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Trifluoromethyl-containing *N*-acylmethylenequinone imines as novel highly electrophilic agents

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Abstract

The strategy of searching for highly electrophilic agents in a class of chemically inert compounds – methylenequinone imines – was developed and successfully performed. The first representative of such electrophiles – *N*-acyl-α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinone imine **6** – was synthesized. Its reactions with N-, O- and C-nucleophiles were investigated that gave various derivatives of α-trifluoromethyl-α-amino(oxy) acids as well as ß,ß,ß-trifluoropropionic acids. 3-Chloro-3-trifluoro-1,3-dihydroindol-2-ones were first obtained and their reactions with nucleophiles were studied with 1-aza-3-trifluoroindene-2-ones being formed as intermediates.

Keywords: *N*-Acylmethylenequinone imines; 1-Azainden-2-ones; Electrophiles; 1,3-Dihydroindol-2-ones

1. Introduction

The quarternary salts of *N*,*N*-dialkyl-α,α-aryl substituted *p*-methylenequinone imines were first obtained by Fischer and Fischer [1]. *N*-Phenyl-α,α-aryl substituted *p*-methylenequinone imines were synthesized by Bayer in the beginning of the last century [2]. Recently their *N*-alkyl analogues have been patented by Mitsubischi Chem. Ind. [3] and described in [4]. The compounds of this type and their quaternary salts are well known to form a large family of triphenylmethane dyes [5]. However, the reactivity of the *p*-methylenequinone imine system of these compounds has been studied only by two examples, namely, addition of water and methanol in the presence of HCl that gave 4-(*N*-phenyl)triphenylcarbinol and its methyl ether, respectively [2].

At present there is the only publication concerning *N*-acyl-*p*-methylenequinone imines: hydrochloride and other salts of *N*-{4-[4-acryloylaminophenyl)-(4-diphenylaminonaphthalene-1-yl)methylene]cyclohexa-2,5-dienylidene}acrylamide, containing the donor aryl substituents in the α-position have been patented recently as monomers for production of ink [6].

In literature there is no information about the existence of *N*-acyl-*p*-methylenequinone imines containing either α-alkyl groups or α-accepting substituents and the data concerning their reactivity. In this context, it was interesting to make an attempt to synthesize such quinone imines, since the electron deficiency at the N-atom as a result of the conjugation with the carbonyl group will lead to the qualitative changes in their reactivity, i.e. the loss of the inertness inherent to the dyes and appearance of the features of electrophilic agents similar to those of *p*-methylene quinones [7]. Of course, this effect will be enhanced by the electron accepting trifluoromethyl and methoxycarbonyl groups in the α-position of the *N*-acyl-*p*-methylenequinone imines **A** (Fig. 1).

The electronic structure of *N*-alkyl(aryl)-*p*-methylenequinone imines (**B**) differs from that of the *p*-methylenequine

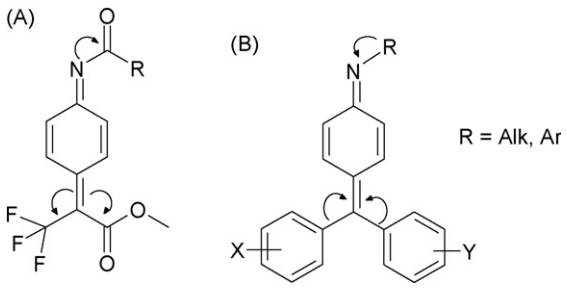

Fig. 1. The differences in electron structure of (A) and (B).

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imines **A** by the presence of the alkyl(aryl) groups (X,Y = OAlk, $NAlk_2$) that donate electrons into the conjugated system to result in the low reactivity towards nucleophiles.

2. Results and discussion

2.1. Method for synthesis of N-acyl-p-methylenequinone imines

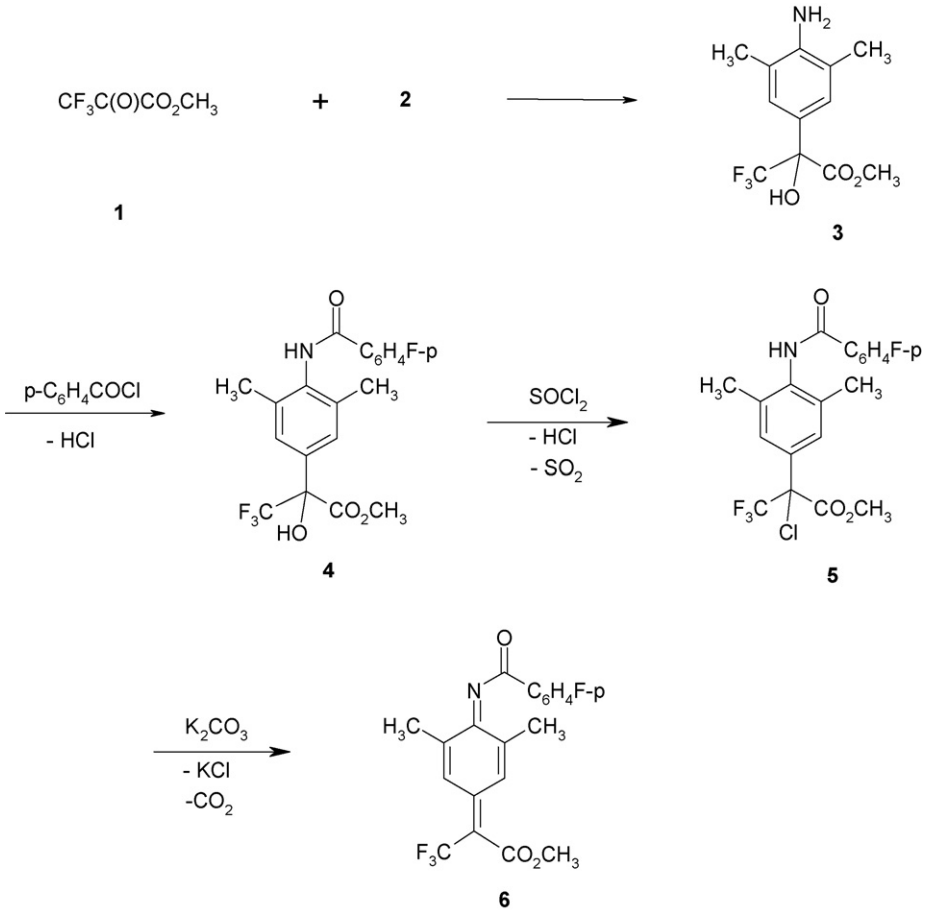
We used the described scheme for synthesizing α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinones [8] as the basis for the synthesis of *N*-acyl-*p*-methylenequinone imines. The starting methyl 2-(4-amino-3,5-dimethylphenyl)-3,3,3-trifluoro-2-hydroxypropionate **3** was prepared by C-alkylation of 2,6-dimethylaniline **2** with methyl trifluoropyruvate **1** [9]. It should be noted that ester **1** was first synthesized by Knunyants et al. [10]. The ester **3** was *N*-acylated with *p*-fluorobenzoyl chloride. Substitution of the OH group in the resulting amide **4** by the chlorine using thionyl chloride gave the corresponding 4-acylaminobenzyl chloride **5**. Heating of product **5** with dehydrochlorinating agents such as pyridine, tertiary amines, and alkali metal hydroxides and carbonates leads to the target *N*-(*p*-fluorobenzoyl)-α- methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinones imine **6** (TLC monitoring) (Scheme 1)

Our numerous attempts to synthesize *N*-acyl-*p*-methylenequinone imines that had failed and some literature data [11] resulted in some doubts concerning the existence of a compound with such an electron-deficient conjugated system. However, compound **6** containing the above system proved to be a stable material under common conditions having distinct melting point.

2.2. NMR data

The ^{1}H and ^{13}C NMR data for the compound **6** are given in Section 4. The signal assignments have been performed using the attached proton test experiment and two-dimensional correlated NMR spectroscopy gs-HSQC and gs-NOESY. These assignments were not trivial and based on the following results (Fig. 2).

In the ^{13}C NMR spectra, splitting of the signals for ^{13}C nuclei due to the spin–spin coupling with ^{19}F nuclei of the CF_3 group is observed not only for the ^{13}C nuclei in positions 21 and 11, but also through three bonds for the carbons in positions 4 and 12. In addition, the ^{13}C NMR spectrum shows the long-range coupling through 4 bonds with the coupling constant being equal to 2 Hz. At the same time this coupling is observed only for one of the ^{13}C nuclei (positions 3 or 5). Since it is known that spin–spin coupling is better transmitted for the



Scheme 1.

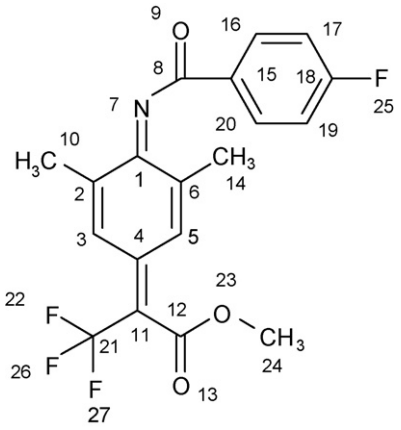


Fig. 2. Numeration of atoms in compound **6**.

trans-position, the signal at 128.0 ppm appears to be assigned to the ^{13}C nuclear in position 5.

To confirm this conclusion and to assign the signals of the quaternary carbons in positions 2 and 6 we used gradient-selected (gs)-HMBC.

In the ^{13}C NMR spectrum of compound **6**, there are cross-peaks between the high field signal of the methyl group and two signals of ^{13}C carbons at 130.1 and 140.0 ppm. The low field signal of the methyl group gives the cross peaks with the signals of the ^{13}C nuclei at 128.0 and 139.4 ppm. In addition, both methyl groups give cross-peaks with ^{13}C nuclear in position 1 at 154.6 ppm.

Further the NOESY spectrum (Fig. 3) shows correlation peaks between the high field signal of the methyl group at 2.067 ppm and the high field signal of the CH proton (6.935 ppm) as well as between the low field signal of the methyl group at 2.117 ppm and the low field signal of the CH proton (7.166 ppm). The 2D H,C-correlation spectrum HSQC indicates that the CH-proton at 7.166 ppm is bound with the ^{13}C nuclear at 128.0 ppm in position 5. Therefore, the signal at 2.117 ppm is assigned to the methyl group in position 6.

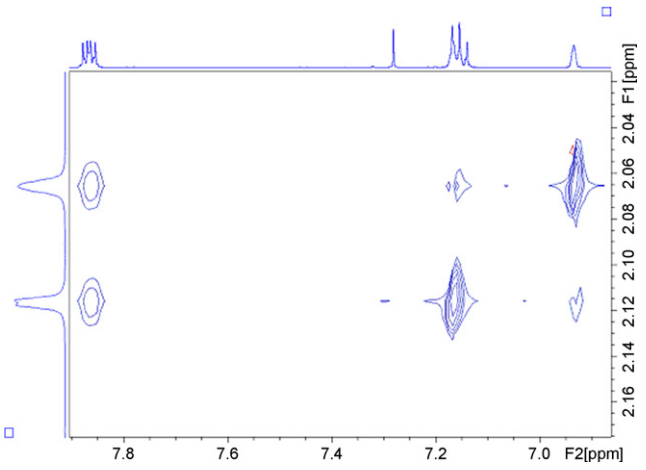


Fig. 3. A portion of the two-dimensional 600 MHz gs-NOESY spectrum of **6**. The 600 MHz ^{1}H spectrum is shown at the top and the left-hand edges.

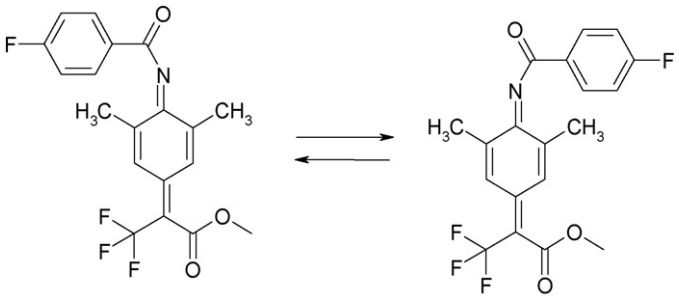


Fig. 4. The possible orientation of the *p*-fluorobenzoyl substituent in compound **6**.

The ^{1}H and ^{13}C nuclei of CH_3 and CH groups in positions 3 and 5 as well as ^{13}C nuclei in positions 2 and 6 of the cyclohexadiene moiety are not magnetically equivalent. At the same time, in the $^{19}F\{^{1}H\}$ spectrum of compound **6**, each of the CF_3- and 4-FC_6H_4-groups gives one signal at −105.30 and −54.55 ppm, respectively.

On one hand, the presence of one set of signals of the indicator ^{1}H, ^{13}C and ^{19}F nuclei suggests that compound **6** exists in the form of one stereoisomer. On the other hand, in the NOESY spectrum, the correlation peaks were unexpectedly found between the signals assigned to the aromatic CH-protons in the 4-fluorophenyl radical (multiplets at 7.867 ppm, positions 16 and 20) with the signals of protons of both methyl groups. The correlation peaks with only one methyl group in the *sin*-position would have been observed if compound **6** had existed in the form of one isomer, stable on the NMR time scale where the 4-fluorobenzoyl radical and the carbomethoxy group could be oriented either to one side or different sides (Fig. 4).

In case the compound **6** had been a mixture of such isomers, the above signals of the indicator groups would have appeared in the form of double set of signals, but this is not observed in the NMR experiments.

The above spectral picture can be explained if we assume a fast NMR transfer on the time scale between these two isomers (Fig. 4). In this case the observed in the NMR spectra magnetic non-equivalence of the indicator nuclei is resulted from the different electron and anisotropic effects of the carbomethoxy and trifluoromethyl groups. In this connection it is necessary to emphasize that a similar magnetic nonequivalence was also observed for methyl 2-(3,5-dimethyl-4-oxocyclohexa-2,5-dienylidene)-3,3,3-trifluoropropionate **7**, which is a structure analogue of compound **6** (Fig. 5) [7].

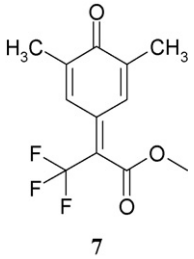


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Fig. 5. Methylenequinone **7**.

Further we are planning to study the structure of compound **6** using dynamic NMR method.

2.3. Reactions with nucleophiles

The *N*-acylmethylenequinone imine **6** that we synthesized proved to be very reactive towards various N-, O- and C-nucleophiles (Scheme 2). For instance, when compound **6** was dissolved in an ammonia metanolic solution **8**, the specific yellow colour of compound **6** disappeared for a moment and after diluting the reaction mixture with water, methyl ester of substituted amino acid **9** precipitated in quantitative yield. Methylenequinone imine **6** reacts with aniline **10** similarly, the reaction carried out in CCl_4 completed for 1 h to give methyl ester of the substituted *N*-phenylalanin **11** in 84% yield.

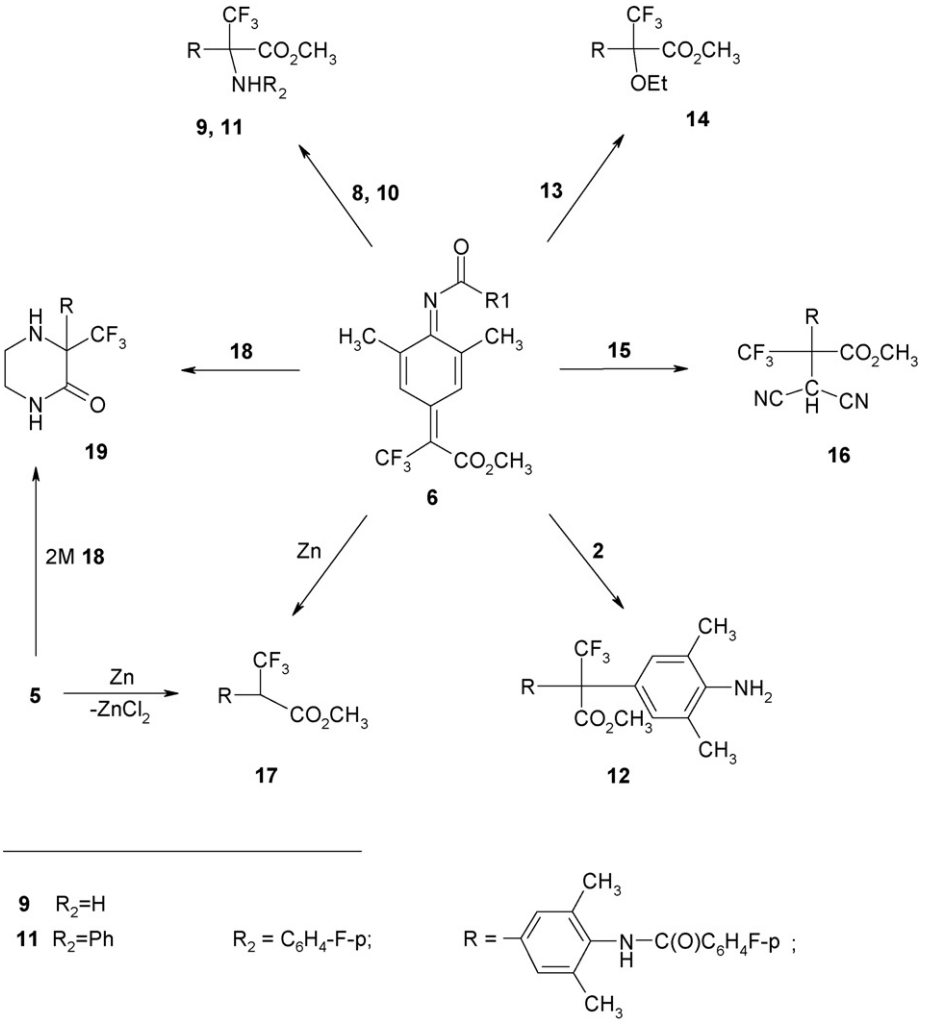
An unexpected result was obtained in the reaction of methylenequinone imine **6** with 2,6-dimethylaniline **2**. In this case, the product of its 4-C-alkylation **12** was formed in a quantitative yield, instead of the expected product of *N*-alkylation. The reaction completed within 5 to 10 min (TLC monitoring).

Reaction of compound **6** with sodium ethoxide **13** in ethanol occurs unambiguously. At 20 °C the reaction completed just after mixing to give ester **14**. The presence of bulk substituents at the α-carbon of the ester **14** hinders conformational transformations. As a result the hydrogens in the OCH_2 group are not equivalent and gave two signals with different chemical shifts in the ^1H NMR spectrum (see Section 4.7.).

The high reactivity of compound **6** in C-alkylations allowed us to hope that its reaction with CH-acids would be successful. Reaction of methylenequinone imine **6** with malonodinitrile **15** is actually performed easily in the presence of triethylamine at ambient temperature to give ester **16**.

Derivatives of 2-phenylpropionic acid are known to exhibit a wide spectrum of biological activity [12]. Recently it has been shown that the presence of CF_3-group in 1-(indol-3-yl)-2,2,2-trifluoropropionic acid inhibits its fast oxidation by horseradish peroxydase to prolong its effect as plant growth regulator [13]. In this respect a search for novel convenient synthesis method for the compounds containing the 1-aryl-2,2,2-trifluoropropionic acid moiety is very important.

It was found that Zn smoothly reduced compound **6** at ambient temperature in glacial acetic acid to form methyl ester



Scheme 2.

17 in quantitative yield. It should be noted that boiling of methyl 2-chloro-3,3,3-trifluoropropionate **5** with zinc in acetic acid for 2 h also gives the ester **17**.

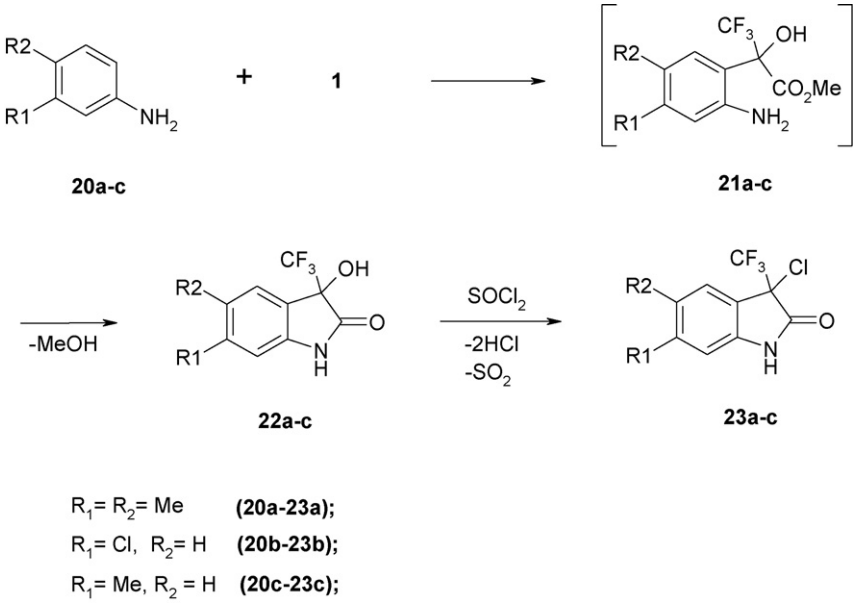
Compounds of the A-type contain the second reactive centre – the methoxycarbonyl group – in addition to the *p*-methylenequinone imine system; this fact makes it possible to consider them promising compounds for heterocyclizations with 1,3- and 1,4-dinucleophiles. Short-term boiling of compound **6** with ethylenediamine **18** in ethanol actually leads to the formation of trifluoromethylpiperazin-2-one **19** in high yield. The reaction of chloroderivative **5** with an excess of ethylenediamine **18** under the similar conditions gives the same result. Probably, the reaction medium is sufficiently basic to dehydrochlorinate ester **5** and the resulting product **6** enters heterocyclization with the second ethylenediamine molecule to form cycloadduct **19**.

2.4. N-Acyl-o-methylenequinone imines in the synthesis of 3-trifluoromethy-1,3-dihydroindol-2-one

In the course of studying the synthesis potential of *N*-acyltrifluoromethylmethylenequinone imines for preparing other CF_3-containing compounds we considered it interesting to synthesize *o*-analogues of compounds A.

It was found earlier that if the *p*-position in anilines **20a–c** is substituted or sterically hindered by a *m*-substituent, methyl trifluoropyrivate **1** C-oxyalkylates these compounds in the *o*-position. In this case the reaction is accompanied by spontaneous cyclization at the expense of the methoxycarbonyl group and the amino group of the intermediates **21a–c** to form the corresponding 3-hydroxy-3-trifluoromethyl-1,3-dihydroindol-2-ones **22a–c** and methanol (Scheme 3).

Lactams **22a–c** are the products of intramolecular *N*-acylation and they are the starting compounds for the synthesis of trifluoromethyl-*o*-methylenequinone imines **24a–c** (Scheme 4). Lactams **22a–c** can be converted quantitatively to 3-chloro-3-trifluoromethyl-1,3-dsihydroindol-2-ones **23a–c** by a short-term reaction with an excess of thionyl chloride in the presence of pyridine. However, we faced some problems when attempted to dehydrochlorinate the resulting chlorolactams **23a–c**. The reaction was monitored by TLC and ^{19}F NMR. The action of pyridine, quinoline, and tertiary amines on the above lactams at 20 °C and boiling of them in THF with NEt_3 did not give the desired result. Only in the case of heating **23b** in pyridine at 80–90 °C the reaction mixture became yellow, this colour is characteristic for *p*-methylenequinone imine **6**. However, the ^{19}F NMR spectrum had only one signal for the CF_3 group assigned to the starting compound **23b**. A prolonged boiling of compound **23b** in the above mentioned dehydroclorinating agents led to resinification and formation of a mixture of products. Only in the case of stirring **23b** with potash either in ether or in THF, a broad singlet at −66.28 ppm typical of the CF_3 group at the double bond appeared in the ^{19}F NMR spectrum of the reaction mixture in addition to the signal of CF_3 group (at −75.12 ppm) of lactam **23b**. The reaction mixture became brightly yellow. As the intensity of the second signal increased, one more signal (−75.17 ppm) appeared in the form of the broad singlet assigned to the CF_3 group of the unknown compound. With the course of time the intensity of this signal (−75.17 ppm) increased as the intensities of the signal of the starting **23b** and the signal at −66.28 ppm decreased. It can be suggested that the generated trifluoromethyl-*o*-methylenequinone imine **24b** underwent transformation to give another product. It is interesting to note that the reaction mixture gradually loses yellow colour while it is moving along the silica gel plate to leave a characteristic trace visible in UV-light. Obviously, product **24b** is so reactive that it decomposes when it is moving in silica gel. A similar picture was observed when we attempted to obtain pure *o*-methylenequinone imines **24a** and **24c** from compounds **23a** and **23c**.



Scheme 3.

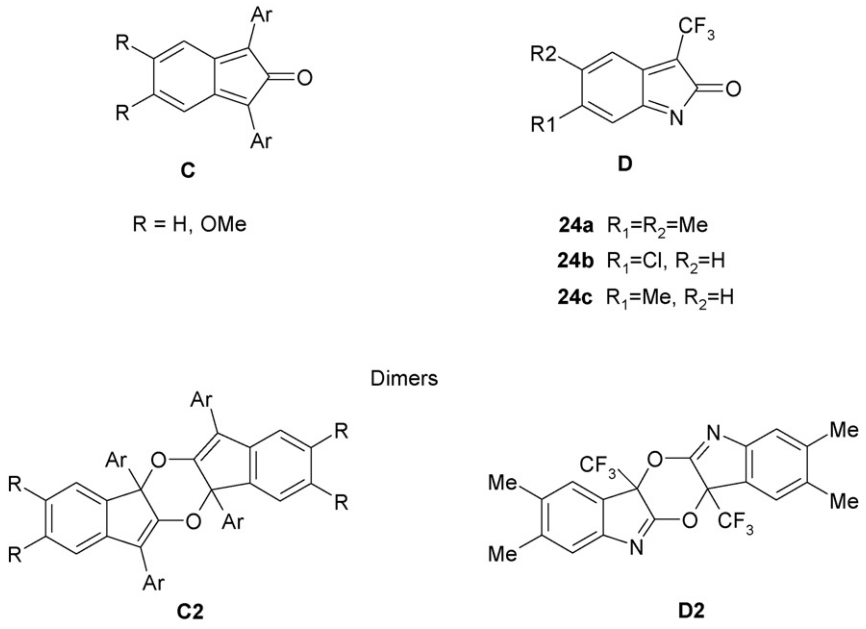


Fig. 6. The structure of compounds C and D and their dimers.

The analysis of the literature showed that the target compounds **D** are aza analogues of methastable inden-2-ones **C** [14] (Fig. 6).

It was shown that 1,3-diphenylinden-2-ones **C** not having substituents R in the benzene ring dimerize even at ambient temperature; their 5,6-dimethoxy derivatives are more stable, but they also undergo dimerization within 1 h [15]. It is worth noting that when 5,6-dimethyl-3-chloro-3-trifluoromethyl-1,3-dihydroindol-2-one **23a** was treated with potash in anhydrous THF at 20 °C, the MS spectrum of the reaction mixture had, in addition to the major ion [261–263] M^+ of the starting **23a**, ions [227] M^+ и [454] M^+ that appear to be assigned to 1-aza-5,6-dimethylinden-2-one **24a** and its dimer **D2** (*cf.* **C2**) (Fig. 6). In this connection we attempted to generate 1-aza-3-trifluoromethylinden-2-one of the **D** type *in situ*. When a nucleophile reacts with 3-chloro-3-trifluoromethyl-1,3-dihydroindol-2-ones **23a–c** (molar ratio 2:1) in a solution, one mole of the nucleophile is consumed for dehydrochlorination and the second one adds to the resulting 1-azainden-2-one **24a–c**. For example, a short-term boiling of compound **23a** (1 mole) in benzene with morpholine **25** (2 moles) gave 5,6-dimethyl-3-morpholin-4-yl-3-trifluoromethyl-1,3-dihydroindol-2-one **26** in high yield (Scheme 4).

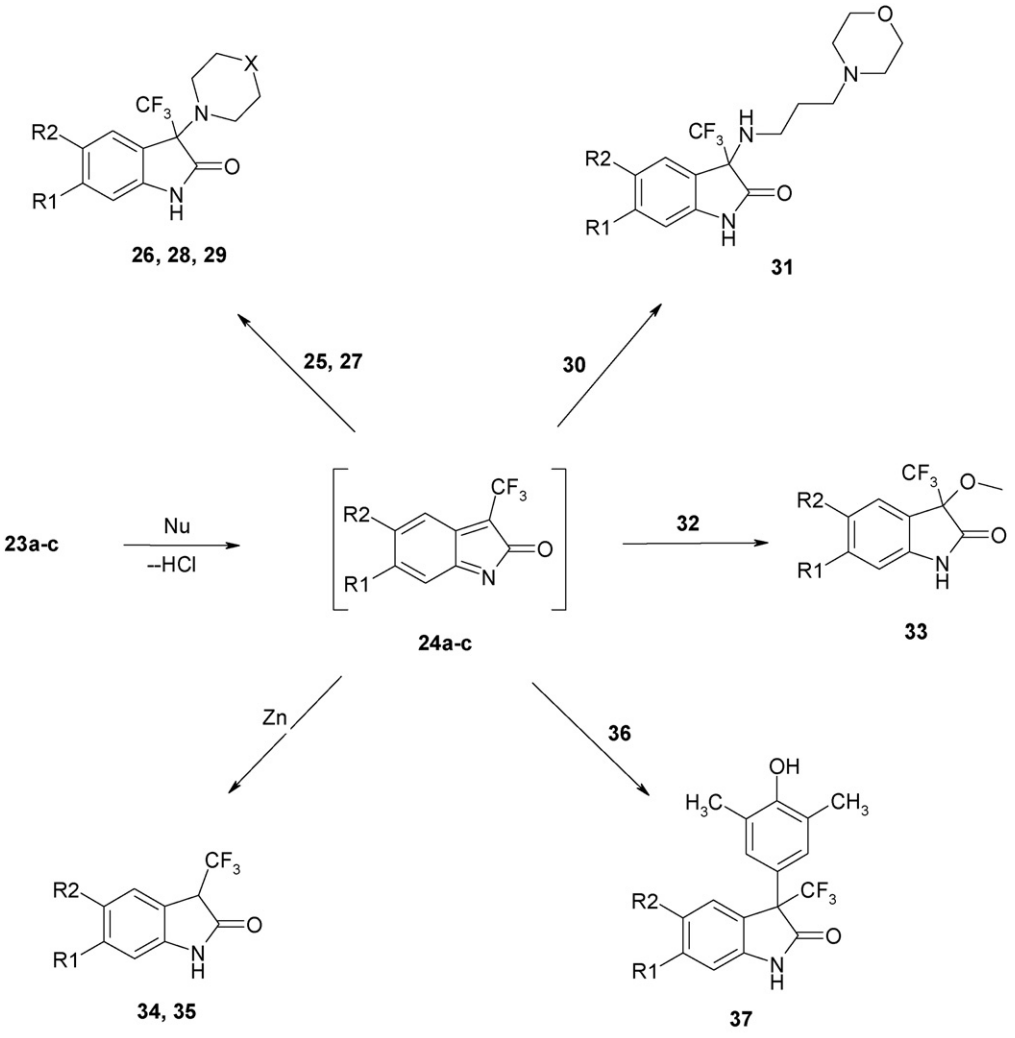
Conversion of the starting 3-chloro-1,3-dihydroindol-2-one was 100%, and the morpholine hydrochloride precipitated (Scheme 4). The reaction of **23b** and **23c** with *N*-phenylpiperazine **27** occurs in a similar manner to give 6-chloro(methyl)-3-(4-phenylpiperazin-1-yl)-3-trifluoromethyl-1,3-dihydroindol-2-ones **28** and **29**, respectively, in good yields. Compound **23a** reacts similarly with equimolecular amount of 3-(4-morpholino)-1-propylamine **30** in ethanol. In this case there is no need to use the second mole of the amine, because the nitrogen in morpholine acts as an acceptor of hydrogen chloride.

It is interesting to note that when compound **23a** is dissolved in metanolic solution of sodium methoxide, the reaction mixture becomes brightly yellow and the intensity of the colour decreases in time. Probably, in this case the rate of formation of intermediate 1-aza-5,6-dimethyl-3-trifluoromethylinden-2-one **24a** is higher than the rate of addition of methanol **32** to it. After neutralization of the reaction mixture and the subsequent diluting it with water spectroscopically pure 3-methoxy-3-trifluoromethyl-1,3-dihydroindol-2-one **31** precipitated in quantitative yield. The ^{19}F NMR monitoring in D4-methanol of the above reaction actually showed the presence of two signals of small intensity as singlets at −67.49 ppm and −60.47 ppm in 5 spectra of the reaction mixture recorded at 3 min intervals. In this case, we observed a gradual disappearance of the signal (at −76.30 ppm) of the starting compound **23a** in addition to the correlating increase in the intensity of the signal (78.02 ppm) assigned to the methoxy derivative **33** that formed.

We cannot say with confidence that the formation of 3-trifluoromethyl-1,3-dihydroindol-2-ones **34**, **35** must be preceded by dehydrochlorination of the starting 3-chloroderivatives **23b**, **23c** under the action of Zn in glacial acetic acid. It would appear reasonable that this process occurs with the formation of Reformatskii adducts as the intermediates. For instance, interaction of **23b** and **23c** with excess Zn under these conditions for 2–3 h gave the products of their reduction **34** and **35**, respectively in almost quantitative yields.

Complex $BF_3{\cdot}NEt_3$ is known to be one of the strongest dehydrohalogenating agents [16]. When compound **23a**, triethylamine, and 2,6-dimethylphenol **36** are boiled in boron trifluoride etherate, 5,6-dimethyl-3-(4-hydroxy-3,5-dimethylphenyl)-3-trifluoromethyl-1,3-dihydroindol-2-one **37** is actually formed in high yield.

The ability of the newly synthesized *N*-acylmethylenequinone imines to C-alkylate aromatic compounds shows that they actually are strong electrophilic agents.



Scheme 4.

3. Conclusion

We have developed a convenient method for the synthesis of new highly electrophilic agents – CF_3-containing *N*-acyl-*p*-methylenequinone imines – by the example of the synthesis of compound **6**. Their high electrophilicity was demonstrated in reactions with ammonia, primary and secondary amines, alkoxides, aromatic compounds and CH-acids. They can be used in heterocyclizations. 3-Chloro-3-trifluoromethyl-1,3-dihydroindol-2-ones were synthesized which are precursors of methastable *N*-acyl-*o*-methylenequinone imines. A method for the synthesis of substituted 3-trifluoromethyl-1,3-dihydroindol-2-ones from the above chloroderivatives has been developed.

Our results make it possible to hope for a successful search for the highly electrophilic CF_3-containing agents such as *N*-sulfoxyalkyl(aryl)-, *N*-carbamoyl-, and *N*-phosphorylylmethylenequinone imines, among compounds related to the class of methylenequinone imines.

4. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance™ 600 (600.22 and 150.93 MHz) and Bruker AMX-400 (400.13 and 100.61 MHz, respectively) spectrometers. Me_4Si was used as an internal standard. ^{19}F NMR spectra were recorded on a Bruker Avance™ 300 (282.38 MHz) instrument and referenced against external CCl_3F. Preliminary assignments in

the spectra were performed using NMR DEPT, HSQC and NOESY procedures. Mass-spectra were obtained on a Kratos MS-30 instrument (EI, 70 eV). Elemental analyses were performed on a Carlo Erba 1106 instrument.

*4.1. Methyl 3.3,3-trifluoro-2-[4-(4-fluorobenzylamino)-3,5-dimethylphenyl]-2-hydroxypropionate (**4**)*

A mixture of compound **3** (2.87 g, 10 mmol), toluene (20 ml), and 4-fluorobenzoyl chloride (1.59 g, 10 mmol) was refluxed until liberation of HCl stopped (for about 1.5 h). The reaction mixture was chilled and filtered to separate the precipitate, which was washed with benzene and hexane to give compound **4** (3.2 g, 8 mmol, 91%), white solid: mp 163–164 °C. ^{1}H NMR (DMSO-d_6): δ 2.20 (6H, *s*), 3.80 (3H, *s*), 7.40 (2H, *s*), 7.50 (2H, *m*), 7.95 (1H, *s*), 8.15 (2H, *m*); 9.90 (1H, *s*). ^{19}F NMR (DMSO-d_6): δ −108.72 (m, 1F), −75.12 (s, 3F). Anal. calculated for $C_{19}H_{17}F_4NO_4$: C, 57.15; H, 4.29; N, 3.51. Found: C, 57.25; H, 4.11; N, 3.35.

*4.2. Methyl 2-chloro-3.3,3-trifluoro-2-[4-(4-fluorobenzylamino)-3,5-dimethylphenyl]-2-propionate (**5**)*

A mixture of compound **4** (2.0 g, 5 mmol), thionyl chloride (2.4 g, 20 mmol), and 3 drops of pyridine was refluxed until liberation of HCl stopped (for about 1 h). An excess of $SOCl_2$ was removed under vacuum, crystallization of the residue gave compound **5** (1.7 g, 4.1 mmol) as a white solid, mp 211–212 °C. Yield 81.3%. ^{1}H NMR (DMSO-d_6): δ 2.21 (6H, *s*), 3.90 (3H, *s*), 7.30 (2H, *s*), 7.41 (2H, *m*), 7.95 (1H, *s*), 8.10 (2H, *m*), 9.92 (1H, *s*). ^{19}F NMR (DMSO-d_6): δ −108.27 (m, 1F), −71.22 (s, 3F). Anal. calculated for $C_{19}H_{16}ClF_4NO_3$: C, 54.62; H, 3.86; N, 3.35. Found: C, 54.25; H, 3.53; N, 3.71.

*4.3. Methyl 3,3,3-trifluoro-2-[4-(4-fluorobenzylamino)-3,5-dimethylcyclohexa-2,5-dienylidene]propionate (**6**) (Fig. 2)*

A mixture of compound **5** (1.25 g, 3 mmol), KOH (0.56 g, 10 mmol) in adhydrous diethyl ether (30 ml) was stirred by a magnetic stirrer at 20 °C for 1.5 h and filtered to separate the precipitate of inorganic salts. The filtrate was evaporated under vacuum, the resulting crude product was purified by column chromatography on Merck silica gel 60 (230–400 mesh ASTM), eluent $CHCl_3$–CCl_4 (1:2) to give pure compound **6** (0.92 g, 2.42 mmol) as a yellow solid: mp 100–101 °C (hexane). Yield 81%. ^{1}H NMR ($CDCl_3$-d_6): δ 2.07 (s, 3H), 2.12 (d, ^4J = 1.1 Hz, 3H), 3.98 (s, 3H), 6.94 (bs, 1H), 7.16 (m, 2H), 7.17 (bs, 1H), 7.87 (m, 2H). ^{13}C NMR (150.93 MHz) δ 20.0 (10–C), 20.2 (14-C), 53.3 (24-C), 115.9 (d, $^2J_{C\text{-}F}$ = 22 Hz, 17(19)-C), 121.8 (q, $^1J_{C\text{-}F}$ = 273 Hz, 21-C), 125.2 (q, $^2J_{C\text{-}F}$ = 33 Hz, 11-C), 128.0 (q, $^4J_{C\text{-}F}$ = 2 Hz, 5-C), 129.4 (d, $^4J_{C\text{-}F}$ = 3 Hz, 15-C), 130.1 (3-C), 131.3 (d, $^3J_{C\text{-}F}$ = 9 Hz, 16(20)-C), 136.7 (q, $^3J_{C\text{-}F}$ = 3 Hz, 4-C), 139.4 (6-C), 140.0 (2-C), 154.6 (1-C), 163.6 (q, $^4J_{C\text{-}F}$ = 3 Hz, 12-C), 165.7 (d, $^1J_{C\text{-}F}$ = 253 Hz, 18-C), 176.0 (8-C). ^{19}F NMR ($CDCl_3$) δ: −105.30 (m, 1F); −54.05 (s, 3F). EIMS, *m/z*: 381[M]$^+$. Anal. calculated for $C_{19}H_{15}F_4NO_3$: C, 59.85; H, 3.96; N, 3.67. Found: C, 59.65; H, 3.84; N, 3.59.

*4.4. Methyl 2-amino-3,3,3-trifluoro-2-[4-(4-fluorobenzoylamino)-3,5-dimethylphenyl]propionate (**9**)*

Compound **6** (0.38 g, 1 mmol) was dissolved in a 20% solution of ammonia in methanol (2 ml) and kept at 0–5 °C until the yellow colour of the reaction mixture disappeared (for 5–10 min). Removal of the solvent under vacuum gave compound **9** (0.40 g, 1 mmol, 100%) as a white solid: mp 168–169 °C. ^{1}H NMR (DMSO-d_6): δ 2.24 (6H, *s*), 3.38 (2H, *s*), 3.80 (3H, *s*), 7.33 (2H, *s*), 7.42 (2H, *m*), 8.10 (2H, *m*), 9.87 (1H, *bs*). ^{19}F NMR (DMSO-d_6): δ −108.99 (m, 1F), −73.72 (s, 3F). Anal. calculated for $C_{19}H_{18}F_4N_2O_3$: C, 57.29; H, 4.55; N, 7.03. Found: C, 57.45; H, 4.33; N, 7.29.

*4.5. Methyl 3,3,3-trifluoro-2-[4-(4-fluorobenzoylamino)-3,5-dimethylphenyl]-2-phenylaminopropionate (**11**)*

Aniline (0.10 g, 1.1 mmol) was added to a solution of compound **6** (0.38 g, 1 mmol) in CCl_4 (2 ml) and kept at ambient temperature for 1 h. The crystalline precipitate that formed was filtered off, washed with hexane and dried under vacuum to give compound **11** (0.40 g, 0.84 mmol, 84%), white solid: mp 102–103 °C. ^{1}H NMR (DMSO-d_6): δ 2.28 (6H, *s*), 3.38 (2H, *s*), 3.79 (3H, *s*), 5.19 (2H, *s*), 6.52 (2H, *d*, J_1 = 8.0 Hz), 6.74 (1H, *t*, J_1 = 7.0 Hz), 7.04 (1H, *t*, J_1 = 7.3 Hz), 7.16 (2H, *m*), 7.35 (2H, *s*), 7.40 (1H, *bs*), 7.90 (2H, *m*). ^{19}F NMR ($CDCl_3$): δ −107.00 (m, 1F), −68.60 (s, 3F). Anal. calculated for $C_{25}H_{22}F_4N_2O_3$: C, 63.29; H, 4.67; N, 5.90. Found: C, 63.45; H, 4.43; N, 5.79.

*4.6. Methyl 2-(4-amino-3,5-dimethylphenyl)-3,3,3-trifluoro-2-[4-(4-fluorobenzoylamino)-3,5-dimethylphenyl-propioate (**12**)*

2,6-Dimethylaniline (0.13 g, 1.1 mmol) was added to a solution of compound **6** (0.38 g, 1 mmol) in CCl_4 (1.5 ml) and kept at ambient temperature for 1 h. The crystalline precipitate that formed was filtered off, washed with hexane and dried under vacuum to give compound **12** (0.40 g, 0.80 mmol, 80%), white solid: mp 218–219 °C. ^{1}H NMR ($CDCl_3$-d_6): δ 2.16 (s, 6H), 2.24 (s, 6H), 3.83 (s, 3H), 3.84 (bs, 2H), 6.84 (s, 2H), 7.04 (s, 2H), 7.17 (m, 2H), 7.33 (bs, 1H), 7.91 (m, 2H). ^{19}F NMR ($CDCl_3$): δ −107.16 (m, 1F), −62.41 (s, 3F). Anal. calculated for $C_{27}H_{26}F_4N_2O_3$: C, 64.54; H, 5.22; N, 5.57. Found: C, 64.43; H, 5.41; N, 5.74.

*4.7. Methyl 2-ethoxy-3,3,3-trifluoro-2-[4-(4-fluorobenzoylamino)-3,5-dimethylphenyl propionate (**14**)*

Compound **6** (0.38 g, 1 mmol) was dissolved in a freshly prepared solution of NaH (0.024 g, 1 mmol) in anhydrous ethanol (4 ml) and stirred for 2 min at ambient temperature. Then acetic acid (0.1 g) and water (6 ml) were added to the reaction mixture. The precipitate that formed was filtered off, washed with water, and dried under vacuum to give compound **14** (0.42 g, 0.98 mmol, 98%), white solid: mp 208–209 °C. ^{1}H NMR (DMSO-d_6): δ 1.26 (bt, 3H, J = 7.1 Hz), 2.22 (s, 6H,),

3.59 (m, 1H, J = 7.1 Hz), 3.23 (m, 1H, J = 7.1 Hz), 3.90 (bs, 3H), 7.20 (bs, 2H), 7.39 (m, 2H), 8.07 (m, 2H), 9.87 (bs, 1H). ^{19}F NMR (DMSO-d_6): δ −110.09 (s, 1F), −72.86 (s, 3F). Anal. calculated for $C_{21}H_{21}F_4NO_4$: C, 59.02; H, 4.95; N, 3.28. Found: C, 59.15; H, 4.74; N, 3.21.

4.8. Methyl 3,3-dicyano-2-[4-(4-fluorobenzoylamino)-3,5-dimethylphenyl]-2-trifluoromethylpropionate (**16**)

Malonodinitrile and triethylamine (3 drops) were added to a solution of compound **6** (0.38 g, 1 mmol) in anhydrous THF (2 ml) and kept at ambient temperature for 30 min. The reaction mixture was diluted with water (10 ml), the water layer was decanted, the residue was dissolved in EtOAc (5 ml), dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was crystallized from CCl_4 to give compound **16** (0.35 g, 0.78 mmol, 78%), white solid: mp 116–117 °C. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 6H,), 3.50–6.00 (bs, 1H), 3.99 (s, 3H), 7.12 (s, 2H), 7.19 (m, 2H), 7.65 (bs, 1H), 7.95 (m, 2H). ^{19}F NMR ($CDCl_3$): δ −106.76 (m, 1F), −63.66 (bs, 3F). Anal. calculated for $C_{22}H_{17}F_4N_3O_3$: C, 59.06; H, 3.83; N, 9.39. Found: C, 59.24; H, 3.61; N, 9.58.

4.9. Methyl 3,3,3-trifluoro-2-[4-(4-fluorobenzoylamino)-3,5-dimethylphenyl]propionate (**17**)

(A) Zinc (0.65 g, 10 mmol) was added to a solution of compound **6** (0.38 g, 1 mmol) in glacial acetic acid (2 ml) and magnetically stirred at ambient temperature until the yellow colour of the reaction mixture disappeared. The excess of Zn and inorganic salts were filtered off, the filtrate was evaporated under vacuum. The solid residue was dissolved in EtOAc (10 ml) and filtered through silica gel. The solvent was removed under vacuum to give compound **17** (0.38 g, 1 mmol, 100%), white solid: mp 148–149 °C.

(B) Zinc (1.95 g, 30 mmol) was added to a solution of compound **5** (1.25 g, 3 mmol) in glacial acetic acid (6 ml) and refluxed for 1.5 h with stirring. The reaction mixture was treated (as desribed in (A)) to give compound **17** (1.13 g, 3 mmol, 100%), white solid: mp 148–149 °C. ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 6H), 3.77 (s, 3H,), 4,27 (q, 1H, $J_{H\text{-}F}$ = 8.5 Hz), 7.15 (m, 2H), 7.18 (s, 2H), 7.46 (bs, 1H), 7.90 (m, 2H). ^{19}F NMR ($CDCl_3$): δ −107.4 (m, 1F), −67.52 (d, $J_{H\text{-}F}$ = 8.5 Hz). Anal. calculated for $C_{19}H_{17}F_4NO_3$: C, 59.53; H, 4.47; N, 3.65. Found: C, 59.65; H, 4.66; N, 3.45.

4.10. N-[2,6-Dimethyl-4-(3-oxo-2-trifluoromethylpiperazin-2-yl)phenyl]-4-fluorobenzamide (**19**)

(A) Ethylenediamine (0.13 g, 2.2 mmol) was added to a solution of compound **6** (0.76 g, 2 mmol) in anhydrous EtOH (5 ml) and refluxed for 20 min. The reaction mixture was evaporated to half its volume and diluted with water until crystallization of the target product started. The precipitate was filtered off, washed with water and dried under vacuum to give compound **19** (0.70 g, 1.7 mmol, 85%), white solid: mp 147–148 °C.

(B) Ethylenediamine (0.13 g, 2.2 mmol) was added to a solution of compound **5** (0.42 g, 2 mmol) in anhydrous EtOH (3 ml) and refluxed for 20 min. The product was isolated as described in (A). Compound **19** (0.70 g, 1.7 mmol) was obtained in 85% yield, white solid: mp 147–148 °C. ^{1}H NMR (DMSO-d_6): δ 2.19 (s, 6H,), 2.60 (m, 1H), 2.85–3.03 (m, 2H), 3.29 (m, 1H), 4.05 (s, 1H), 7.38 (m, 2H), 7.48 (s, 2H), 8.06 (m, 2H), 8.16 (s, 1H), 9.81 (s, 1H). ^{19}F NMR (DMSO-d_6): δ −108.82 (m, 1F), −71.88 (s, 3F). Anal. calculated for $C_{20}H_{19}F_4N_3O_2$: C, 58.68; H, 4.68; N, 10.26. Found: C, 58.54; H, 4.43; N, 10.49.

4.11. 3-Hydroxy-5,6-dimethyl-3-trifluoromethyl-1,3-dihydroindol-2-one (**22a**)

Compound **20b** (3.5 g, 1.45 mmol, 71.4%) was obtained by boiling of ketoester **1** (3.43 g, 22 mmol) and 3,4-dimethylaniline (2.14 g, 20 mmol) in *m*-xylene (10 ml) for 9 h, product **22a** was isolated by a procedure used for the synthesis of **22b** and **22c** [9]. **22a**: white solid: mp 260 °C (subl). ^{1}H NMR (DMSO-d_6): δ 2.17 (s, 3H,), 2.20 (s, 3H,), 6.71 (s, 1H), 7.15 (s, 1H), 7.49 (s, 1H), 10.72 (bs, 1H). ^{19}F NMR (DMSO-d_6): δ −76.75 (s, 3F). Anal. calculated for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 54.05; H, 4.23; N, 5.49.

4.12. 3-Hydroxy-6-methyl-3-trifluoromethyl-1,3-dihydroindol-2-one (**22c**)

Compound **22b** (3.43 g, 22 mmol) was obtained in 69.3% yield from ketoester **1** (3.43 g, 22 mmol) and 3-methylaniline (2.14 g, 20 mmol) by a procedure similar to that used for the synthesis of **22a**. **22c** was obtained as a white solid: mp 205–206 °C (lit. mp 207 °C [9]).

4.13. 3-Chloro-5,6-dimethyl-3-trifluoromethyl-1,3-dihydroindol-2-one (**23a**)

Compound **22a** (2.45 g, 10 mmol), thionyl chloride (3.6 g, 30 mmol) and pyridine (6 drops) were refluxed in a flask fitted a reflux condenser until liberation of HCl stopped (for about 1 h). An excess of $SOCl_2$ was removed under vacuum, the residue was dissolved in benzene, passed through a 5 mm silica gel layer. The solvent was removed under vacuum, the solid residue was crystallized from hexane to give compound **23c** (2.5 g, 0.95 mmol, 95%), white solid: mp 191–192 °C. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H,), 2.35 (s, 3H,), 6.88 (s, 1H), 7.32 (s, 1H), 8.91 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −74.67 (s, 3F). Anal. calculated for $C_{11}H_9ClF_3NO$: C, 50.11; H, 3.44; N, 5.31. Found: C, 49.95; H, 3.63; N, 5.25.

4.14. 3,6-Dichloro-3-trifluoromethyl-1,3-dihydroindol-2-one (**23b**)

Product **23b** (2.5 g, 0.93 mmol, 93%) was obtained from compound **22b** (2.51 g, 10 mmol) and thionyl chloride

(3.6 g, 30 mmol) by a procedure used for the synthesis of **23a**. Compound **23b** was obtained as a white solid: mp 159–160 °C. ^{1}H NMR ($CDCl_3$): δ 7.07 (d, 1H, J_1 = 1.5 Hz), 7.15 (dd, 1H, J_1 = 8.20 Hz, J_2 = 1.50 Hz), 7.45 (d, 1H, J_1 = 8.20 Hz), 9.12 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −74.58 (s, 3F). Anal. calculated for $C_9H_4Cl_2F_3NO$: C, 40.03; H, 1.49; N, 5.19. Found: C, 39.95; H, 1.63; N, 5.35.

*4.15. 3-Chloro-6-methyl-3-trifluoromethyl-1,3-dihydroindol-2-one (**23c**)*

Product **23c** (2.3 g, 0.92 mmol, 92,4%) was obtained from compound **22c** (2.31 g, 10 mmol) and thionyl chloride (3.6 g, 30 mmol) by a procedure used for the synthesis of **23a**. Compound **23c** was obtained as a white solid: mp 156–157 °C. ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H,), 6.85 (s, 1H), 6.95 (d, 1H, J_1 = 10,4 Hz), 7.38 (d, 1H, J_1 = 10.4 Hz), 8.90 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −74.70 (s, 3F). Anal. calculated for $C_{10}H_7ClF_3NO$: C, 48.12; H, 2.83; N, 5.61. Found: C, 48.05; H, 2.63; N, 5.45.

*4.16. 5,6-Dimethyl-3-morpholin-4-yl-3-trifluoromethyl-1,3-dihydroindol-2-one (**26**)*

Morpholine (0.19 g, 2.2 mmol) was added to a solution of compound **23a** (0.53 g, 2 mmol) in benzene (5 ml) and refluxed for 20 min. The precipitate of morpholine hydrochloride was filtered off; to the filtrate benzene (10 ml) was added and passed through a 5 mm layer of silica gel. The solvent was removed and the solid residue was crystallized from CCl_4 to give compound **26** (0.50 g, 1.6 mmol, 80%), white solid: mp 177–178 °C. ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H,), 2.26 (s, 3H,), 2.76 (m, 4H), 3.72 (m, 4H), 6.77 (s, 1H), 7.18 (s, 1H), 8.98 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −68.69 (s, 3F). Anal. calculated for $C_{15}H_{17}F_3N_2O_2$: C, 57.32; H, 5.45; N, 8.91. Found: C, 57.75; H, 5.54; N, 8.51.

*4.17. 6-Chloro-3-(4-phenylpiperazin-1-yl)-3-trifluoromethyl-1,3-dihydroindol-2-one (**28**)*

Phenylpiperazine (0.65 g, 4 mmol) was added to a solution of compound **23b** (0.54 g, 2 mmol) in benzene (5 ml) and refluxed for 20 min. The precipitate of the hydrochloride was filtered off; to the filtrate benzene (15 ml) was added and passed through a layer of silica gel. The solvent was removed and the solid residue was crystallized from CCl_4 to give compound **28** (0.52 g, 1.3 mmol, 66%), white solid: mp 125–126 °C. ^{1}H NMR ($CDCl_3$): δ 2.94 (m, 4H,), 3.21 (m, 4H,), 6.84-6.90 (m, 3H), 6.98 (d, 1H, J_1 = 1.8 Hz), 7.12 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.8 Hz), 7.22–7.28 (m, 2H), 7.40 (d, 1H, J_1 = 8.0 Hz), 8.49 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −68.62 (s, 3F). Anal. calculated for $C_{19}H_{17}ClF_3N_3O$: C, 57.66; H, 4.33; N, 10.62. Found: C, 57.73; H, 4.55; N, 10.40.

*4.18. 6-Methyl-3-(4-phenylpiperazin-1-yl)-3-trifluoromethyl-1,3-dihydroindol-2-one (**29**)*

N-Phenylpiperazine (0.65 g, 4 mmol) was added to a solution of compound **23c** (0,5 g, 2 mmol) in benzene (5 ml) and refluxed for 20 min. The precipitate was filtered off; benzene (15 ml) was added to the filtrate and passed through a layer of silica gel. The solvent was removed and the solid residue was crystallized from CCl_4 to give compound **29** (0.48 g, 1.3 mmol, 64%), white solid: mp 176–177 °C. ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H,), 2.95 (m, 4H,), 3.21 (m, 4H), 6.82–6.94 (m, 4H), 7.22–7.27 (m, 2H), 7.34–7.37 (m, 2H). ^{19}F NMR ($CDCl_3$): δ −68.74 (s, 3F). Anal. calculated for $C_{20}H_{20}F_3N_3O$: C, 63.99; H, 5.37; N, 11.19. Found: C, 63.75; H, 5.54; N, 10.98.

*4.19. 5,6-Dimethyl-3-(3-morpholin-4-yl)propylamino)-1,3-dihydroindol-2-one (**31**)*

3-(Morpholine-4-yl)propylamine (0.29 g, 2 mmol) was added to a solution of compound **23a** (0.53 g, 2 mmol) in EtOH (5 ml) and refluxed for 25 min. The ethanol was removed under vacuum; the residue was treated with a mixture of benzene (20 ml) and a saturated $NaHCO_3$ solution (10 ml). The organic layer was separated, dried over Na_2SO_4 and passed through a silica gel layer. The solvent was removed and the solid residue was crystallized from CCl_4 to give compound **31** (0.52 g, 1.4 mmol, **7**0%), white solid: mp 71–72 °C. ^{1}H NMR ($CDCl_3$): δ 1.50–1.60 (m, 1H), 1.65–1.75 (m, 1H), 2.27 (s, 3H,), 2.28 (s, 3H,), 2.30–2.60 (m, 8H), 3.70-3.85 (m, 5H), 6.75 (s, 1H), 7.23 (s, 1H), 8.67 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −76.48 (s, 3F). Anal. calculated for $C_{18}H_{24}F_3N_3O_2$: C, 58.21; H, 6.51; N, 11.31. Found: C, 58.01; H, 6.30; N, 11.04.

*4.20. 3-Methoxy-5,6-dimethyl-3-trifluoromethyl-1,3-dihydroindol-2-one (**33**)*

Sodium hydride (0.029 g, 1.2 mmol) was dissolved in anhydrous methanol (2 ml), compound **23a** (0.26 g, 1 mmol) was added and the mixture was kept for 1 h at ambient temperature. Then AcOH (50 mg) and H_2O (6 ml) were added to the reaction mixture. The precipitate that formed was filtered off, washed and dried under vacuum to give compound **33** (0.25 g, 0.97 mmol, 97%), white solid: mp 189–190 °C. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H,), 2.29 (s, 3H,), 3.23 (s, 3H), 6.80 (s, 1H), 7.21 (s, 1H), 8.74 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −78.02 (s, 3F). Anal. calculated for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.75; H, 4.54; N, 5.21.

*4.21. 6-Chloro-3-trifluoromethyl-1,3-dihydroindol-2-one (**34**)*

A mixture of compound **23b** (0.27 g, 1 mmol) and Zn (0.65 g, 10 mmol) in anhydrous AcOH (2 ml) was magnetically stirred at ambient temperature for 2 h. An excess of Zn and the salts that formed were filtered off and washed AcOH (2 ml × 3). The resulting filtrate was rotor evaporated to achieve a 1 ml volume and diluted with water until precipitation was completed. The precipitate was filtered off, washed with water and dried under vacuum to give product **34** (0.22 g, 0.91 mmol, 91%), white solid: mp 170–171 °C. ^{1}H NMR ($CDCl_3$): δ 4.14 (q, 1H, $J_{H\text{-}F}$ = 9.4 Hz), 7.00 (d, 1H,

J_1 = 1.6 Hz), 7.09 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.32 (d, 1H, J_1 = 8.0 Hz), 8.74 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −66.94 (d, 3F, $J_{H\text{-}F}$ = 9,4 Hz). Anal. calculated for $C_9H_5ClF_3NO$: C, 45.88; H, 2.14; N, 5.95. Found: C, 45.98; H, 1.99; N, 6.04.

*4.22. 6-Methyl-3-trifluoromethyl-1,3-dihydroindol-2-one (**35**)*

A mixture of compound **23c** (0.25 g, 1 mmol) and Zn (0.65 g, 10 mmol) in anhydrous AcOH (2 ml) was magnetically stirred at ambient temperature for 2 h. An excess of Zn and the salts that formed were filtered off and washed AcOH (2 ml × 3). The resulting filtrate was rotor evaporated to achieve a 1 ml volume and diluted with water until precipitation was completed. The precipitate was filtered off, washed with water and dried under vacuum to give product **35** (0.20 g, 0.93 mmol, 93%), white solid: mp 139–140 °C. ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H,), 4.85 (q, 1H, $J_{H\text{-}F}$ = 9.5 Hz), 6.78 (s, 1H), 6.90 (d, 1H, J_1 = 7.5 Hz), 7.24 (d, 1H, J_1 = 7.5 Hz), 10.89 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −67.7 (d, $J_{H\text{-}F}$ = 9.5 Hz, 3F). Anal. calculated for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.95; H, 3.66; N, 6.45.

*4.23. 3-(4-Hydroxy-3,5-dimethylphenyl)-5,6-dimethyl-3-trifluoromethyl-1,3-dihydroindol-2-one (**37**)*

Compound **23a** (0.53 g, 2 mmol) and 2,6-dimethylphenol (0.25 g, 2 mmol) were dissolved in 2 ml of $BF_3{\cdot}OEt_2$, then NEt_3 (0.2 g, 2 mmol) was added and refluxed for 10 min. An excess of $BF_3{\cdot}OEt_2$ and volatile reaction products were removed using a rotor evaporator. The residue was treated with 20 ml of a mixture EtOAc-water (1:1). The organic layer was separated, dried over Na_2SO_4 and passed through a 5 mm layer of silica gel. The solvent was rotor evaporated, the residue was crystallized from benzene to give compound **37** (0.54 g, 1,54 mmol, 77%), white solid: mp 204–206 °C. ^{1}H NMR ($CDCl_3$): δ 2.21 (bs, 6H, $2CH_3$), 2.29 (d, 6H, $2CH_3$), 4.74 (bs, 1H, OH), 7.25 (s, 1H), 7.25 (bt, 3H), 8.19 (bs, 1H). ^{19}F NMR ($CDCl_3$): δ −68.69 (s, 3F). Anal. calculated for $C_{12}H_{12}F_3NO_2$: C, 65.32; H, 5.19; N, 4.01. Found: C, 65.15; H, 4.98; N, 3.71.

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