Journal of Fluorine Chemistry 143 (2012) 272–280

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

# A new synthesis of N-substituted o-trifluoroacetylanilines

Alexander F. Shidlovskii, Alexander S. Golubev *, Dmitrii V. Gusev, Kyrill Yu. Suponitsky, Alexander S. Peregudov, Nikolai D. Chkanikov

*A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov St. 28, GSP-1, Moscow, Russian Federation*

ARTICLE INFO

*Article history:*
Received 20 April 2012
Received in revised form 30 June 2012
Accepted 5 July 2012
Available online 16 July 2012

*Keywords:*
N-substituted isatoic anhydrides
Ruppert–Prakash reagent
N-substituted o-trifluoroacetylanilines
9-Trifluoromethylacridines

ABSTRACT

A method for the synthesis of N-substituted o-trifluoroacetylanilines by the reaction of N-substituted isatoic anhydrides with (trifluoromethyl)trimethylsilane (Ruppert–Prakash reagent) has been developed. This method provides easy access to both N-alkyl-o-trifluoroacetylanilines and N-aryl-o-trifluoroacetylanilines in high yields. Cyclisation of N-aryl-o-trifluoroacetylanilines in trifluoroacetic acid gives 9-trifluoromethylacridines.



## 1. Introduction

o-Trifluoroacetylanilines are widely used for the synthesis of physiologically active heterocycles including HIV-1 reverse transcriptase inhibitors [1], antidiabetic drugs [2], fluorinated analogues of cytotoxic alkaloid luotonine [3], homocamptothecin [4], selective androgen receptor modulator [5], and T-type calcium channel antagonists [6]. o-Trifluoroacetylanilines exhibit antiherpetic activity [7], they are extensively studied as molecular sensors [8].

Several approaches towards the synthesis of o-trifluoroacetylanilines exist. o-Trifluoroacetylation of lithiated anilines bearing a N-protecting and *ortho*-directing group (usually Piv- or Boc-group) [9], nucleophilic substitution by N-nucleophiles of fluorine in 2-fluoro-α,α,α-trifluoroacetophenones [10] and dimethylamino group in N,N-dimethyl-2-trifluoroacetyl-naphthylamines or N,N-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamines [11], and insertion of arynes in the C–N bond of N-aryltrifluoroacetamides to give N-aryl-o-trifluoroacetylanilines [12] can be considered as most important methods for the synthesis of o-trifluoroacetylanilines.

The above mentioned approaches make it possible to synthesize o-trifluoroacetylanilines containing various substituents in the aromatic ring, as well as their N-substituted analogues. However all these methods have their own limitations. In particular, in the synthesis of o-trifluoroacetylanilines by trifluoroacetylation of lithiated N-Piv(N-Boc)-anilines, strong bases such as *n*-BuLi or *tert*-BuLi are used for obtaining dilithio intermediates in the first stage of the synthesis [9]. As a result, the lithiation reaction of N-Piv-toluidine leads to lateral rather than nuclear lithiation [13]. For 3,4-dichloroaniline, the yield of the target 1-(2-amino-5,6-dichlorophenyl)-2,2,2-trifluoroethanone is rather low (19%) because of a side reaction of HCl elimination. The same limitation operates when other 3-chloroanilines are applied [9c]. o-Trifluoroacetylanilines with a nitro group are not available by aniline lithiation approach. They can be obtained by a tedious multistep synthesis, which includes a Weinreb amide reduction step [14]. Most 2-fluoro-α,α,α-trifluoroacetophenones used for the synthesis of o-trifluoroacetylanilines were obtained by lithiation (in this case with LDA) of the corresponding fluorobenzenes [10]. The reaction operates at cryogenic temperatures and suffers often from lack of regioselectivity [15]. Nucleophilic substitution by N-nucleophiles of dimethylamino group in N,N-dimethyl-2-trifluoroacetyl-naphthylamines is restricted to the naphthalene nucleus, as N,N-dimethyl-2,4-bis(trifluoroacetyl)aniline does not react [11]. Insertion of arynes proceeds in the C–N bond of N-aryltrifluoroacetamides. No examples were given for obtaining of N-alkyl o-trifluoroacetylanilines by this method [12].

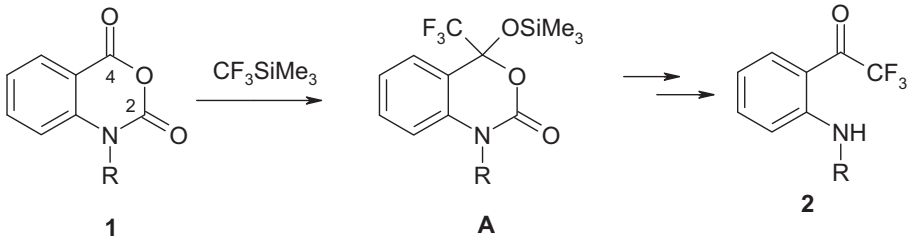
Moreover, a general method for synthesizing N-substituted o-trifluoroacetylanilines does not exist.

## 2. Results and discussion

Our approach to the synthesis of N-substituted o-trifluoroacetylanilines is based on the reaction of isatoic anhydride derivatives (2H-3,1-benzoxazine-2,4(1H)-diones **1**) with Ruppert–Prakash

* Corresponding author. Tel.: +7 499 135 9358; fax: +7 499 135 0176.
*E-mail address:* golubev@ineos.ac.ru (A.S. Golubev).

0022-1139/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2012.07.002




**Scheme 1.**

reagent ($CF_3SiMe_3$ [16]) (Scheme 1). We envisioned that a nucleophilic attack of Ruppert–Prakash reagent would occur predominantly at position *4* of heterocycle **1**, rather than at position *2* to provide high regioselectivity of the process as a result. We also assumed that intermediate compound A should be sufficiently stable under the reaction conditions to hinder the second attack of Ruppert–Prakash reagent with formation of bis(trifluoromethyl)carbinols as a by-product.

When our research in this direction had been almost completed, Braese and co-workers published a paper [17] where their attempt to realize a similar synthetic idea was described. They studied reaction of 2-methyl-(4H)3,1-benzoxazin-4-one with Ruppert–Prakash reagent in various solvents in the presence of tetrabutylammonium fluoride (TBAF) as catalyst. Dimethylsulfoxide proved to be the solvent of choice. The yields of o-trifluoroacetylanilines were low (13–53%) even when applying a 3-fold excess of Ruppert–Prakash reagent [17].

In this paper we show our results on the synthesis of various N-substituted o-trifluoroacetylanilines by the reaction of Ruppert–Prakash reagent with N-substituted 2H-3,1-benzoxazine-2,4(1H)-diones **1**. After initial experiments, we selected DMF as the solvent of choice, because the transfer of the $CF_3$ group in DMF is rather fast, and the treatment of the reaction mixture is very simple. We used a combination of KF and tetrabutylammonium bromide (TBAB) as catalyst. This combination is rather cheap, and provides reliable catalysis for $CF_3$-group transfer, and it does not bring water into the reaction mixture. Tetrabutylammonium fluoride (TBAF), which is usually used for such reactions, should be additionally dried, because otherwise the water it contains hydrolyses the starting reactants under the reaction conditions. In all reactions studied, we used a 30% excess of Ruppert–Prakash reagent to achieve the full conversion of starting benzoxazin-2,4-diones **1**.

We have discovered that N-alkylisatoic anhydrides **1a–d** reacted with Ruppert–Prakash reagent in DMF in the presence of KF + TBAB at room temperature to give N-substituted o-trifluoroacetylanilines **2a–d** in high yields (85–90%, Table 1).

The reaction was monitored by $^{19}F$ NMR spectroscopy. As reaction occured, the intensity of the signal at −65.1 ppm ($CF_3SiMe_3$) decreased while the signal at about −85.0 ppm (assigned to compound A, Scheme 1) increased. Conversion of benzoxazin-2,4-diones **1a–d** was estimated by TLC. The reaction was treated with a 5% solution of HCl to remove the trimethylsilyl moiety in ketal **A**, then with a 10% solution of sodium carbonate to decompose desilylated ketal **A**, which is quite stable in solutions of mineral acids [18].

In all cases, the content of by-products in the reaction mixture did not exceed 5% (according to $^{19}F$ NMR data). By the example of reaction of benzoxazine-2,4-dione **1a**, we found out formation of bis(trifluoromethyl)carbinol **3a** to account for side reaction to a great extend. Carbinol **3a** was isolated from the reaction mixture and characterized. Its structure was also confirmed independently by the reaction of Ruppert–Prakash reagent with *o*-aminoketone **2a** (Scheme 2).

We failed to avoid the formation of by-product **3a** at all by either decreasing the excess of Ruppert–Prakash reagent or varying the solvent. The commercial TBAF led to somewhat worse results in comparison with the combination KF + TBAB, and the presence of NaOAc resulted in formation of several by-products. The use of THF decreased the yield of product **2a** as a result of incomplete conversion even upon prolonged (for 24 h) stirring. The low yield of product **2a** was observed in methylene chloride because of low conversion of starting **1a**.

We failed to isolate N-cyanomethylated o-trifluoroacetylaniline from the reaction of N-cyanomethylisatoic anhydride with Ruppert–Prakash reagent. Probably, an enhanced acidity of the cyanomethyl fragment prevents KF + TBAB (and also TBAF) from catalysis of $CF_3$-group addition reaction. Isatoic anhydride itself did not react with Ruppert–Prakash reagent under the aforesaid conditions.

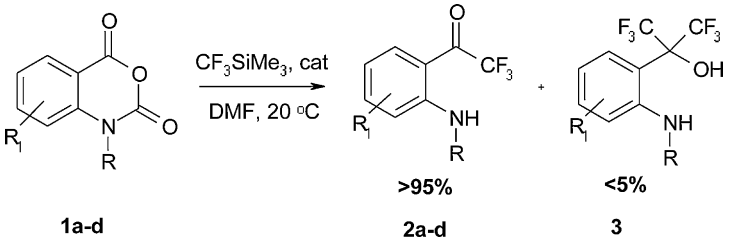
We extended a set of the N-alkylsubstituted o-trifluoroacetylanilines obtained by modifying the aromatic ring. For instance, N-methyl-4-bromo-2-trifluoroacetylaniline **2b** gave 4-phenyl derivatives **2e** in 95% yield. Therefore the N-alkylamino- and *o*-trifluoroacetyl groups do not hinder the Suzuki reaction (Scheme 3).

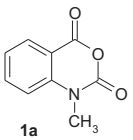
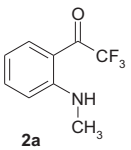
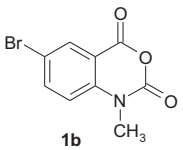
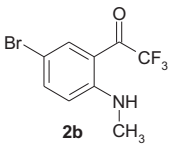
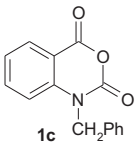
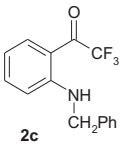
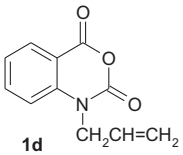
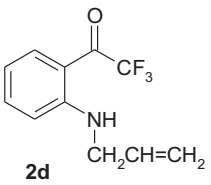
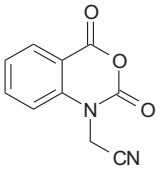
We have also found that N-arylisatoic anhydrides **4a–d** reacted with Ruppert–Prakash reagent in DMF in the presence of KF + TBAB at room temperature to give N-arylated o-trifluoroacetylanilines **5a–d** in good to high yields (Table 2).

In contrast to N-alkylisatoic anhydrides **1a–d**, reaction of N-phenylisatoic anhydride **4a** with Ruppert–Prakash reagent proceeded much more slowly. It took usually about 16 h to reach a high conversion of **4a** at 25 °C. Moreover, we observed clear evidences of instability of the initial cyclic ketal **A** (Scheme 1, R = Ph) in DMF. Monitoring the reaction by $^{19}F$ NMR spectroscopy detected along with the signal at −65.1 ppm ($CF_3SiMe_3$) and the signal at about −85.0 ppm (assigned to cyclic ketal **A**, Scheme 1), three other intensive signals, a singlet at −67.8 ppm (ketone **5a**), a singlet at −72.81 ppm, and a broad singlet at −66.17 ppm. While reaction is proceeding, the intensity of the signal at −85.0 ppm decreases, a singlet at −67.8 ppm (ketone **5a**) increases, and arises a new signal – a singlet at −71.25 ppm. After $CF_3SiMe_3$ was consumed and the reaction was treated by diluted HCl (an additional treatment with $Na_2CO_3$ was excessive in this case), all 4 initial signals collapsed to a singlet at −67.87 ppm (ketone **5a**). And only the singlet at −71.25 ppm went unchanged after acidic treatment of the reaction and clearly indicated presence of a by-product in this reaction in notable amounts (up to 8%). We isolated this by-product. Its structure as bridged diazocine **6a** was confirmed by X-ray diffraction method (Fig. 1) [19]. We found that the content of the by-product **6a** in the reaction mixture was increased to 20–25% when running the reaction at 35 °C.

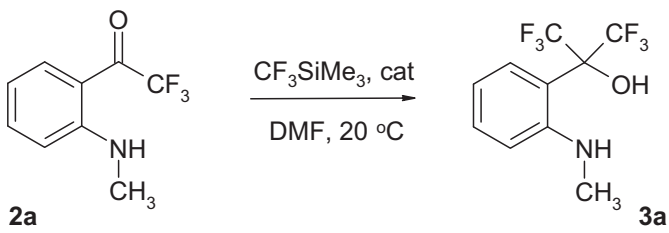
All these observations testify to the fact that instability of the initial cyclic ketal **A** in DMF and the formation of by-product **6a** are intrinsically connected. To mention, on monitoring the reaction of benzoxazin-2,4-diones **1a–d** with $CF_3SiMe_3$ to give quite stable

**Table 1**
Reaction conditions and yields for the reaction of N-alkylbenzoxazin-2,4-diones **1a–d** with Ruppert's reagent.

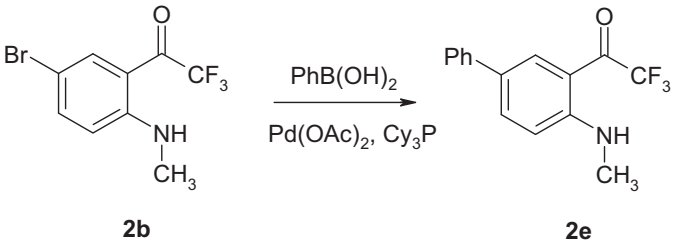



| 2H-3,1-benzoxazin-2,4(1H)-dione | Solvent | Catalyst | Product | Isolated yield, % |
|---|---|---|---|---|
|  **1a** | DMF | KF + TBAB[a] |  **2a** | 87[b] |
| **1a** | DMF | TBAF | **2a** | 73 |
| **1a** | DMF | NaOAc | **2a** | 65[c] |
| **1a** | THF | TBAF | **2a** | 61[d] |
| **1a** | $CH_2Cl_2$ | KF + TBAB[a] | **2a** | 40[c,e] |
|  **1b** | DMF | KF + TBAB[a] |  **2b** | 80 |
|  **1c** | DMF | KF + TBAB[a] |  **2c** | 85 |
|  **1d** | DMF | KF + TBAB[a] |  **2d** | 90 |
|  | DMF | KF + TBAB[a] or TBAF | traces of product | – |
| Isatoic anhydride | DMF | KF + TBAB[a] | no reaction | – |

[a] 30 mol% referred to a N-alkylbenzoxazin-2,4-dione, in a ratio 1:1.
[b] Compound **3a** (2%) was also isolated.
[c] In addition to by-products (according to $^{19}F$ NMR spectral data).
[d] Incomplete conversion for 24 h.
[e] Incomplete conversion for 164 h.




**Scheme 2.**

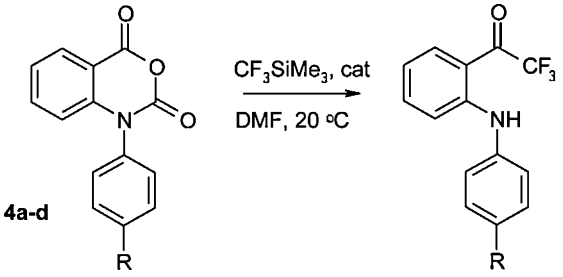


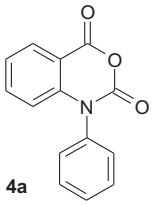
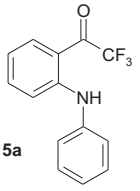
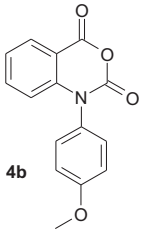
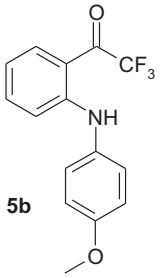
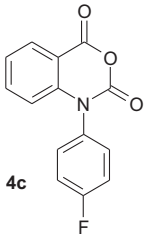
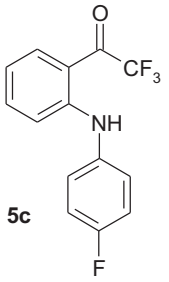
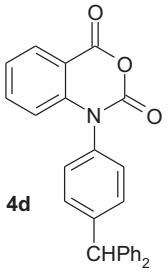
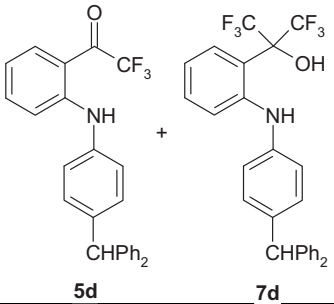

**Scheme 3.**

cyclic ketals A (R = alkyl, Scheme 1), no analogous to **6a** by-products were detected. A plausible mechanism for the formation of **6a** is shown in Scheme 4.

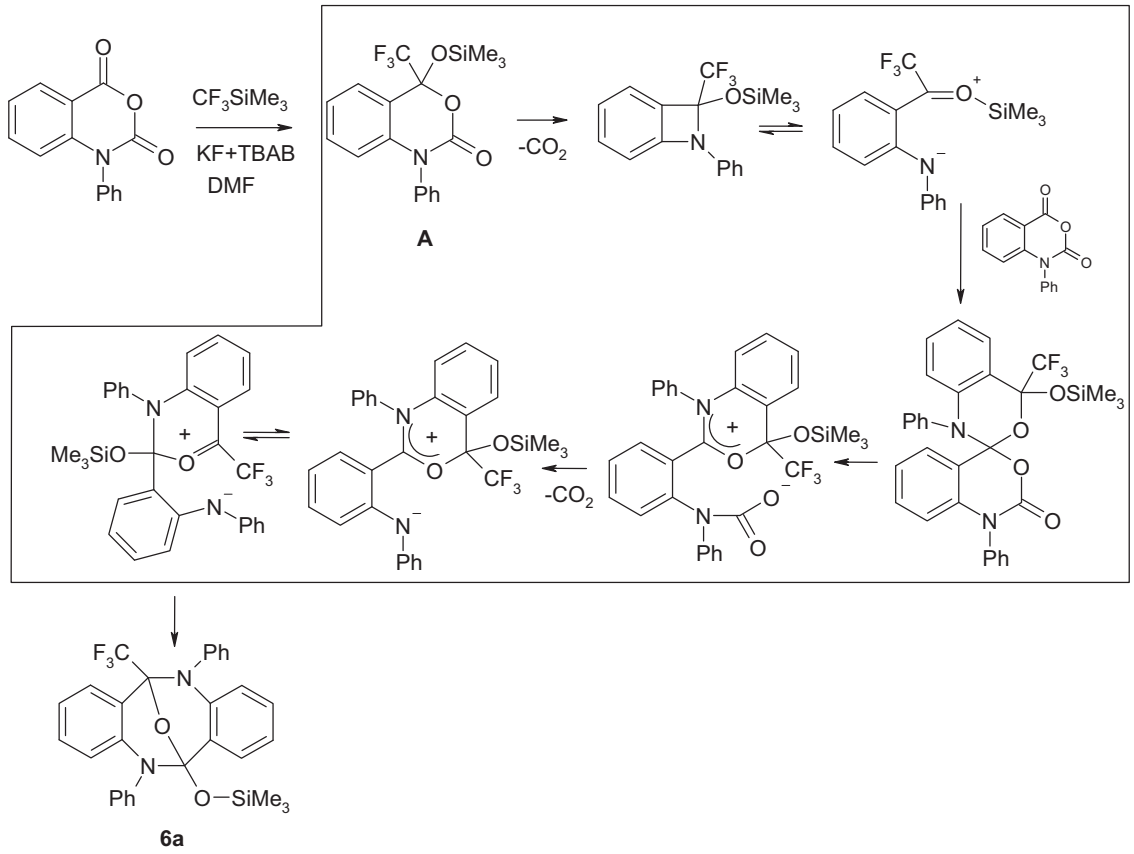
N-phenylisatoic anhydride was identified as carbonyl dipolarophile [20]. Apparently spectroscopically observed instable in DMF cyclic ketal **A** decarboxylates to provide a putative intermediate, which can act as 1,4-dipole [21]. 1,4-Cycloadduct decarboxylates again to afford via a cascade process the formal [4 + 4] dimer **6a**. We found that N-phenyl-*o*-trifluoroacetylaniline **5a** did not react with N-phenylisatoic anhydride in DMF in presence of KF + TBAB even at 75 °C. It means that the formation of **6a** by a reaction sequence including a nucleophilic attack of the nitrogen atom of N-phenyl-*o*-trifluoroacetylaniline **5a** on the C-4 atom of N-phenylisatoic anhydride followed by intramolecular cyclisation with formation of diazocine ring can be excluded. Further investigations to provide support to our interpretation and to make use of this unusual reaction for diazocine synthesis are under way.

**Table 2**
Reaction conditions and yields for the reaction of N-arylbenzoxazin-2,4-diones **4a**–**d** with Ruppert's reagent.




| 2H-3,1-benzoxazin-2,4(1H)-dione | Solvent | Catalyst | Product | Isolated yield, % |
|---|---|---|---|---|
|  **4a** | DMF | KF + TBAB[a] |  **5a** | 74[b] |
|  **4b** | DMF | KF + TBAB[a] |  **5b** | 83 |
|  **4c** | DMF | KF + TBAB[a] |  **5c** | 67 |
|  **4d** | DMF | KF + TBAB[a] |  **5d** + **7d** | 77 (5d)<br>5% (7d)[c] |

[a] 30 mol % referred to a N-arylbenzoxazin-2,4-dione, in a ratio 1:1.
[b] Compound **6a** (6%) was isolated.
[c] Compound **8d** (5%) was also isolated.




**Scheme 4.**

Reaction of N-arylisatoic anhydrides **4b–d** with Ruppert–Prakash reagent proceeded faster than with N-phenylisatoic anhydride **4a**. The highest yield was obtained for anhydride **4b** (Table 2). Analogous to **6a** by-product was detected in the reaction of N-(*p*-fluorophenyl)isatoic anhydride, but it was not isolated. In the case of oxazin-2,4-dione **4d**, we isolated another minor component – bis(trifluoromethyl)carbinol **7d** from the reaction mixture (about 5%).

We also observed the formation of a minor fluorinated component of another type in the reaction of benzoxazine-2,4-diones **4a–d** with Ruppert–Prakash reagent. A by-product of this type gave a singlet (at about $\delta$ −49 ppm) in the $^{19}$F NMR spectrum, its content was up to 5%. In the case of benzoxazin-2,4-dione **4d**, we isolated this minor component and characterized it as 9-trifluoromethylacridine **8d**.

9-Trifluoromethylacridines as representatives of important class of acridines [22] are of undoubted practical interest. To our surprise, there is no any method for the synthesis of 9-trifluoromethylacridines in literature [23]. We have found that N-arylsubstituted o-trifluoroacetylanilines **5a–d** underwent intramolecular cyclisation to give 9-trifluoromethylacridines **8a–d** in 50–70% yield upon prolonged (for 3–7 days) stirring in trifluoroacetic acid [23a] (Scheme 5).

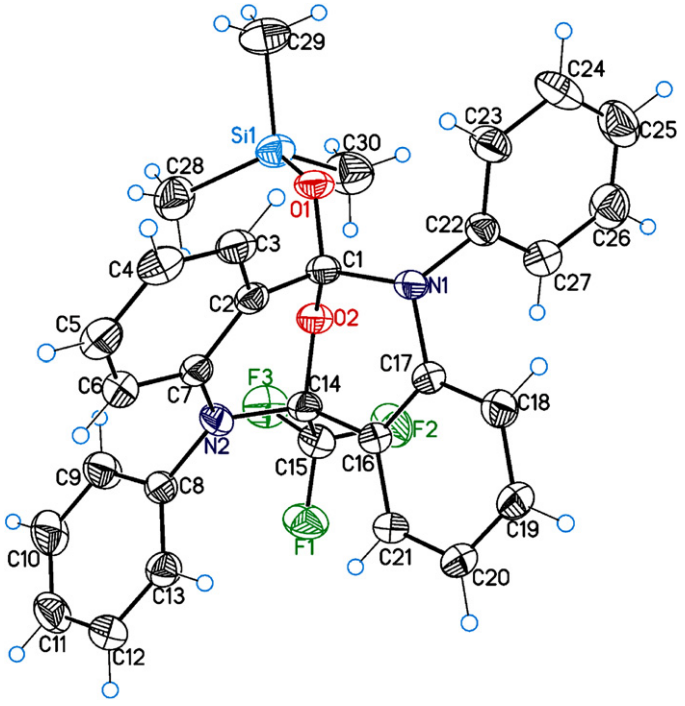
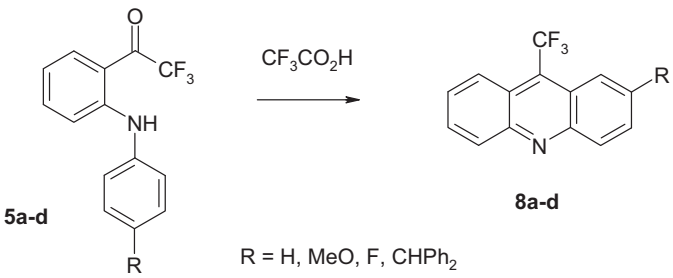



**Fig. 1.** ORTEP view (drawn at 30% probability of thermal displacement ellipsoids) of **6a**.




**Scheme 5.**

## 3. Conclusion

Therefore, we have developed a general and efficient method for the synthesis of N-substituted o-trifluoroacetylanilines by the reaction of N-substituted isatoic anhydrides with Ruppert–Prakash reagent. This method provides easy access to both N-alkyl-o-trifluoroacetylanilines and N-aryl-o-trifluoroacetylanilines in high yields. Various N-alkyl- and N-arylisatoic anhydrides are commercially available or can be easily prepared [24]. This makes it possible to synthesize a wide variety of N-substituted o-trifluoroacetylanilines using the developed method. A method for the synthesis of 9-trifluoromethylacridines has been developed using the intramolecular cyclisation of N-aryl-o-trifluoroacetylanilines in trifluoroacetic acid.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C{$^1$H} NMR spectra were recorded on a Bruker Avance™ 300 spectrometer (300.13 MHz and 75.46 MHz, respectively), and on a Bruker Avance™ 600 spectrometer (600.21 MHz and 150.93 MHz, respectively). Chemical shifts for protons and $^{13}$C nuclei were determined with respect to the residual signal for chloroform (7.27 ppm) or the signal for $CDCl_3$ (77.0 ppm), respectively and recalculated from the $SiMe_4$ signal. Chemical shifts were determined with accuracy no less than 0.001 ppm and 0.03 ppm, respectively. $^{19}$F NMR spectra were recorded on a Bruker Avance™ 300 spectrometer (282.38 MHz). Chemical shifts for $^{19}$F nuclei were determined with respect to trifluoroacetic acid as an external standard with accuracy no less than 0.01 ppm and recalculated relative to $CFCl_3$.

Mass spectra were obtained on a Finnigan Polaris Q instrument (ion trap, 70 eV, the DIP procedure was used for the sample injection). Silica gel with the particle size of 0.06—0.20 mm (Merck Kieselgel 60) was used for column chromatography. Monitoring the reaction course and purity of products obtained was performed using Merck Kieselgel 60 $F_{254}$ TLC plates. N,N-dimethylformamide (99.8%, Panreac) was used as received.

Compounds **1a**–**1d** and **4a**–**d** were synthesized according to the literature [24].

### 4.2. General procedure for the synthesis of compounds ***2a–d***

To a solution of the corresponding 1-alkyl-2H-3,1-benzoxazine-2,4(1H)-dione (N-alkylisatoic anhydride) **1a**–**d** (10 mmol), KF (174 mg, 3 mmol) and TBAB (967 mg, 3 mmol) in dry DMF (20 ml) was added trimethyl(trifluoromethyl)silane (1.85 g, 13 mmol) dropwise at 0 °C under argon. After completion of addition, the reaction mixture was allowed to warm to rt and stirred for 5 h. The reaction was quenched with 5% aq HCl solution (10 ml) at 0 °C, allowed to warm to rt, and stirred for 0.5 h. To the reaction mixture was added 10% aq $Na_2CO_3$ solution (50 ml) with vigorous stirring, and stirring was continued for 1 h at rt. The resulting emulsion was extracted with hexanes (60 ml × 3). The organic layer was separated, washed with brine (30 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure.

#### 4.2.1. 2,2,2-Trifluoro-1-[2-(methylamino)phenyl]ethanone (***2a***)

Yellow oil. Yield 87%. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 8.79 (1H, br. s, N*H*Me), 7.84 (1H, dqd, $J_1$ = 7.8 Hz, $^5J_{H,F}$ = 2.5 Hz, $J_2$ = 1.4 Hz, Ar), 7.55 (1H, ddd, $J_1$ = 8.8 Hz, $J_2$ = 7.3 Hz, $J_3$ = 1.4 Hz, Ar), 6.84 (1H, br. d, $J$ = 8.8 Hz, Ar), 6.71 (1H, ddd, $J_1$ = 7.8 Hz, $J_2$ = 7.3 Hz, $J_2$ = 1.4 Hz, Ar), 3.05 (3H, d, $J$ = 5.0 Hz, NH*Me*). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 180.4 (q, $^2J_{C,F}$ = 33 Hz, *C*(O)$CF_3$), 154.4, 137.3, 132.1 (q, $^3J_{C,F}$ = 4 Hz, *C*C(O)$CF_3$), 117.3 (q, $^1J_{C,F}$ = 291 Hz, $CF_3$), 114.8, 111.9, 110.5, 29.5 (NH*Me*).$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −67.69 (d, $^5J_{H,F}$ = 2.5 Hz, 3F, $CF_3$). EIMS 70 eV, *m/z*: 204 $[M+H]^+$ (33), 203 $[M]^+$ (32), 134 $[M-CF_3]^+$ (100), 106 $[M-CF_3-CO]^+$ (28). Anal. Calcd for C9H8F3NO: C, 53.21; H 3.97. Found C, 52.95; H, 4.22.

The aqueous layer from the above reaction was extracted with EtOAc (15 ml × 3), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (toluene/hexanes/EtOAc = 2:1:1) to give 1,1,1,3,3,3-hexafluoro-2-[2-(methylamino)phenyl]propan-2-ol (**3a**) (42 mg, 0.15 mmol, yield 2%) as a yellowish powder. Mp 80–81 °C. $^1$H NMR (300.13 MHz, $Me_2SO$-$d_6$): $\delta$ 9.82 (1H, br s, N*H*Me), 7.29 (2H, m, Ar), 6.78 (1H, d, $J$ = 8.8 Hz, Ar), 6.72 (1H, m, Ar), 6.15 (1H, br s, OH), 2.79 (3H, d, $J$ = 4.2 Hz, NH*Me*). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 147.3, 130.8, 128.7 m, $^3J_{C,F}$ = 3 Hz, CC(OH)$(CF_3)_2$, 125.8, 125.5, 123.4, 123.3 (q, $^1J_{C,F}$ = 291 Hz, $CF_3$), 80.3 (sept, $^2J_{C,F}$ = 30 Hz, C$(CF_3)_2$), 36.2 (NH*Me*).$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −74.43 (s, 6F, $(CF_3)_2$). EIMS 70 eV, *m/z*: 274 $[M+H]^+$ (12), 273 $[M]^+$ (58), 204 $[M-CF_3]^+$ (100), 186 $[M-CF_3-H_2O]^+$ (52), 166 $[M-CF_3-H_2O-HF]^+$ (90). Anal. Calcd for C10H9F9NO: C, 43.97; H 3.32; N 5.13. Found C, 43.62; H, 3.08; N, 4.88.

#### 4.2.2. 2,2,2-Trifluoro 1-[5-bromo-2-(methylamino)phenyl]ethanone (***2b***)

Yellow powder. Yield 80%. Mp 101–102 °C. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 8.79 (1H, br s, N*H*Me), 7.91 (1H, pent, $J$ = 2.0 Hz, Ar), 7.60 (1H, dd, $J_1$ = 9.3 Hz, $J_2$ = 2.0 Hz, Ar), 6.76 (1H, d, $J$ = 9.3 Hz, Ar), 3.05 (3H, d, $J$ = 5.3 Hz, NH*Me*). $^{13}$C (100.61 MHz, $CDCl_3$): $\delta$ 179.4 (q, $^2J_{C,F}$ = 33 Hz, *C*(O)$CF_3$), 152.9, 139.7, 133.5 (q, $^3J_{C,F}$ = 4 Hz, *C*C(O)$CF_3$), 116.7 (q, $^1J_{C,F}$ = 291 Hz, $CF_3$), 113.7, 111.7, 105.9, 29.4 (NH*Me*).$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −67.87 (d, $^5J_{H,F}$ = 2.0 Hz, 3F, $CF_3$). EIMS 70 eV, *m/z*: 284 $[M+H]^+$ (7), 283 $[M+]^+$ (28), 282 $[M+H]^+$ (10), 281 $[M+]^+$ (31), 279 $[M]^+$ (52), 215 $[M+H-CF_3]^+$ (9), 214 $[M-CF_3]^+$ (70), 213 $[M+H-CF_3]^+$ (8), 212 $[M-CF_3]^+$ (77), 134 $[M+H-CF_3-Br]^+$ (14), 133 $[M-CF_3-Br]^+$ (100). Anal. Calcd for C9H7BrF3NO: C, 38.33; H 2.50; N 4.97. Found C, 38.55; H, 2.80; N, 4.62.

#### 4.2.3. 2,2,2-Trifluoro-1-[2-(benzylamino)phenyl]ethanone (***2c***)

Yellow powder. Yield 85%. Mp 51–52 °C. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 9.20 (1H, br s, $NHCH_2$), 7.87 (1H, m, Ar), 7.42 (6H, m, Ar), 6.82 (1H, d, $J$ = 8.6 Hz, Ar), 6.74 (1H, dd, $J_1$ = 8.1 Hz, $J_2$ = 7.3 Hz, Ar), 4.59 (3H, d, $J$ = 5.5 Hz, $NHCH_2$). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 180.7 (q, $^2J_{C,F}$ = 33 Hz, *C*(O)$CF_3$), 153.3, 137.5, 137.3, 132.2 (q, $^3J_{C,F}$ = 4 Hz, *C*C(O)$CF_3$), 128.89, 127.8, 127.1, 117.3 (q, $^1J_{C,F}$ = 291 Hz, $CF_3$), 115.4, 112.8, 110.8, 47.0 ($NHCH_2$).$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −76.53 (br. s, 3F, $CF_3$). EIMS 70 eV, *m/z*: 280 $[M+H]^+$ (13), 279 $[M]^+$ (52), 210 $[M-CF_3]^+$ (100), 208 $[M-CF_3-2H]^+$ (32), 132 $[M-CF_3-Ph]^+$ (83). Anal. Calcd for C15H12F3NO: C, 64.51; H 4.33; N 5.02. Found C, 64.33; H, 4.37; N, 5.12.

#### 4.2.4. 2,2,2-Trifluoro-1-[2-(allylamino)phenyl]ethanone (***2d***)

Isolated by column chromatography on silica gel (chloroform/hexanes = 1:3). Yellow oil. Yield 90%. $^1$H NMR (400.13 MHz, $CDCl_3$): $\delta$ 8.74 (1H, br s, $NHCH_2CH{=}CH_2$), 7.83 (1H, m, $J_1$ = 7.8 Hz, $J_2$ = 1.5 Hz, Ar), 7.47 (1H, ddd, $J_1$ = 8.8 Hz, $J_2$ = 7.6 Hz, $J_3$ = 1.5 Hz, Ar), 6.80 (1H, br. d, $J$ = 8.8 Hz, Ar), 6.69 (1H, ddd, $J_1$ = 7.8 Hz, $J_2$ = 7.6 Hz, $J_2$ = 1.0 Hz, Ar), 5.98 (1H, m, $CH{=}CH_2$), 5.32 (2H, m, $CH{=}CH_2$), 3.98 (2H, m, $NHCH_2CH{=}CH_2$). $^{13}$C (100.61 MHz, $CDCl_3$): $\delta$ 180.4 (q, $^2J_{C,F}$ = 33 Hz, *C*(O)$CF_3$), 153.2, 137.0, 133.0, 131.9 (q, $^3J_{C,F}$ = 5 Hz, *C*C(O)$CF_3$), 117.1 (q, $^1J_{C,F}$ = 291 Hz, $CF_3$), 116.6, 114.9, 112.5, 110.6, 44.9 (s, $NHCH_2CH{=}CH_2$).$^{19}$F NMR: (282.38 MHz, $CDCl_3$) $\delta$ −67.71 (br. s, 3F, $CF_3$). EIMS 70 eV, *m/z*: 230 $[M+H]^+$ (11), 229 $[M]^+$ (33), 160 $[M-CF_3]^+$ (58), 132 $[M-CF_3-CO]^+$ (100), 130 $[M-CF_3-CO-2H]^+$ (30), 117 $[M-CF_3-CO-CH_3]^+$ (30). Anal. Calcd for C11H10F3NO: C, 57.64; H 4.40; N 6.11. Found C, 57.95; H, 4.67; N, 6.32.

*4.2.5. Synthesis of 2,2,2-trifluoro-1-[2-(methylamino)phenyl]ethanone (2a) by the reaction in THF*

To a solution of 1-methyl-2H-3,1-benzoxazine-2,4(1H)-dione **1a** (0.61 g, 3.45 mmol) and trimethyl(trifluoromethyl)silane (638 mg, 4.49 mmol) in dry THF (15 ml) was added TBAF (1M in THF; 0.52 ml, 0.52 mmol) dropwise at 0 °C under argon. After completion of addition, the reaction mixture was allowed to warm to rt and stirred for 24 h. The reaction was quenched with 5% aq HCl solution (10 ml) at 0 °C, allowed to warm to rt, and stirred 0.5 h.To the reaction mixture was added 10% aq $Na_2CO_3$ solution (50 ml) under vigorous stirring, and stirring was continued for 1 h at rt. The resulting solution was extracted with hexanes (60 ml × 3). The organic layer was washed with brine (30 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford ethanone **2a** (0.43 g, 61% yield) as a yellow oil.

*4.3. Synthesis of 1,1,1,3,3,3-hexafluoro-2-[2-(methylamino)phenyl]propan-2-ol (**3a**) by reaction of Ruppert's reagent with compound **2a***

To a solution of compound **2a** (0.36 g, 1.77 mmol), KF (30 mg, 0.52 mmol) and TBAB (168 mg, 0.52 mmol) in dry DMF (4 ml) was added trimethyl(trifluoromethyl)silane (0.71 g, 5.00 mmol) dropwise at 0 °C under argon. After completion of addition, the reaction mixture was allowed to warm to rt and stirred for 20 h. The reaction was quenched with 10% aq HCl solution (10 ml) at 0 °C, allowed to warm to rt, and stirred 2 h. The resulting solution was extracted with EtOAc (15 ml × 3). The organic layer was washed with brine (15 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (toluene/hexanes/EtOAc = 2:1:1) to afford compound **3a** (266 mg, 55% yield) as a yellowish powder.

*4.4. Synthesis of 2,2,2-trifluoro-1-[4-(methylamino)biphenyl-3-yl]ethanone (**2e**) by Suzuki coupling.*

Bromide **2b** (630 mg, 2.23 mmol), phenylboronic acid (410 mg, 3.35 mmol), tricyclohexyl phosphine ($Cy_3P$) (60 mg, 0.21mmol) and $K_3PO_4{}^*H_2O$ (1.94 g, 8.43 mmol) were combined in water (2.1 ml) and toluene (15 ml). To the mixture obtained was added $Pd(OAc)_2$ (25 mg, 0.11 mmol) and reaction stirred for 1.5 h at rt under argon. When the reaction completed, the reaction mixture was filtered through Celite, washed with toluene (40 ml) and water (10 ml). The organic layer was washed with a satd $NaHCO_3$ solution (20 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (toluene/hexanes = 3:7) to afford compound **2e** (590 mg, 2.12 mmol, 95% yield) as an orange powder. Mp 86–87 °C.$^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 8.82 (1H, br s, N*H*Me), 8.06 (1H, pent, $J$ = 2.0 Hz, Ar), 7.83 (1H, dd, $J_1$ = 9.1 Hz, $J_2$ = 2.2 Hz, Ar), 7.59 (2H, m, Ar), 7.51 (2H, m, Ar), 7.40 (1H, m, Ar), 6.91 (1H, d, $J$ = 9.1 Hz, Ar), 3.11 (3H, d, $J$ = 5.1 Hz, NH*Me*). $^{13}$C (100.15 MHz, $CDCl_3$): $\delta$ 180.4 (q, $^2J_{C,F}$ = 33 Hz, *C*(O)$CF_3$), 153.5, 139.6, 136.1, 129.8 (q, $^3J_{C,F}$ = 6 Hz, *C*C(O)$CF_3$), 128.8, 127.7, 126.7, 126.0, 117.2 (q, $^1J_{C,F}$ = 291 Hz, $CF_3$), 112.4, 110.7, 29.4 (NH*Me*).$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −67.51 (d, $^5J_{H,F}$ = 2.2 Hz, 3F, $CF_3$). EIMS 70 eV, *m/z*: 280 $[M+H]^+$ (14), 279 $[M]^+$ (66), 211 $[M+H-CF_3]^+$ (17), 210 $[M-CF_3]^+$ (100), 182 $[M-CF_3-CO]^+$ (33), 165 $[M-CF_3-CO-NH_3]^+$ (33). Anal. Calcd for C15H12F3NO: C, 64.51; H 4.33; N 5.02. Found C, 64.35; H, 4.37; N, 5.23.

*4.5. General procedure for synthesis of compounds **5a–d***

To a solution of the corresponding 1-aryl-2H-3,1-benzoxazine-2,4(1H)-dione (N-arylisatoic anhydride) (**4a–d**) (10 mmol), KF (174 mg, 3 mmol) and TBAB (967 mg, 3 mmol) in dry DMF (20 ml) was added trimethyl(trifluoromethyl)silane (1.85 g, 13 mmol) dropwise at 0 °C under argon. After completion of addition, the reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched with 5% aq HCl solution (10 ml) at 0 °C, allowed to warm to rt, and stirred 0.5 h.

*4.5.1. 2,2,2-Trifluoro-1-(2-anilinophenyl)ethanone (**5a**)*

The isolation proceeded as follows. The reaction mixture treated as above was extracted with hexanes (60 ml × 3). The organic layer was washed with brine (30 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in 20 ml n-hexane, stored at −20 °C overnight. Precipitate that formed was filtered off to afford 5,11-diphenyl-6-(trifluoromethyl)-12-[(trimethylsilyl)oxy]-5,6,11,12-tetrahydro-6,12-epoxydi-benzo[b,f][1,5]diazocine (**6a**) (150 mg, 0.28 mmol, 6%) as a yellowish powder. Mp 168 °C.$^1$H NMR (600.21 MHz, $CDCl_3$): $\delta$ 7.5–7.2 (12H, m, Ar), 7.10 (1H, td, $J_1$ = 7.6 Hz, $J_2$ = 1.1 Hz, Ar), 6.97 (1H, td, $J_1$ = 7.6 Hz, $J_2$ = 1.5 Hz, Ar), 6.81 (1H, t, $J$ = 7.8 Hz, Ar), 6.77 (1H, t, $J$ = 7.8 Hz, Ar), 6.58 (1H, d, $J$ = 8.4 Hz, Ar), 6.20 (1H, d, $J$ = 8.1 Hz, Ar), 0.02 (9H, s, $SiMe_3$). $^{13}$C NMR (150.93 MHz, $CDCl_3$): $\delta$ 145.1, 143.9, 142.7, 142.2, 132.7, 132.1, 131.1, 129.6, 128.9, 128.8, 128.5, 128.0, 126.8, 126.4, 126.0, 122.9 (q, $^1J_{C,F}$ = 286 Hz, $CF_3$), 120.3, 119.7, 119.5, 119.4, 117.2, 101.6, 88.8 (q, $^2J_{C,F}$ = 30 Hz, C–$CF_3$), 0.9 ($SiMe_3$).$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −71.84 (s, 3F, $CF_3$). EIMS 70 eV, *m/z*: 532 $[M]^+$ (27), 517 $[M-CH_3]^+$ (12), 463 $[M-CF_3]^+$ (22), 440 $[M-CH_3-Ph]^+$ (16), 373 $[M-CF_3-CH_3-Ph+2H]^+$ (47), 345 $[M-CH_3-2Ph-F+H]^+$ (19), 324 $[M-CH_3-2Ph-2F+H]^+$ (100). Anal. Calcd for C30H27F3N2O2Si: C, 67.65; H 5.11; N 5.26. Found C, 67.25; H, 4.98; N, 5.02.

The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (toluene/hexanes 1:25) on silica gel to afford ethanone **5a**. Orange oil [22b]. Yield 74%. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 10.31 (1H, br s, NHPh), 7.92 (1H, dqd, $J_1$ = 8.4 Hz, $^5J_{H,F}$ = 2.1 Hz, $J_2$ = 1.4 Hz, Ar), 7.47 (3H, m, Ar), 7.30 (4H, m, Ar), 6.83 (1H, ddd, $J_1$ = 8.4 Hz, $J_2$ = 7.0 Hz, $J_3$ = 1.1 Hz, Ar). $^{13}$C NMR spectral data completely agreed with the data reported in the literature [12]. $^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −67.87 (d, $J$ = 2.1 Hz, 3F, $CF_3$).

*4.5.2. 2,2,2-Trifluoro-1-{2-[(4-methoxyphenyl)amino]phenyl}ethanone (**5b**)*

The reaction time was 5 h. The isolation proceeded as follows. When stirred, the reaction mixture treated as above formed a precipitate, which was filtered off, washed with water (50 ml) and dried in vacuum to give **5b**. Yellow powder. Yield 83%. Mp 80 °C, ref. [12] mp 77–78 °C. $^1$H NMR (600.21 MHz, $CDCl_3$): $\delta$ 10.15 (br s, 1H, NHPh), 7.85 (d, $J$ = 7.8 Hz, 1H, Ar), 7.37 (t, $J$ = 7.8 Hz, 1H, Ar), 7.21 (d, $J$ = 8.7 Hz, 2H, Ar), 7.00 (d, $J$ = 7.8 Hz, 1H, Ar), 6.97 (d, $J$ = 8.7 Hz, 2H, Ar), 6.73 (d, $J$ = 7.8 Hz, 1H, Ar), 3.86 (s, 3H, OMe). $^{13}$C NMR spectral data completely agreed with the data reported in the literature [12]. $^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −67.84 (br. s, 3F, $CF_3$).

*4.5.3. 2,2,2-Trifluoro-1-{2-[(4-fluorophenyl)amino]phenyl}ethanone (**5c**)*

The reaction time was 5 h.The isolation proceeded as follows. The reaction mixture was treated as above, extracted with hexanes (60 ml × 3). The organic layer was washed with brine (30 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (PhH/hexanes/EtOAc 1:40:5) on silica gel to afford ethanone **5c**. Yellow powder. Yield 67%. Mp 65–66 °C. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 10.19 (1H, br s, NHAr), 7.92 (1H, m, Ar), 7.45 (3H, m, Ar), 7.30 (2H, m, Ar), 7.14 (3H, m, Ar), 6.82 (1H, ddd, $J_1$ = 8.4 Hz, $J_2$ = 6.9 Hz, $J_3$ = 1.0 Hz, Ar). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 181.1 (q,

$^{2}J_{C,F}$ = 33 Hz, *C*(O)$CF_3$), 160.6 (d, $^{1}J_{C,F}$ = 245 Hz, C–F), 151.8, 137.0, 134.7 (d, $^{4}J_{C,F}$ = 3 Hz), 132.0 (q, $^{3}J_{C,F}$ = 4 Hz, *C*C(O)$CF_3$), 126.8 (d, $^{3}J_{C,F}$ = 9 Hz), 117.1 (q, $^{1}J_{C,F}$ = 291 Hz, $CF_3$), 116.9, 116.5 (d, $^{2}J_{C,F}$ = 27 Hz), 114.1, 111.7. $^{19}$F {$^{1}$H} NMR (282.38 MHz, $CDCl_3$): $\delta$ −67.91 (s, 3F, $CF_3$), −114.86 (s, 1F, 4-$FC_6H_4$). EIMS 70 eV, *m/z*: 284 $[M+H]^+$ (14), 283 $[M]^+$ (87), 215 $[M-CF_3]^+$ (16), 214 $[M-CF_3]^+$ (100), 186 $[M-CF_3-CO]^+$ (8), 185 $[M-CF_3-CO-H]^+$ (35), 166 $[M-CF_3-CO-HF]^+$ (17). Anal. Calcd for C14H9F4NO: C, 59.37; H 3.20; N 4.95. Found C, 59.05; H, 3.18; N, 5.12.

#### 4.5.4. 2,2,2-Trifluoro-1-(2-{[4-(diphenylmethyl)phenyl]amino}phenyl)ethanone (**5d**)

The reaction time was 10 h. The isolation proceeded as follows. The reaction mixture was treated as above, extracted with hexanes (60 ml × 3). The organic layer was washed with brine (30 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/toluene/EtOAc 7:2:1) on silica gel to afford compound **5d**. Yellow–orange oil. Yield 77%. $^{1}$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 10.30 (1H, s, NHAr), 7.91 (1H, m, Ar), 7.51–7.21 (16H, m, Ar), 6.82 (1H, m, Ar), 5.64 (1H, s, $CHPh_2$).$^{13}$C (75.46 MHz, $CDCl_3$): $\delta$ 180.9 (q, $^{2}J_{C,F}$ = 33 Hz, *C*(O)$CF_3$), 151.3, 143.7, 141.3, 137.0, 136.9, 132.0 (q, $^{3}J_{C,F}$ = 4 Hz, *C*C(O)$CF_3$), 130.6, 129.4, 128.4, 126.5, 124.2, 117.2 (q, $^{1}J_{C,F}$ = 291 Hz, $CF_3$), 116.8, 114.6, 111.8, 56.4. $^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −67.85 (br. s, 3F, $CF_3$). EIMS 70 eV, *m/z*: 432 $[M+H]^+$ (32), 431 $[M]^+$ (100), 413 $[M+H-F]^+$ (29), 363 $[M+H-CF_3]^+$ (29), 362 $[M-CF_3]^+$ (90), 354 $[M-Ph]^+$ (80), 284 $[M-HCF_3-Ph]^+$ (24). Anal. Calcd for C27H20F3NO: C, 75.16; H 4.67; N 3.25. Found C, 75.44; H, 4.89; N, 3.42.

By the further eluation of the column was isolated 2-(2-{[4-(diphenylmethyl)phenyl]amino}phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**7d**). Brown oil, yield 5%. $^{1}$H NMR (600.21 MHz, $CDCl_3$): $\delta$ 7.74 (1H, d, *J* = 7.7 Hz, Ar), 7.45 (1H, dd, $J_1$ = 7.5 Hz, $J_2$ = 7.0 Hz, Ar), 7.38 (1H, dd, $J_1$ = 7.7 Hz, $J_2$ = 7.5 Hz, Ar), 7.33–7.14 (11H, m, Ar), 7.05 (2H, d, *J* = 8.1 Hz, Ar), 6.76 (2H, d, *J* = 8.1 Hz, Ar), 5.53 (1H, s, $CHPh_2$). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 143.8, 143.4, 143.2, 138.7, 131.1, 130.5, 130.1, 129.4, 128.7, 128.4, 127.3, 126.4, 125.6, 123.1 (q, $^{1}J_{C,F}$ = 290 Hz, $CF_3$), 118.9, 80.0 (sept, $^{2}J_{C,F}$ = 31 Hz, $C(CF_3)_2$), 56.2.$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −74.12 (s, 6F, $(CF_3)_2$). EIMS 70 eV, *m/z*: 502 $[M+H]^+$ (33), 501 $[M]^+$ (99), 424 $[M-Ph]^+$ (100), 336 $[M-Ph-CF_3-H_2O-H]^+$ (25), 229 $[M-2Ph-H_2O]^+$ (43). Anal. Calcd for C28H21F6NO: C, 67.06; H 4.22; N 2.79. Found C, 67.35; H, 4.37; N, 2.49.

By the further eluation of the column was isolated 2-(diphenylmethyl)-9-(trifluoromethyl)acridine (**8d**). Brown powder. Yield 5%. Mp 131–132 °C. $^{1}$H NMR (600.21 MHz, $CDCl_3$): $\delta$ 8.46 (1H, d, *J* = 9.0 Hz, Ar), 8.31 (1H, d, *J* = 9.0 Hz, Ar), 8.23 (1H, d, *J* = 9.0 Hz, Ar), 8.16 (1H, br. s, Ar), 7.82 (1H, dd, $J_1$ = 6.6 Hz, $J_2$ = 9.0 Hz,Ar), 7.70 (1H, dd, $J_1$ = 9.0 Hz, $J_2$ = 1.3 Hz, Ar), 7.64 (1H, ddd, $J_1$ = 6.6 Hz, $J_2$ = 9.0 Hz, $J_3$ = 1.3 Hz), 7.37 (4H, m, Ar), 7.31 (2H, m, Ar), 7.24 (4H, m, Ar), 5.81 (1H, s, $CHPh_2$). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 148.7, 148.3, 144.0, 142.7, 132.4, 130.6, 130.4, 129.7, 129.5, 129.1 (q, $^{2}J_{C,F}$ = 29 Hz, $^{9}CCF_3$), 128.6, 128.1, 126.9, 125.5 (q, $^{1}J_{C,F}$ = 279 Hz, $CF_3$), 124.3 (q, $^{4}J_{C,F}$ = 6 Hz), 123.8 (q, $^{4}J_{C,F}$ = 6 Hz), 123.0, 122.7, 57.5.$^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −48.98 (s, 3F, $CF_3$). EIMS 70 eV, *m/z*: 414 $[M+H]^+$ (28), 413 $[M]^+$ (100), 412 $[M-H]^+$ (61), 336 $[M-Ph]^+$ (35), 266 $[M-Ph-HCF_3]^+$ (31). Anal. Calcd for C27H18F3N: C, 78.44; H 4.39; N 3.39. Found C, 78.73; H, 4.47; N, 3.12.

### 4.6. General procedure for synthesis of acridines **8a–d**

To a solution of ethanone **5a–d** (3 mmol) in $CHCl_3$ (7 ml) was added TFA (4.0 g) and reaction mixture stirred for the specified time. The solvents were removed under reduced pressure, the residue was diluted by EtOAc (50 ml) and a satd aq $NaHCO_3$ solution (30 ml). The organic layer was washed with brine (20 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by recrystallization from acetone to give acridine **8a–d**.

#### 4.6.1. 9-(Trifluoromethyl)acridine (**8a**)

Reaction time 72 h. Yellowish powder. Yield 86%. Mp 108 °C (acetone). $^{1}$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 8.56 (2H, br. d, *J* = 9.0 Hz, H-1, H-8), 8.36 (2H, d, *J* = 9.0 Hz, *J* = 1.0 Hz, H-4, H-5), 7.89 (2H, dt, *J* = 9.0 Hz, *J* = 1.0 Hz, H-3, H-6), 7.64 (2H, ddd, $J_1$ = 9.0 Hz, $J_2$ = 7.0 Hz, $J_3$ = 1.0 Hz, H-2, H-7). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 148.5, 130.3, 130.1, 129.8 (q, $^{2}J_{C,F}$ = 28 Hz, $^{9}CCF_3$), 128.2, 128.1, 125.5 (q, $^{1}J_{C,F}$ = 279 Hz, $CF_3$), 124.3 (q, $^{4}J_{C,F}$ = 6 Hz, C-1, C-8), 122.7. $^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −48.93 (s, 3F, $CF_3$). EIMS 70 eV, *m/z*: 248 $[M+H]^+$ (18), 247 $[M]^+$ (100), 198 $[M+H-CF_2]^+$ (11), 197 $[M-CF_2]^+$ (64), 178 $[M-CF_3]^+$ (9). Anal. Calcd for C14H8F3N: C, 68.02; H 3.26; N 5.67. Found C, 67.95; H, 3.37; N, 5.42.

#### 4.6.2. 2-Methoxy-9-(trifluoromethyl)acridine (**8b**)

Reaction time 120 h. Green powder. Yield 64%. Mp 91–92 °C (acetone). $^{1}$H NMR (600.21 MHz, $CDCl_3$): $\delta$ 8.39 (1H, d, *J* = 9.0 Hz, Ar), 8.25 (1H, d, *J* = 9.0 Hz, Ar), 8.15 (1H, d, *J* = 9.4 Hz, Ar), 7.73 (1H, dd, $J_1$ = 6.6 Hz, $J_2$ = 9.0 Hz,Ar), 7.62 (1H, ddd, $J_1$ = 6.6 Hz, $J_2$ = 9.0 Hz, $J_3$ = 1.1 Hz), 7.54 (1H, br. s, Ar), 7.46 (1H, dd, $J_1$ = 6.6 Hz, $J_2$ = 9.0 Hz,Ar), 3.97 (3H, s, $OCH_3$). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 158.7, 146.7, 146.0, 131.9, 130.4, 128.8, 128.2, 126.8 (q, $^{2}J_{C,F}$ = 29 Hz, C-9), 125.8 (q, $^{1}J_{C,F}$ = 277 Hz, $CF_3$), 125.5, 124.1, 123.8 (q, $^{4}J_{C,F}$ = 6 Hz, C-8), 123.1, 99.9 (q, $^{4}J_{C,F}$ = 6 Hz, C-1), 55.5. $^{19}$F NMR (282.38 MHz, $CDCl_3$): $\delta$ −49.73 (s, 3F, $CF_3$). EIMS 70 eV, *m/z*: 278 $[M+H]^+$ (18), 277 $[M]^+$ (100), 247 $[M-OCH_2]^+$ (8), 234 $[M-COCH_3]^+$ (81), 214 $[M-HF-COCH_3]^+$ (11), 184 $[M-CF_2-COCH_3]^+$ (16). Anal. Calcd for C15H10F3NO: C, 64.98; H 3.64; N 5.05. Found C, 64.63; H, 3.47; N, 5.66.

#### 4.6.3. 2-Fluoro-9-(trifluoromethyl)acridine (**8c**)

Reaction time 168 h. Yellowish powder. Yield 53%. Mp 82–83 °C (acetone). $^{1}$H NMR (600.21 MHz, $CDCl_3$): $\delta$ 8.45 (1H, d, *J* = 9.0 Hz, Ar), 8.31 (1H, dd, *J* = 9.0 Hz, *J* = 6.2 Hz, Ar), 8.29 (1H, d, *J* = 9.0 Hz Ar), 8.10 (1H, d, $J_{H-F}$ = 11.5 Hz, Ar), 7.83 (1H, dd, $J_1$ = 6.6 Hz, $J_2$ = 9.0 Hz, Ar), 7.70 (1H, ddd, $J_1$ = 6.6 Hz, $J_2$ = 9.0 Hz, $J_3$ = 1.1 Hz, Ar), 7.64 (1H, m, Ar). $^{13}$C (150.93 MHz, $CDCl_3$): $\delta$ 161.1 (d, $^{1}J_{C,F}$ = 252 Hz, C–F), 148.3 (d, $^{4}J_{C,F}$ = 3 Hz), 146.4, 134.7 (d, $^{4}J_{C,F}$ = 3 Hz), 132.0 (q, $^{3}J_{C,F}$ = 4 Hz, *C*C(O)$CF_3$), 133.5 (d, $^{3}J_{C,F}$ = 10 Hz), 128.9 (dq, $^{2}J_{C,F}$ = 25 Hz, $^{4}J_{C,F}$ = 8 Hz, C-9), 128.8, 125.4 (q, $^{1}J_{C,F}$ = 279 Hz, $CF_3$), 123.4 (q, $^{4}J_{C,F}$ = 6 Hz), 123.1, 123.0, 121.9 (d, $^{2}J_{C,F}$ = 28 Hz), 107.2 (dq, $^{2}J_{C,F}$ = 28 Hz, $^{4}J_{C,F}$ = 7 Hz, C-1). $^{19}$F {$^{1}$H} NMR (282.38 MHz, $CDCl_3$): $\delta$ −49.63 (s, 3F, $CF_3$), −106.53 (s, 1F, 4-$FC_6H_4$). EIMS 70 eV, *m/z*: 266 $[M+H]^+$ (18), 265 $[M]^+$ (100), 246 $[M-F]^+$ (9), 216 $[M+H-CF_2]^+$ (11), 215 $[M-CF_2]^+$ (72), 195 $[M-H-CF_3]^+$ (10). Anal. Calcd for C14H7F4N: C, 63.40; H 2.66; N 5.28. Found C, 63.25; H, 2.47; N, 5.12.

#### 4.6.4. 2-(Diphenylmethyl)-9-(trifluoromethyl)acridine (**8d**)

Reaction time 72 h. Brown powder. Yield 83%.

### 4.7. X-ray diffraction experiment

Yellow single crystal samples of **6a** in the form of thin plates suitable for the X-ray study were obtained by slow evaporation of solution of **6a** in diethyl ether. At room temperature (294K), crystals **6a** ($C_{30}H_{27}F_3N_2O_2Si$) are triclinic, space group *P*-1: *a* = 9.169(3) Å, *b* = 11.706(4) Å, *c* = 13.853(5) Å, $\alpha$ = 86.544(8), $\beta$ = 73.189(7), $\gamma$ = 67.937(7), *V* = 1317.1(8) Å$^3$, *Z* = 2, $d_{calc}$ = 1.343 g cm$^{-3}$, $\mu$ = 0.141 mm$^{-1}$. The 7660 reflections were collected at SMART APEX2 CCD difractometer ($\lambda$(Mo-K$\alpha$) = 0.71073 Å, graphite monochromator, ω-scans, $2\theta < 60$) at 294 K. An analysis

of measured intensities was carried out with the SAINT and SADABS programs included in the APEX2 program package [25]. The structure was solved by the direct methods and refined by the full-matrix least-squares procedure against $F^2$ in anisotropic approximation. The 5046 independent reflections ($R$(int) = 0.0376) were used in the refinement procedure that was converged to $wR_2$ = 0.1066 calculated on $F^2_{hkl}$ (GOF = 0.987, $R_1$ = 0.0513 calculated on $F_{hkl}$ using 2511 reflections with $I > 2\sigma(I)$). The refinement was carried out with the SHELXTL program [26]. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Any request to the CCDC should quote the full literature citation and the reference number 876706.

## Acknowledgment

This work was financially supported by the Russian Foundation for Basic Research (Project ofi-ts no. 08-04-13562).

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.07.002.

## References

[1] (a) N.A. Magnus, P.N. Confalone, L. Storace, M. Patel, C.C. Wood, W.P. Davis, R.L. Parsons Jr., Journal of Organic Chemistry 68 (2003) 754–761;
(b) M.E. Pierce, R.L. Parsons Jr., L.A. Radesca, Y.S. Lo, S. Silverman, J.R. Moore, Q. Islam, A. Choudhury, J.M.D. Fortunak, D. Nguyen, C. Luo, S.J. Morgan, W.P. Davis, P.N. Confalone, Journal of Organic Chemistry 63 (1998) 8536–8543.
[2] S. Ishikawa, T. Mizutani, T. Nagase, N. Sato, H. Takahashi, Benzoxazinone derivative, European Patent Application, 2210880 (2010).
[3] A.S. Golubev, V.O. Bogomolov, A.F. Shidlovskii, L.G. Dezhenkova, A.S. Peregudov, A.A. Shtil, N.D. Chkanikov, Russian Chemical Bulletin International Edition 59 (2010) 209–218.
[4] L. Zhu, Z. Miao, C. Sheng, W. Guo, J. Yao, W. Liu, X. Che, W. Wang, P. Cheng, W. Zhang, European Journal of Medicinal Chemistry 45 (2010) 2726–2732.
[5] N.S. Mani, J.-H. Chen, J.P. Edwards, M. Wu, P. Chen, R.I. Higuchi, Tetrahedron Letters 49 (2008) 1903–1905.
[6] J.C. Barrow, R.V. Cube, P.L. Ngo, K.E. Rittle, Z. Yang, S.D. Young, Quinazolinone T-type calcium channel antagonists, WO Application, 2006098969.
[7] D.L. Flynn, J. Zablocki, K. Williams, S.L. Hockerman, Electrophilic ketones for the treatment of herpesvirus infections, US Patent Application, 20030119721.
[8] (a) D.-S. Kim, Y.-M. Chung, M. Jun, K.H. Ahn, Journal of Organic Chemistry 74 (2009) 4849–4854;
(b) D.-S. Kim, H. Miyaji, B.-Y. Chang, S.-M. Park, K.H. Ahn, Chemical Communications (2006) 3314–3316.
[9] (a) A.S. Thompson, E.G. Gorley, M.F. Huntington, E.J.J. Grabowski, Tetrahedron Letters 36 (1995) 8937–8940;
(b) M. Patel, S.S. Ko, R.J. McHugh Jr., J.A. Markwalder, A.S. Srivastava, B.C. Cordova, R.M. Klabe, S. Erickson-Viitanen, G.L. Trainor, S.P. Seitz, Bioorganic and Medicinal Chemistry Letters 9 (1999) 2805–2810;
(c) J.W. Corbett, S.S. Ko, J.D. Rodgers, L.A. Gearhart, N.A. Magnus, L.T. Bacheler, S. Diamond, S. Jeffrey, R.M. Klabe, B.C. Cordova, S. Garber, K. Logue, G.L. Trainor, P.S. Anderson, S.K. Erickson-Viitanen, Journal of Medicinal Chemistry 43 (2000) 2019–2030;
(d) F. Leroux, O. Lefebvre, M. Schlosser, European Journal of Organic Chemistry (2006) 3147–3151;
(e) L. Zhu, Z. Miao, C. Sheng, J. Yao, C. Zhuang, W. Zhang, Journal of Fluorine Chemistry 131 (2010) 800–804.
[10] T. Mizutani, S. Ishikawa, T. Nagase, H. Takahashi, T. Fujimura, T. Sasaki, A. Nagumo, K. Shimamura, Y. Miyamoto, H. Kitazawa, M. Kanesaka, R. Yoshimoto, K. Aragane, S. Tokita, N. Sato, Journal of Medicinal Chemistry 52 (2009) 7289–7300.
[11] (a) M. Hojo, R. Masuda, E. Okada, Tetrahedron Letters 28 (1987) 6199–6200;
(b) E. Okada, N. Tsukushi, Y. Otsuki, S. Nishiyama, T. Fukuda, Synlett (1999) 126–127;
(c) E. Okada, N. Tsukushi, N. Shimomura, Synthesis (2000) 237–242.
[12] Z. Liu, R.C. Larock, Journal of the American Chemical Society 127 (2005) 13112–13113.
[13] W. Fuhrer, H. Gschwend, Journal of Organic Chemistry 44 (1979) 1133–1136.
[14] M. Patel, R.J. McHugh Jr., B.C. Cordova, R.M. Klabe, S. Erickson-Viitanen, G.L. Trainor, S.S. Ko, Bioorganic and Medicinal Chemistry Letters 9 (1999) 3221–3224.
[15] (a) W.M. Owton, Tetrahedron Letters 44 (2003) 7147–7149;
(b) Y-M. Zhang, P.J. Connoly, S.-C. Lin, M.J. Maclelag, Amino-pyrrolidine-azetidine diamines as monoacylglycerol lipase inhibitors, US Patent Application, 20120101081.
[16] (a) R.P. Singh, J. Shreeve, Tetrahedron 56 (2000) 7613–7632;
(b) G.K.S. Prakash, A.K. Yudin, Chemical Reviews 97 (1997) 757–786.
[17] N. Allendörfer, M. Es-Sayed, M. Nieger, S. Bräse, Tetrahedron Letters 53 (2012) 388–391.
[18] A.J. Cocuzza, D.R. Chidester, B.C. Cordova, S. Jeffrey, R.L. Parsons, L.T. Bacheler, S. Erickson-Viitanen, G.L. Trainor, S.S. Ko, Bioorganic and Medicinal Chemistry Letters 11 (2001) 1177–1179.
[19] Y. Wang, J. Ai, G. Liu, M. Geng, A. Zhang, Organic and Biomolecular Chemistry 9 (2011) 5930–5933 (Parent diazocines are known).
[20] A.M. D'Souza, N. Spiccia, J. Basutto, P. Jokisz, L.S.-M. Wong, A.G. Meyer, A.B. Holmes, J.M. White, J.H. Ryan, Organic Letters 13 (2011) 486–489.
[21] (a) D.H. Aue, D. Thomas, Journal of Organic Chemistry 40 (1975) 2360–2365;
(b) S.R. Turner, L.J. Guilbault, G.B. Butler, Journal of Organic Chemistry 36 (1971) 2838–2840.
[22] (a) D.C. Rognes, R.C. Larock, Journal of Organic Chemistry 75 (2010) 2289–2295, and references therein;
(b) D.G. Pintori, M.F. Greaney, Organic Letters 12 (2010) 168–171.
[23] (a) M. Hojo, R. Masuda, E. Okada, T. Tomofuji, N. Imazaki, Synthesis (1990) 1135–1137, 9-CF3-benz[c]acridines;
(b) T.N. Vasilevskaja, I.I. Baturina, M.I. Kollegova, T.N. Gerasimova, V.A. Barkhash, Russian Journal of Organic Chemistry 7 (1971) 1230–1239, The only 9-CF3-acridine isolated as a by-product.
[24] (a) G.M. Coppola, Journal of Heterocyclic Chemistry 24 (1987) 1249–1251;
(b) G.E. Hardtmann, G. Koletar, O.R. Pfister, Journal of Heterocyclic Chemistry 12 (1975) 565–572.
[25] APEX2 and SAINT, Bruker AXS Inc., Madison, WI, USA, 2005.
[26] G.M. Sheldrick, Acta Crystallographica A64 (2008) 112.