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THE CONCERTED MECHANISM OF ACYLAMIDATION. SYN-STEREOSPECIFICITY OF THE REACTION.

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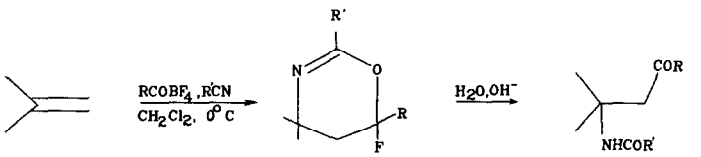
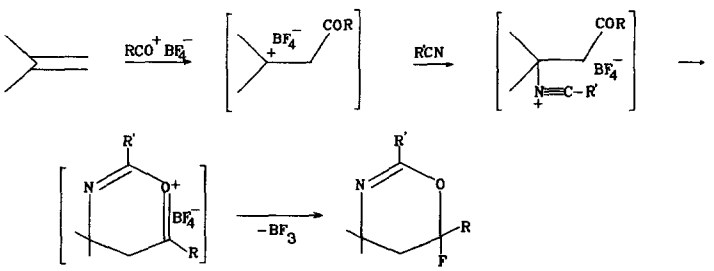
Key Words: 6-fluoro-5,6-dihydro-1,3-oxazines; β-amidoketones; acylation; acylamidation; cycloaddition.

Abstract: *The concerted mechanism for the new reaction of acylamidation of alkenes and alkynes is proposed on the basis of syn-stereospecifity observed and the study of the reagent structure.*

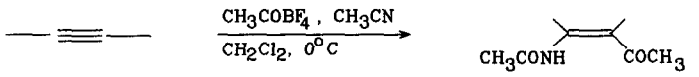
Earlier we have reported on the new reaction of acylamidation of alkenes and alkynes. The reagent used in this reaction is the mixture of acyl tetrafluoroborate and nitrile in methylene chloride [1-4]:



Analogously to the other reactions of acyl tetrafluoroborates [5-8] we have proposed Ad_E-mechanism for this reaction [1-4]:



Nevertheless, the acylamidation of 1-methylcyclopentene proved to be syn-stereospecific [3], which is most unusual for the electrophylic addition. The acylamidation of acetylenes is also syn-stereospecific [4]:



This work deals with more careful investigation of stereochemistry and mechanism of the acylamidation reaction.

Study of the reagent.

The addition of the excess of acetonitrile to the suspension of acetyl tetrafluoroborate affords solution active in the acylamidation reaction. In Table 1 the NMR data for this solution as well as for acetylfluoride, acetonitrile, their BF_3-complexes, trimethyldiazapirilium tetrafluoroborate 1 and trimethyltriazine 2, which can coexist in the conditions concerned.

Table 1. The NMR study of the reagent.

Compound	δ ^1H, ppm (J_{HF}, Hz)	δ ^{13}C, ppm (J_{CF}, Hz)
CH_3COF	2.35 (7.5)	17.52 (59.3), 160.13 (349.0)
CH_3COBF_4	3.10[a]	7.55, 150.13[b]
CH_3CN	1.96[c]	0.66,[c] 117.09[c]
$CH_3CN \cdot BF_3$	2.47	1.74 117.81
1	2.13, 2.25	24.92, 25.95, 173.18, 170.15
2[d]	2.33	23.16, 168.12
The reagent[e]	2.30 (7.5)	17.39 (59.3), 160.23(349.0)
	2.51	1.27 116.79

[a] [9]. [b] [10]. [c] [11]. [d] [12]. [e] $t=0^oC$.

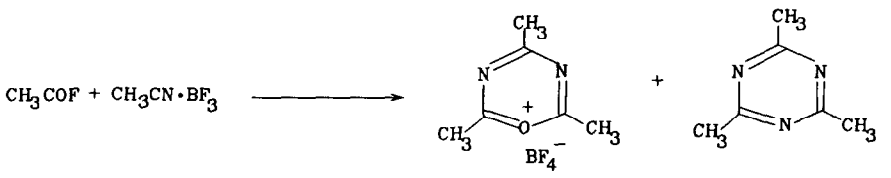
Table 1 reveals the same values of J_{HF} and J_{CF} in acetylfluoride and reactive solution. This fact points to the absence of the bonding between CH_3COF and BF_3, i.e. the addition of acetonitrile to the suspension of CH_3COBF_4 in CH_2Cl_2 causes the following exchange reaction:

$$CH_3COBF_4 + CH_3CN \longrightarrow CH_3COF + CH_3CN \cdot BF_3$$

This process is irreversible since we could not detect any dynamic effects in NMR spectra of the reactive solution in the temperature interval -60-0^oC.

The complex $CH_3CN \cdot BF_3$ can be easily obtained from the reactive solution in crystalline form by evaporation of the solvent and acetylfluoride in vacuo. Satisfactory microanalysis was obtained for this compound.

When the reactive solution is stored at room temperature in a sealed tube, the slow formation of diazapirilium salt 1 and triazine 2 takes place:



1 2

The purple solution formed does not react with unsaturated hydrocarbons.

Thus, NMR investigation of the solution, active in the acylamidation reaction revealed the absence of acetyl tetrafluoroborate in this solution, which excludes the possibility of the Ad_E-mechanism for this reaction. The data obtained enable to propose another possibility: the reagent is the acetylfluoride acylated by the complex $CH_3CN \cdot BF_3$ as it is shown on the Figure 1. The acylating properties of the similar complexes ($RCN \cdot BX_3$, X=Cl, Br) were earlier reported [13, 14].

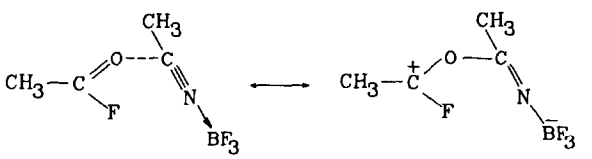


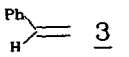
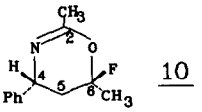
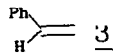
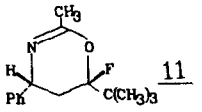
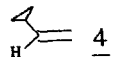
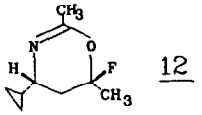
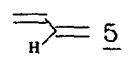
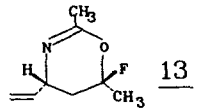
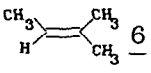
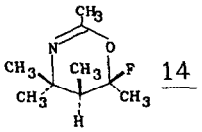
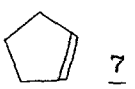
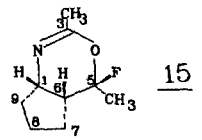
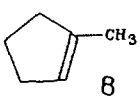
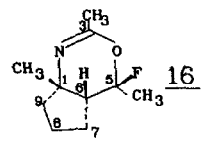
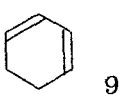
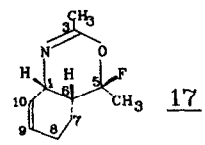
Fig 1 The proposed structure of the reagent

The stereochemistry of acylamidation.

The results of the stereochemistry investigation are summarized in Table 2.

The structure of the fluorooxazines 10-14 was determined by NMR spectroscopy using the values of coupling constants $^3J_{HF}$ and $^3J_{HH}$ given in Table 3. The great distinctions in the values of coupling constants $^3J_{H^A F}$ and $^3J_{H^B F}$ (see Figure 2) enable the assignment of the protons H^A and H^B and the determination of the relative position of H^A, H^B and F atoms [13]. Further, the comparison of the values $^3J_{H^A H^C}$ and $^3J_{H^B H^C}$ gives the relative position of the protons H^A, H^B and H^C. Thus, the configuration of the fluorooxazines 10-13 is adequately determined – the radicals in positions 4 and 6 are cis-disposed. The fluoroxazine 11 obtained from pivaloyl tetrafluoroborate and acetonitrile has the same configuration. The structure of fluorooxazine 14 is apparent from the value $^3J_{H^A F}$ - the methyl radicals in positions 5 and 6 are trans-disposed.

Table 2. The structure of fluorooxazines obtained by acylamidation reaction.

Substrate	t, °C	Product	Yield ,%
 3	0	 10	62
 3	0	 11	52
 4	−10	 12	35
 5	−10	 13	33
 6	0	 14	57
 7	0	 15	48[a]
 8	0	 16	66[a]
 9	−20	 17	25[b]

[a] About 20% of corresponding 3-acetylcyclopentene was separated

[b] Yield is low due to the polymerisation of the product.

The structure assignment for the compound **16** was previously described [3]. The configurations of the compounds **15**, **17** were determined on the basis of the values $^{3}J_{H^1H^6}$ (7.2 and 5.4 Hz respectively) [15] and $^{3}J_{C^7F}$ (8.7 and 8.2 Hz) [16].

Thus, in all the cases investigated the stereospecifity of acylamidation is observed. We could not detect the presence of more than 2% of any other isomers in the reaction mixtures by means of NMR and chromato-mass spectrometry.

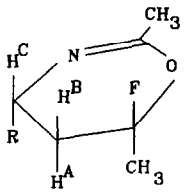


Fig 2 The configuration of the compounds **10**–**14**

Table 3. Chemical shifts (δ, ppm) and the characteristic coupling constants (J, Hz) in compounds **10**-**14**.

Compound	δH^A	δH^B	δH^C	$^{2}J_{H^AH^B}$	$^{3}J_{H^AH^C}$	$^{3}J_{H^AF}$	$^{3}J_{H^BH^C}$	$^{3}J_{H^BF}$
10	1.27	2.07	4.83	-12.5	13.8	33.3	7.4	3.8
11	1.51	2.21	4.50	-12.6	13.8	34.3	4.1	4.1
12	0.99	1.69	4.10	-12.5	13.9	32.7	4.8	3.4
13	1.45	2.15	2.50	-12.6	13.4	35.0	5.1	4.0
14	-	-	-	-	-	30.3	-	-

The mechanism of acylamidation.

The strict stereospecifity of the acylamidation reaction and the NMR study of the reagent enable to propose for this reaction the mechanism of concerted [2π+2π+2π] cycloaddition. Figure 3 shows the intermediate complex proposed for the acylamidation reaction. It is clear that the interaction between the alkene and the acetylfluoride, acylated by $CH_3CN \cdot BF_3$ can lead directly to the corresponding 6-fluoro-5,6-dihydro-1,3-oxazine.

Moreover, the stereochemistry observed can be rationalized using the concept of "chair-like" intermediate complex for the concerted reactions [17-19].The preferential equatorial disposition of all three radicals (CH_3, R^1 and R^2) [17] in the intermediate complex shown on the Figure 3 leads to the observed stereochemistry of the reaction.

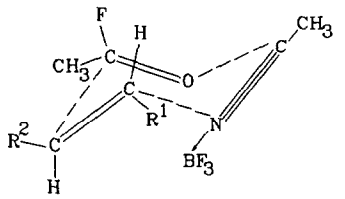


Fig 3 The transition state for the acylamidation reaction

Therefore, the acylamidation reaction is a new stereospecific concerted [2π+2π+2π] cycloaddition reaction which enables the synthesis of 6-fluoro-5,6-dihydro-1,3-oxazines, saturated and unsaturated β-amidoketones from the simple unsaturated hydrocarbons.

Acknoledments: The authors express their gratitude for Drs I.F.Lechsheva, A.V. Buevich, V.A.Chertkov and I.A.Bolkunov for the registration of high resolution NMR spectra.

EXPERIMENTAL

All solvents were dried and distilled over calcium hydride. IR spec tra were recorded by the UR-20 spectrofotometer. NMR spectra were obtained using Jeol FX-100, Varian VXR-300, Brucker AM-360 and Varian VXR-400 spectrometers. Chromato-mass experiments were performed on Finnigan MAT 112 S spectrometer.

General procedure for the synthesis of fluorooxasines.

The solution of 0.02 mole of acetylfluoride was saturated by gaseous BF_3 at -60°C. Then 0.06 mole of acetonitrile was added. The temperature was raised up to 0°C and 0.02 mole of corresponding alkene was added dropwise. The raction mixture was stirred for 0.5 h, and then was added to the mixture of ether and aqueous $NaHCO_3$. The organic layer was separated, the aqueous one was extracted with ether (2x100 ml). The solvent was evaporated and the residual oil was distilled in vacuo.

6-Fluoro-2,6-dimethyl-4-phenyl-5,6-dihydro-1,3-oxazine 10, yield 62%, b.p. 110°C (1mm Hg). IR (ν, cm^{-1}): 1690 (C=N). ^1H NMR (300 MHz, C_6D_6, δ ppm): 1.375 ddd (1H, $^3J_{HF}$ 33.3 Hz; $^2J_{HH}$ -12.5 Hz; $^3J_{HH}$ 13.8 Hz), 1.38 d (3H, CH_3, $^3J_{HF}$ 17.1 Hz), 2.07 ddd (1H, $^3J_{HF}$ 3.8 Hz, $^2J_{HH}$ -12.5 Hz, $^3J_{HH}$ 7.5 Hz), 2.01 s (3H, CH_3), 4.83 dm (1H, $^3J_{HH}$ 13.8 Hz), 7.2-7.4 m (5H, C_6H_5). ^{13}C NMR (25 MHz, $CDCl_3$, δ ppm): 153.40 d (C=N, $^3J_{CF}$ 2.0 Hz), 142.38, 127.59, 126.06, 125.67 (C_6H_5), 108.28 d (C^6, $^1J_{CF}$ 218.8 Hz), 51.03 d (C^4, $^3J_{CF}$ 3,7 Hz), 36.9 d (C^5, $^2J_{CF}$ 25.0 Hz), 24.28 d (CH_3, $^2J_{CF}$ 28.5 Hz), 20.23 (CH_3). Mass-spectrum (m/z): 207 (M^+).

6-Fluoro-2-methyl-4-phenyl-6-tret-butyl-5,6-dihydro-1,3-oxazine 11, yield 52%, b.p. 170-175°C (1 mm Hg). IR (ν, cm^{-1}): 1680 (C=N). ^1H NMR (400 MHz, CD_2Cl_2, δ ppm): 0.96 s (9H, $3CH_3$), 1.51 ddd (1H, $^3J_{HF}$ 34.26 Hz, $^2J_{HH}$ -12.6

Hz, $^{3}J_{HH}$ 13.8 Hz), 1.98 d (3H, CH_3, $^{5}J_{HH}$ 1.80 Hz), 2.21 ddd (1H, $^{3}J_{HF}$ 4.11 Hz, $^{3}J_{HH}$ 4.11 Hz), 4.50 ddq (1H, $^{3}J_{HH}$ 13.8, 4.11 Hz, $^{5}J_{HH}$ 1.80 Hz), 7.20-7.35 m (5H, C_6H_5). ^{13}C NMR (75 MHz, CD_2Cl_2, δ ppm): 156.03 (C=N), 144.06, 126.68, 127.17, 126.88 (C_6H_5), 52.43 d (C^4, $^{3}J_{CF}$ 5.3 Hz), 38.21 d ($C^{qu.}$, $^{2}J_{CF}$ 24.9 Hz), 32.78 d (C^5, $^{2}J_{CF}$ 26.2 Hz), 24.30 ($3CH_3$), 21.40 (CH_3). Mass-spectrum (m/z): 249 (M^+), 57 ($C_4H_9^+$).

6-Fluoro-2,6-dimethyl-4-cyclopropyl-5,6-dihydro-1,3-oxazine 12, yield 35%, b.p. 100°C (7 mm Hg). IR (ν, cm^{-1}): 1685 (C=N). ^{1}H NMR (360 MHz, CD_2Cl_2, δ ppm): 0.41 m, 0.50 m (5H of cyclopropane), 1.45 ddd (1H, $^{3}J_{HF}$ 35.1 Hz, $^{2}J_{HH}$ -12.3 Hz, $^{3}J_{HH}$ 13.4 Hz), 2.14 ddd (1H, $^{3}J_{HF}$ 4.0 Hz, $^{2}J_{HH}$ -12.3 Hz, $^{3}J_{HH}$ 5.1 Hz), 1.55 d (3H, CH_3, $^{3}J_{HF}$ 17.8 Hz), 1.90 s (3H, CH_3), 2.75 m (1H). Mass-spectrum (m/z): 171 (M^+).

6-Fluoro-2,6-dimethyl-4-vinyl-5,6-dihydro-1,3-oxazine 13,yield 33%, b.p. 74°C (7 mm Hg), n_D^{18} 1.4453. IR (ν, cm^{-1}): 1680 (C=N). ^{1}H NMR (300 MHz, C_6D_6, δ ppm): 1.00 ddd (1H, $^{3}J_{HF}$ 32.7 Hz, $^{2}J_{HH}$ -12.5 Hz, $^{3}J_{HH}$ 13.9 Hz), 1.22 d (3H, CH_3, $^{3}J_{CF}$ 18.0 Hz), 1.69 ddd (1H, $^{3}J_{HF}$ 3.4 Hz, $^{2}J_{HH}$ -12.5 Hz, $^{3}J_{HH}$ 4.8 Hz), 1.80 d (3H, CH_3, $^{5}J_{HH}$ 1.0 Hz), 4.09 dm (1H, $^{3}J_{HH}$ 13.9 Hz), 5.05 dt (1H, $^{2}J_{HH}$ 2.1 Hz, $^{3}J_{HH}$ 8.8 Hz), 5.24 dt (1H, $^{2}J_{HH}$ 2.1 Hz, $^{3}J_{HH}$ 15.0 Hz), 5.86 ddd (1H, $^{3}J_{HH}$ 15.0, 8.8, 4.9 Hz). ^{13}C NMR (25 MHz, $CDCl_3$, δ ppm): 153.92 (C=N), 139.03 (CH=), 114.67 (CH_2=), 109.84 d (C-F, $^{1}J_{CF}$ 236.0 Hz), 50.11 d (C^4, $^{3}J_{CF}$ 3.1 Hz), 35.24 d (C^5, $^{2}J_{CF}$ 24.8 Hz), 25.07 d (CH_3, $^{2}J_{CF}$ 28.8 Hz), 20.86 (CH_3). Mass-spectrum (m/z): 167 (M^+).

6-Fluoro-2,4,4,5,6-pentamethyl-5,6-dihydro-1,3-oxazine 14,yield 57%, b.p. 61°C (7 mm Hg), n_D^{21} 1.4317. IR (ν, cm^{-1}) 1680 (C=N). ^{1}H NMR (360 MHz, CD_2Cl_2, δ ppm): 1.03 d (3H, 4-CH_3, $^{5}J_{HF}$ 1.1 Hz), 1.11 (3H, 5-CH_3, $^{3}J_{HH}$ 9.8 Hz), 1,21 s (3H, 4-CH_3), 1,44 d (3H, 6-CH_3, $^{3}J_{HF}$ 18.0 Hz), 1.60 dq (1H, H^5, $^{3}J_{HF}$ 30.4 Hz, $^{3}J_{HH}$ 9.8 Hz), 1.78 s (3H, 2-CH_3). ^{13}C NMR (25 MHz, $CDCl_3$, δ ppm): 150.29 d (C=N, $^{3}J_{CF}$ 1.4 Hz), 106.42 d (C-F, $^{1}J_{CF}$ 214.2 Hz), 51.92 (C^4), 41.98 d (C^5, $^{2}J_{CF}$ 23.4 Hz), 31.04 (4-CH_3), 24.39 (2-CH_3), 22.72 d (4-CH_3, $^{4}J_{CF}$ 6.9 Hz), 21.49 d (6-CH_3, $^{2}J_{CF}$ 22.7 Hz), 9.88 d (5-CH_3, $^{3}J_{CF}$ 1.5 Hz). Mass-spectrum (m/z): 173 (M^+).

Cis-5-fluoro-3,5-dimethyl-2-aza-4-oxa-cis-bicyclo[4.3.0]non-2-ene 15, yield 48%, b.p. 70°C (7 mm Hg), $n^{20}{}_D$1.4490. IR (ν, cm^{-1}): 1690 (C=N). ^{1}H NMR (360 MHz, $CDCl_3$, δ ppm): 1.31 m (1H of cyclopentane), 1.54 d (3H, CH_3, $^{3}J_{HF}$ 17.9 Hz), 1.6-2.9 m (5H of cyclopentane), 2.22 dddd (1H, H^6, $^{3}J_{HF}$ 4.8 Hz, $^{3}J_{HH}$ 10.3, 5.4, 7.3 Hz), 1.96 s (3H,CH_3), 3.81 m (1H, H^1). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 153.89 (C=N), 111.217 d (C^5, $^{1}J_{CF}$ 216.2 Hz), 54.64 (C^1), 42.71 d (C^6, $^{2}J_{CF}$ 24.8 Hz), 33.22 (C^9), 25.22 d (C^7, $^{3}J_{CF}$ 7.28 Hz), 24.11 d (CH_3, $^{2}J_{CF}$ 28.1 Hz), 23.36 (C^8), 21.04 (CH_3). Mass-spectrum (m/z): 171 (M^+).

Cis-5-fluoro-1,3,5-trimethyl-2-aza-4-oxa-cis-bicyclo[4.3.0]non-2-ene 16, yield 66%, the compound was earlier described [11].

Cis-5-fluoro-3,5-dimethyl-2-aza-4-oxa-cis-bicyclo[4.3.0]deca-2,9-diene 17, yield 25%, b.p. 95°C (7 mm Hg). IR (ν, cm^{-1}): 1690 (C=N). ^1H NMR (300 MHz, C_6D_6, δ ppm): 1.13 dddd (H^7), 1.25 dm (H^{7a}), 1.36 d (3H, CH_3, ^3JHF 18.7 Hz), 1.50-1.90 m (2H, H^8, H^{8a}), 2.11 m (1H, H^6, $^3J_{H^6H^1}$ 5.4 Hz, $^3J_{H^6H^9}$ 9.8 Hz, $^5J_{HH}$ 2.0 Hz [20]), 4.23 m (1H, H^1), 5.69 m (1H, H^9), 6.13 dddd (1H, H^{10}). ^{13}C NMR (75 MHz, C_6D_6, δ ppm): 151.57 (C^3), 128.16 (C^{10}), 127.92 (C^9), 111.74 d (C^5, $^1J_{CF}$ 216.7 Hz), 47.61 d (C^1, $^3J_{CF}$ 3.3 Hz), 37.42 d (C^6, $^2J_{CF}$ 25.4 Hz), 25.09 (CH_3), 22.81 d (CH_3, $^2J_{CF}$ 27.8 Hz), 20.80 (C^8), 19.60 d (C^7, $^3J_{CF}$ 8.18 Hz). Mass-spectrum (m/z): 183 (M^+).

REFERENCES AND NOTES:

1. Shastin, A.V.; Balenkova, E.S. *Zh.Org.Khim.*,1984, 20, 1357.
2. Gridnev,I.D.; Shastin, A.V.; Balenkova, E.S. *Zh.Org.Khim.*, 23, 1546.
3. Gridnev, I.D.; Buevich, A.V.; Sergeyev, N.M.; Balenkova, E.S. *Tetrahedron Letts.* 1989, 30, 1987.
4. Gridnev, I.D.;Balenkova, E.S. *Zh.Org.Khim.*, 1988, 24, 1605.
5. Al-Talib, M.; Tashtoush, H. *Org.Prep.Proceed.Int.* 1990,22, 1.
6. Hoffman, H.M.R.; Tsushima, T. *J.Am.Chem.Soc.*, 1977, 99, 6008.
7. Lubinskaya, O.V; Smit, W.A.; Shashkov, A.S.; Chertkov, V.A.; Kanichshev, M.I.; Kucherov, V.F. *Izv.Acad.Nauk SSSR, Ser. Khim.* 1978, 2, 397.
8. Kanischev, M.I.; Schegolev, A.A.; Smit, W.A.; Caple, R.; Kelner, M.I. *J.Am.Chem.Soc.*, 1979, 101, 5660.
9. Olah, G.A.; Kuhn, S.J.; Tolgyesi W.S.; Baker E.B. *J.Am.Chem.Soc.*, 1962, 84, 2733.
10. Olah, G.A.; White, A.M. *J.Am.Chem.Soc.*, 1969, 91, 5801.
11. Levi, G.C.; Nelson, G.L. "Carbon-13 NMR for organic chemists", Wiley-Interscience, N.Y. 1972.
12. Tadashi, T.; Fraenkel, G. *J.Am.Chem.Soc.*, 1969, 91, 5005.
13. Hamana, H.; Sugasawa, Ts. *Chem.Letts.*, 1985, 5, 571.
14. Hamana, H.; Sugusawa, Ts. *Chem.Letts.*, 1985, 5, 575.
15. Melnick, M.J.; Weinreb S.M. *J.Org.Chem*, 1988, 53, 850.
16. Subbotin, O.A.; Sergeyev, N.M. *J.Am.Chem.Soc.*, 1975, 97, 1080.
17. Masamune, S.; Ali, S.A.; Snitman, D.L.; Garvey, D.S. *Angew.Chem.*, 1980, 92, 573.
18. Heathcock, C.H.; White C.T. *J.Am.Chem.Soc.*, 1980, 102, 573.
19. Hoffman, R.W.; Sander, T. *Chem.Ber.*, 1990, 123, 145.
20. The values of coupling constants were obtained by double resonance.