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Short communication

# Polyfluorinated 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepines: Synthesis and new rearrangement into polyfluorodihydrobenzimidazo[1,2-*a*]quinolines

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ABSTRACT

Interaction of polyfluorinated chalcones (pentafluorobenzalacetophenone, benzalpentafluoroacetophenone and decafluorochalcone) with 1,2-diaminobenzene in alcohols in the presence of triethylamine or quaternary ammonium salt (TEBAC) has been investigated. In the presence of TEBAC in 2-propanol polyfluorinated 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepines are formed. Some of them undergo intramolecular fluorine substitution and unusual rearrangement into a previously unknown polyfluoro-containing tetracyclic compounds—(6a*R*)-1,2,3,4-tetrafluoro-6a-aryl-6a,7-dihydrobenzimidazo[1,2-*a*]quinolines, under the reaction conditions as well as in absence of TEBAC. The structures are established on NMR spectra and confirmed by X-ray.

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## 1. Introduction

1,5-Diazepines are an important class of heterocycles with a wide range of biological activity such as antidepressant, anti-inflammatory, anticonvulsant, antifidant, antibacterial and analgesic agents [1–5]. One of the basic methods to obtain benzo-1,5-diazepines is the reaction of α,β-unsaturated carbonyl compounds, including chalcones, with 1,2-diaminobenzene in the presence of bases, acids or salts as catalysts [1,6]. Polyfluorinated benzo-1,5-diazepines are not described. The introduction of fluorine atoms into biologically active compounds is a well-known method to enhance their therapeutically effect [2,7,8].

## 2. Results and discussion

Previously we studied the reactions of polyfluorinated chalcones with nitrogen-containing binucleophiles–hydrazines [9], 2-aminothiophenol and its zinc salt [10], resulting in azaheterocycles formation or fluorine substitution. In this paper, we report the reactions of polyfluorochalcones **1a-c** (Fig. 1) with 1,2-diaminobenzene.

The reactions were carried out in ethyl and 2-propyl alcohols in the presence of triethylamine (TEA) or benzyltriethylammonium chloride (TEBAC) in excess or in catalytic amounts. An excess of 1,2-diaminobenzene (7 eq.) was used to avoid "crosslinking" of two or more chalcone molecules due to the high fluorine mobility in perfluorophenyl rings. In addition, complete conversion of starting chalcones was not achieved at equimolar ratio.

It was shown that the reaction mixture composition depended on the structure of the starting chalcone and the reaction conditions. Pentafluorobenzalacetophenone **1a** reacted with an excess of 1,2-diaminobenzene in boiling ethanol in the presence of triethylamine (TEA) forming a mixture of two compounds—probably Michael aza-adduct 3-(2-aminophenyl)amino-3-(perfluorophenyl)-1-phenyl-propan-1-one (**2a**) and 2-(perfluorophenyl)-4-phenyl-2,3-dihydro-1*H*-benzo-1,5-diazepine (**3a**) (Scheme 1), with the significant amount of starting **1a** remaining unchanged.

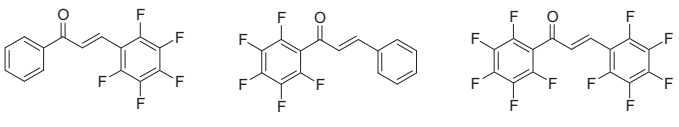


**Fig. 1.** The structures of starting chalcones.

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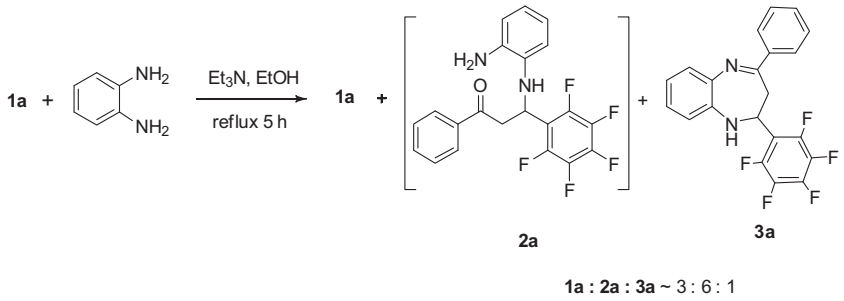
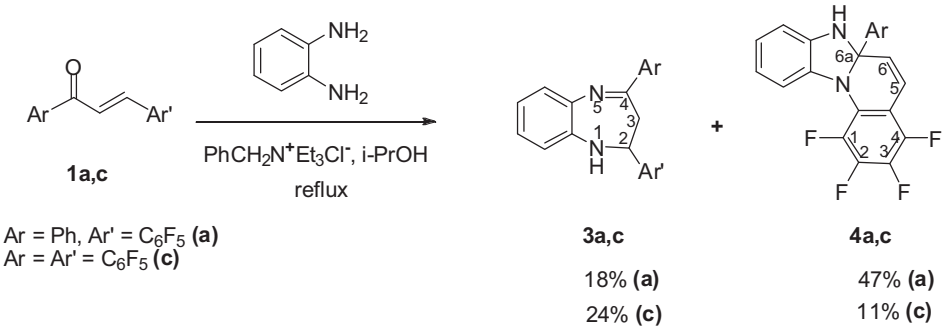



**Scheme 1.**




**Scheme 2.**

Increasing of the reaction time up to 28 h led to the single product—benzodiazepine **3a**, which was isolated with the yield 67%.

Compound **2a** could not be isolated as a pure substance. When we tried to separate the reaction product by column chromatography on alumina, **2a** possibly decomposed or transformed into diazepine **3a**. The proposed structure of **2a** was established in the mixture on the NMR spectra which were similar to the spectra of bis-aza-adduct from chalcone **1a** and piperazine [11] as well as of thia-adduct [10]. Thus, in the $^1$H NMR spectrum of aza-adduct **2a** there are ABX-system signals—multiplet of CH-proton at 5.54 ppm with $^1J$ = 10 Hz (C<u>H</u>–NH) and $^2J = {}^3J$ = 7 Hz (C<u>H</u>–$CH_2$), and two doublets of doublets of adjacent $CH_2$-protons with $J_{gem}$ = 17 Hz and $J_{vic}$ = 7 Hz. Furthermore, there is a doublet of NH-group with $J$ = 11 Hz and the multipletes of aromatic protons. $^{19}$F NMR spectrum contains three signals of pentafluorophenyl group at −162.7 (*meta*-F), −156.3 (*para*-F) and −144.4 (*ortho*-F) ppm.

Benzalpentafluoroacetophenone **1b** didn't react with 1,2-diaminobenzene under the same conditions. Less influence of $C_6F_5$-group on β-C-electrophilicity in **1b** compared with **1a** may be explained by the fact that perfluorophenyl ring near the carbonyl group does not lie in the conjugation plane (for example, dihedral angle is about 57° in $C_6F_5COCH_3$ [12] and 60.3° in decafluorochacone [13]). Decafluorochalcone **1c** gave a complex mixture of unidentifiable compounds under the same conditions.

Reflux of pentafluorobenzalacetophenone **1a** with an excess of 1,2-diaminobenzene and TEBAC in 2-propanol gave a mixture of benzodiazepine **3a** and the compound with unexpected structure—(6a*R*)-1,2,3,4-tetrafluoro-6a-phenyl-6a,7-dihydrobenzimidazo[1,2-*a*]quinoline **4a**. Decafluorochalcone **1c** formed two similar products – **3c** and **4c** (Scheme 2) – and numerous minor unidentifiable impurities, i.e. the reason of low yields.

The use of catalytic quantities of TEBAC (10 mol% to chalcone) in both cases did not change significantly the ratio of benzodiazepine **3** to benzimidazoquinoline **4**, but more starting chalcones remained, which made chromatographic separation of reaction mixture difficult.

The structures of **4a,c** were established from NMR spectra and high resolution mass spectrometry. $^{19}$F NMR spectrum of **4a** contains four signals with equal intensity. In the $^1$H NMR spectrum there are two doublets of double bond protons (6.38 and 6.74 ppm, $J$ = 9.9 Hz), singlet of NH-group at 4.41 ppm and the multipletes of aromatic protons.

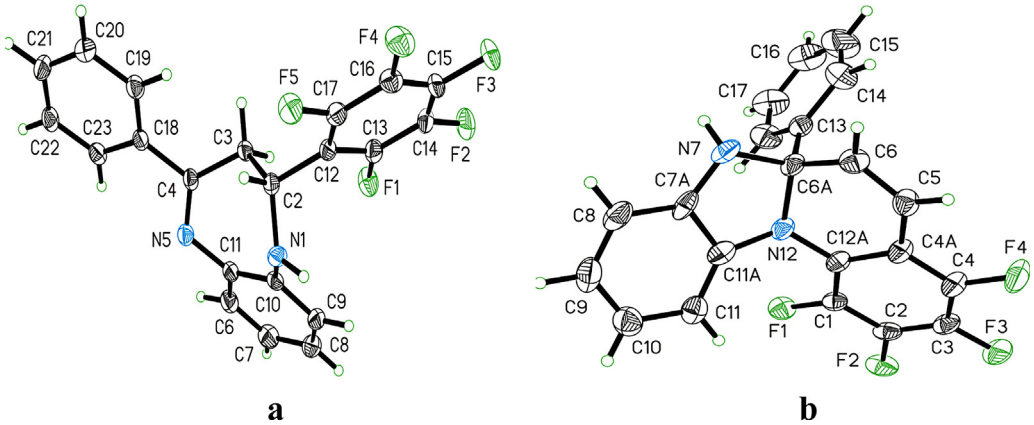
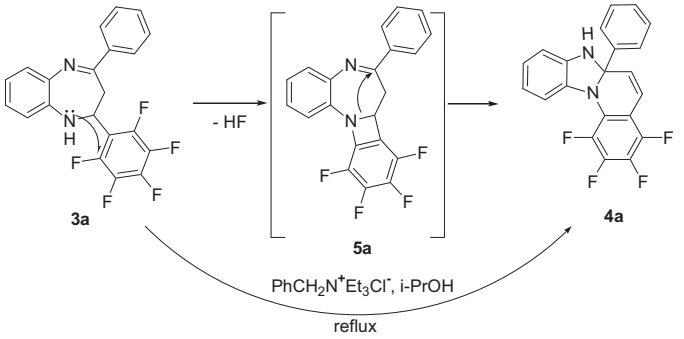
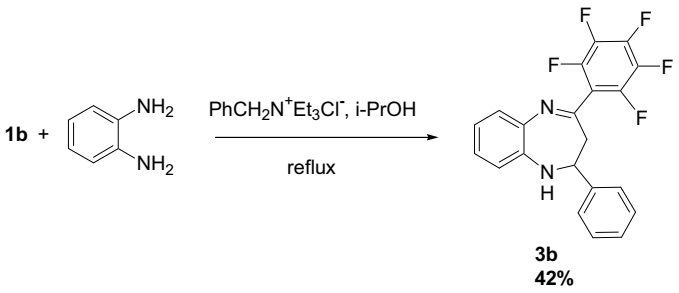



**Fig. 2.** Crystal structures of **3a** (**a**) and **4a** (**b**).




Scheme 3.




Scheme 5.

The structure of **3a** was independently confirmed by X-ray crystal structure analysis (Fig. 2a). The 2,4-diphenyl-2,3-dihydro-1*H*-benzo-1,5-diazepine derivatives are well studied by XRD; however, in the Cambridge Structural database (CSDB) there is no data available on the structure of benzodiazepine containing perfluorophenyl group. The diazepine cycle of **3a** has a boat conformation with pseudo-axial perfluorophenyl and the pseudo-equatorial phenyl. The same conformation is observed in 2-(2,5-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine [14]. In a crystal, the molecules are linked into chains by hydrogen bonds N1–H...N5 (distance H...N 2.28(2), 2.39(2) Å, NHN angles 171(2), 175(2)°, respectively for two independent molecules). Note the π...π interactions of perfluorophenyl-phenyl(C18–C23), and perfluorophenyl-benzo(C6–C11) with intercentroid distances 3.746(1) and 3.680(1) Å.

The structure of **4a** was confirmed by X-ray crystal structure analysis (Fig. 2b). In CSDB there is no data available on a structure of 6a,7-dihydrobenzimidazo[1,2-*a*]quinoline derivatives. The benzimidazole fragment of molecule **4a** is planar within ±0.080 Å. The conformation of dihydropyridine cycle is a distorted boat with deviations of C6 and C6A atoms by 0.287(8), 0.266(8) and 0.649(8), 0.581(8) Å, respectively for the two independent molecules. The hydrogen bond N7–H...N7 (H...N 2.52 Å, NHN 163°) and short contact F2...F3 2.703(4) Å should be noted.

The formation of compound **4a** may be explained by intramolecular cyclization of initially formed benzodiazepine **3a** via *o*-fluorine substitution by NH-group to unstable intermediate tetracyclic compound **5a**; the latter undergoes a skeletal rearrangement to **4a** (Scheme 3). To confirm this hypothesis, we showed that benzodiazepine **3a** transformed almost completely into the compound **4a** under the reaction conditions or without TEBAC in boiling 2-propanol.

An alternative way to **4a** may be considered—through initial 1,2-addition of 1,2-diaminobenzene to carbonyl group leading to imine **6a** and then to cyclic aminal **7a**, which closes six-member cycle due to intramolecular fluorine substitution (Scheme 4). Such a sequence is less likely for the following reasons. First, chalcones react usually with 1,2-diaminobenzene at the first stage as conjugative 1,4-addition, but not 1,2-addition [15]. Second, steric hindrance may also prevent the formation of **7a** and its cyclization in **4a**.

We believe that transformation of **3a** into **4a** in reaction conditions is a direct confirmation of reaction way given in Scheme 3. It is difficult to clarify how TEBAC acts as a catalyst in this reaction because the process is homogeneous. However, TEBAI was applied for obtaining of 1,5-diazepine [16].

Such structures as **4** including fluorine-containing benzimidazo[1,2-*a*]quinolones have been described [8,17–19], but the compounds **4a,c** are new and have been obtained by the original method.

Benzalpentafluoroacetophenone **1b** gave at the same conditions only 4-(perfluorophenyl)-2-phenyl-2,3-dihydro-1*H*-benzo-1,5-diazepine **3b**, which was not able to *o*-fluorine substitution (Scheme 5).

## 3. Conclusions

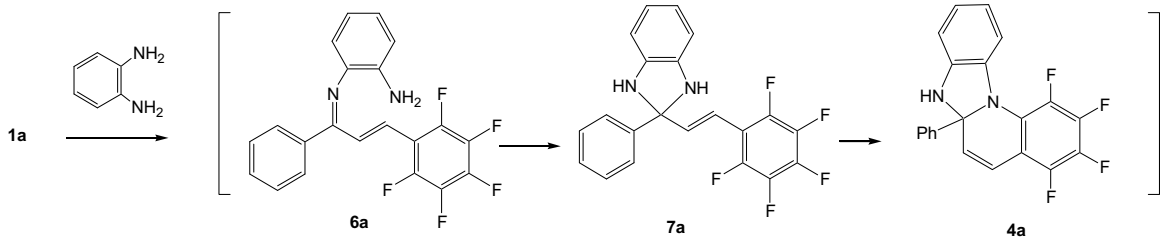
The reaction of polyfluorochalcones with 1,2-diaminobenzene in the presence of triethylamine (TEA) or benzyltriethylammonium chloride (TEBAC) can be used to obtain new polyfluorinated benzo-1*H*-1,5-diazepines. Some of them undergo intramolecular cyclization by means of *o*-fluorine substitution and following rearrangement to form fluorine-containing benzimidazoquinoline.

## 4. Experimental

### 4.1. Materials and methods

Chalcones **1a-c** were synthesized using the method described in [20]. 1,2-Diaminobenzene is a commercially available product. NMR spectra were recorded in $CDCl_3$ on a Bruker AC-300 spectrometer ($^1H$: 300.13 MHz, $^{19}F$: 282.37 MHz). Chemical shifts ($\delta$) are reported in ppm relative to TMS for $^1H$ spectra with residual protons of $CHCl_3$ ($\delta_H$ = 7.24 ppm) and to $CCl_3F$ for $^{19}F$ spectra with $C_6F_6$ as internal standard. Mass spectra were recorded on a high resolution mass spectrometer DFS in direct input. Single crystals of **3a** and **4a** were grown from ethanol.

Yields of isolated compounds are given. The products ratio on Scheme 1 was calculated from NMR $^{19}F$ spectra.




Scheme 4.

*4.2. Reaction of pentafluorobenzalacetophenone (**1a**) with 1,2-diaminobenzene in the presence of triethylamine (TEA)*

*4.2.1. Pentafluorobenzalacetophenone **1a***

Pentafluorobenzalacetophenone (**1a**, 0.5 g, 1.68 mmol) was added to a solution of 1,2-diaminobenzene (1.27 g, 11.7 mmol) and TEA (1.62 ml, 11.7 mmol) in ethanol (10 ml). The mixture was refluxed at stirring for 5 h; after cooling to room temperature it was poured in crushed ice. The sticky product was extracted with diethyl ether, washed with distilled water and dried ($MgSO_4$); the solvent was evaporated in vacuum. The oily product (0.66 g) was analyzed by $^1$H NMR and $^{19}$F NMR (see Section 2), products ratio is given in Scheme 1.

*4.2.2. Benzodiazepine **3a***

Benzodiazepine **3a** was obtained with the yield 0.26 g (67%) from 0.3 g (1.0 mmol) pentafluorobenzalacetophenone **1a**, 0.76 g (7.0 mmol) 1,2-diaminobenzene and 0.98 ml (7.0 mmol) TEA after boiling in 10 ml ethanol for 28 h and processing as described above.

*4.3. 2-(Perfluorophenyl)-4-phenyl-2,3-dihydro-1*H*-benzo-1,5-diazepine **(3a)** and (6a*R*)-1,2,3,4-tetrafluoro-6a-phenyl-6a,7-dihydrobenzimidazo[1,2-*a*]quinoline **(4a)***

Pentafluorobenzalacetophenone (**1a**, 0.6 g, 2.0 mmol) was added to the solution of 1,2-diaminobenzene (1.52 g, 14.0 mmol) and TEBAC (3.14 g, 14.0 mmol) in 2-propanol (20 ml). The mixture was refluxed under stirring for 5 h, and after cooling to room temperature it was poured in crushed ice. The precipitate was filtered, washed with distilled water and dried on air. The product (0.68 g) was analyzed by $^1$H NMR and $^{19}$F NMR. Thin layer chromatography of the product on alumina (benzene/hexane = 1/1) gave two compounds. The first fraction**—4a** (0.35 g, 47%), yellow solid, mp 105–108 °C (from EtOH). $^1$H NMR ($CDCl_3$): δ 4.41 (s, 1H, NH), 6.38 (d, 1H, $J$ = 9.9, –CH=), 6.63–6.71 (m, 2$H_{Ar}$), 6.74 (dd, 1H, –CH=, $^1J$ = 9.9, $^2J$ = 1.3), 6.78–6.88 (m, 2$H_{Ar}$), 7.27–7.35 (m, 3$H_{Ar}$), 7.48–7.53 (m, 2$H_{Ar}$) ppm. $^{19}$F NMR ($CDCl_3$): δ −164.1 (t, 1F, $J_{FF}$ = 21.2, F3), −157.3 (b.t, 1F, $^1J$ = 21.2, $^2J$ = 20.4, F2), −148.6 (dd, 1F, $^1J$ = 21.2, $^2J$ = 11.0, F4), −146.7 (m, 1F, F1) ppm. HRMS: calcd. for $C_{21}H_{12}N_2F_4$ [$M^+$]: 368.0931; found: 368.0938. Anal. Calcd for $C_{21}H_{12}N_2F_4$: C, 68.48; H, 3.28; F, 20.63; N, 7.61. Found: C, 68.48; H, 3.08; F, 20.63; N, 7.09. The second fraction gave **3a** (0.14 g, 18%), yellow solid, mp 155–157 °C (from EtOH). $^1$H NMR ($CDCl_3$): δ 3.22 (dd, 1H, $^1J$ = 13.1, $^2J$ = 3.5, $CH_2$, ABX), 3.27 (dd, 1H, $^1J$ = 13.1, $^2J$ = 11.1, $CH_2$, ABX), 3.60 (br.s, 1H, NH); 5.64 (dd, 1H, CH, $^1J$ = 11.1, $^2J$ = 3.5, ABX), 6.71–6.79 (m, 1$H_{Ar}$), 7.00–7.09 (m, 2$H_{Ar}$), 7.32–7.37 (m, 1$H_{Ar}$), 7.43–7.49 (m, 3$H_{Ar.}$), 7.92–7.99 (m, 2$H_{Ar}$) ppm. $^{19}$F NMR ($CDCl_3$): δ −161.9 (2F), −155.3 (1F), −142.7 (2F) ppm. HRMS: calcd. for $C_{21}H_{13}N_2F_5$ [$M^+$]: 388.0993; found: 388.0990. Anal. Calcd. for $C_{21}H_{13}N_2F_5$: C, 64.95; H, 3.37; F, 24.46; N, 7.21. Found: C, 64.91; H, 3.32; F, 24.46; N, 7.21.

*4.4. Conversion of **3a** into **4a***

The solution of **3a** (0.03 g) in 2-propanol (2 ml) was refluxed 2 h, cooled to room temperature and poured in crushed ice. The product was extracted with $CHCl_3$, dried ($CaCl_2$), the solvent was evaporated in vacuum, and the residue was analyzed by $^{19}$F NMR. The product contained 81% of **4a** and 19% of **3a**.

*4.5. 4-(Perfluorophenyl)-2-phenyl-2,3-dihydro-1*H*-benzo-1,5-diazepine **(3b)***

Benzalpentafluoroacetophenone (**1b**, 1.0 g, 3.3 mmol) was added to the solution of 1,2-diaminobenzene (2.54 g, 23.1 mmol) and TEBAC (5.22 g, 23.1 mmol) in 2-propanol (20 ml). The mixture was refluxed at stirring for 14 h, and after cooling to room temperature it was poured in crushed ice. The sticky product was extracted with chloroform, washed with distilled water and dried ($CaCl_2$); the solvent was evaporated in vacuum. The residue (1.78 g) was purified by column chromatography on alumina (benzene/hexane = 1/1) to give **3b** (0.55 g, 42%), a yellow solid, mp 115–117 °C (from EtOH). $^1$H NMR ($CDCl_3$): δ 3.01 (dd, 1H, $CH_2$, $^1J$ = 14.3, $^2J$ = 3.0, ABX), 3.13 (dd, 1H, $CH_2$, $^1J$ = 14.3, $^2J$ = 8.9, ABX), 4.06 (br.s, 1H, NH), 5.07 (dd, 1H, CH, $^1J$ = 8.9, $^2J$ = 3.0, ABX), 6.78 (d, 1$H_{Ar}$, $J$ = 7.9), 6.95 (t, 1$H_{Ar}$, $J$ = 7.9), 7.11 (t, 1$H_{Ar}$, $J$ = 7.9), 7.27–7.39 (m, 6$H_{Ar}$) ppm. $^{19}$F NMR, ($CDCl_3$): δ −162.7 (2F), −154.9 (1F), −142.8 (2F) ppm. HRMS: calcd. for $C_{21}H_{13}N_2F_5$ [$M^+$]: 388.0993; found: 388.0991. Anal. Calcd for $C_{21}H_{13}N_2F_5$: C, 64.95; H, 3.37; F, 24.46; N, 7.21. Found: C, 64.98; H, 3.23; F, 24.46; N, 7.42.

*4.6. 2,4-Bis(perfluorophenyl)-2,3-dihydro-1*H*-benzo-1,5-diazepine **(3c)** and (6a*S*)-1,2,3,4-tetrafluoro-6a-(perfluorophenyl)-6a,7-dihydrobenzimidazo[1,2-*a*]quinoline **(4c)***

Decafluorochalcone (**1c**, 0.3 g, 0.77 mmol) was added to the solution of 1,2-diaminobenzene (0.58 g, 5.4 mmol) and TEBAC (1.23 g, 5.4 mmol) in 2-propanol (6 ml). The mixture was refluxed under stirring for 5 h, and after cooling to room temperature it was poured in crushed ice. The oily product was extracted with chloroform, washed with distilled water and dried ($CaCl_2$), the solvent was evaporated in vacuum. The residue (0.38 г) was separated by thin layer chromatography on alumina (benzene/hexane = 1/2). First fraction gave **4c** (0.04 г, 11%), red solid, mp 130–133 °C (from EtOH). $^1$H NMR ($CDCl_3$): δ 5.25 (br.s, 1H, NH), 6.77 (dd, 1H, –CH=, $^1J$ = 7.4, $^2J$ = 1.6), 7.06–7.18 (m, 2$H_{Ar}$), 7.26–7.39 (m, 3H, –CH=, 2$H_{Ar}$) ppm. $^{19}$F NMR, ($CDCl_3$): δ −163.9 (t, 1F, $^1J$ = $^2J$ = 22.6), −163.2 (m, 2F), −159.2 (ddm, 1F, $^1J$ = 22.6, $^2J$ = 10.6), −154.3 (t, 1F, $^1J$ = $^2J$ = 20.9), −152.9 (td, 1F, $^1J$ = $^2J$ = 22.6, $^3J$ = 5.5), −141.6 (m, 2F), −134.9 (m, 1F) ppm. HRMS: calcd. for $C_{21}H_7F_9N_2$ [$M^+$]: 458.0457; found: 458.0460. Anal. Calcd for C, 55.03; H, 1.54; F, 37.31; N, 6.11. Found: C, 55.40; H, 1.09; F, 37.26; N, 6.06. Second fraction gave **3c** (0.087 г, 24%), yellow solid, mp 155–158 °C (from EtOH). $^1$H NMR ($CDCl_3$): δ 2.89 (dd, 1H, $CH_2$, $^1J$ = 14.1, $^2J$ = 2.9, ABX), 3.43 (dd, 1H, $CH_2$, $^1J$ = 14.1, $^2J$ = 10.8, ABX), 3.85 (br. s, 1H, NH); 5.60 (dd, 1H, CH, $^1J$ = 10.8, $^2J$ = 2.9, ABX), 6.73 (dd, 1$H_{Ar}$, $^1J$ = 7.9, $^2J$ = 1.0), 7.00 (td, 1$H_{Ar}$, $^1J$ = $^2J$ = 7.6, $^3J$ = 1.3), 7.12 (td, 1$H_{Ar}$, $^1J$ = $^2J$ = 7.6, $^3J$ = 1.6), 7.32 (dd, 1$H_{Ar}$, $^1J$ = 7.9, $^2J$ = 1.6) ppm. $^{19}$F NMR, ($CDCl_3$): δ −162.2 (m, 2F), −161.5 (m, 2F), −154.4 (t, 1F, $^1J$ = $^2J$ = 21.3), −154.0 (t, 1F, $^1J$ = $^2J$ = 20.6), −142.9 (m, 4F) ppm. HRMS: calcd. for $C_{21}H_8F_{10}N_2$ [$M^+$]: 478.0525; found: 478.0522. Anal. Calcd for $C_{21}H_8F_{10}N_2$: C, 52.73; H, 1.69; F, 39.72; N, 5.86. Found: C, 52.71; H, 1.76; F, 40.22; N, 5.62.

*4.7. X-ray crystallography*

The details of the crystallographic data collection and refinement are given in Table 1. Data collection used a Bruker Kappa Apex II CCD diffractometer fitted with monochromated Mo Ka radiation (λ = 0.71073 Å). The structures were solved by direct methods (SHELXS-97) and refined by least squares methods (SHELXL-97) [21]. All non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms refined isotropically on calculated positions using a riding model. The H atom bonded to N was identified in later electron-density maps for compound **3a**. Low quality of compound **4a** crystals should be noted.

CCDC 972629-972630 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Table 1**
Crystallographic data for **3a** and **4a**.

| | Compound **3a** | Compound **4a** |
|---|---|---|
| $T$ [K] | 150 (2) | 200(2) |
| Crystal system | Monoclinic | Triclinic |
| Space group | $P2_1/n$ | $P$-1 |
| $a$ [Å] | 8.1812 (3) | 11.4884 (7) |
| $b$ [Å] | 21.2756 (8) | 11.5612 (7) |
| $c$ [Å] | 19.2775 (6) | 13.4008 (7) |
| $\alpha$ [°] | 90 | 101.361 (2) |
| $\beta$ [°] | 97.893 (1) | 107.779 (2) |
| $\gamma$ [°] | 90 | 89.764 (2) |
| $V$ [Å$^3$] | 3323.7 (2) | 1658.7 (2) |
| $Z$ | 8 | 4 |
| $\rho_{calc}$ [mg mm$^{-3}$] | 1.552 | 1.475 |
| $\mu$ [mm$^{-1}$] | 0.131 | 0.119 |
| Observed reflections [$I > 2\sigma(I)$] | 6289 | 4569 |
| Data/restraints/parameters | 8480/0/514 | 5853/0/487 |
| $R_1$, $wR_2$ [$I > 2\sigma(I)$] | 0.0430, 0.1128 | 0.0971, 0.2879 |
| $R_1$, $wR_2$ [all data] | 0.0663, 0.1371 | 0.1156, 0.3154 |
| Largest diff. peak, hole [e·Å$^{-3}$] | 0.47, −0.32 | 0.99, −0.53 |

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