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SYNTHESIS OF 3-SUBSTITUTED 4-PIPERIDONES

G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, and I. A. Ivanova

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It has been shown that the addition of methyl acrylate and acrylonitrile to the pyrrolidine enamines of 1-methyl-, (1S)-α-phenylethyl-, (1S)-sec-butyl-, 1,2-dimethyl-, and 1,3-dimethyl-4-piperidone results in the formation of 3- or 5-substituted 4-piperidones, depending on the reaction conditions and the structure of the enamine. The formation of a pair of diastereomers of the 3-substituted 4-piperidones in a 1:1 ratio takes place when there is a chiral substituent on the nitrogen atom in the piperidone ring.

In the framework of the study of asymmetric reactions in a series of 4-piperidones, we investigated the possibility of the transmission of the asymmetric effect of a chiral substituent on the nitrogen atom when a new carbon—carbon bond forms. As a model reaction we selected the formation of 3-substituted 4-piperidones by the addition of methyl acrylate and acrylonitrile to enamines of 4-piperidones. Since there is only one report in the literature on the cyanoethylation of the pyrrolidine enamine of 1-methyl-4-piperidone [1], it was necessary to work out the conditions and to establish the stereochemical laws for the addition of methyl acrylate and acrylonitrile to the pyrrolidine enamines of 4-piperidones. The addition of methylacrylate and acrylonitrile to the pyrrolidine enamines and 1-methyl- (IIa), (1S)-α-phenylethyl- (IIb), (1S)-sec-butyl- (IIc), 1,2-dimethyl- (IId), and 1,3-dimethyl-4-piperidone (IIe).

The enamines of type II were obtained by boiling the 4-piperidones (I) with a 0.5-molar excess of pyrrolidine in absolute benzene in an argon atmosphere. It should be noted that all the enamines of type II are unstable and readily decompose on silica gel and during storage. The structure of enamines IIa-c was confirmed by the presence in the PMR spectra of a characteristic triplet of the vinyl proton at 4 ppm and by the presence in the IR spectra of bands of the stretching vibrations of the enamino group at 1660-1670 cm^{-1}. Two enamines, IIdA and IIdB, form from 1,2-dimethyl-4-piperidone, since two signals, viz., a triplet at 4.1 and a doublet at 3.91 ppm, are observed in the PMR spectrum in the region of the vinyl protons, the ratio between their integrated intensities being 1:1. According to the PMR data, only enamine IIe forms from 1,3-dimethyl-4-piperidone. This was established on the basis of

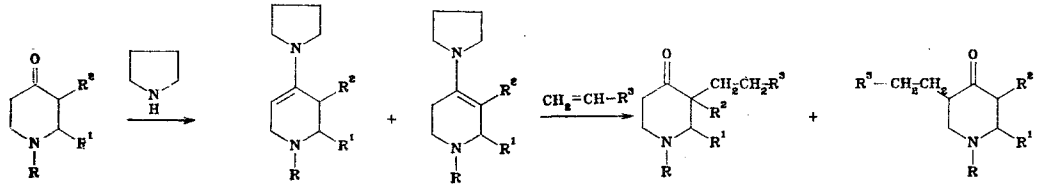
M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1510-1514, November, 1983. Original article submitted May 17, 1983.

TABLE 1. Properties of Enamines of 4-Piperidones

Compound	R	R^1	R^2	bp, deg C (mm)	IR spectrum, cm^{-1}	PMR spectrum, ppm (J, Hz), without a solvent			Yield, %
						=C—H |	N—R	2-CH_3 or 3-CH_3	
IIa	CH_3	H	H	78—80 (1)	1665[a]	4,1, t (3), 1H	2,18, 3H, CH_3	—	75
IIb	$CH(CH_3)C_6H_5$	H	H	—	1660	4,3, t (3), 1H[b]	1,44, d (6), 3H, CH_3 7,4, s, 5H, C_6H_5	—	100[c]
IIc	$CH(CH_3)C_2H_5$	H	H	—	1670	4,3, t (3), 1H[b]	0,85—1,1 (m)	—	100[c]
IIdA,B	CH_3	CH_3	H	78—80 (2)	1670	3,91, d (3), 1H 4,1, t (3), 1H	2,18, s, 6H, CH_3	1,14, d (6), 6H	78
IIe[d]	CH_3	H	CH_3	80—82 (1)[e]	1660	4,23, t (3), 1H	2,38, s, 3H, CH_3	1,33, d (6), 3H	65

[a]IR spectrum: 1650 cm^{-1} [1]. [b]PMR spectrum of crude substances in $CDCl_3$. [c]The yield is given for the unpurified substance. [d]Carbon-13 NMR chemical shifts relative to TMS in benzene: 46.34 (1'-C), 60.23 (2-C), 32.99 (3-C), 20.04 (3'-C), 145.97 (4-C), 47.41 (4'-C), 24.71 (4"-C), 92.21 (5-C), 55.62 ppm (6-C). The assignment of the signals was determined by incomplete decoupling from the protons. [e]bp 67-70°C (1). PMR spectrum: 1.23 (3H, d, 2-CH_3), 2.33 (3H, s, N-CH_3), 4.28 ppm (1H, t, =C—H) [2].

the presence of a triplet of the vinyl proton at 4.08 and a doublet of the 3-CH_3 group at 1.16 ppm. A similar conclusion was drawn on the basis of an analysis of the ^{13}C NMR spectrum of enamine IIe. The presence of the signals of nine carbon atoms confirms the formation of only one of the enamines, and the chemical shifts of the $C_{(3)}$ (32.99 ppm) and $C_{(5)}$ (92.21 ppm) carbon atoms in the piperidone ring and of the 3-CH_3 group (20.04 ppm) correspond to the structure of enamine IIe (Table 1).



Ia—e IIa—c, e IIdA IIdB IIIa—e, IIIfA, IIIhA IIIfB—IIIiB

Ia, IIa, IIIa,b R=CH_3, R^1=R^2=H; Ib, IIb, IIIc, d R=$CH(CH_3)C_6H_5$, R^1=R^2=H; Ic, IIc; IIId R=$CH(CH_3)C_2H_5$, R^1=R^2=H; Id, IIdA, B, III A, B, IIIg A, B R=R^1=CH_3, R^2=H; Ie, IIe, IIhA, B IIIiB R=R^2=CH_3, R^1=H; IIIa,c,e,f A,B,hA, B R^3=$COOCH_3$; IIIb,d, g A, B, iB R^3=CN

The addition of methyl acrylate and acrylonitrile to the enamines of type II takes place when equimolar amounts of the enamines and methyl acrylate or acrylonitrile are boiled in absolute benzene for 2-7 h. It was found that the hydrolysis of the alkylation products of the enamines of type II readily occurs upon contact with silica gel; therefore, the decomposition of the reaction mixture and the isolation of the piperidones of types III and IV were carried out with the aid of column or preparative thin-layer chromatography on silica gel. The structure and composition of the piperidones of types III and IV were established according to data from gas-chromatographic–mass spectrometry, PMR, IR spectroscopy, and elemental analysis (Table 2).

The addition of methyl acrylate and acrylonitrile to the enamines of piperidones IIa-c without substituents on the ring in benzene results in the formation of 3-substituted piperidones IIIa-e. In the case of enamine IIb in methanol, 3,5-disubstituted piperidones IVaA and IVaB also form along with 3-substituted IIIc according to the gas-chromatographic–mass-spectrometric and PMR data, and they were isolated with the aid of preparative chromatography on silica gel in a 2:1 ratio.

The 3- and 5-substituted piperidones IIIfA, IIIfB, IIIgA, and IIIgB form in a 1:1 ratio from a mixture of the enamines of 1,2-dimethyl-4-piperidone IIdA and IIdB in benzene, as was established according to the data from TLC on Silufol plates.

The reaction of the enamine of 1,3-dimethylpiperidone with methyl acrylate under the same conditions does not have unique course, and the 3-substituted piperidone IIIhA and an N-alkylation product, viz., N-carbomethoxyethylpyrrolidine, also form along with the expected piperidone IIIhB, as was established according to gas-chromatographic–mass-spectrometric data. The mixture of the compounds formed was separated in a column or on plates with silica gel,

TABLE 2. Properties of 3(or 5)-Carbomethoxyethyl-4-piperidones

Compound	R	R¹	R²	R³	Solvent, time, h	R_f	IR spectrum, cm^{-1}		PMR spectrum, ppm (J, Hz) in $CDCl_3$			M^+	Found, %		Empirical formula	Calc., %		Yield, %
							C=O	C≡N	N—R	2-CH_3 or 3-CH_3	O—CH_3		C	H		C	H	
IIIa	CH_3	H	H	$COOCH_3$	Benzene, 7	0,57[a]	1720, 1745	—	2,33, s, 3H, CH_3	—	3,6,s , 3H	199	60,5	8,4	$C_{10}H_{17}NO_3$	60,2	8,6	57
IIIb[b]	CH_3	H	H	C≡N	Benzene, 2	0,35[a]	1730	2250	2,36, s, 3H, CH_3	—	—	166	—	—	—	—	—	75
IIIc[c]	$CH(CH_3)C_6H_5$	H	H	$COOCH_3$	Benzene, 4	0,6[a]	1730, 1745	—	1,39, d (6,5), 3H, 7,36, s, 5H, C_6H_5	—	3,63,s , 3H	289	70,3	8,4	$C_{17}H_{23}NO_3$	70,2	8,3	41
IIId	$CH(CH_3)C_6H_5$	H	H	C≡N	Benzene, 7	0,5[a]	1730	2245	1,43, d (7), 3H, CH_3 3,7, q (7), 1H, CH 3,72, q (7), 1H, CH 7,34, s, 5H, C_6H_5	—	—	—	75,1	8,3	$C_{13}H_{17}NO$	75,0	7,9	65
IIIe	$CH(CH_3)C_2H_5$	H	H	$COOCH_3$	Benzene, 5	0,45[d]	1735, 1750	—	0,95, d (7), 3H, CH_3, 0,91, d (7), 3H, CH_3 1,18—1,72, m	—	3,60, s, 3H	241	64,4	9,9	$C_{13}H_{23}NO_3$	64,7	9,6	76
IIIf A, B	CH_3	CH_3	H	$COOCH_3$	Benzene, 2	0,44[d] 0,39	1720, 1750	—	2,33, s , 3H, CH_3	1,1—1,2, m	3,61, s, 3H	213	45,5	5,1	$C_{17}H_{22}N_4O_{10}$[e]	46,1	5,0	36
IIIg A, B	CH_3	CH_3	H	C≡N	Benzene, 6	0,42[d]	1720	2245	2,33, s, 3H, CH_3	0,86, d (6), 3H, 1,05, d (6), 3H	—	180	46,5	4,9	$C_{16}H_{19}N_5O_8$[e]	46,9	4,7	77
IIIh A	CH_3	H	CH_3	$COOCH_3$	Benzene, 5	0,54[d]	1720, 1750	—	2,3, s, 3H, CH_3	1,03,s , 3H,	3,63, s , 3H,	213,	46,1	4,7	$C_{17}H_{22}N_4O_{10}$[f]	46,1	5,0	34
IIIhB	CH_3	H	CH_3	$COOCH_3$		0,33	1740, 1755	—	2,3, s, 3H, CH_3	1,02, d (6), 3H	3,63, s, 3H	213						
IIIiB	CH_3	H	CH_3	C≡N	Methanol,7	0,45[d]	1725	2260	2,34, s, 3H, CH_3	0,96, d (6), 3H	—	180	45,1	4,4	$C_{16}H_{19}N_5O_8$	46,9	4,7	48

[a]Silufol, 3:1 benzene—acetone. [b]Literature data [1]. [c]Yield and properties are given for piperidone IIIc, and the yield and properties of both isomers isolated for (1S)-α-phenylethyl-3,5-dicarbomethoxyethyl-4-piperidone, IVaA and IVaB, are given in the experimental part. [d]Silufol, 1:1:0.5 benzene—acetone—chloroform saturated with ammonia. [e]Picrate of the isomer mixture. [f]Picrate of individual isomer.

TABLE 3. Carbon-13 NMR Chemical Shifts[a] of 4-Piperidones in ppm Relative to TMS in C_6D_6

Compound	R	2-C	3-C	5-C	6-C	N—R			3-CH_2'—CH_2''—$COOCH_3$		
						CH_3	CH_2	CH	CH_2'	CH_2''	O—CH_3
IIIc	$CH(CH_3)C_6H_5$	56,13 55,64	49,17 —	40,99 —	50,76 50,03	19,26 18,53	— —	63,21 62,84	23,28 —	31,60 —	50,76 —
IIIe	$CH(CH_3)C_2H_5$	55,86 52,81	50,12 —	41,58 —	49,87 47,07	13,89 13,62 11,49	31,81 27,05	60,27 —	26,69 —	41,82 —	50,85 —

[a]The signals were assigned by incomplete decoupling from the protons and comparison with the data in the literature [4].

and the structure of each substance was confirmed by data from gas-chromatographic—mass spectrometry, elemental analysis, PMR, and IR spectroscopy. The addition of acrylonitrile to enamine IIe in benzene results in the formation of a mixture of 5-cyanoethyl-4-piperidone (IIIiB) and N-cyanoethylpyrrolidine. The unexpected formation of the 3-substituted piperidone IIIhA from the enamine of 1,3-dimethyl-4-piperidone IIe is probably attributable to the existence of imine—enamine tautomerism [3].

In order to ascertain the possibility of the transmission of the asymmetric effect upon the formation of a new carbon—carbon bond, we investigated the addition of methyl acrylate and acrylonitrile to enamines IIb and IIc, which have chiral substituents on the nitrogen atom. The reaction of methyl acrylate or acrylonitrile with emanime IIb in benzene or in dioxane results in the formation of pairs of diastereomers of the 3-substituted piperidones IIIc and IIId in equal amounts. For example, the PMR spectrum of the diastereomeric pair of IIId showed two quartets of the methine proton of the α-phenylethyl substituent at 3.70 and 3.72 ppm, respectively. The ^{13}C NMR spectrum of piperidone IIIc showed doubling of the signals of the $C_{(2)}$ and $C_{(6)}$ atoms of the piperidone ring and the signals of the carbon atoms in the methine and methyl groups in the (1S)-α-phenylethyl substituent. Similarly, the formation of a pair of diastereomers in a 1:1 ratio was established on the basis of the doubling of the signal of the $C_{(2)}$ atom of the piperidone ring and the signals of the carbon atoms of the methine and methyl groups in the sec-butyl substituent in the ^{13}C NMR spectrum of (1S)-sec-butyl-3-carbomethoxyethyl-4-piperidone (IIIe) (Table 3). The diastereomers formed in the corresponding pairs of IIIc-IIIe are characterized by an identical chromatographic mobility, and it is, therefore, impossible to separate them into the individual isomers.

It should be noted that in the literature there is no information at all on the separation of substituted 4-piperidones into optical isomers; therefore, the data obtained on the formation of chiral diastereomeric pairs of 3-substituted 4-piperidones IIIc-IIIe and the subsequent, for example, reductive modification of the keto group can provide a convenient path for the synthesis of optically active derivatives of 4-piperidones with a required stereochemistry.

EXPERIMENT

The PMR spectra of the enamines of type II were recorded without a solvent and for solutions in $CDCl_3$, and the PMR spectra of the 4-piperidones of types III and IV were recorded in $CDCl_3$ solutions with TMS as the internal reference on a Varian T-60 instrument. The ^{13}C NMR spectra were recorded on a CFT-20 instrument in C_6D_6 solutions, the IR spectra were recorded on thin layers on a UR-20 instrument, and the mass spectra were recorded on a Varian MAT-44 instrument with introduction of the sample through a chromatograph. The chromatography was carried out in a glass capillary column with an SE-54 liquid phase and programming of the column temperature from 100 to 250°C.

1,2-Dimethyl-4-pyrrolidinyl-4-piperidiene (IIdA) and 1,2-Dimethyl-4-pyrrolidinyl-3-piperideine (IIdB). A mixture of 3.17 g (25 mmole) of 1,2-dimethyl-4-piperidone (Id) and 2.62 g (37 mmole) of pyrrolidine in 10 ml of benzene was boiled with a Dean—Stark trap in an argon atmosphere until the evolution of water ceased. The benzene and the pyrrolidine excess were distilled off, the residue was vacuum-distilled, and 2.98 g (78%) of a mixture of enamines IIdA and IIdB with bp 78-80°C (2 mm Hg) were obtained.

Enamines IIa–IIc and IIe were obtained in a similar manner. Their properties are given in Table 1. Enamines IIb and IIc were introduced into the reactions without preliminary distillation.

1-Methyl-3-carbomethoxyethyl-4-piperidone (IIIa). A mixture of 0.66 g (4 mmole) of enamine IIa and 0.34 g (4 mmole) of methyl acrylate in 2 ml of absolute benzene was boiled for 7 h in an argon atmosphere. Chromatographic monitoring on Silufol in a 3:1 benzene–acetone system demonstrated the formation of a new compound with R_f 0.57. The reaction mixture was introduced into a column with silica gel and diluted by dry ether. The chromatographically homogeneous fractions were combined. After the removal of the ether in a vacuum, 0.46 g (57%) of piperidone IIIa was obtained.

Piperidones IIIb–IIIi were obtained in a similar manner, and their properties are given in Table 2. Piperidones IIIb, IIIc, IIIf, and IIIh were recovered in a similar manner. Elution by a 5:1 benzene–acetone system was used for the recovery of piperidone IIIe, a 10:1 benzene–acetone system was used for piperidone IIId, and a 6:1 petroleum ether–acetone system was used for piperidone IIIi.

(1S)-α-Phenylethyl-3-carbomethoxyethyl-4-piperidone (IIIc) and (1S)-α-Phenylethyl-3,5-dicarbomethoxyethyl-4-piperidones (IVaA and IVaB). A mixture of 1.54 g (6 mmole) of enamine IIb and 0.51 g (6 mmole) of methyl acrylate in 5 ml of absolute methanol was boiled under argon for 17 h. The formation of two new compounds with R_f 0.75 and 0.6 was observed upon chromatography of the reaction mixture on Silufol in a 3:1 benzene–acetone system. The methanol was distilled off, and 2.16 g of the oil were dissolved in 3 ml of benzene and applied to nine 18 × 24 (cm) plates with a silica gel layer having a thickness equal to 2 mm. Elution was carried out by a 3:1 benzene–acetone system. The chromatographically homogeneous layers were combined, and the substances were eluted by acetone and dried by anhydrous potassium carbonate. Removal of the solvent gave 0.08 g (3.5%) of piperidone IVaA with R_f 0.75 and 0.85 g of a mixture of two substances, which were separated in an analogous manner with elution by a 5:1 petroleum ether–acetone system. This yielded 0.35 g (21%) of piperidone IIIc with R_f 0.2 (Silufol, 1:10 acetone–petroleum ether) and 0.14 g (6.2%) of piperidone IVaB with R_f 0.1 (Silufol, 1:10 acetone–petroleum ether). Piperidone IVaA with R_f 0.75 (Silufol, 3:1 benzene–acetone), M^+ 375. PMR spectrum: 1.42 (3H, d, J = 6.5 Hz, CH_3); 1.37 (3H, d, J = 6.5 Hz, CH_3); 3.64 (3H, s, OCH_3); 3.66 (3H, s, OCH_3); 7.32 (5H, s, C_6H_5). IR spectrum: 1720, 1745 cm^{-1} (C=O, $COOCH_3$). Piperidone IVaB, R_f 0.1 (Silufol, 1:10 acetone–petroleum ether), R_f 0.5 (Silufol, 3:1 benzene–acetone), M^+ 375. PMR spectrum: 1.41 (6H, d, J = 6.5 Hz, two CH_3); 3.64 (3H, s, OCH_3); 3.66 (3H, s, OCH_3); 7.35 ppm (5H, s, C_6H_5). IR spectrum: 1720, 1745 cm^{-1} (C=O, $COOCH_3$).

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