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New β-amino-α-trifluoromethyl alcohols and their exploration in the synthesis of trifluoromethylated imidazole derivatives

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ABSTRACT

Racemic and enantiomerically pure β-amino-α-trifluoromethyl alcohols were obtained via sequential nucleophilic trifluoromethylation of selected α-imino ketones, derived from arylglyoxals, and subsequent removal of the MeO or Ph(Me)CH substituent, respectively, located at the N-atom. The obtained products, containing a primary amino group, were used for the synthesis of imidazole *N*-oxides bearing a trifluoromethyl group as a part of the *N*(1)-alkyl chain. Imidazole *N*-oxides with an electron-withdrawing ester group at C(4) underwent spontaneous isomerization under the reaction conditions, and the corresponding imidazol-2-ones derivatives were isolated as final products.

1. Introduction

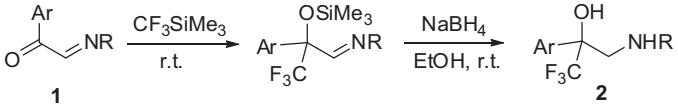
The importance of β-amino-α-trifluoromethyl alcohols is well established, and our recent review summarizes methods of their synthesis as well as applications for the preparation of heterocycles and biologically active compounds [1]. The elaboration of simple and efficient methods for their synthesis is a challenging task. Particular attention is focused on amino compounds, which contain the trifluoromethyl group in α-position [2]. Very likely, the same relationship is valid for trifluoromethylated imidazole derivatives, with the CF_3 group attached directly to C(2) [3] of the imidazole ring or in a side chain attached to N(1) [4].

Regioselective nucleophilic trifluoromethylation of imines **1** derived from arylglyoxals with subsequent reduction of the C=N bond was described as a convenient protocol for the preparation of β-amino-α-trifluoromethyl alcohols **2** with a secondary amino group [5] (Scheme 1). These products were applied for the preparation of aziridines as well as five- and six-membered O,N-heterocycles [6].

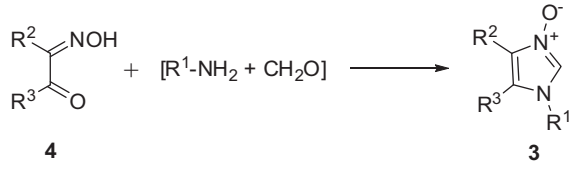
The synthesis and reactivity of 2-unsubstituted imidazole *N*-oxides **3** are of current interest as they are useful building blocks for the preparation of diverse imidazole derivatives, including enantiomerically pure compounds [7]. The straightforward method for their synthesis is based on the condensation of α-hydroxyimino ketones **4** with formaldehyde and a corresponding primary amine (Scheme 2).

In a previous paper, we showed that the primary amine can be replaced by a β-amino alcohol and the imidazole *N*-oxide obtained in this case contains a β-hydroxyalkyl residue at N(1) [7e].

The goal of the present study was the elaboration of a method for the preparation of amino alcohols of type **2** with a primary amino group (R=H) via nucleophilic trifluoromethylation [8] of properly selected arylglyoxalimines. Furthermore, the obtained β-amino-α-trifluoromethyl alcohols should be used as starting materials for the synthesis of new imidazole *N*-oxides **3**, bearing a



Scheme 1.



Scheme 2.

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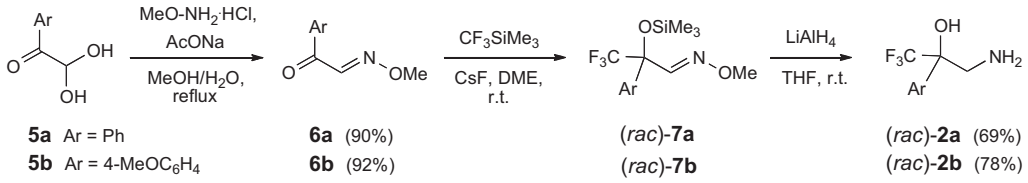


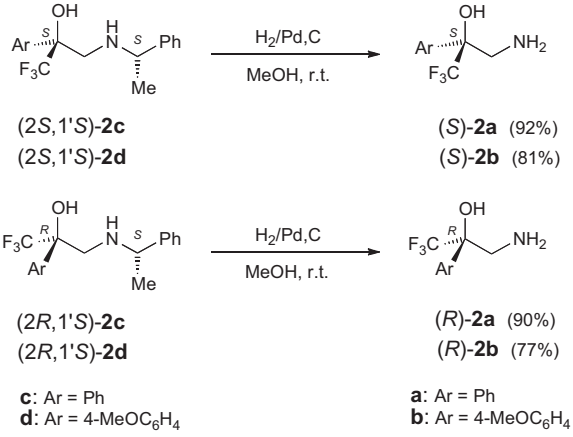
5a Ar = Ph
5b Ar = 4-MeOC$_6$H$_4$

6a (90%)
6b (92%)

(*rac*)-**7a**
(*rac*)-**7b**

(*rac*)-**2a** (69%)
(*rac*)-**2b** (78%)

Scheme 3.



(2*S*,1'*S*)-**2c**
(2*S*,1'*S*)-**2d**

(*S*)-**2a** (92%)
(*S*)-**2b** (81%)

(2*R*,1'*S*)-**2c**
(2*R*,1'*S*)-**2d**

(*R*)-**2a** (90%)
(*R*)-**2b** (77%)

c: Ar = Ph
d: Ar = 4-MeOC$_6$H$_4$

a: Ar = Ph
b: Ar = 4-MeOC$_6$H$_4$

Scheme 4.

β-hydroxy-β-trifluoromethyl substituent at N(1). Moreover, optically active imidazole *N*-oxides with this substitution pattern should be also prepared.

2. Results and discussion

Searching for suitably substituted arylglyoxalimines, the model compounds **6**, bearing a methoxy group at the N-atom, were selected. They were obtained by treatment of arylglyoxal hydrates **5a**,**b** with *O*-methyl hydroxylamine hydrochloride in the presence of sodium acetate. The subsequent nucleophilic trifluoromethylation was carried out under typical conditions using an equimolar amount of CF_3SiMe_3 (Ruppert-Prakash reagent [8]) in dimethoxyethane (DME) in the presence of catalytic amounts of CsF. The crude reaction mixtures were examined by ^{19}F-NMR spectroscopy, which evidenced the presence of only one CF_3 signal in each case. Additionally, the IR and ^{13}C-NMR spectra indicated that the obtained products contained still the C=N bond, in accordance with the structure of the *O*-silylated 1:1 adducts **7** (Scheme 3).

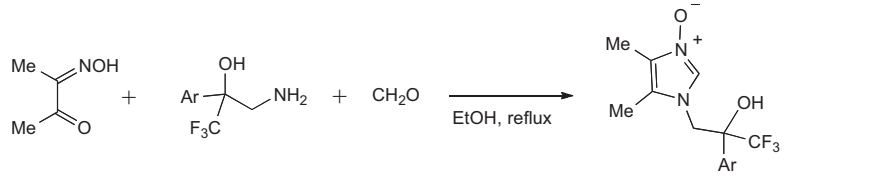
The attempted desilylation/reduction step using $NaBH_4$ [5] led in both cases to complex mixtures. The alternative protocol with $LiAlH_4$ in THF gave the expected amino (trifluoromethyl)alcohols **2a**,**b** in 69 and 78% yield, respectively.

Another approach suitable for the preparation of amino alcohols with a primary amino group is the debenzylation of the initially obtained secondary *N*-benzylated amines **2**. Especially important in this case is the exploration of *N*-(α-methylbenzyl) derivatives, which opens access to optically active amino alcohols. The preparation of optically active amino alcohols **2c**,**d**, synthesized from (*S*)-α-methylbenzylamine and arylglyoxal hydrates **5a**,**b**, has already been reported [5]. The separated diastereoisomers were treated with H_2/Pd, C in methanol at room temperature to give the enantiomerically pure amino alcohols (*R*)-**2a**, (*S*)-**2a**, (*R*)-**2b**, and (*S*)-**2b** (Scheme 4).

The enantiomeric purity of the obtained chiral amino alcohols (*R*)- and (*S*)-**2a** and (*R*)- and (*S*)-**2b** was established spectroscopically by running the ^{1}H- and ^{19}F-NMR spectra in $CDCl_3$ in the presence of the optically pure (*S*)-(*tert*-butyl)(phenyl)phosphonothioic acid [9] (see also [5,7f,10].

The synthesis of imidazole derivatives was carried out first with racemic amino alcohols **2a** and **2b** using formaldehyde and diacetyl monooxime (**4a**). After heating the mixture in boiling ethanol for 3 h, imidazole *N*-oxides **3a** and **3b** were isolated in 70 and 82% yield, respectively (Scheme 5).

On the other hand, the same procedure applied for (*rac*)-**2b** and ethyl 2-hydroxyimino-3-oxobutanoate (**4b**) led to imidazolone (*rac*)-**8a**, which was obtained as the sole product (Scheme 6). Based

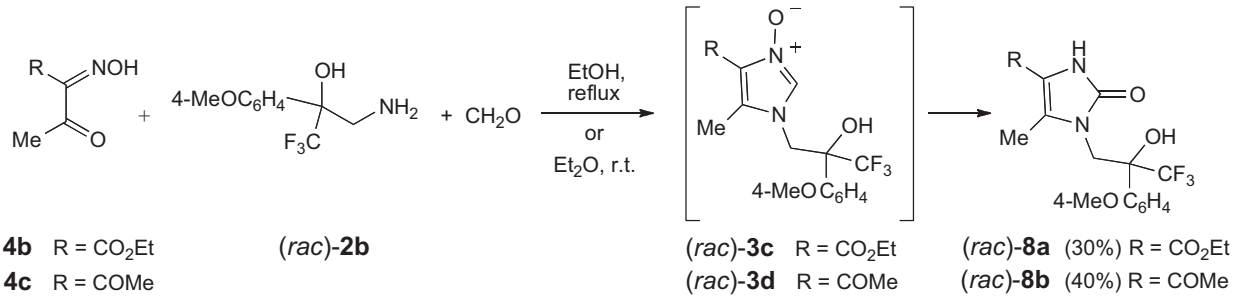


4a

(*rac*)-**2a**
(*rac*)-**2b**

(*rac*)-**3a** (70%) Ar = Ph
(*rac*)-**3b** (82%) Ar = 4-MeOC$_6$H$_4$

Scheme 5.

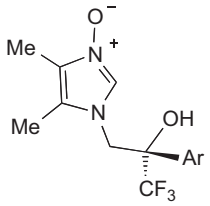


Scheme 6.

on our earlier observation, the formation of (*rac*)-**8a** in this case can be rationalized by the isomerisation of the initially formed *N*-oxide (*rac*)-**3c**.

In general, 2-unsubstituted imidazole *N*-oxides bearing an electron withdrawing substituent at C(4) tend to undergo spontaneous isomerization to the corresponding imidazolones already at room temperature [10]. Otherwise, the isomerization requires heating of the *N*-oxide [11a], irradiation with UV light [11b], or treatment with acetic anhydride [7b]. The experiment with **4b** and (*rac*)-**2b** was repeated in ether at room temperature, but also in this case only (*rac*)-**8a** was obtained. Similarly, the reaction performed with 3-hydroxyiminopentane-2,4-dione (**4c**) led to imidazolone derivative (*rac*)-**8b** (Scheme 6).

Finally, the enantiomerically pure amino alcohols (*S*)-**2a** and (*S*)-**2b** were used in the reaction with formaldehyde and **4a** in boiling ethanol. The optically active imidazole *N*-oxides (*S*)-**3a** and (*S*)-**3b** were isolated in 52 and 50% yield.



(*S*)-**3a** Ar = Ph

(*S*)-**3b** Ar = 4-MeOC$_6$H$_4$

3. Conclusions

The presented results show that properly substituted imino derivatives of arylglyoxals can be used for the nucleophilic trifluoromethylation with the Ruppert-Prakash reagent and subsequent treatment with $LiAlH_4$ or reduction/debenzylation lead to β-amino-α-trifluoromethyl alcohols possessing a primary amino group. The reduction/debenzylation procedure with the imine derived from enantiomerically pure (*S*)-α-methylbenzyl-amine opens a convenient access to enantiomerically pure trifluoromethylated amino alcohols. Both racemic and enantiomerically pure amino alcohols **2** can be used as new building blocks for the preparation of imidazole derivates. Depending on the substitution pattern of α-hydroxyimino ketone used in these reactions, either 2-unsubstituted imidazole *N*-oxides or the isomeric imidazol-2-ones were obtained. The structure of the obtained imidazole derivatives relates to some known biologically active compounds and, therefore, they may be of interest for future applications.

4. Experimental part

4.1. General experimental procedures

General. Melting points were determined on a Melt-Temp. II apparatus (Aldrich) in capillary and they are uncorrected. The ^{1}H, ^{13}C{^{1}H} and ^{19}F NMR spectra were recorded on Bruker Avance III 600 or Varian Gemini BB 200 spectrometers using solvent signals as reference. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. The IR spectra were measured using a NEXUS FT-IR spectrophotometer. The MS spectra (ESI, ESI-HRMS) were obtained using Varian 500-MS or Bruker Esquire LC spectrometers. Elemental analyses were performed in the Microanalytical Laboratory of the Centre of Molecular and Macromolecular Studies PAS in Łódź. Optical rotations were measured on a PERKIN-ELMER 241 MC spectropolarimeter for λ = 589 nm.

4.2. Materials

Commercial paraformaldehyde, (trifluoromethyl)trimethylsilane, methoxyamine hydrochloride, lithiumaluminium hydride (1 M solution in THF) and palladium on charcoal (10%) were purchased from Sigma–Aldrich. α-(Hydroxyimino)ketones **4a** [12a], **4b** [12b], and **4c** [12c], as well as 2,2-dihydroxy-1-arylethanones **5a**,**b** [13] were prepared according to known protocols. (2*R*/2*S*,1′*S*)-1,1,1-Trifluoro-3-[1-(1-phenylethyl-amino)]-2-arylpropan-2-ols **2c**,**d** were prepared according to the published procedure [5]. Dimethoxyethane (DME) and tetrahydrofurane (THF) were dried over sodium with benzophenone and they were freshly distilled prior to their use.

4.3. Syntheses of α-(methoxyimino)ketones 6

General procedure. 1-Aryl-2,2-dihydroxyethanone **6a**,**b** (5 mmol), methoxyamine hydrochloride (5.05 mmol), and sodium acetate were dissolved in MeOH/H_2O 4:1 (10 ml). The mixture was gently heated to reflux for 30 min. Then, the mixture was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the solutions were evaporated to dryness (room temperature bath). Products **6**, contaminated with ca. 5% (by ^{1}H NMR) of unidentified impurities, were used for further transformations without purification.

2-(*Methoxyimino)-1-phenyl)ethanone* (**6a**). Yield: 0.73 g (90%). Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.10 (s, 3H, CH_3O), 7.45–7.49 (m, 2 arom. CH), 7.58–7.63 (m, 1 arom. CH), 7.95 (s, 1H, HC=N), 8.07–8.09 (m, 2 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 63.4 (CH_3O), 128.3, 130.1, 133.4 (5 arom. CH), 135.9 (1 arom. C), 147.1 (HC=N), 188.1 (C=O). IR (film): *ν* 3061*w*, 2979*m*, 2900*w*,

2822*w*, 1656*vs* (C=O), 1598*s* (C=N), 1448*s*, 1328*s*, 1278*s*, 1233*m*, 1182*m*, 1036*s*, 1020*s*, 926*m* cm^{-1}.

2-(Methoxyimino)-1-(4-methoxyphenyl)ethanone (**6b**). Yield: 0.89 g (92%). Pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 3.89, 4.09 (2s, 6H, 2 CH_3O), 6.94–6.98 (m, 2 arom. CH), 7.94 (s, 1H, HC=N), 8.10–8.15 (m, 2 arom. CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.1, 62.9 (2 CH_3O), 113.5, 132.2 (4 arom. CH), 128.5, 146.9 (2 arom. C), 163.8 (HC=N), 185.9 (C=O). IR (film): ν 3073*w*, 3000*w*, 2944*w*, 1640*vs* (C=O), 1604*vs* (C=N), 1511*m*, 1424*w*, 1293*s*, 1260*vs*, 1186*m*, 1177*m*, 1037*s*, 839*s* cm^{-1}.

4.4. Synthesis of β-amino-α-trifluoromethyl alcohols 2

4.4.1. Reactions of α-iminoketones 6a,b with (trifluoromethyl)trimethylsilane – general procedure

A solution of the corresponding α-methoxyimino ketone **6a**,**b** (1 mmol) in anhydrous DME (1.5 ml), was placed in a dry, two-necked flask, equipped with septum and a tube filled with anhydrous $CaCl_2$. Next, a catalytic amount (3–5 mg) of freshly dried CsF and (trifluoromethyl)trimethylsilane (0.17 ml, 157 mg, 1.1 mmol) were added. The mixture was stirred at room temperature for ca. 1 h and subsequently quenched with water (5 ml). The solution was extracted with CH_2Cl_2 three times. The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated and the crude, oily products **7a**,**b** were used for further reactions without purification.

4.4.2. Reduction of adducts 7a,b with lithium aluminium hydride – general procedure

To a magnetically stirred solution of the corresponding adduct **7a**,**b** in anhydrous THF (3 ml), 1 M solution of $LiAlH_4$ (1.0 ml, 1 mmol) was added dropwise while cooling, and the mixture was stirred for 12 h at room temperature. After this time, a portion of water (ca. 5 ml) was added carefully while cooling the reaction flask in an ice-bath. Next, a solution of saturated aqueous NaOH and solid KOH were added, and subsequently the products were extracted with Et_2O. The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated and the crude products were purified by column chromatography on SiO_2.

3-Amino-1,1,1-trifluoro-2-phenylpropan-2-ol ((*rac*)-**2a**). Yield: 141 mg (69%). Colourless crystals, m.p. 84–86 °C (hexane). ^1H NMR (600 MHz, $CDCl_3$): δ 2.71 (br. s, 2H, OH, NH), 3.04, 3.52 (2d, $^2J_{H,H}$ = 13.2 Hz, 2H, CH_2), 7.35–7.41 (m, 3 arom. CH), 7.58–7.59 (m, 2 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 45.7 (CH_2), 74.3 (q, $^2J_{C,F}$ = 27.2 Hz, C_q), 126.0 (q, $^1J_{C,F}$ = 285.3 Hz, CF_3), 126.4, 128.5, 128.7 (5 arom. CH), 137.6 (1 arom. C). ^{19}F NMR (565 MHz, $CDCl_3$): δ −78.3 (s, CF_3). IR (KBr): ν 3388*s* (O–H), 3095*m*, 3068*m*, 2904*m*, 1603*w*, 1458*m*, 1273*m*, 1196*s*, 1163*vs*, 1152*vs*, 1071*m*, 942*m* cm^{-1}. ESI-MS *m/z* (rel. int.): 206 (45, $[M+1]^+$), 188 (100, $[M-18+1]^+$). Anal. Calcd. for $C_9H_{10}F_3NO$ (205.18): C, 51.07; H, 5.14. Found: C, 50.79; H, 5.14.

3-Amino-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol ((*rac*)-**2b**). Yield: 183 mg (78%). Colourless crystals, m.p. 94–96 °C (hexane/Et_2O). ^1H NMR (600 MHz, $CDCl_3$): δ 3.03, 3.51 (2d, $^2J_{H,H}$ = 13.2 Hz, 2H, CH_2), 3.82 (s, 3H, CH_3O), 6.92–6.93 (m, 2 arom. CH), 7.49–7.51 (m, 2 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 45.6 (CH_2), 55.5 (CH_3O), 73.9 (q, $^2J_{C,F}$ = 27.2 Hz, C_q), 113.9, 127.7 (4 arom. CH), 126.0 (q, $^1J_{C,F}$ = 286.8 Hz, CF_3), 129.6, 159.9 (2 arom. C). ^{19}F NMR (565 MHz, $CDCl_3$): δ −78.7 (s, CF_3). IR (KBr): ν 3342*s* (O–H), 3312*m* (N–H), 3017*m*, 2972*m*, 2913*m*, 1692*w*, 1515*s*, 1465*m*, 1305*m*, 1254*s*, 1183*s*, 1154*vs*, 1112*m*, 1036*m*, 960*m* cm^{-1}. ESI-MS *m/z* (rel. int.): 236 (27, $[M+1]^+$), 218 (100, $[M-18+1]^+$). Anal. Calcd for $C_{10}H_{12}F_3NO_2$ (235.21): C, 52.69; H, 4.91. Found: C, 52.68; H, 4.95.

4.4.3. Hydrogenolysis of β-amino-N-phenylethyl-α-trifluoromethyl alcohols 2c,d

To a solution of the corresponding amino alcohol (2*S*, 1′*S*)- or (2*R*, 1′*S*)-**2c**,**d** (1.0 mmol) in MeOH (2 ml), 10% Pd/C (150 mg) was added, and the flask was closed with a septum. Then, hydrogen was bubbled through the mixture via a needle from a rubber balloon, and the suspension was stirred for ca. 3 h under atmospheric pressure. Next, the solvent was evaporated under vacuum, and the products were isolated after filtration through celite and silica gel pads using a mixture hexane/CH_2Cl_2 (1:1) as the eluent.

(S)-*3-Amino-1,1,1-trifluoro-2-phenylpropan-2-ol* ((*S*)-**2a**). Yield: 189 mg (92%). Colourless crystals, m.p. 86–88 °C (hexane), $[\alpha]_D$ = +43 (*c* 1.0, CH_2Cl_2). Spectroscopic data identical with data for (*rac*)-**2a**.

(R)-*3-Amino-1,1,1-trifluoro-2-phenylpropan-2-ol* ((*R*)-**2a**). Yield: 185 mg (90%). Colourless crystals, m.p. 84–86 °C (hexane), $[\alpha]_D$ = –42 (*c* 1.0, CH_2Cl_2). Spectroscopic data identical with data for (*rac*)-**2a**.

(S)-*3-Amino-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*S*)-**2b**). Yield: 190 mg (81%). Colourless crystals, m.p. 97–99 °C (hexane/Et_2O), $[\alpha]_D$ = +28 (*c* 1.0, CH_2Cl_2). Spectroscopic data identical with data for (*rac*)-**2b**.

(R)-*3-Amino-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*R*)-**2b**). Yield: 181 mg (77%). Colourless crystals, m.p. 98–100 °C (hexane/Et_2O). $[\alpha]_D$ = –29 (*c* 1.0, CH_2Cl_2). Spectroscopic data identical with data for (*rac*)-**2b**.

4.5. Syntheses of imidazole derivatives 3 and 8

4.5.1. Reactions of β-amino-α-trifluoromethyl alcohols 2a,b with paraformaldehyde and α-(hydroxyimino)ketone 4a – general procedure

A solution of a β-amino-α-trifluoromethyl alcohol **2a**,**b** (1.0 mmol) and paraformaldehyde (32 mg, 1.05 mmol) in EtOH was stirred at room temperature for 12 h. The solution was filtered, α-(hydroxyimino)ketone **4a** (1.1 mmol) was added, and the mixture was heated to reflux for 6 h. Then, the solvent was evaporated, the residue was treated with Et_2O, and the crystalline product was separated and washed several times with Et_2O. Pure products were obtained after crystallization from an appropriate solvent.

3-(4,5-Dimethyl-3-oxido-1H-imidazol-1-yl)-1,1,1-trifluoro-2-phenyl-propan-2-ol ((*rac*)-**3a**). Yield: 210 mg (70%). Colourless crystals, m.p. 239–241 °C (decomp.; iPr_2O/MeOH). ^1H NMR (600 MHz, CD_3OD): δ 1.96, 2.06 (2s, 6H, 2 CH_3), 4.55 (s, 2H, CH_2), 7.41–7.44 (m, 3 arom. CH), 7.55–7.57 (m, 2 arom. CH), 7.78 (s, 1 CH imidazol). ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.5, 7.1 (2 CH_3), 49.6 (CH_2), 76.6 (q, $^2J_{C,F}$ = 27.4 Hz, C_q), 123.2, 124.8, 135.0 (2C imidazole, 1 arom. C), 125.2 (q, $^1J_{C,F}$ = 285.4 Hz, CF_3), 126.1, 128.3, 129.0 (5 arom. CH), 126.6 (1 CH imidazol). ^{19}F NMR (565 MHz, CD_3OD): δ −75.6 (s, CF_3). IR (KBr): ν 3153*br.m*, 3061*br.m*, 2930*w*, 2630*br.m*, 1632*w*, 1450*m*, 1444*w*, 1404*m*, 1341*m*, 1267*s*, 1250*s*, 1172*vs*, 1155*vs*, 1079*m*, cm^{-1}. ESI-HRMS: Calcd for $C_{14}H_{15}F_3N_2O_2Na^+$ ($[M+23]^+$): *m/z* 323.09783; found: *m/z* 323.09778. Calcd for $C_{14}H_{16}F_3N_2O_2^+$ ($[M+1]^+$): *m/z* 301.11584; found: *m/z* 301.11606.

(S)-*3-(4,5-Dimethyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-phenyl-propan-2-ol* ((*S*)-**3a**). Yield: 190 mg (63%). Colourless crystals, m.p. 240–242 °C (decomp.; iPr_2O/MeOH). $[\alpha]_D$ = +16.0 (*c* 1.0, MeOH). Spectroscopic data identical with data for (*rac*)-**3a**.

*3-(4,5-Dimethyl-3-oxido-1*H*-imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*rac*)-**3b**). Yield: 271 mg (82%). Colourless crystals, m.p. 235–237 °C (decomp.; iPr_2O/MeOH). ^1H NMR (600 MHz, CD_3OD): δ 1.93, 2.04 (2s, 6H, 2 CH_3), 3.80 (s, CH_3O), 4.49 (s, 2H, CH_2), 6.93–6.96, 7.43–7.44 (2m, 4 arom. CH), 7.72 (s, 1 CH imidazol). ^{13}C NMR (150 MHz, CD_3OD): δ 7.1, 8.7 (2 CH_3), 51.1

(CH_2), 55.9 (CH_3O), 78.0 (q, $^2J_{C,F}$ = 27.5 Hz, C_q), 115.2, 129.0 (4 arom. CH), 128.1 (1 CH imidazol), 126.8 (q, $^1J_{C,F}$ = 285.3 Hz, CF_3), 125.2, 125.3, 126.3, 162.0 (2C imidazole, 2 arom. C). ^{19}F NMR (565 MHz, CD_3OD): δ −77.9 (s, CF_3). IR (KBr): ν 3162*br.m*, 3018*br.m*, 2845*br.w*, 2614*br.w*, 1613*m*, 1516*s*, 1444*w*, 1340*w*, 1305*m*, 1250*s*, 1173*vs*, 1154*vs*, 1030*m*, 841*m* cm^{-1}. ESI-HRMS: Calcd. for $C_{15}H_{18}F_3N_2O_3^+$ ([M+1]$^+$): *m/z* 331.12640; found: *m/z* 331.12662.

(*S*)-*3-(4,5-Dimethyl-3-oxido-1*H-*imidazol-1-yl)]-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*S*)-**3b**). Yield: 202 mg (61%). Colourless crystals, m.p. 234–236 °C (decomp.; *i*Pr_2O/MeOH). $[\alpha]_D$ = +13.7 (*c* 1.0, MeOH). Spectroscopic data identical with data for (*rac*)-**3b**.

4.5.2. Reactions of β-amino-α-trifluoromethyl alcohol 2b with paraformaldehyde and α-(hydroxyimino)ketones 4b,c – general procedure

A solution of a β-amino-α-(trifluoromethyl)alcohol **2a**,**b** (1.0 mmol) and paraformaldehyde (32 mg, 1.05 mmol) in EtOH was stirred at room temperature for 12 h. Then, the solution was filtered, **4b** or **4c** (1.1 mmol) was added, and the mixture was stirred in room temperature for 48 h. The white precipitate was filtered off and washed several times with Et_2O.

*3-(4-Ethoxycarbonyl-2,3-dihydro-5-methyl-2-oxo-1*H-*imidazol-1-yl)-1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol* ((*rac*)-**8a**). Yield: 125 mg (30%). Colourless crystals, m.p. 196–198 °C (decomp.). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.23 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, CH_3CH$_2$), 2.22 (s, 3H, CH_3), 3.76 (s, CH_3O), 4.17 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, CH_3CH_2), 4.21, 4.32 (2d, 2H, $^2J_{H,H}$ = 15.6 Hz, 2H, CH_2), 6.95–6.96, 7.52–7.54 (2m, 4 arom. CH), 7.58 (s, 1H, OH), 10.92 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 9.9 (CH_3), 14.2 (*C*H_3CH$_2$), 46.7 (CH_2), 55.1 (CH_3O), 60.0 (CH_3*C*H$_2$), 76.7 (q, $^2J_{C,F}$ = 27.4 Hz, C_q), 125.3 (q, $^1J_{C,F}$ = 286.8 Hz, CF_3), 113.6, 128.1 (4 arom. CH), 127.7, 127.9 131.5, 154.6 (2C imidazole, 2 arom. *C*), 159.5 ($CH_3CH_2CO_2$ and C=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ −76.4 (s, CF_3). IR (KBr): ν 3280*br.s* (N–H + O–H), 1693*vs* (C=O), 1636*vs* (C=O), 1605*s*, 1514*m*, 1443*m*, 1308*m*, 1254*m*, 1180*s*, 1173*vs*, 1153*vs*, 1144*s*, 1111*m*, 1029*m* cm^{-1}. ESI-HRMS: Calcd. for $C_{17}H_{19}F_3N_2O_5Na^+$ ([M+23]$^+$): *m/z* 411.11383; found: *m/z* 411.11384.

*3-(4-Acetyl-2,3-dihydro-5-methyl-2-oxo-1*H-*imidazol-1-yl)-1,1,1-trifluoro-(4-methoxphenyl)propan-2-ol* ((*rac*)-**8b**). Yield: 155 mg (40%). Colourless crystals, m.p. 222–225 °C (decomp.). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.25, 2.26 (2s, 6H, CH_3 + CH_3CO), 3.76 (CH_3O), 4.23, 4.35 (2d, 2H, $^2J_{H,H}$ = 15.0 Hz, 2H, CH_2), 6.95–6.97, 7.53–7.55 (2m, 4 arom. CH), 7.51 (s, 1H, OH), 10.89 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 10.5 (CH_3), 28.1 (*C*H_3CO), 46.3 (CH_2), 55.1 (CH_3O), 76.6 (q, $^2J_{C,F}$ = 27.2 Hz, C_q), 125.2 (q, $^1J_{C,F}$ = 288.3 Hz, CF_3), 113.5, 127.6 (4 arom. CH), 118.8, 127.5, 131.2, 153.7 (2C imidazole, 2 arom. C), 159.4 (C=O), 186.6 (CH_3*C*O). ^{19}F NMR (565 MHz, DMSO-d_6): δ −76.1 (s, CF_3). IR (KBr): ν 3280*br.s* (N–H + O–H), 1693*vs* (C=O), 1636*vs* (C=O), 1605*s*, 1514*m*, 1443*m*, 1308*m*, 1254*m*, 1180*s*, 1173*vs*, 1153*vs*, 1144*s*, 1111*m*, 1029*m* cm^{-1}. ESI-HRMS: Calcd for $C_{16}H_{17}F_3N_2O_4Na^+$ ([M+23]$^+$): *m/z* 381.10326; found: *m/z* 381.10346.

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