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SYNTHESIS AND STEREOCHEMISTRY OF TRIFLUOROMETHYL-CONTAINING ISOXAZOLIDINES

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The reaction of trifluoromethyl-containing enones with hydroxylamine under various conditions is studied. The products in basic medium are equilibrating mixtures of isoxazolidine diastereomers in an ~1:1 ratio. The energy of the nitrogen atom inversion barrier in these compounds is 50-60 kJ/mol. Broadened signals are observed at room temperature in the ^{1}H and ^{13}C NMR.

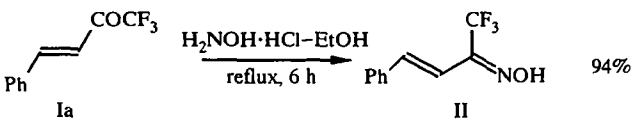
Isoxazole derivatives (isoxazolines and isoxazolidines) frequently exhibit a wide spectrum of biological activity [1]. Furthermore, they are employed to synthesize bifunctional compounds (by opening the ring) [2] and have been used for the total synthesis of natural products [3]. The preparation of trifluoromethyl-containing derivatives of isoxazole is of great interest [4, 5].

The reactions of trifluoromethyl- and perfluoroalkyl-containing β-diketones [6], β-alkoxy- [7-9] and β-amino-substituted [10] enones, and acetylenic ketones [11] with hydroxylamine have been previously studied. The products are isoxazolines that contain a stable hemiacetal moiety –NH–O–C(OH)R_f that is stabilized by the electron-accepting influence of the perfluoroalkyl group. Furthermore, the 1,3-dipolar cycloaddition of trifluoroacetonitrile oxide to alkenes and alkynes [12-14] has been applied to the preparation of trifluoromethyl-containing isoxazolines and isoxazoles. The reaction of trifluoromethyl-containing arylvinylsulfones with nitrones [15] has been used to prepare isoxazolidines.

The reaction of trifluoromethyl-containing α,β-enones without such substituents as RO– and R^1R^2N– with hydroxylamine has not previously been studied. The reactions of their unfluorinated analogs produce mixtures of isomeric isoxazolines and the oxime, the ratio of which depends on the structure of the starting enone and the reaction conditions [16]. Unfluorinated enones with a labile substituent in the β-position {RO–, RNH– [17], RS– [18] (R = Alk, Ar), CH_3COO– [19]} or a bromine in the α-position [20] have been studied more. In these instances one of the isomeric isoxazoles can be formed regioselectively by varying the reaction conditions. The formation of isoxazolidines through the reaction of α,β-unsaturated ketones with hydroxylamine has not previously been observed.

According to the literature, unfluorinated enones in addition to β-alkoxy-substituted trifluoromethyl-containing enones react to form isoxazolines both in acidic and basic medium [7-9, 16-18].

We studied the reaction of enone I with hydroxylamine in acidic medium by boiling it with the hydrochloride in ethanol. The reaction produced almost quantitatively the corresponding oxime II, which exhibits no tendency to cyclize in either acidic or basic medium (bases such as NaOH and sodium ethoxide were used).



Ia II

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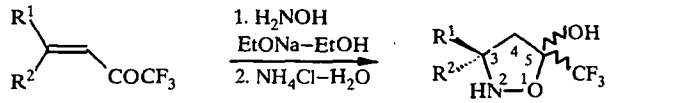
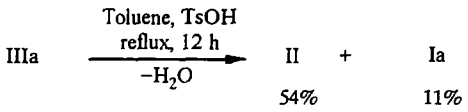
Performing the reaction in near-neutral medium (in the presence of sodium acetate) gives a mixture of II and the isoxazolidine IIIa. Therefore, we studied the reaction of a series of trifluoromethyl-containing α,β-enones with hydroxylamine in basic medium. The reaction of these enones with hydroxylamine in the presence of an equimolar amount of sodium ethoxide produces the isoxazolidines III in good yields (Table 1).



Ia–j IIIa–j 72...93%

The observed dependence of the reaction path on the conditions agrees with the literature for the reaction of acetylenic ketones with hydroxylamine with the difference that oxime IV, which is prepared from an acetylenic ketone, cyclizes on boiling in benzene to form the isoxazole V [11]. In our experiments, oxime II undergoes no reaction under these conditions. This is probably explained by the fact that an aromatic compound (isoxazole V) is formed in the first instance.

We used IIIa as an example for studying the dehydration of isoxazolidines. As it turned out, boiling in toluene with azeotropic removal of water in the presence of *p*-toluenesulfonic acid produces oxime II in moderate yield. The starting enone Ia is produced as a side product. The corresponding isoxazoline does not form.



The isoxazolines VI, which are prepared from β-alkoxy-substituted enones or acetylenic ketones, are dehydrated under acidic conditions to give the isoxazoles VII [8, 9]. Apparently in this case the ability to form an aromatic system plays a deciding role in determining the reaction path. If an aromatic system cannot be formed, the formation of the oxime is apparently the most favorable path under these conditions.

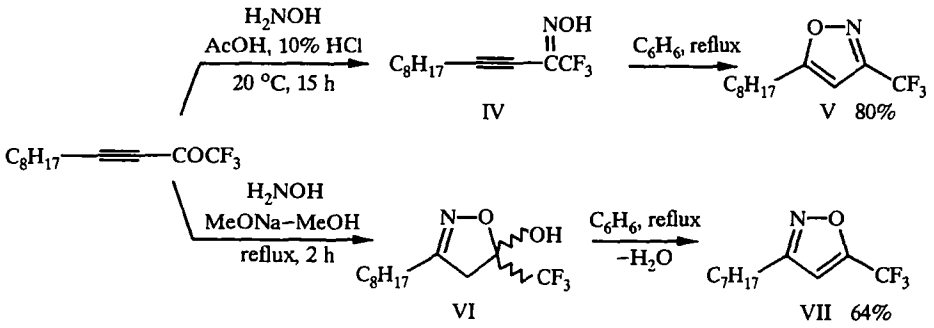


TABLE 1. Reactions of α,β-Enones with Hydroxylamine in Basic Medium

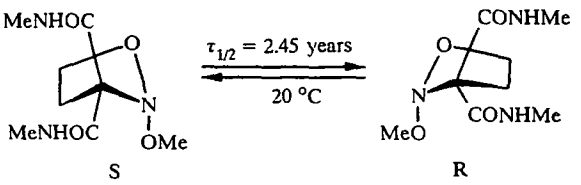
Enone	R^1	R^2	Isoxazolidine	Yield, %
Ia	Ph	H	IIIa	81
Ib	Indol-3-yl	H	IIIb	87
Ic	Pyrrol-2-yl	H	IIIc	72
Id	N-Methylpyrrol-2-yl	H	IIId	84
Ie	2-Phenylindol-3-yl	H	IIIe	93
If	Thien-2-yl	H	IIIf	80
Ig	Fur-2-yl	H	IIIg	76
Ih	Ph	Me	IIIh	88
Ii		$-(CH_2)_3-$	IIIi	74
Ij		2,2-Adamantyl	IIIj	90

The ^{1}H and ^{13}C NMR data indicate that isoxazolidines IIIi and IIIj, which have a symmetric substituent in the 3-position, exist as one diastereomer at room temperature. The ^{1}H and ^{13}C NMR spectra of IIIa-h, which have an aromatic substituent on $C_{(3)}$, contain two sets of signals of approximately equal intensity. These data are consistent with a mixture of two diastereomers (~1:1) for IIIa-h at room temperature. The diastereomers have a different relative configuration on $C_{(3)}$ and $C_{(5)}$. Furthermore, the reaction occurs regiospecifically to form exclusively the 5-CF_3-isoxazolidines. This is indicated by the presence of characteristic quadruplets for $C_{(5)}$ near 104-107 ppm with a spin-spin coupling constant (SSCC) $^{2}J_{C-F}$ = 31-33 Hz whereas the spectra of CF_3-heterocycles of similar structure, but possessing the –NHC(OH)CF_3 moiety have the analogous signal for $C_{(5)}$ at 92-95 ppm ($^{2}J_{C-F}$ = 29.5 Hz) [21].

One feature of the prepared isoxazolidines is that the ^{13}C NMR of IIIi, which exists as one diastereomer, has signals for $C_{(3)}$ and $C_{(4)}$ in addition to the two CH_2 groups of the cyclobutane moiety that are very broad (Fig. 1).

Broadened signals were also seen in the spectra of the remaining isoxazolidines with the exception of IIIj. This effect is evident to differing degree for the diastereomers and depends on the nature of the substituent(s) in the 3-position. Thus, the ^{1}H NMR of IIIa has doublets of doublets for the 3-H and 4-H protons. The signals for the 3-H proton of one diastereomer and one of the 4-H protons for both diastereomers are broadened. The same situation is observed in the NMR spectra of the remaining compounds. We propose that the broadening is a result of a dynamic equilibrium between the two diastereomers with a different configuration for the asymmetric nitrogen atom. In the isoxazolidines, which have two different substituents on $C_{(3)}$, there are three chiral centers: two asymmetric carbon atoms and one nitrogen atom. Thus, the existence of four diastereomers for these compounds is theoretically possible. Compounds with a symmetric spiro substituent have one asymmetric carbon atom and an asymmetric nitrogen atom. Thus, they can exist as two disatereomers.

In most instances the stereoisomers with an asymmetric nitrogen atom cannot be isolated because of the facile pyramidal inversion (the "umbrella" effect). However, introduction of electronegative substituents increases the energy of the barrier to inversion. Thus, pure enantiomers of N-alkoxyisoxazolidines were isolated. The half-life for conversion of these compounds at room temperature is of the order of several years. The energy of the barrier to inversion is 90-100 kJ/mol [22, 23].



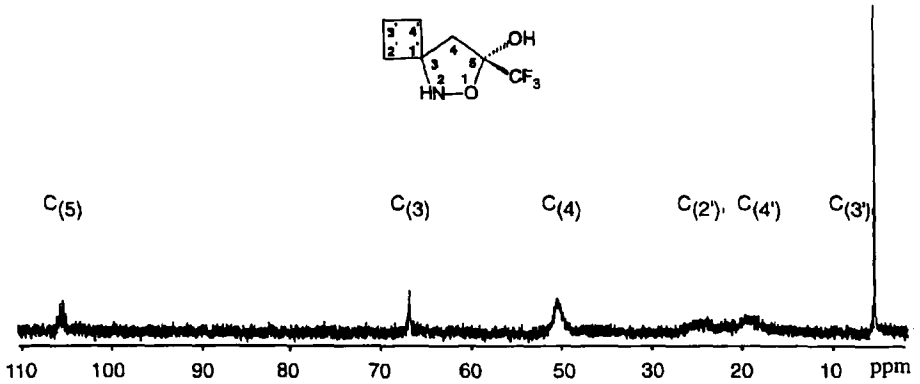


Fig. 1. A fragment of the ^{13}C NMR spectrum (CD_3CN, 100 MHz) of IIIi at room temperature.

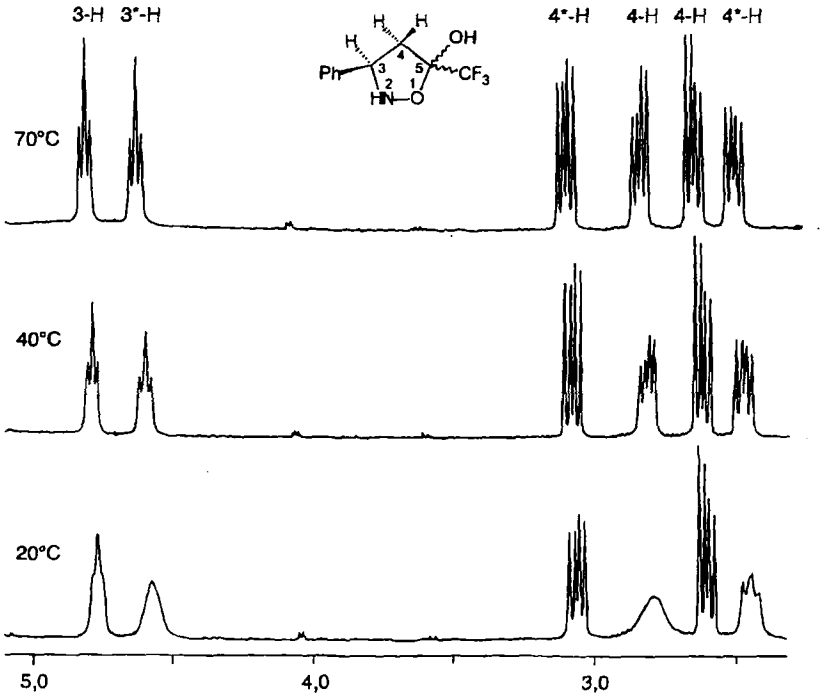


Fig. 2. A fragment of the ^{1}H NMR spectrum (CD_3CN, 400 MHz) of IIIa at variable temperature.

The energy of the barrier to inversion of the nitrogen atom in the isoxazolidines prepared by us is probably sufficiently high to decrease the rate of inversion. As a result the usually observed sharp signals from a certain "average" configuration for the nitrogen atom become broadened.

Steric effects apparently are responsible for the different behavior of IIIi and IIIj. The bulky adamantane moiety in IIIi increases the energy of both diastereomers whereas the energy of the transition state in which the isoxazolidine ring is planar and the repulsion of the substituents is minimal does not increase. Therefore, the energy of the barrier to nitrogen atom inversion in IIIj is lower than in IIIi. The latter has a cyclobutane moiety, which does not cause steric hindrance.

We studied the temperature dependence of the NMR spectra of IIIa and IIIh (Figs. 2-4). A comparison of the spectra of IIIa at various temperatures indicates that the broadened signals of the 4-H protons change into a doublet of doublets at elevated temperature. Apparently the nitrogen atom inversion is sufficiently fast at high temperature (70°C). At low temperature the rate of inversion of the diastereomers (nitrogen atom inversion) decreases, causing the signals to broaden (Fig. 2).

At room temperature very broad signals of two diastereomers are seen in the ^{1}H and ^{13}C NMR of IIIh. At low temperature (-40°C), the ^{1}H NMR spectrum of this compound contains signals of three diastereomers. The signal for the CH_3 group of one of these is significantly broadened (Fig. 3).

The ^{13}C NMR spectrum of IIIj at room temperature contains signals of two diastereomers. At reduced temperature (down to -40°C), signals for $C_{(4)}$ and the CH_3 group indicate four diastereomers (Fig. 4).

Thus, the rate of nitrogen atom inversion at a sufficiently low temperature is decreased so much that signals of four diastereomers are observed in the NMR spectra of IIIh. These diastereomers have different configurations at the two carbon atoms and the nitrogen atom. The diastereomers with different configurations at the nitrogen atom exst sufficiently long because they are "frozen" out. This phenomenon is very interesting because it suggests that stereoisomers with different configurations at the nitrogen atom can exist for compounds of different classes that are not required to have a small ring or an electronegative substituent [22, 23].

We estimated the energy of the barrier to nitrogen inversion in IIIh at a temperature where the signals of the diastereomers with different configurations at the nitrogen atom coalesce [~0°C (273 K)]. The approximate values of ΔG calculated on the basis of the ^{1}H and ^{13}C NMR spectra are 51 and 55 kJ/mol, respectively. Taking

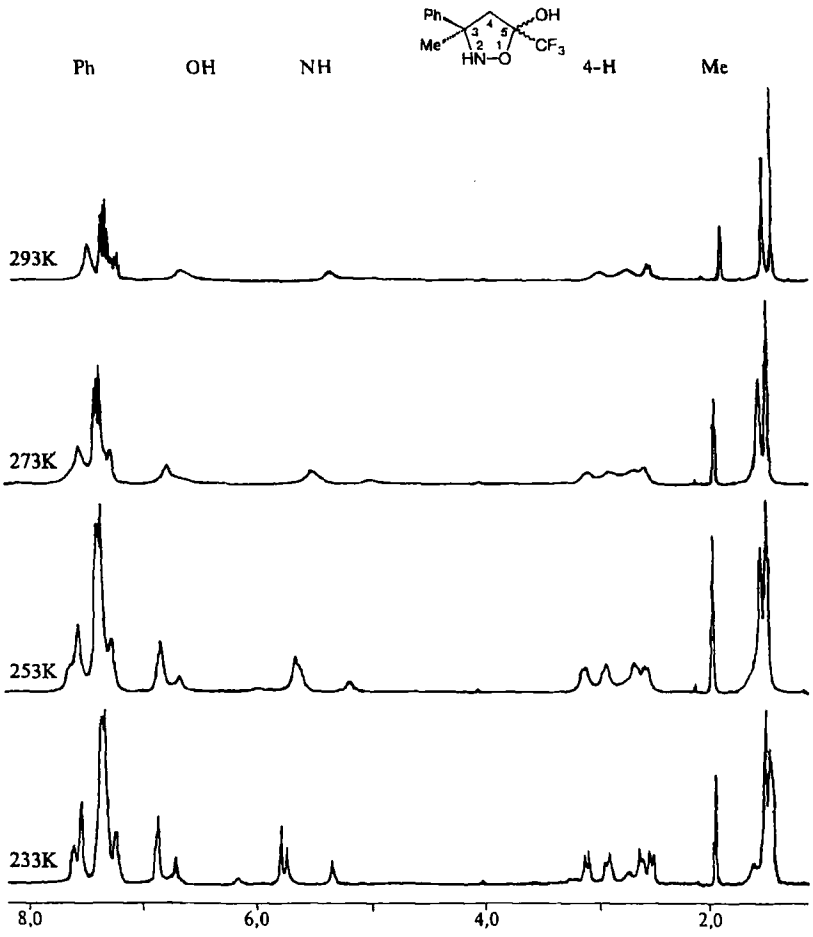
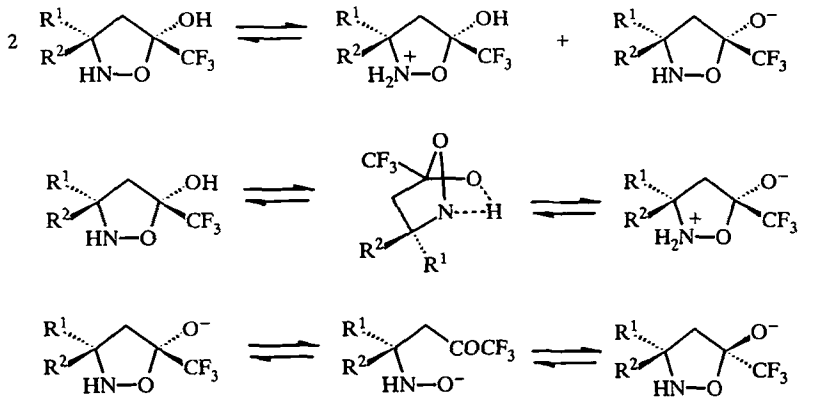


Fig. 3. ^{1}H NMR spectra (CD_3CN, 400 MHz) of IIIh at variable temperature.

into account the uncertainty in determining the coalescence temperature, it can be assumed that the energy of the barrier to nitrogen atom inversion in IIIh is of the order of 50-60 kJ/mol. This is almost two times less than in the isoxazolidines described in the literature [22, 23].



The saturation-shift-transfer (SST) method demonstrated that suppressing the signal for the 3-H proton of one diastereomer of IIIa in the ^{1}H NMR caused the intensity of the signal of the 3-H proton in the other diastereomer to change. This suggests that the diastereomers with different relative configurations at $C_{(3)}$ and $C_{(5)}$ interconvert. However, this process is much slower than inversion at the nitrogen atom and is not evident in the

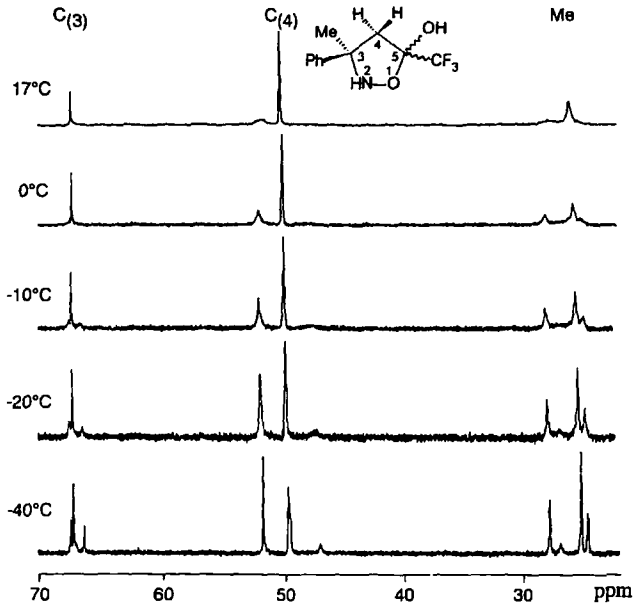


Fig. 4. Temperature dependence of ^{13}C NMR spectra (CD_3CN, 100 MHz) for IIIh.

NMR spectra. A possible mechanism for the conversion of one diastereomer into the other is the transfer of a proton onto the nitrogen atom. This could be both inter- and intramolecular. The result is the formation of an anion or zwitter-ion, the reversible opening of which can transform one diastereomer into the other.

An example of ring-chain isomerism for cyclic hemiacetals with the $-OC(OH)CF_3$ moiety has been reported [24, 25]. In our instance, the signals of the acyclic form (the most characteristic of which would be the signal of the carbonyl group of $COCF_3$ in the ^{13}C NMR spectrum, a quadruplet near 180-190 ppm) were not observed. Nevertheless, any proposed mechanism for the conversion of the diastereomers should include the formation of such a species although its concentration is apparently too low to be detected by NMR spectroscopy.

TABLE 2. Properties of Synthesized Isoxazolidines

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
IIIa	$C_{10}H_{10}F_3NO_2$	51,28 / 51,51	4,25 / 4,32	6,05 / 6,01	114...115 (dec.)	81
IIIb	$C_{12}H_{11}F_3N_2O_2$	52,74 / 52,95	3,96 / 4,07	*	193...194 (dec.)	87
IIIc	$C_{18}H_{15}F_3N_2O_2$	61,82 / 62,07	4,10 / 4,34	*	205...210 (dec.)	93
IIId	$C_8H_9F_3N_2O_2$	43,18 / 43,25	4,09 / 4,08	12,51 / 12,61	134...135 (dec.)	72
IIIe	$C_9H_{11}F_3N_2O_2$	45,80 / 45,77	4,68 / 4,69	11,93 / 11,86	111...112 (dec.)	84
IIIf	$C_8H_8F_3NO_2S$	40,18 / 40,17	3,21 / 3,37	5,90 / 5,86	111...112 (dec.)	80
IIIg	$C_8H_8F_3NO_3$	42,87 / 43,06	3,51 / 3,61	*	85...86 (dec.)	76
IIIh	$C_{11}H_{12}F_3NO_2$	53,26 / 53,44	4,92 / 4,89	5,69 / 5,67	117...118 (dec.)	88
IIIi	$C_7H_{10}F_3NO_2$	42,47 / 42,11	5,16 / 5,11	7,16 / 7,10	104...105 (dec.)	74
IIIj	$C_{13}H_{18}F_3NO_2$	56,39 / 56,31	6,50 / 6,54	4,88 / 5,05	144...145 (dec.)	90

* Elemental analysis for nitrogen was not performed.

TABLE 3. Spectral Characteristics of Isoxazolidines III

Compound	IR spectrum, (ν, cm^{-1})	^1H NMR spectrum, δ, ppm			^{13}C NMR, δ, ppm		
		First diastereomer	Second diastereomer	Common signals	First diastereomer	Second diastereomer	Common signals
1	2	3	4	5	6	7	8
IIIa	2700...3200 (OH) 3220 (NH)	5,03 (1H, t, ^3J = 7,4 Hz, 3-H); 3,06 (1H, dd, ^2J = 13,1, ^3J = 7,0 Hz, 4-H); 2,87 (1H, dd, ^2J = 13,4, ^3J = 7,7 Hz, 4-H)	4,83 (1H, t, ^3J = 8,1 Hz, 3-H); 3,32 (1H, dd, ^2J = 13,9, ^3J = 8,0 Hz, 4-H); 2,72 (1H, dd, ^2J = 13,9, ^3J = 8,3 Hz, 4-H)	7,75...7,55 (5H, m, Ph) 6,84 (1H, br. s, NH) 5,75 (1H, br. s, OH)	128,81 (2C Ph) 128,31 (C Ph); 127,49 (2C Ph); 123,42 (CF_3, q, $^1J_{C-F}$ = 283 Hz) 63,30 ($C_{(3)}$, br. s)	128,62 (2C Ph) 127,82 (C Ph) 126,79 (2C Ph) 123,58 (CF_3, q, $^1J_{C-F}$ = 283 Hz) 62,10 ($C_{(3)}$, br. s)	104,20 ($C_{(5)}$, q, $^1J_{C-F}$ = 31,5 Hz) 45,19 ($C_{(4)}$)
IIIb	2700...3200 (OH) 3230 (NH) 3350 (NH indol.)	7,75 (1H, d, ^3J = 7,9 Hz); 7,44 (1H, d, ^3J = 8,0 Hz, 4-H or 7-H indol.); 7,33 (1H, d, J = 2,4 Hz, 2-H, indol.); 4,81 (1H, br.s, 3-H); 3,08 (1H, dd, ^2J = 13,8, ^3J = 7,7 Hz, 4-H); 2,63 (1H, dd, ^2J = 13,8, ^3J = 9,9 Hz, 4-H)	7,68 (1H, d, ^3J = 7,8 Hz); 7,45 (1H, d, ^3J = 8,1 Hz, 4-H or 7-H indol.); 7,23 (1H, s, 2-H, indol.); 5,02 (1H, br.s, 3-H); 2,84...2,72 (2H, m, 4-H)	6,41 (1H, br. s, NH indol.); 7,22...7,16 (1H, m); 7,11...7,07 (1H, m, 5-H or 6-H indol.); 6,39 and 6,21 (1H, br. s, OH, NH)	138,61 (C quar. indol.); 119,91 112,91; 59,71 ($C_{(3)}$) 45,40 ($C_{(4)}$)	138,49 (C quar. indol.); 119,79 112,80; 57,79 ($C_{(3)}$, br. s); 44,52 ($C_{(4)}$, br. s)	127,91 (C quar. indol.); 124,30 (br. s) 124,81; 123,29 (C indol.); 123,00 (CF_3, q, $^1J_{C-F}$ = 281 Hz) 120,69 (C indol.) 104,53 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,4 Hz)
IIIc	2700...3200 (OH) 3180 (NH) 3390 (NH pyrrol.)	4,75 (1H, t, ^3J = 7,1 Hz, 3-H); 3,00 (1H, dd, ^2J = 13,6, ^3J = 7,6 Hz, 4-H) 2,51 (1H, br. s, 4-H)	4,57 (1H, br. s, 3-H) 2,67 (2H, br. s, 4-H)	9,40 (1H, br. s, NH pyrrol.); 6,76 (1H, dd, ^3J = 4,1, J = 2,6 Hz, CH pyrrol.); 6,28 (1H, br. s, NH or OH); 6,20 (1H, s, CH pyrrol.) 6,13...6,07 (1H, m, CH pyrrol.); 5,65 (1H, br. s, NH or OH)	122,94 (CF_3, q, $^1J_{C-F}$ = 283 Hz) 104,15 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,2 Hz) 58,43 ($C_{(3)}$, br. s) 43,98 ($C_{(4)}$)	123,55 (CF_3, q, $^1J_{C-F}$ = 283 Hz) 104,60 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,2 Hz) 56,80 ($C_{(3)}$, br. s) 43,06 ($C_{(4)}$, br. s)	118,80; 108,01 106,59 (C pyrrol.)
IIId	2700...3200 (OH) 3240 (NH)	4,53 (1H, br. s, 3-H) 3,63 (3H, s, CH_3) 3,00 (1H, dd, ^2J = 13,9, ^3J = 7,4 Hz, 4-H); 2,54 (1H, t, J = 12,4 Hz, 4-H)	4,74 (1H, br. s, 3-H) 3,63 (3H, s, CH_3) 2,71...2,63 (2H, 2 br. s, 4-H)	6,68 (1H, t, J = 2,0 Hz, pyrrol.); 6,21 (1H, dd, ^3J = 3,5, J = 1,5 Hz, CH pyrrol.); 6,15 (1H, br. s, NH or OH); 6,03 (1H, t, J = 3,2 Hz, CH pyrrol.); 5,88 (1H, br. s, NH or OH)	57,19 ($C_{(3)}$) 42,40 ($C_{(4)}$)	55,51 ($C_{(3)}$, br. s) 43,59 ($C_{(4)}$)	122,75 (CF_3, q, $^1J_{C-F}$ = 283 Hz) 124,01; 107,10 106,88; 106,71 (C pyrrol.); 103,95 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,5 Hz); 33,33 (CH_3)

TABLE 3 (continued)

1	2	3	4	5	6	7	8
IIIe*	2700...3200 (OH) 3220 (NH) 3340 (NH indol.)	5,05 (1H, t, ^3J = 9,0 Hz, 3-H) 3,18 (1H, dd, ^2J = 13,8, ^3J = 9,1 Hz, 4-H) 3,04 (1H, dd, ^2J = 13,8, ^3J = 9,1 Hz, 4-H)	5,36 (1H, br. s, 3-H) 3,48 (1H, br. s, 4-H) 2,69 (1H, br. s, 4-H)	8,27 (1H, d, ^3J = 7,0 Hz, CH indol.) 7,82...7,77 (2H, m, arom.); 7,70...7,57 (4H, m, arom.) 7,38...7,27 (2H, m, arom.)	60,12 ($C_{(3)}$) 44,28 ($C_{(4)}$)	59,15 ($C_{(3)}$, br. s) 43,84 ($C_{(4)}$, br. s)	138,44; 133,82(C quar. arom.); 130,38 (C arom.); 130,22 (2C Ph); 130,15 (2C Ph); 129,69 (C arom.) 127,40 (C quar. arom.); 124,45 (CF_3, q, $^1J_{C-F}$ = 282 Hz) 123,44 (C arom.) 123,39 (C quar. arom.); 121,02 (C arom.); 120,22 (C quar. arom.) 113,16 (C arom.) 104,80 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,4 Hz)
IIIf	2700...3200 (OH) 3230 (NH)	7,40 and 7,15 (2H, br. s, CH thiophen.) 7,05 (1H, t, J = 4,2 Hz, CH thiophen.) 4,99 (1H, br. s, 3-H) 2,82 and 2,76 (2H, 2 br. s, 4-H)	7,34 (1H, br. s, CH thiophen.); 7,01 (2H, br. s, CH thiophen.) 4,79 (1H, br. s, 3-H) 3,12 and 2,54 (2H, br. s, 4-H)	6,43 and 5,58 (2H, br. s, OH, NH)	58,39 ($C_{(3)}$) 45,60 ($C_{(4)}$)	59,82 ($C_{(3)}$, br. s) 46,15 ($C_{(4)}$, br. s)	127,20; 126,99 126,75; 126,01 (C thiophen., br. s) 122,82 (CF_3, q, $^1J_{C-F}$ = 282 Hz) 104,21 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,4 Hz)
IIIg	2700...3300 (OH) 3200 (NH)	7,52 (1H, br. s, furan.) 4,79 (1H, br. s, 3-H) 2,80 and 2,68 (2H, br. s, 4-H)	7,48 (1H, br. s, furan.) 4,61 (1H, br. s, 3-H) 2,97 and 2,58 (2H, br. s, 4-H)	6,60...6,35 (3H, m, 2-H furan., NH or OH); 5,52 (1H, s, NH or OH)	56,42 ($C_{(3)}$) 42,21 ($C_{(4)}$)	58,28 ($C_{(3)}$, br. s) 42,80 ($C_{(4)}$, br. s)	143,25 (C furan., br. s); 124,23 (CF_3, q, $^1J_{C-F}$ = 283 Hz) 110,60; 110,49 109,21 (C furan., br. s); 104,02 ($C_{(5)}$, q, $^2J_{C-F}$ = 32,5 Hz)
IIIh	2700...3300 (OH) 3220 (NH)	3,00 (1H, br. s, 4-H) 2,56 (1H, d, ^2J = 12,7 Hz, 4-H); 1,47 (3H, s, CH_3)	2,77 (1H, br. s, 4-H) 1,54 (3H, s, CH_3)	7,55...7,20 (5H, m, Ph) 6,66...5,77 (1H, br. s, OH, NH)	129,19 (2C Ph) 127,76 (C Ph); 126,38 (2C Ph); 106,43 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,8 Hz) 68,33 ($C_{(3)}$); 51,45 ($C_{(4)}$); 27,3 (CH_3, br. s)	129,49 (2C Ph); 128,22 (C Ph); 126,66 (2C Ph); 106,33 ($C_{(5)}$, q, $^2J_{C-F}$ = 32,1 Hz) 68,35 ($C_{(3)}$, br. s) 53,90 ($C_{(4)}$, br. s) 29,2 (CH_3, br. s)	123,75(CF_3, q, $^1J_{C-F}$ = 283 Hz)
IIIi	2700...3300 (OH) 3220 (NH)	6,46 (1H, br. s); 5,29 (1H, br. s) (OH, NH); 2,75...1,75 (8H, m, 4-H, $3CH_2$ cyclobut.)			124,07 (CF_3, q, $^1J_{C-F}$ = 283 Hz); 105,27 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,7 Hz) 66,86 ($C_{(3)}$, br. s); 50,36 ($C_{(4)}$, br. s); 34,5 (CH_2 cyclobut., br. s) 29,0 (CH_2 cyclobut., br. s); 15,56 (CH_2 cyclobut., br. s)		
IIIj	2700...3300 (OH) 3240 (NH)	5,57 (1H, br. s); 5,08 (1H, br. s) (OH, NH); 250 (1H, d, ^3J = 14,2 Hz, 4-H) 2,24 (1H, br. s, adamant.); 2,19 (1H, d, $3J$ = 14,2 Hz, 4-H) 2,01... 1,68 (13H, m, adamant.)			123,95 (CF_3, q, $^1J_{C-F}$ = 283 Hz); 105,78 ($C_{(5)}$, q, $^2J_{C-F}$ = 31,5 Hz) 69,99 ($C_{(3)}$); 48,58 ($C_{(4)}$); 38,18, 36,46, 36,13, 35,65, 34,76, 34,54, 34,14, 28,03, 27,84 (9C adamant.)		

* ^1H and ^{13}C spectra were taken in CD_3OD.

It is noteworthy that the nature of the substituent has little effect on the ratio between the two diasteromers of isoxazolidines IIIa-h, which have a different relative configuration at $C_{(3)}$ and $C_{(5)}$. Apparently the energy difference between the diasteromers in this case is less than in the trifluoromethyl-containing carbo- and heterocycles with a six-membered ring, in which primarily one of the isomers forms [26].

Thus, the reaction of trifluoromethyl-containing α,β-enones without labile for substitution groups with hydroxylamine in basic medium produces isoxazolidines. The products in solution at room temperature exist as a mixture of equilibrating diastereomers (~1:1). The energy of the barrier to inversion of the nitrogen atom in the products is sufficiently high (of the order of 50-60 kJ/mol) that broadened signals are observed at room temperature in the ^1H and ^{13}C NMR spectra.

EXPERIMENTAL

Varian VXR-400 and Bruker AMX 400 (working frequency for ^{13}C 100 MHz) spectrometers were used to record ^1H and ^{13}C NMR spectra in CD_3CN and CD_3OH with TMS internal standard. IR spectra were obtained on a UR-20 spectrometer in mineral oil. TLC analysis was performed on Silufol UV-254 plates with visualization in acidified $KMnO_4$ solution and iodine vapor. The trifluoromethyl-containing enones were prepared according to the literature [27-30].

(*E*)-1,1,1-Trifluoro-4-phenyl-3-buten-2-one Oxime (II). Yield 94%; mp 152-153°C. IR spectrum: 1630 (C=N), 2900-3400 cm^{-1} (OH). ^1H NMR spectrum (CD_3COCD_3): 7.23 (1H, dq, H-3, ^{3D}J = 17.2, $^4J_{C-F}$ = 1.2 Hz), 7.39-7.29 (4H, m, $3H_{Ph}$ and 4-H), 7.63-7.57 ppm (2H, m, Ph). ^{13}C NMR spectrum (CD_3COCD_3): 111.02 ($C_{(3)}$), 121.95 (CF_3, q, $^1J_{C-F}$ = 274 Hz), 128.01 (2C, Ph), 129.50 (2C, Ph), 130.29 (C, Ph), 136.31 (C quat., Ph), 138.60 ($C_{(4)}$), 145.14 ppm ($C_{(2)}$, q, $^2J_{C-F}$ = 30.5 Hz). Found, %: C 55.97; H 3.68. $C_{10}H_8F_3NO$. Calculated, %: C 55.82; H 3.75.

Synthesis of Isoxazolidines. Mixture of hydroxylamine hydrochloride (15 mmol) and sodium ethoxide (20 mmol) in ethanol (25 ml) was boiled for 20 min. The appropriate trifluoromethyl-containing enone (10 mmol) was added after cooling to room temperature. The mixture was held at room temperature for 10 h, after which it was poured into saturated NH_4Cl solution (30 ml). The reaction products were extracted with CH_2Cl_2 (5×20 ml). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The isoxazolidines were crystallized by adding hexane (20-30 ml) to the solid.

Yields, elemental analyses, and melting points of the III series of compounds are given in Table 2. IR and ^1H and ^{13}C spectra are reported in Table 3.

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