV was filtered off. The aqueous layer was extracted with chloroform (4 × 20 ml) and dried with magnesium sulfate. After driving off the chloroform, we obtained 0.21 g compound IV, white crystals, T_{mp} 130-132°C (from hexane), R_f 0.45 (Alufol, ethylacetate—hexane, 1:1). Overall yield of compound V, 0.45 g (83%). IR spectrum: 3600 cm^{-1} (OH). Mass spectrum: M^+ 207.

2-Hydroxyiminomethyl-4-methyl-5-(α-methyl-β-methylaminoethyl)pyrrole (V, $C_{10}H_{17}N_3O$). A mixture of 0.34 g (1.8 mmoles) compound III, 0.25 g (3.6 mmoles) hydroxylamine hydrochloride, and 0.73 g (5.4 mmoles) sodium acetate was boiled for 9 h in 15 ml ethanol (monitored by TLC). 10 ml water was added to the residue after driving off the alcohol, and it was made alkaline with 10% aqueous sodium hydroxide up to pH 8. This was extracted with chloroform and dried with sodium sulfate. After driving off the chloroform, the residue was crystallized from hexane. Obtained: 0.28 g (80%) compound V, cream-colored crystals, T_{mp} 105-107°C, R_f 0.1 (Silufol, alcohol). IR spectrum: 3700 cm^{-1} (OH). Mass spectrum: M^+ 195.

2-Cyano-4-methyl-5-(α-methyl-β-N-methyl-N-acetylaminoethyl)pyrrole (VI, $C_{12}H_{17}N_3O$). 0.05 g (0.24 mmoles) oxime V was boiled in 10 ml acetic anhydride. After driving off the anhydride, the residue was crystallized from hexane. Obtained: 0.045 g (86%) compound VI, cream-colored crystals, T_{mp} 120-122°C, R_f 0.35 (Alufol, ethylacetate—hexane, 1:1). IR spectrum: 1630 C=O, 2210 cm^{-1} (CN). Mass spectrum: M^+ 219.

1,2,3,4-Tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidin-7-azine (VII, $C_{22}H_{32}N_6$). A solution of 0.05 g (0.26 mmoles) compound III and 0.026 g (0.52 mmoles) hydrazine hydrate in 10 ml alcohol was stirred at 20°C in the presence of two drops of glacial acetic acid. The precipitated crystals were filtered. Obtained: 0.035 g (73%) compound VII, yellow crystals, T_{mp} 190-192°C (from alcohol). R_f 0.5 (Silufol, ethylacetate). Mass spectrum: M^+ 380, 190.

This research was carried out with the financial support of the State Committee of the Russian Federation on Fine Organic Synthesis.

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