Reactions of 1,3,3-trimethyl-3,4-dihydroisoquinolines with polyhaloalkanonitriles*

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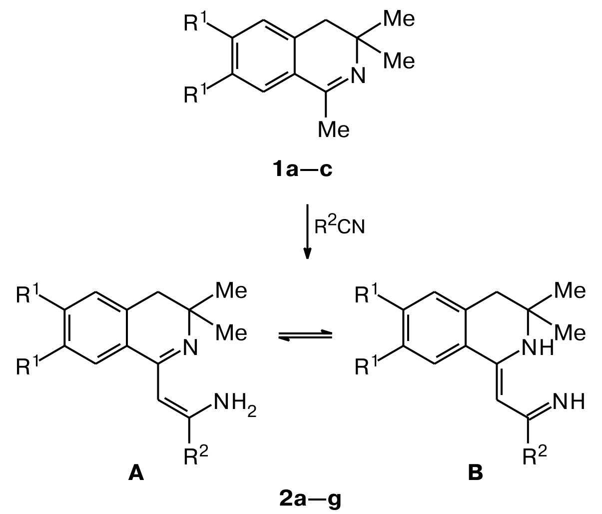
The reactions of 1,3,3-trimethyl-3,4-dihydroisoquinolines with halogenated nitriles afford β-aminovinylimines, which undergo acid hydrolysis to form 1-(polyhaloacylmethylene)-3,3-dimethyl-3,4-dihydroisoquinolines.

Key words: 1,3,3-trimethyl-3,4-dihydroisoquinolines, halogenated nitriles, β-aminovinylimines, 1-(polyhaloacylmethylene)-3,3-dimethyl-3,4-dihydroisoquinolines.

β-Diimines exist mainly in the form of β-aminovinylimines (enaminoimines, 4-amino-1-azabutadienes) and are valuable substrates for syntheses of various nitrogen-containing heterocyclic compounds.[1—6] They can be synthesized by the reactions of ketimines with aromatic and aliphatic nitriles in the presence of $AlCl_3$,[7] addition of zinc derivatives of Schiff's bases to nitriles,[8] and treatment of 1-aryl-4,6-disubstituted pyrimidin-2(1*H*)-ones with alkaline metal alkoxides.[9] Fluorine-containing enaminoimines have been first synthesized by the condensation of methylketimines with fluorinated imidoyl chlorides in the presence of lithium diisopropylamide,[10] while the reactions of amines with partially fluorinated β-diketones and of methylketimines with nitriles activated by polyfluoroalkyl groups do not afford R^F-containing β-aminovinylimines. In the first case, regioisomeric β-aminovinyl ketones[11] are formed, depending on the structures of amine and β-diketone. In the second case, the reaction affords 2,4-bis(polyfluoroalkyl)pyrimidines, which are the products of the reaction of primarily formed enaminoimines with excess R^FCN.[12] The reactions of trifluoroacetonitrile with enamines occur similarly.[13] Therefore, it was of interest to study the reactions of polyhaloalkanonitriles with 1,3,3-trimethyl-3,4-dihydroisoquinolines **1a—c**, which can react with electrophilic substrates[14,15] as *C*-nucleophiles or 1,3-*C*,*N*-dinucleophiles[15—17] due to imino-enamine tautomerism of the methylketimine fragment. Taking into account structural features of these compounds, one could expect that the reaction would stop at the step of nucleophilic addition to the activated nitrile group of halonitriles and would afford new 3,4-dihydroisoquinoline derivatives with the polyhaloalkyl-containing enaminoimine system.

Results and Discussion

It has previously[15] been shown that 1,3,3-trimethyl-3,4-dihydroisoquinolines **1a,c** readily add to the carbonyl group of hexafluoroacetone and methyl trifluoropyruvate due to the highly reactive enamine moiety. We found that the reactions of dihydroisoquinolines **1a—c** with excess CCl_3CN without a solvent occur at ~20 °C for 5 h, whereas the reactions with R^FCN in a chloroform solution at the same temperature in a sealed ampule occur for 3 h. In



1	R1	2	R1	R2	2	R1	R2
a	H	a	H	CCl_3	e	MeO	$(CF_2)_2H$
b	Me	b	H	CF_3	f	MeO	CF_3
c	MeO	c	H	$(CF_2)_2H$	g	MeO	CCl_3
		d	Me	CCl_3			

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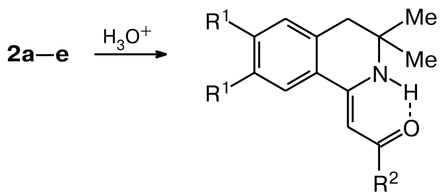
this case, due to the methyl group in position 1, isoquinolines **1a—c** add to the nitrile group of halonitriles and yield compounds **2a—g** in 52—81% yields. Compounds **2a—g** contain the labile prototropic enaminoimine system, which can be used for further transformations in the dihydroisoquinoline series, including syntheses of substances with potential biological activity.[18]

The ^{1}H NMR spectra of products **2** in $CDCl_3$ solutions (Table 1) contain signals of aromatic protons, singlets of the *gem*-dimethyl group (δ 1.27—1.31), methylene group (δ 2.72—2.84), and ethylenic protons (δ 5.39—5.90), and a broadened two-proton singlet of the amino group at δ 8.9—9.6 (when CD_3CO_2D is added, this signal disappears, and the intensity of the signal of the ethylenic proton decreases to 0.3 H), which indicates the absence of the β-diimine moiety and presence of compounds **2** as an equilibrium mixture of two tautomeric enaminoimine moieties **A** and **B**. It is known[12,19] that the replacement of $CDCl_3$ by DMSO-d$_6$ in such mobile tautomeric systems favors the shift of the prototropic equilibrium toward tautomer **B** with the geminal arrangement of the imino group and polyhaloalkyl substituent. In our case, this conclusion is indicated by the value of the $^3J_{H,F}$ constant of the $(CF_2)_2H$ group in compounds **2c,e**. In a DMSO-d$_6$ solution, this constant is 5.5—5.6 Hz, which is characteristic of the HCF_2CF_2—C(C)=N fragment.[19,20] In a solution of compounds **2c,e** in $CDCl_3$, the $^3J_{H,F}$ value decreases to 3.9—4.0 Hz, and the triplet of the terminal proton of the $(CF_2)_2H$ group appears at 5.88—5.89 ppm, which can indirectly confirm that in this solvent the equilibrium shifts toward tautomer **A** with the HCF_2CF_2—C(N)=C fragment for which the values $^3J_{H,F}$ = 2.5—3.8 Hz and δ_H = 5.85—6.05 are given.[19]

As has already been mentioned, the reactions of R^FCN with imines obtained from aryl methyl ketones and isopropylamine do not stop at the step of enaminoimine formation but lead to the formation of 2,4-bis(polyfluoroalkyl)pyrimidines.[12] In the case of compounds **2**, no similar heterocyclization was observed even with an increase in excess R^FCN and duration and temperature of the reaction.

The acid hydrolysis of enaminoimines **2a—e**, which was carried out in aqueous THF in the presence of a catalytic amount of concentrated H_2SO_4 at ~20 °C for 3 min, affords polyhaloacyl derivatives **3a—e** in high yields (65—85%). The ^{1}H NMR spectra of these compounds in $CDCl_3$ solutions exhibit singlets of the *gem*-dimethyl group (δ 1.36—1.37), methylene group (δ 2.84—2.92), and ethylenic proton (δ 5.91—6.34) and a broadened singlet of the NH proton involved in intramolecular hydrogen bond formation (δ 11.1—11.6)[21] (see Table 1). The ketoenamine (not iminoenol) structures of the hydrolysis products follow from the consideration of the values of the $^3J_{H,F}$ constant and chemical shift of the terminal proton of the $(CF_2)_2H$ group in compounds **3c,e**, which are equal to 5.6 Hz and 6.18—6.20 ppm, respectively. These values agree well with the data for β-aminovinyl ketones with the $(CF_2)_2H$ group at the carbonyl carbon atom.[19] The IR spectra of compounds **3** contain absorption bands at 1620—1530 cm^{-1}, which are characteristic of the aminoenone system[22] (see Table 1).



3a—e

	R^1	R^2		R^1	R^2		R^1	R^2
a	H	CCl_3	**c**	H	$(CF_2)_2H$	**e**	MeO	$(CF_2)_2H$
b	H	CF_3	**d**	Me	CCl_3			

Thus, the condensation of polyhaloalkylnitriles with 1,3,3-trimethyl-3,4-dihydroisoquinolines is a simple and convenient method for syntheses of new CCl_3- and R^F-containing β-aminovinylimines and β-aminovinyl ketones of the dihydroisoquinoline series.

Experimental

IR spectra were recorded on an IKS-29 in Nujol. ^{1}H NMR spectra were obtained on a Bruker DRX-400 spectrometer in $CDCl_3$ or DMSO-d$_6$ with a working frequency of 400.13 MHz using Me_4Si as internal standard. The starting 1,3,3-trimethyl-3,4-dihydroisoquinolines **1a—c** were synthesized according to a previously described procedure.[23] Trifluoroacetonitrile and 2,2,3,3-tetrafluoropropionitrile were synthesized by heating of the corresponding amides with P_2O_5. The yields, melting points, and data of elemental analysis and ^{1}H NMR and IR spectra for the compounds synthesized are presented in Table 1.

1-(3,3-Dimethyl-3,4-dihydroisoquinolin-1-yl)-3,3,3-trichloroprop-1-ene-2-amine (2a). A mixture of dihydroisoquinoline **1a** (0.52 g, 3.0 mmol) and CCl_3CN (1.30 g, 9.0 mmol) was stirred and left to stay for 5 h at ~20 °C. Then the reaction mixture was triturated with cold EtOH (5 mL), and the crystalline product was filtered off, washed with EtOH (3 mL), dried, and recrystallized from hexane. Compounds **2d,g** were synthesized according to a similar procedure.

1-(3,3-Dimethyl-3,4-dihydroisoquinolin-1-yl)-3,3,3-trifluoroprop-1-ene-2-amine (2b). Dihydroisoquinoline **1a** (0.36 g, 2.1 mmol) and $CHCl_3$ (5 mL) were placed in an ampule, and CF_3CN, obtained by heating of CF_3CONH_2 (3.0 g) with P_2O_5 (5 g) on cooling to –95 °C, was condensed into the ampule. The sealed ampule was left for 3 h at ~20 °C. Then chloroform and nitrile excess were evaporated, the residue was mixed with cold 70% EtOH (5 mL), and the crystalline product was filtered off and recrystallized from hexane. Compounds **2c,e,f** were synthesized according to a similar procedure.

Table 1. Physicochemical characteristics and element composition of compounds **2a—g** and **3a—e**

Compound	Yield (%)	M.p./°C	Found/Calculated (%)			Molecular formula	^{1}H NMR (CDCl$_3$, δ, *J*/Hz)	IR, ν/cm^{-1}
			C	H	N			
2a	81	124—125	53.17 52.94	4.67 4.76	8.88 8.82	$C_{14}H_{15}Cl_3N_2$	1.31 (s, 6 H, 2 Me); 2.84 (s, 2 H, CH$_2$); 5.90 (s, 1 H, =CH); 7.17 (dd, 1 H, H(5), J_o = 7.3, J_m = 0.8); 7.30 (td, 1 H, H(7), J_o = 7.5, J_m = 1.4); 7.36 (td, 1 H, H(6), J_o = 7.4, J_m = 1.4); 7.72 (d, 1 H, H(8), J_o = 7.6); 9.60 (br.s, 2 H, NH$_2$)	3350, 1610, 1565, 1550
2b	65	59—60	62.77 62.68	5.65 5.64	10.35 10.44	$C_{14}H_{15}F_3N_2$	1.28 (s, 6 H, 2 Me); 2.80 (s, 2 H, CH$_2$); 5.61 (s, 1 H, =CH); 7.16 (d, 1 H, H(5), J_o = 7.3); 7.29 (td, 1 H, H(7), J_o = 7.6, J_m = 1.3); 7.35 (td, 1 H, H(6), J_o = 7.4, J_m = 1.3); 7.64 (d, 1 H, H(8), J_o = 7.5); 8.90 (br.s, 2 H, NH$_2$)	3510, 3345, 1655, 1630, 1570
2c	80	72—73	59.88 60.00	5.49 5.37	9.34 9.33	$C_{15}H_{16}F_4N_2$	CDCl$_3$: 1.27 (s, 6 H, 2 Me); 2.79 (s, 2 H, CH$_2$); 5.53 (s, 1 H, =CH); 5.88 (tt, 1 H, CF$_2$CF$_2$H, $^2J_{H,F}$ = 53.6, $^3J_{H,F}$ = 3.9); 7.15 (d, 1 H, H(5), J_o = 7.3); 7.28 (td, 1 H, H(7), J_o = 7.6, J_m = 1.2); 7.35 (td, 1 H, H(6), J_o = 7.3, J_m = 1.2); 7.61 (d, 1 H, H(8), J_o = 7.6); 8.90 (br.s, 2 H, NH$_2$). DMSO-d$_6$: 1.17 (s, 6 H, 2 Me); 2.72 (s, 2 H, CH$_2$); 5.56 (s, 1 H, =CH); 6.74 (tt, 1 H, CF$_2$CF$_2$H, $^2J_{H,F}$ = 52.1, $^3J_{H,F}$ = 5.5); 7.23 (d, 1 H, H(5), J_o = 7.5); 7.33 (td, 1 H, H(7), J_o = 7.5, J_m = 1.3); 7.40 (td, 1 H, H(6), J_o = 7.4, J_m = 1.2); 7.65 (d, 1 H, H(8), J_o = 7.7); 8.90 (br.s, 2 H, NH$_2$)	3495, 3345, 1645, 1620, 1555
2d	83	138—139	55.61 55.59	5.53 5.54	7.93 8.10	$C_{16}H_{19}Cl_3N_2$	1.30 (s, 6 H, 2 Me); 2.28, 2.30 (both s, 3 H each, Me); 2.76 (s, 2 H, CH$_2$); 5.85 (s, 1 H, =CH); 6.93, 7.46 (both s, 1 H each, H(5), H(8)); 9.60 (br.s, 2 H, NH$_2$)	3330, 1615, 1570, 1560
2e	71	141—143	56.80 56.66	5.64 5.59	7.64 7.77	$C_{17}H_{20}F_4N_2O_2$	CDCl$_3$: 1.28 (s, 6 H, 2 Me); 2.72 (s, 2 H, CH$_2$); 3.92, 3.93 (both s, 3 H each, MeO); 5.39 (s, 1 H, =CH); 5.88 (tt, 1 H, CF$_2$CF$_2$H, $^2J_{H,F}$ = 53.6, $^3J_{H,F}$ = 4.0); 6.64, 7.09 (both s, 1 H each, H(5), H(8)); 9.00 (br.s, 2 H, NH$_2$). DMSO-d$_6$: 1.16 (s, 6 H, 2 Me); 2.64 (s, 2 H, CH$_2$); 3.81, 3.82 (both s, 3 H each, MeO); 5.49 (s, 1 H, =CH); 6.76 (tt, 1 H, CF$_2$CF$_2$H, $^2J_{H,F}$ = 52.1, $^3J_{H,F}$ = 5.6); 6.85, 7.13 (both s, 1 H each, H(5), H(8)); 9.0 (br.s, 2 H, NH$_2$)	3460, 3330, 1660, 1625, 1610, 1600, 1590, 1540
2f	64	155—156	58.27 58.53	5.78 5.83	8.44 8.53	$C_{16}H_{19}F_3N_2O_2$	1.29 (s, 6 H, 2 Me); 2.73 (s, 2 H, CH$_2$); 3.92, 3.94 (both s, 3 H each, MeO); 5.45 (s, 1 H, =CH); 6.64, 7.10 (both s, 1 H each, H(5), H(8)); 9.00 (br.s, 2 H, NH$_2$)	3400, 1660, 1620, 1580
2g	52	173—175	51.05 50.88	5.05 5.07	7.32 7.42	$C_{16}H_{19}Cl_3N_2O_2$	1.31 (s, 6 H, 2 Me); 2.76 (s, 2 H, CH$_2$); 3.92, 3.94 (both s, 3 H each, MeO); 5.75 (s, 1 H, =CH); 6.64, 7.17 (both s, 1 H each, H(5), H(8)); 9.60 (br.s, 2 H, NH$_2$)	3320, 1625, 1610, 1580, 1560

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)			Molecular formula	^{1}H NMR (CDCl$_3$, δ, *J*/Hz)	IR, ν/cm^{-1}
			C	H	N			
3a	82	180—181	52.75 52.77	4.35 4.43	4.36 4.40	$C_{14}H_{14}Cl_3NO$	1.37 (s, 6 H, 2 Me); 2.92 (s, 2 H, CH$_2$); 6.34 (s, 1 H, =CH); 7.23 (d, 1 H, H(5), J_o = 7.4); 7.37 (t, 1 H, H(7), J_o = 7.2); 7.48 (td, 1 H, H(6), J_o = 7.5, J_m = 1.2); 7.78 (d, 1 H, H(8), J_o = 7.7); 11.10 (br.s, 1 H, NH)	1615, 1600, 1565, 1530
3b	80	58—59	62.24 62.45	5.47 5.24	4.96 5.20	$C_{14}H_{14}F_3NO$	1.37 (s, 6 H, 2 Me); 2.92 (s, 2 H, CH$_2$); 5.94 (s, 1 H, =CH); 7.24 (s, 1 H, H(5), J_o = 7.5); 7.37 (t, 1 H, H(7), J_o = 7.6); 7.49 (td, 1 H, H(6), J_o = 7.5, J_m = 1.2); 7.75 (d, 1 H, H(8), J_o = 7.7); 11.60 (br.s, 1 H, NH)	1620, 1600, 1570, 1530
3c	80	73—74	59.54 59.80	5.00 5.02	4.58 4.65	$C_{15}H_{15}F_4NO$	1.36 (s, 6 H, 2 Me); 2.92 (s, 2 H, CH$_2$); 6.05 (s, 1 H, =CH); 6.18 (tt, 1 H, CF$_2$CF$_2$H, $^2J_{H,F}$ = 53.3, $^3J_{H,F}$ = 5.6); 7.23 (dd, 1 H, H(5), J_o = 7.5, J_m = 0.6); 7.36 (td, 1 H, H(7), J_o = 7.7, J_m = 1.2); 7.49 (td, 1 H, H(6), J_o = 7.5, J_m = 1.2); 7.77 (d, 1 H, H(8), J_o = 7.7); 11.6 (br.s, 1 H, NH)	1620, 1605, 1590, 1570, 1530
3d	85	114—115	55.47 55.43	5.22 5.23	3.94 4.04	$C_{16}H_{18}Cl_3NO$	1.35 (s, 6 H, 2 Me); 2.31, 2.32 (both s, 3 H each, Me); 2.83 (s, 2 H, CH$_2$); 6.30 (s, 1 H, =CH); 6.99, 7.50 (both s, 1 H each, H(5), H(8)); 11.10 (br.s, 1 H, NH)	1620, 1600, 1570, 1530
3e	65	99—100	56.50 56.51	5.43 5.30	3.59 3.88	$C_{17}H_{19}F_4NO_3$	1.36 (s, 6 H, 2 Me); 2.84 (s, 2 H, CH$_2$); 3.94, 3.95 (both s, 3 H each, MeO); 5.91 (s, 1 H, =CH); 6.20 (tt, 1 H, CF$_2$CF$_2$H, $^2J_{H,F}$ = 53.3, $^3J_{H,F}$ = 5.6); 6.68, 7.17 (both s, 1 H each, H(5), H(8)); 11.6 (br.s, 1 H, NH)	1615, 1600, 1565, 1540

3-[3,3-Dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene]-1,1,1-trichloroacetone (3a). Enaminoimine **2a** (130 mg, 0.41 mmol) and concentrated H_2SO_4 (1 drop) were added to a THF—H_2O (1 : 1) mixture (1 mL). After stirring for 3 min at ~20 °C, the reaction mixture was diluted with water (5 mL), and the crystallized product was filtered off, washed with water, dried, and recrystallized from hexane. Compounds **3b—e** were synthesized according to a similar procedure.

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