Synthesis of Novel 5,6-Dihydropyrrolo[2,1-*a*]isoquinolines *via* Grob Reaction between (*E*)-1,1,1-Trifluoro-3-nitro-2-butene and 3,4-Dihydroisoquinolines

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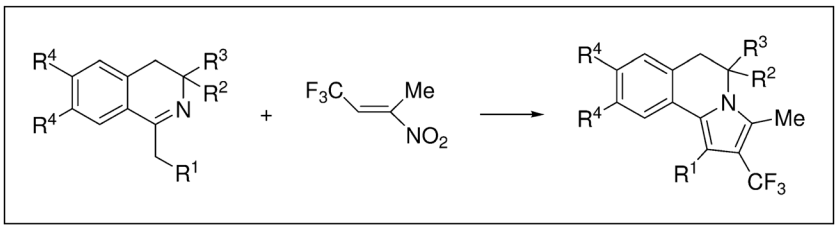
Received December 29, 2010
DOI 10.1002/jhet.881
View this article online at wileyonlinelibrary.com.



Uncatalyzed cycloaddition of 3,4-dihydroisoquinolines to (*E*)-1,1,1-trifluoro-3-nitro-2-butene *via* Grob reaction provide a simple one-step route to the 5,6-dihydropyrrolo[2,1-*a*]isoquinolines, which represent the basic structural framework of the antitumor active alkaloid crispine.

J. Heterocyclic Chem., **49**, 856 (2012).

INTRODUCTION

In the last decades, considerable interest has been devoted to the synthesis of partially fluorinated heterocycles, many of which have used as agrochemicals and drugs [1]. However, reports on the use of polyfluoroalkylated nitroalkenes as substrates for organic synthesis are very scarce [2], although conjugated nitroolefins are versatile intermediates in organic synthesis. The convertibility of the nitro group into a variety of functional groups such as carbonyl (Nef reaction), oxime, hydroxylamine, amine, and hydrogen (*via* desamination reaction) enhances the usefulness of the trihalomethylated nitroolefins in synthetic organic chemistry [3]. In continuation of our studies on the chemical properties of CX_3-nitroalkenes (X = F and Cl), which turned out to be highly reactive substrates in the hetero-Diels–Alder reaction [4] and in reactions with some N-, O-, and C-nucleophiles [5], we decided to investigate the reaction of (*E*)-1,1,1-trifluoro-3-nitro-2-butene (**1**) with 1-methyl- and 1-benzyl-3,4-dihydroisoquinolines **2**, which are capable of reacting with electrophilic substrates as C-nucleophiles or 1,3-C, N-dinucleophiles *via* the enamine tautomeric form [6]. Although much attention has been paid to the chemistry of 3,4-dihydroisoquinolines **2** [7], mainly due to their use as excellent building blocks for the preparation of a variety of complex heterocyclic compounds [6,8], there is only one report on the reaction of ethyl-(6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)acetate with 2-nitro-1-phenylpropene and 1-nitro-1,2-diphenylethene leading to the corresponding 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives [9]. Moreover, the reactivity of (*E*)-1,1,1-trifluoro-3-nitro-2-butene (**1**) is nearly unexplored, as only a handful of articles describing some reaction with N- and O-nucleophiles is present in the literature [10].

A reaction involving the addition of enaminoesters to nitroolefins followed by intramolecular displacement of the nitro group by the amino group to yield pyrroles was disclosed by Grob and coworkers [11]. This method makes use of easily prepared reagents and is particularly suitable for a combinatorial approach to the synthesis of substituted pyrroles [9,12]. As imines and 3,4-dihydroisoquinolines have been shown to react with β-nitrostyrene and 3-nitro-2*H*-chromenes to give the corresponding pyrroles [8,13], it was expected that Michael addition of **2a–f**, including dihydropapaverine (**2d**) and drotaverine (**2e**) (the hydrochloride of **2e** is a well-known spasmolytic agent widely used in medicine and known as No-Spa) to the nitrobutene **1**, followed by ring closure and aromatization (Grob reaction) could provide a direct route to 5,6-dihydropyrrolo[2,1-*a*] isoquinolines **3a–f** (Fig. 1).

This heterocyclic system constitutes the basic structural framework of the recently isolated two pyrrolo[2,1-*a*] isoquinoline alkaloids, crispine A and crispine B (Fig. 1), which inhibit the growth of some human cancer lines *in vitro* and show a significant cytotoxic activity [14]. As a result of this potent antitumor activity, various synthetic methods have been developed for the synthesis of crispine A, in both racemic [15] and enantiomerically pure form [16], and many analogs have

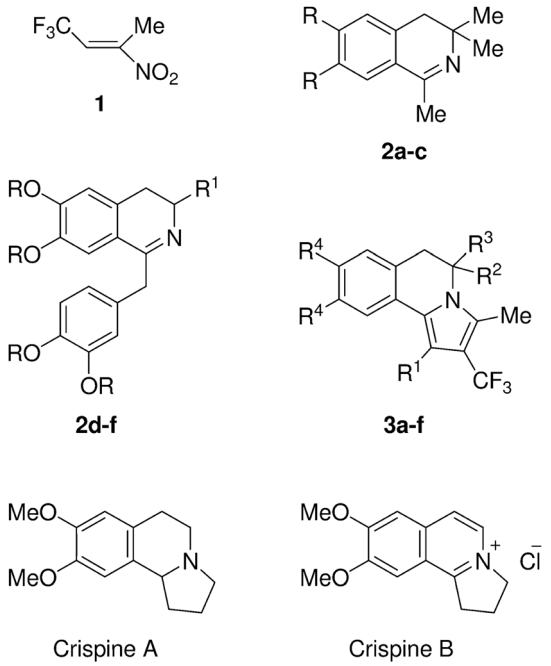


Figure 1. Starting materials for the synthesis of crispine derivatives.

been prepared [17]. In view of the unique biological properties displayed by crispines on one hand and by many fluorine-containing heterocycles [1] on the other hand, it was of interest to obtain a series of 5,6-dihydropyrrolo[2,1-*a*] isoquinolines **3** with an electron-withdrawing CF_3 group. In this context, we regarded (*E*)-1,1,1-trifluoro-3-nitro-2-butene (**1**) as a useful CF_3-containing building block.

RESULTS AND DISCUSSION

We found that nitroalkene **1** reacted with dihydroisoquinolines **2a–f** in isobutanol at 80°C for 0.5 h to produce pyrrolo[2,1-*a*]isoquinolines **3a–f** in 54–68% yields (method *A*). As compounds **2a–f**, especially **2d–f**, are prone to air oxidation, all operations should be performed in an inert atmosphere. The synthesis of **3a–e** has been also achieved in high yields (67–80%) by the reaction of **1** with **2a–e** in toluene at room temperature for 24 h (method *B*). Under these conditions, the Michael adducts **4** could not be isolated and underwent spontaneous cyclization to form the fused pyrrole ring (Scheme 1, Table 1). The double bond of **1** is so reactive that no catalyst was necessary. However, reactions of 1,1,1-trichloro-3-nitro-2-butene and 1-nitro-3,3,3-trichloro(trifluoro)propenes with 3,4-dihydroisoquinolines **3a**,**b** did not give the corresponding pyrrole derivatives and only resinification was observed even at room temperature.

In accordance with the proposed mechanism [11(b)], the Michael adduct **A** through intermediate **B** undergoes intramolecular displacement of the nitro group by the NH group; thus, affording pyrrolo[2,1-*a*]isoquinoline system **3** *via* elimination of water and hyponitrous acid $H_2N_2O_2$ (Scheme 1). Compound **3** can serve as a basis for the preparation of new physiologically active compounds. For example, taking into account that the pyrrole ring of **3** can easily be reduced by the catalytic chemoselective hydrogenation [15(b)], this is a simple method for preparing CF_3-substituted crispine derivatives.

The structures of **3a–f** were characterized by ^1H, ^{19}F, and ^{13}C NMR spectra and elemental analyses. For compounds **3d**,**e**, a characteristic feature of the ^1H and ^{19}F NMR spectra in $CDCl_3$ is the presence of quartet at δ 2.40–2.42 ppm for Me-3 group and quartet at δ 109.9 ppm (HFB) for CF_3 group with $^5J_{H,F}$ = 1.4 Hz. The ^{13}C NMR spectrum of **3d** exhibited a quartet ($^4J_{C,F}$ = 1.9 Hz) at 10.4 ppm due to the Me-3 group, indicating that the Me-3 and CF_3 groups were spatially close to each other. Finally, the structure of compound **3d** was confirmed by X-ray crystallographic analysis, which revealed that the aromatic group on the pyrrole is almost orthogonal to the rest of the relatively planar tricyclic system (Fig. 2). Keeping this fact in mind and in making the ^1H NMR assignments, we have assumed that the ring current of the phenyl ring attached at C-1 causes shielding of the proton at C-10 (δ 6.41–6.44 ppm for **3d–f** and 6.96 ppm for **3c**). Note that the ^1H NMR spectra of **3f** displayed broad signals for the aromatic protons of the 3,4-$(MeO)_2C_6H_3$ substituent and for one of the four MeO groups. This phenomenon may be attributed to the restricted rotation of the aryl moiety about the C1-C1′ bond leading to rotamer formation.

Interestingly, the reaction of 1,3,3,4,4,7-hexamethyl-3,4-dihydroisoquinoline (**2g**) with nitrobutene **1** in toluene

Scheme 1

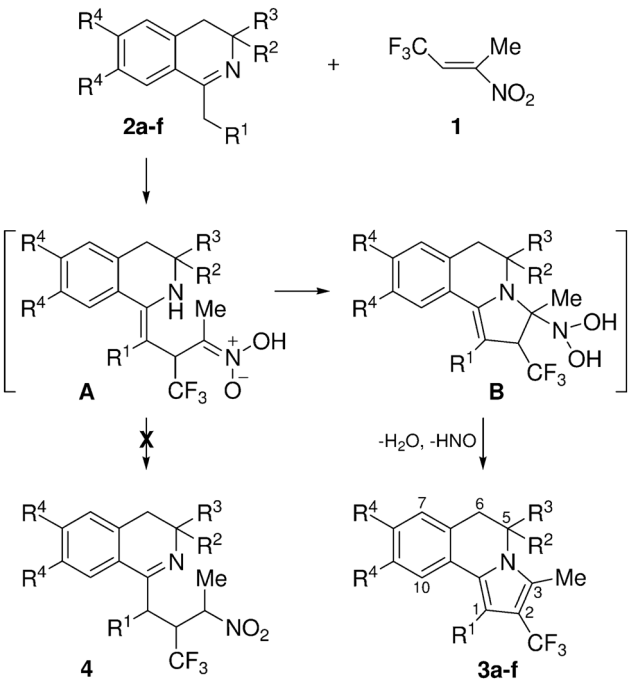


Table 1

Synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines **3a–f**.

Isoquinoline	R^1	R^2	R^3	R^4	Pyrrole	Yield (%) Method *A*	Yield (%) Method *B*
2a	H	Me	Me	H	**3a**	68	80
2b	H	Me	Me	Me	**3b**	56	71
2c	H	Me	Me	MeO	**3c**	55	73
2d	3,4-$(MeO)_2C_6H_3$	H	H	MeO	**3d**	60	67
2e	3,4-$(EtO)_2C_6H_3$	H	H	EtO	**3e**	65	68
2f	3,4-$(MeO)_2C_6H_3$	Me	H	MeO	**3f**	54	–

Method *A*: in isobutanol at 80°C, 0.5 h.
Method *B*: in toluene at 20°C, 12 h.

(method *B*) stopped at the initial stage to give the Michael adduct **4g** as a 53:44:3 mixture of two diastereomers and pyrrole **3g**, respectively, in 81% yield (^{19}F NMR spectrum). When this product was refluxed in isobutanol for 3 h, 5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**3g**) was obtained in 55% yield (Scheme 2).

In conclusion, the reaction of 1,1,1-trifluoro-3-nitro-2-butene with 3,4-dihydroisoquinolines provides a simple and convenient procedure for the preparation of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines, which may be considered as new tricyclic crispine derivatives. The resulting products are of considerable interest as precursors in the synthesis of other biologically and medicinally important organic materials.

EXPERIMENTAL

^1H (400 MHz), ^{19}F (376 MHz), and ^{13}C (126 MHz) NMR spectra were recorded on a Bruker DRX-400 and Bruker Avance II spectrometers in $CDCl_3$ with TMS and HFB as the internal standards. IR spectra were recorded on Perkin–Elmer Spectrum BX-II instrument as KBr disks. Elemental analyses were performed on a Carlo Erba EA 1108 automatic analyzer at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. Flash-chromatography was performed on silica gel (LSL 5/40, Lachema). The starting (*E*)-1,1,1-trifluoro-3-nitro-2-butene (**1**) and 1,3,3-trimethyl-3,4-dihydroisoquinolines **2a–c**,**g** were prepared according to the described procedures [10,18].

General procedure for the synthesis of 5,6-dihydropyrrolo [2,1-*a*]isoquinoline (3a–f). ***Method A.*** A mixture of the corresponding isoquinoline **2** (1.0 mmol) and nitrobutene **1** (0.16 g, 1.0 mmol) was heated at 80°C in isobutanol (2 mL) for 0.5 h. After that, the mixture was concentrated under reduced pressure, chromatographed on silica gel (eluted with chloroform), and the solid formed was recrystallized from isobutanol or hexane to give compound **3** as colorless powder.

Method B. A mixture of the corresponding isoquinoline **2** (1.0 mmol) and nitrobutene **1** (0.16 g, 1.0 mmol) was kept in toluene at ~20°C for 12 h. After that, the mixture was concentrated under reduced pressure, chromatographed on silica gel (eluted with chloroform), and the solid formed was recrystallized from isobutanol or hexane to give compound **3** as colorless powder.

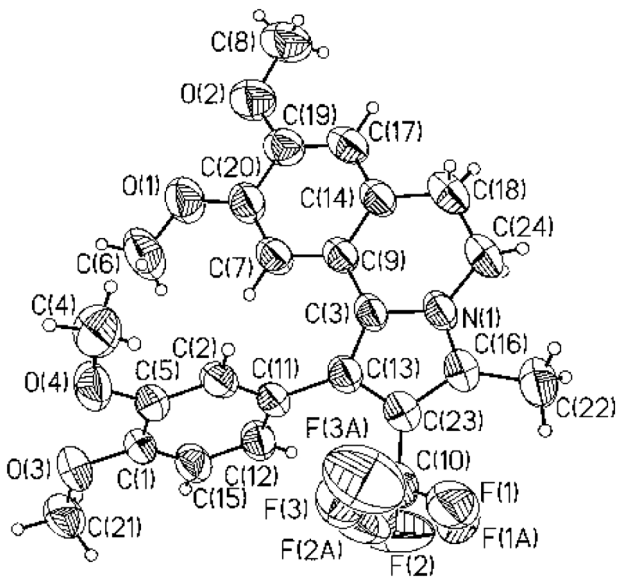
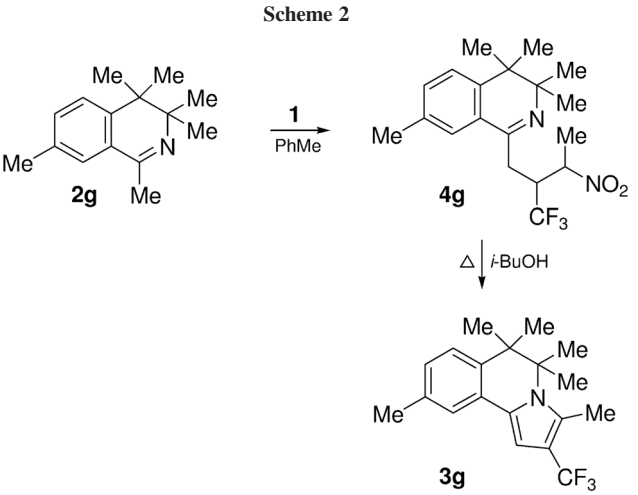


Figure 2. Molecular structure of **3d** (arbitrary numbering, thermal ellipsoids at 50% probability).

Scheme 2



3,5,5-Trimethyl-2-(trifluoromethyl)-5,6-dihydropyrrolo[2,1-a] isoquinoline (3a). Yield 68% (method *A*), 80% (method *B*), mp 69–70°C (hexane); IR (KBr) 1607, 1589, 1574, 1534, 1468, 1452, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 6H, 2 Me), 2.54 (s, 3H, Me), 2.97 (s, 2H, CH_2), 6.67 (s, 1H, H-1), 7.10–7.25 (m, 3H, H-7, H-8, H-9), 7.47 (d, 1H, H-10, J = 7.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ 106.3 (s, CF_3). Anal. Calcd for $C_{16}H_{16}F_3N$: C, 68.81; H, 5.77; N, 5.01. Found: C, 68.99; H, 5.80; N, 5.13.

3,5,5,8,9-Pentamethyl-2-(trifluoromethyl)-5,6-dihydropyrrolo [2,1-a]isoquinoline (3b). Yield 56% (method *A*), 71% (method *B*), mp 119−120°C (hexane); IR (KBr) 1596, 1571, 1535, 1452, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 6H, 2 Me), 2.24, 2.26, 2.52 (all s, 3H, Me), 2.90 (s, 2H, CH_2), 6.61 (s, 1H, H-1), 6.88 (s, 1H, H-7), 7.25 (s, 1H, H-10); ^{19}F NMR (376 MHz, $CDCl_3$): δ 106.4 (s, CF_3). Anal. Calcd for $C_{18}H_{20}F_3N$: C, 70.34; H, 6.56; N, 4.56. Found: C, 70.09; H, 6.70; N, 4.80.

8,9-Dimethoxy-3,5,5-trimethyl-2-(trifluoromethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (3c). Yield 55% (method *A*), 73% (method *B*), mp 104−105°C (hexane); IR (KBr) 1612, 1574, 1538, 1500, 1437 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 6H, 2 Me), 2.53 (s, 3H, Me-3), 2.90 (s, 2H, CH_2), 3.89 (s, 3H, MeO), 3.91 (s, 3H, MeO), 6.54 (s, 1H, H-1), 6.63 (s, 1H, H-7), 6.96 (s, 1H, H-10); ^{19}F NMR (376 MHz, $CDCl_3$): δ 106.4 (s, CF_3). Anal. Calcd for $C_{18}H_{20}F_3N$: C, 63.71; H, 5.94; N, 4.13. Found: C, 63.75; H, 6.09; N, 4.02.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3-methyl-2-(trifluoromethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (3d). Yield 60% (method *A*), 67% (method *B*), mp 122−123°C (isobutanol); IR (KBr) 1610, 1579, 1568, 1544, 1517, 1496, 1469 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (q, 3H, Me-3, $^5J_{H,F}$ = 1.4 Hz), 3.02 (t, 2H, CH_2, J = 6.5 Hz), 3.32, 2.83, 3.85, 3.90 (all s, 3H, Me), 3.97 (t, 2H, CH_2N, J = 6.5 Hz), 6.42 (s, 1H, H-10), 6.66 (s, 1H, H-7), 6.90−6.95 (m, 3H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ 109.9 (q, CF_3, $^5J_{F,H}$ = 1.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 10.4 (q, Me-3, $^4J_{C,F}$ = 1.9 Hz), 28.9, 40.9, 55.1, 55.87, 55.93, 56.0, 107.5, 110.7 (q, C-2, $^2J_{C,F}$ = 32.8 Hz), 110.9, 111.3, 114.2, 118.1 (q, C-1, $^3J_{C,F}$ = 2.2 Hz), 121.7, 123.2, 123.6, 124.9 (q, CF_3, $^1J_{C,F}$ = 268.0 Hz), 125.7, 127.4 (q, C-3, $^3J_{C,F}$ = 3.4 Hz), 128.0, 147.1, 147.5, 148.3, 148.9. Anal. Calcd for $C_{24}H_{24}F_3NO_4$: C, 64.42; H, 5.41; N, 3.13. Found: C, 64.51; H, 5.44; N, 3.08.

1-(3,4-Diethoxyphenyl)-8,9-diethoxy-3-methyl-2-(trifluoromethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (3e). Yield 65% (method *A*), 68% (method *B*), mp 137−138°C (isobutanol); IR (KBr) 1607, 1568, 1576, 1543, 1515, 1494, 1475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15, 1.39, 1.41, 1.46 (all t, 3H, Me, J = 7.0 Hz), 2.40 (q, 3H, Me-3, $^5J_{H,F}$ = 1.4 Hz), 2.98 (t, 2H, CH_2, J = 6.5 Hz), 3.53 (q, 2H, CH_2O, J = 7.0 Hz), 3.95 (t, 2H, CH_2N, J = 6.5 Hz), 4.05 (q, 4H, 2 CH_2O, J = 7.0 Hz), 4.12 (q, 2H, CH_2O, J = 7.0 Hz), 6.44 (s, 1H, H-10), 6.66 (s, 1H, H-7), 6.85−6.91 (m, 3H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ 109.9 (q, CF_3, $^5J_{F,H}$ = 1.4 Hz). Anal. Calcd for $C_{28}H_{32}F_3NO_4$: C, 66.79; H, 6.41; N, 2.78. Found: C, 66.70; H, 6.55; N, 2.76.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3,5-dimethyl-2-(trifluoromethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (3f). This compound was prepared from 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3-methyl-3,4-dihydroisoquinoline (0.39 g, 1.0 mmol) and nitrobutene **1** (0.16 g, 1.0 mmol) in the presence of Et_3N (0.12 g, 1.2 mmol) according to the method *A*. Yield 54%, mp 129−130°C (isobutanol); IR (KBr) 1610, 1564, 1543, 1517, 1494, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, 3H, Me-5, J = 6.6 Hz), 2.44 (s, 3H, Me-3), 2.71 (d, 1H, H-6a, J = 15.3 Hz), 3.35 (dd, 1H, H-6b, J = 15.3, 5.8 Hz), 3.33, 3.85, 3.89 (all s, 3H, MeO), 3.70–3.85 (br s, 3H, MeO), 4.56 (quint, 1H, H-5, J = 6.2 Hz), 6.41 (s, 1H, H-10), 6.65 (s, 1H, H-7), 6.72−7.12 (m, 3H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ 111.2 (s, CF_3). Anal. Calcd for $C_{25}H_{26}F_3NO_4$: C, 65.07; H, 5.68; N, 3.04. Found: C, 64.92; H, 5.50; N, 3.22.

3,5,5,6,6,9-Hexamethyl-2-(trifluoromethyl)-5,6-dihydropyrrolo [2,1-a]isoquinoline (3g). A mixture of isoquinoline **2g** (0.37 g, 1.0 mmol) and nitrobutene **1** (0.16 g, 1.0 mmol) was refluxed in isobutanol (2 mL) for 3 h. After that, the mixture was concentrated under reduced pressure and chromatographed on silica gel (eluted with chloroform). Yield 55%, colorless oil; IR (KBr) 1614, 1592, 1571, 1536, 1487, 1442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04, 1.16, 1.47, 1.84 (all br s, 12H, 4 Me), 2.34 (s, 3H, Me-9), 2.53 (s, 3H, Me-3), 6.64 (s, 1H, H-1), 6.99 (d, 1H, H-8, J = 7.9 Hz), 7.22 (d, 1H, H-7, J = 7.9 Hz), 7.30 (s, 1H, H-10); ^{19}F NMR (376 MHz, $CDCl_3$): δ 106.6 (s, CF_3). Anal. Calcd for $C_{19}H_{22}F_3N$: C, 71.01; H, 6.90; N, 4.36. Found: C, 69.85; H, 6.74; N, 4.43.

3,3,4,4,7-Pentamethyl-1-[3-nitro-2-(trifluoromethyl)butyl]-3,4-dihydroisoquinoline (4g). This compound was prepared from 1,3,3,4,4,7-hexamethyl-3,4-dihydroisoquinoline (**2g**) and nitrobutene **1** according to the method *B*. Yield 81%, yellow oil; IR (KBr) 1642, 1612, 1559, 1442, 1392, 1376, 1364 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ major isomer (55%): 1.0–1.2 (m, 12H, 4 Me), 1.62 (d, 3H, Me, J = 7.0 Hz), 2.38 (s, 3H, Me), 2.91 (dd, 1H, C*H*H, J = 17.2, 8.5 Hz), 3.16 (dd, 1H, CH*H*, J = 17.2, 2.9 Hz), 4.22−4.34 (m, 1H, *CH*Me), 4.98–5.06 (m, 1H, *CH*CF_3), 7.18−7.30 (m, 3H, Ar), minor isomer (45%): 1.0–1.2 (m, 12H, 4 Me), 1.65 (d, 3H, Me, J = 7.1 Hz), 2.38 (s, 3H, Me), 3.05 (d, 2H, CH_2, J = 5.9 Hz), 4.22−4.34 (m, 1H, *CH*Me), 4.87–4.95 (m, 1H, *CH*CF_3), 7.18−7.30 (m, 3H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ major isomer (53%): 94.6 (d, CF_3, $^3J_{F,H}$ = 9.6 Hz), minor isomer (44%): 93.2 (d, CF_3, $^3J_{F,H}$ = 9.2 Hz), **3g** (3%): 106.6 (s, CF_3).

Crystal data for 3d. Diffraction data were collected at 295 K on an Xcalibur 3 automatic single-crystal diffractometer (graphite-monochromated MoKα radiation, ω-scans). The structures were solved by direct methods and refined by the full-matrix least-squares method using the SHELX-97 program package [19]. The H atoms were located geometrically using the riding model.

Crystal data: $C_{24}H_{24}F_3NO_4$, M = 447.44, triclinic, space group P-1, a = 8.4754 (12) Å, b = 11.3587 (10) Å, c = 11.8318 (7) Å, α = 87.090 (6)°, β = 83.664 (8)°, γ = 76.787 (10)°, V = 1101.73 (19) $Å^3$, Z = 2, ρ_{calcd} = 1.349 g/cm^3, μ = 0.108 mm^{-1}, F(0 0 0) = 468. Final R = 0.0466, $wR2$ = 0.1244, S = 1.008 for 320 parameters and 9934 reflections, 5165 unique [$R_{(int)}$ = 0.0163], of which 2278 with $I > 2r(I)$.

Crystallographic data for compound **3d** (CCDC deposition number 804622) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

Acknowledgments. This work was financially supported by the RFBR (grant 10-03-00138) and the Presidium program of the RAS N 21.

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