

Reaction of trifluoromethyl 1,3-dicarbonyl compounds with formaldehyde and esters of natural α -aminoacids

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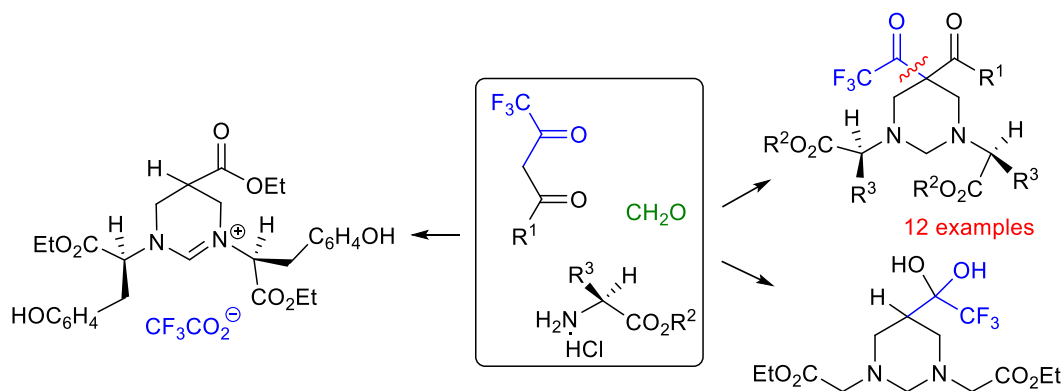
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Abstract

Condensation of fluorinated 1,3-dicarbonyl compounds with formaldehyde and L-amino acid ester hydrochlorides in acetate buffer, AcONa–AcOH (pH 5.9), at room temperature gave chiral hexahydropyrimidines, both containing and lacking a trifluoroacetyl group at position 5 of the heterocycle. In contrast, the reaction of ethyl 3-oxo-4,4,4-trifluorobutanoate with formaldehyde and ethyl (S)-tyrosinate hydrochloride under the same conditions gave a new chiral tetrahydropyrimidinium salt containing the trifluoroacetate anion in good yield. It is interesting that one of the formaldehyde molecules acts as an oxidant in this process.



Keywords: Trifluoromethyl 1,3-dicarbonyl compounds, (S)-aminoesters, hexahydropyrimidines, chirality

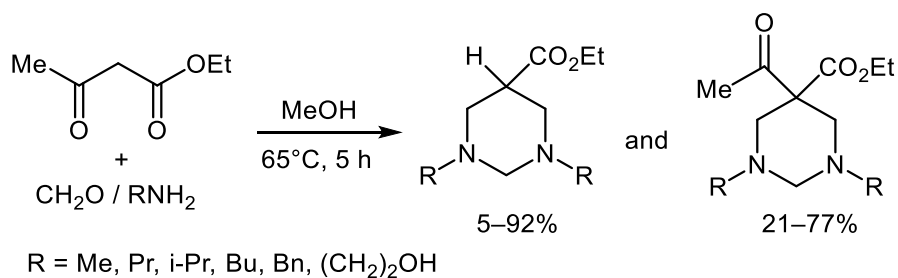
Introduction

The unique properties of the trifluoromethyl group, such as strong electron-withdrawing character, lipophilicity and metabolic stability, are widely used in the synthesis of new compounds for pharmaceutical and agrochemical industries as well as in materials technology.¹ Replacement of a hydrogen atom for a fluorine has little effect on the molecule's geometry due to the similarity of their atomic radii, but the high electronegativity of fluorine strongly affects the overall electron-donating properties of a molecule.² On a molecular level, this results in inhibition of certain metabolic pathways, including a change in membrane permeability and electrostatic interaction with the target. In terms of physiology, an increase in bioavailability and selectivity with respect to the pharmacological target are achieved.³

Hexahydropyrimidines belong to an important class of biologically active heterocycles with a broad range of physiological activity: antitumoral,^{4,5} cytotoxic,^{3,6} antibacterial,⁷ antimicrobial,⁸ antiarrhythmic⁹ and antiviral (against hepatitis C).¹⁰ 5,5-Disubstituted hexahydropyrimidines are efficient against Ehrlich carcinoma and *Staphylococcus aureus*.¹¹ Some hexahydropyrimidines containing a trifluoromethyl group are usually obtained by the Biginelli reaction from ethyl 4,4,4-trifluoroacetoacetate, an aldehyde, and urea or thiourea.^{3,12,13} Several fluorine-containing 2-thia- or 2-oxahexahydropyrimidines manifest cytotoxic³ and antibacterial activity¹² and are promising as selective antitumoral medicines.¹⁴

In this study we suggest a one-pot synthesis of optically active hexahydropyrimidine derivatives by reaction of trifluoromethyl 1,3-dicarbonyl compounds with formaldehyde and natural amino acid ester hydrochlorides under Mannich reaction conditions. Also, a one-pot method for the synthesis of a new chiral tetrahydropyrimidinium salt is presented.

The reactions of CH-acids with aldehydes and primary amines under Mannich reaction conditions are among the convenient methods for synthesizing hexahydropyrimidine derivatives. These reactions are generally carried out in methanol or in water-methanol solutions at 65°C and pH 7.5–8.0^{15,16} (Scheme 1).



Scheme 1. Synthesis of hexahydropyrimidines under Mannich reaction conditions.

Results and Discussion

In continuation of studies¹⁵ on the synthesis of hexahydropyrimidines, we studied the reaction of fluorine-containing 1,3-dicarbonyl compounds, namely ethyl 3-oxo-4,4,4-trifluorobutanoate (**1a**), 1,1,1-trifluoropentane-2,4-dione (**1b**) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**1c**), with formaldehyde and esters of natural amino acids under Mannich reaction conditions. Methyl ester hydrochlorides of (*S*)-alanine (**2b**), (*S*)-valine (**2c**), (*S*)-leucine (**2d**) and ethyl ester hydrochlorides of glycine (**2a**), (*S*)-phenylalanine (**2e**), and (*S*)-tyrosine (**2f**) were used as the amino esters. It was found that in all cases the reaction conditions used

previously for non-fluorinated 1,3-dicarbonyl compounds did not provide tetrasubstituted hexahydropyrimidines due to easy elimination of the CF₃CO group. Still, we succeeded in finding conditions where the trifluoroacetyl group was preserved for certain amino esters. The formation of the 1,3,5,5-tetrasubstituted hexahydropyrimidine moiety occurs most successfully at room temperature under conditions of sequential condensation of trifluoromethyl 1,3-dicarbonyl compounds with formaldehyde and amino ester hydrochlorides with a molar reagent ratio of 1 : 15 : 2 or 1 : 4 : 2 (depending on the CH-acid used) in acetate buffer, AcONa–AcOH (pH 5.9). The use of 1.0 ml acetate buffer for each one-mmol of a CH-acid proved to be the optimum amount for this reaction.

A study of the effect of the nature of the starting reagents on the reaction pathway showed that the amine component considerably affected the likelihood that the trifluoroacetyl group at position 5 of the heterocycle would be preserved. In fact, the reaction of ethyl 3-oxo-4,4,4-trifluorobutanoate (**1a**) with an aqueous solution of formaldehyde and ethyl glycinate hydrochloride (**2a**) or methyl (*S*)-alaninate hydrochloride (**2b**) results in hexahydropyrimidines **3a** or **3b** containing no trifluoroacetyl group (Table 1, entries 1 and 2). In general, this behavior of trifluoroacetyl derivatives is not surprising. For example, it is known¹⁶ that the reaction of ethyl 3-oxo-4,4,4-trifluorobutanoate (**1a**) with benzaldehyde in the presence of pyridine is accompanied by elimination of pyridinium trifluoroacetate.

Table 1. Synthesis of hexahydropyrimidines **3** and **4** from **1a,b**, CH₂O and various α-amino esters

Entry	CH-acid	R ¹	Amino ester	R ²	R ³	Isolated yields (%) ^a
1	1a	OEt	2a	Et	H	3a (62) –
2	1a	OEt	2b	Me	Me	3b (56) –
3	1a	OEt	2c	Me	CHMe ₂	3c (10) 4c (48)
4	1a	OEt	2d	Me	CH ₂ CHMe ₂	3d (26) ^b 4d (40) ^b
5	1a	OEt	2e	Et	CH ₂ Ph	– 4e (46)
6	1b	Me	2a	Et	H	3f (42) ^c –
7 ^d	1b	Me	2a	Et	H	– 4f (70)
8 ^d	1b	Me	2f	Et	CH ₂ C ₆ H ₄ OH-4	3g (46) ^c –

^a Reaction conditions: molar ratio **1** : CH₂O (33% aqueous solution) : **2** = 1 : 15 : 2, rt, 24 h.

^b Results after column chromatography.

^c Yields were determined by NMR spectroscopy (benzene as internal standard).

^d Molar ratio **1b** : CH₂O : **2** = 1 : 4 : 2.

Unlike glycine and alanine esters, the reactions of **1a** with formaldehyde and (*S*)-valine (**2c**) and especially (*S*)-leucine (**2d**) and (*S*)-phenylalanine (**2e**) ester hydrochlorides under the same conditions occurs with preservation of the CF₃CO group.¹⁷ While in the case of (*S*)-valine the reaction mixture contains not only **4c** but also ~10% of defluorinated product **3c** (entry 3), amino esters **2d** and **2e** selectively give fluorinated hexahydropyrimidines **4d** and **4e** in 68 and 46% yields, respectively (entries 4, 5). However, certain precautions are also needed in this case in order to preserve the trifluoroacetyl group in the hexahydropyrimidine ring. For example, isolation of compound **4d** by column chromatography on SiO₂ resulted in deacylation of a proportion of the product to give compounds **3d** and **4d** in 26 and 40% yields, respectively. However, this phenomenon was not observed in the case of chromatography of hexahydropyrimidines **4c** and **4e** on SiO₂.

In order to establish the absence of epimerization and to prove the formation of a single enantiomer we carried out the reaction of **1a** with racemic leucine methyl ester (**2d**). In this case, according to the data of NMR spectra and chiral HPLC analysis, the target compound **4d** is formed as four stereoisomers. Three of them are diastereomers, of which two represent *meso*-forms (Figure 1). At the same time, the corresponding compound obtained from (*S*)-leucine **2d** in the same conditions is formed as one pure (*S,S*)-enantiomer.

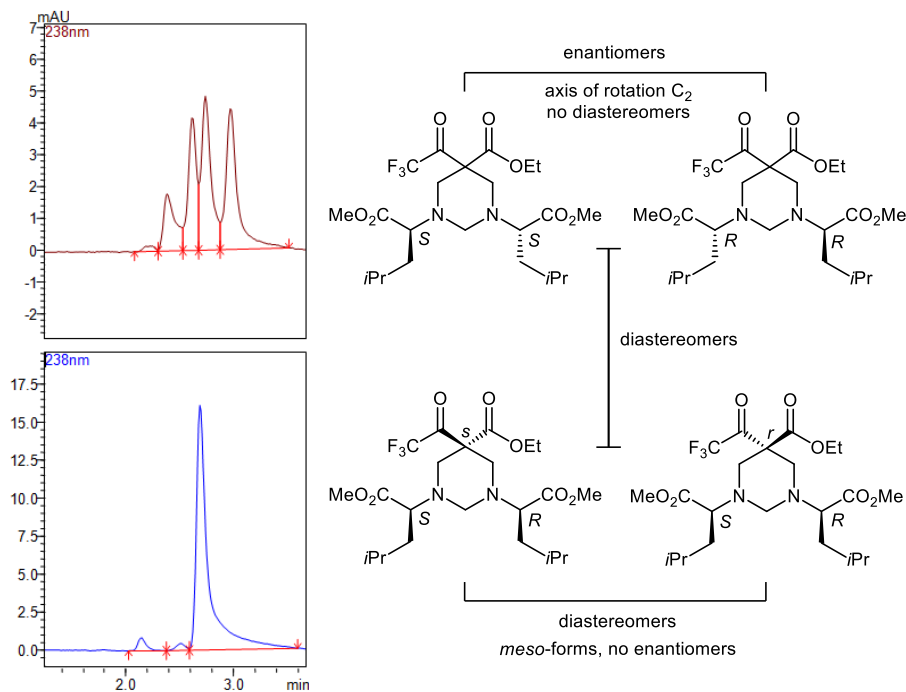


Figure 1. Four stereoisomers of compound **4d** formed in the reaction of racemic leucine methyl ester and chiral HPLC analysis for them (top) in comparison with the same enantiopure (bottom).

The reaction of 1,1,1-trifluoropentane-2,4-dione (**1b**) with formaldehyde and ethyl glycinate hydrochloride (**2a**), similarly to keto ester **1a** under the same conditions, gives 1,3,5-trisubstituted hexahydropyrimidine **3f** containing no trifluoroacetyl group (Table 1, entry 6). However, if the CH-acid : CH₂O : amino ester molar ratio is changed from 1 : 15 : 2 to 1 : 4 : 2, the reaction occurs with retention of the trifluoroacetyl group to give hexahydropyrimidine **4f** in 70% yield (entry 7). It might seem that the reaction of diketone **1b** with formaldehyde and ethyl (*S*)-tyrosinate hydrochloride (**2f**) under the same conditions would have to result in a hexahydropyrimidine with retention of the trifluoroacetyl moiety. However, only deacylated product **3g** was

found after the reaction (entry 8). It cannot be ruled out that this reaction pathway, unlike with the similar amino esters **2c-e**, is favored by the presence of weakly acidic phenol moieties in the amino ester component.

A study of the effect of time on the reaction completeness showed that hexahydropyrimidines were mostly formed in the first several hours. In fact, the yields of compound **3f** in 1, 7 and 24 h are ~30, 39 and 42%, respectively, and almost does not increase after that. An increase in the amount of acetate buffer or addition of dichloromethane (*ca.* 5-fold) in order to increase the solubility of the components favors the homogenization of the reaction mixture but has little effect on the yields of hexahydropyrimidines. The reaction carried out in water, diethyl ether, acetic acid, or in methanol under reflux conditions gave complex mixtures of compounds in which no hexahydropyrimidine derivatives were found.

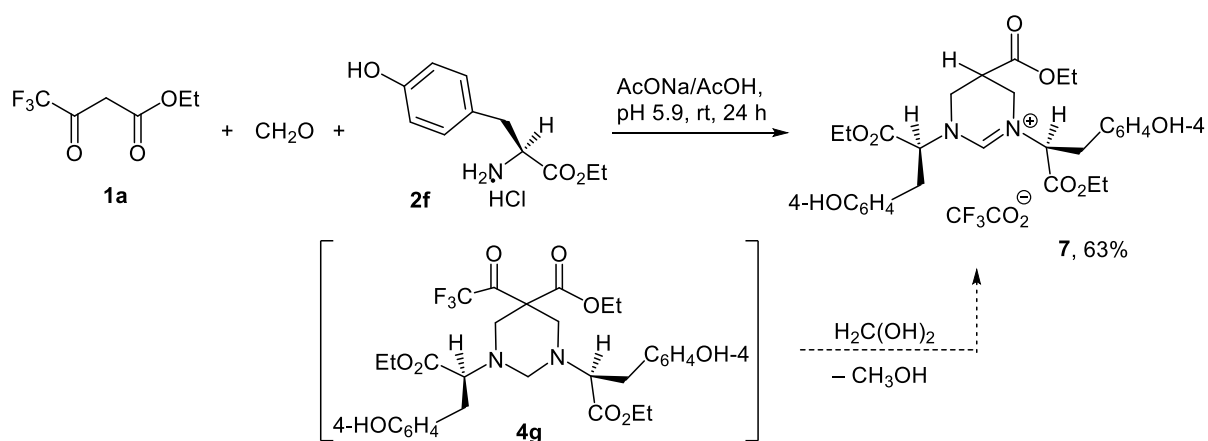
On switching to 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**1c**), an abrupt decrease in the yields of hexahydropyrimidines was observed; moreover, only one trifluoroacetyl group (or its hydrate form) remained in the reaction products. In fact, diketone **1c** entered a Mannich reaction with 33% aqueous formaldehyde and ethyl glycinate hydrochloride at a CH-acid : CH₂O : amino ester molar ratio of 1 : 15 : 2 to give two trifluoromethyl-containing hexahydropyrimidines **5a** and **6** in a total yield of 30% in 1 : 1 ratio (Table 2). By decreasing the amount of formaldehyde (molar ratio **1c** : CH₂O : **2a** = 1 : 4 : 2), we succeeded to obtain the hexahydropyrimidine **6** selectively, but its yield increased insignificantly (to only 18%).

Under similar conditions (Table 2, Entry 3), ethyl (*S*)-tyrosinate hydrochloride (**2f**) as the amine component gave 5-trifluoroacetylhexahydropyrimidine **5f** in 45% yield. Previously,¹⁸ the possibility of involving 1,3-diketones containing two trifluoromethyl groups in the Mannich reaction was denied entirely due to formation of stable tetraols or bis-hemiketals in alcoholic or aqueous media. It is interesting to note that at molar ratio **1c** : CH₂O : **2f** = 1 : 15 : 2 no compounds containing the hexahydropyrimidine frame were isolated.

Table 2. Synthesis of fluorinated hexahydropyrimidines **5** and **6**

Entry	Molar ratio 1c : CH ₂ O : 2	Amino ester	Isolated yields (%)
1	1 : 15 : 2	2a R = H	5a (15) 6 (15)
2	1 : 4 : 2	2a R = H	– 6 (18)
3	1 : 4 : 2	2f R = CH ₂ C ₆ H ₄ OH-4	5f (45) –

Unlike with diketones **1b,c**, a somewhat unexpected result was obtained in the reaction of keto ester **1a** with ethyl (*S*)-tyrosinate hydrochloride (**2f**) in the presence of a 15-fold molar excess of CH₂O. In this case we obtained chiral tetrahydropyrimidinium salt **7** containing the trifluoroacetate anion (Scheme 2). This compound was isolated in 63% yield by column chromatography on SiO₂ as a crystalline compound with m.p. 77–78 °C;¹⁹ none of the expected hexahydropyrimidines was found.



Scheme 2. Preparation of tetrahydropyrimidinium salt **7** using (*S*)-tyrosine derivative **2f**.

A specific feature of this reaction is that the formation of the tetrahydropyrimidinium moiety assumes that a redox process occurs, where one of the formaldehyde molecules acts as the oxidant and is converted to methanol. Formally, the overall result of this transformation corresponds to the cleavage of the prospective compound **4g** under the action of the hydrated formaldehyde (Scheme 2), but how this actually happens we cannot yet explain. Tetrahydropyrimidinium salts are generally obtained either by quaternization of tetrahydropyrimidines or by dehydrogenation of hexahydropyrimidines.²⁰ There are no data in literature on one-pot methods for the synthesis of structures of this kind from simple linear starting compounds.

Though salt **7** forms good crystals, we failed to obtain an X-ray analysis. Nevertheless, its structure was totally confirmed by ¹H, ¹³C, ¹⁵N, and ¹⁹F NMR spectroscopy with the use of 2D techniques and gradient pulse sequences, *viz.*, COSY, TOCSY, NOESY, DOSY, HSQC, HMBC, ¹⁵N-HMBC, ¹⁹F-HMBC and ¹⁹F-HOESY, and the data completely match the ionic form described.

This is also confirmed by HRMS ESI data (in positive mode) that directly show that the cation of this salt is present. It was found that in solution, the trifluoroacetate anion is rather strongly bound with the cation into an ion pair. The 2D ¹H,¹⁹F-HOESY NMR spectra in CDCl₃ solution show ¹H-¹⁹F heteronuclear NOE couplings between the CF₃ group and the protons of aromatic rings, showing that they are rather close in space (Figure 2).

Aside from the unusual formation of an ionic structure itself, salt **7** behaves in a very interesting manner in solutions with various polarities. In low-polar solvents (CDCl₃), compound **7** forms stable associates that strongly affect NMR spectra (Figure 3). In fact, the NOE sign changes from positive to negative, which occurs if the molecular mass of the solution structural unit increases above 1000 Da. Furthermore, due to the formation of associates, the diffusion coefficient in the solution decreases significantly. (The diffusion coefficient was measured using 2D ¹H DOSY NMR spectra, Diffusion Ordered NMR Spectroscopy). It is very difficult to judge on the structure of these associates. Perhaps, they are formed through intermolecular interaction of trifluoroacetate anions with cations that link them into a long chain. The trifluoroacetate anion in CDCl₃ solution is rather strongly bound with the cation into ion pairs and is quite close to it in space, which results in ¹H-¹⁹F Heteronuclear NOE coupling in 2D ¹H,¹⁹F-HOESY NMR spectra (Figure 2).

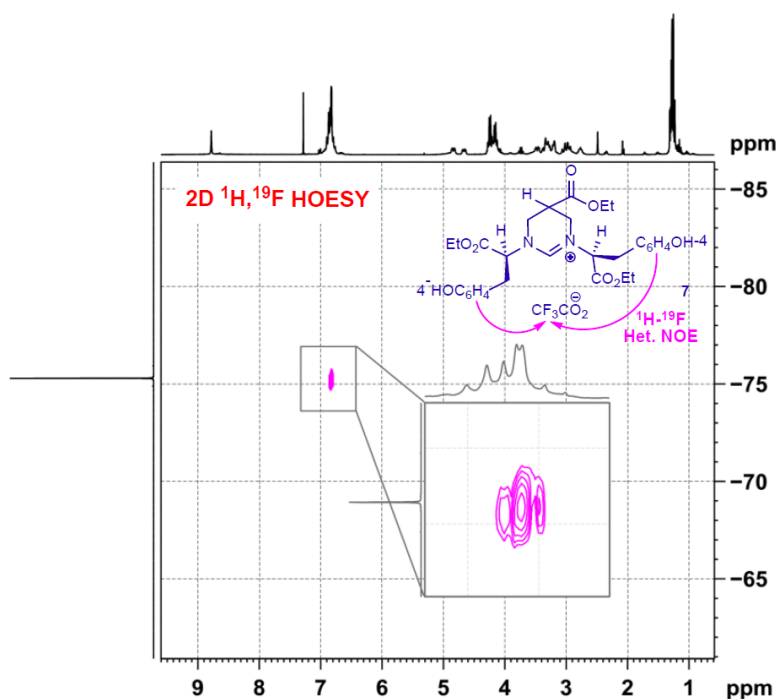


Figure 2. The 2D ^1H , ^{19}F HOESY NMR spectrum (mixing time 2 sec) of salt **7** in CDCl_3 . Enlarged aromatic region of the spectrum is given in the rectangle. ^1H - ^{19}F Heteronuclear NOE correlations are shown in crimson color on the spectrum and by corresponding arrows on the structure.

In more polar solvents (CD_3CN) the associates decompose and compound **7** behaves as an ordinary low-molecular compound. In NMR spectra, the NOE sign becomes positive, while the diffusion coefficient increases considerably. Furthermore, the chemical shifts change strongly in comparison with the solution in CDCl_3 .

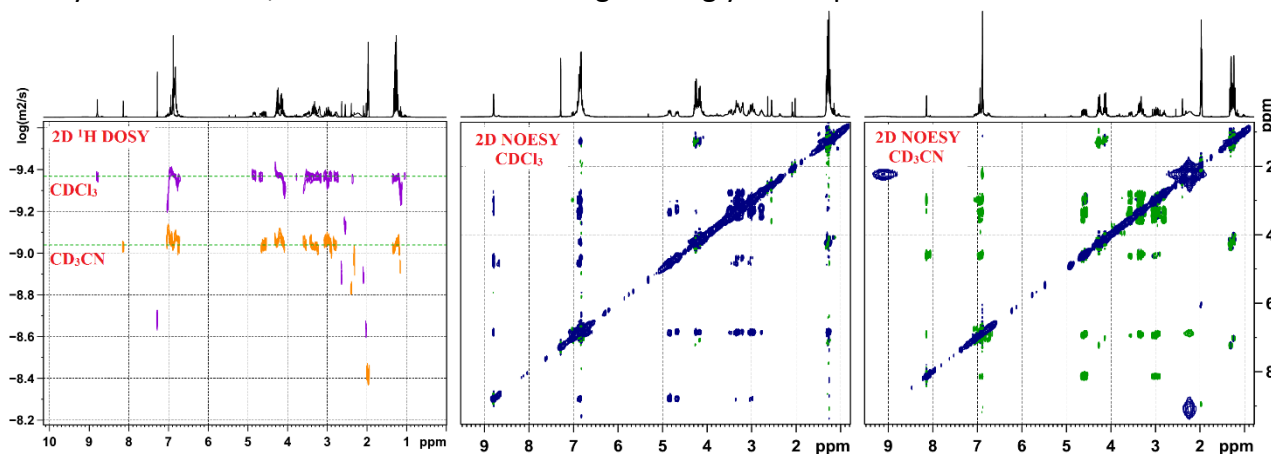


Figure 3. The left image: two imposed 2D ^1H LED-DOSY NMR spectra of salt **7** in CDCl_3 (purple) and CD_3CN (orange); green dashed lines indicate the approximate diffusion coefficients of salt **7**; the associates of **7** in CDCl_3 have higher MW and lower diffusion coefficients. The central and right images: 2D ^1H , ^1H NOESY NMR spectra (mixing time 1 sec) of salt **7** in CDCl_3 (the central image) and CD_3CN (the right image); the color the of cross-peaks indicates the sign of the NOE effect (green – positive, blue – negative); in CDCl_3 all cross-peaks have a negative sign (abnormal for low molecular weight compounds) which indicates the formation of associates.

The chemical shift δ_{H} of the N–CH=N⁺ signal changes most significantly (by 0.7 ppm, *i.e.*, from 8.8 to 8.1). In this case, addition of just a few drops of CD₃CN to a solution in CDCl₃ decomposes the associates to a considerable extent. This apparently occurs due to stabilization of ion pairs by molecules of the polar solvent with formation of a solvate shell.

The formation of associates is demonstrated in the pictures showing the 2D NOESY and 2D DOSY NMR spectra (Figure 3). In fact, two pictures of 2D NOESY in CDCl₃ and CD₃CN demonstrate the NOE sign change (Figure 3, the central and right images; the sign is shown by cross-peaks, green – positive, blue – negative, relative to the diagonal which is always negative; all the signals change their sign). The change in the diffusion coefficients is demonstrated by the 2D ¹H DOSY NMR spectra superimposed on the same scale (Figure 3, the left image; the logarithm of the diffusion coefficient changes from –9.03 in CD₃CN (orange) to –9.37 in CDCl₃ (purple)).

Conclusions

We have studied the reaction of fluorine-containing 1,3-dicarbonyl compounds (ethyl 3-oxo-4,4,4-trifluorobutanoate (**1a**), 1,1,1-trifluoropentane-2,4-dione (**1b**) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**1c**)) with formaldehyde and esters of natural amino acids under Mannich reaction conditions. New derivatives of 1,3,5- and 1,3,5,5-substituted hexahydropyrimidines have been obtained, including those with a trifluoroacetyl group at position 5 of the heterocycle. These compounds show promise as ligands for asymmetric metal-complex catalysis and as chiral synthons for the preparation of biologically active compounds with a broad spectrum of activity. A one-pot method for the synthesis of a new chiral tetrahydropyrimidinium salt, based on the reaction of ethyl 3-oxo-4,4,4-trifluorobutanoate with ethyl (*S*)-tyrosinate and excess formaldehyde at a 1 : 2 : 15 molar ratio of the components in acetate buffer medium (pH 5.9) at room temperature, is suggested.

Experimental Section

General. ¹H and ¹³C NMR spectra were recorded on a Bruker AM-300 (300.1 and 75.5 MHz, respectively) or Bruker Avance-III 500 (500 and 125 MHz, respectively) spectrometers with TMS as internal standard at 25 °C. ¹⁹F NMR spectra were obtained using a Bruker Avance-III 500 spectrometer (470 MHz) with CFCl₃ as external standard. The mass spectra were obtained on a Shimadzu LC-MS-2010EV liquid chromatograph–mass spectrometer in the chemical ionization mode at atmospheric pressure and on a MaXis (Bruker Daltonics) mass spectrometer in the chemical ionization mode. The melting points were determined on a Boetius melting point apparatus. Elemental analysis were performed with a CHNS Euro EA 3000 Elemental Analyzer. Optical rotations were determined with a Perkin Elmer 341 polarimeter (λ 589 nm) at 20 °C. TLC analyses were carried out using Sorbfil plates PTSKh-AF-A plates (*IMID* Ltd.); eluent chloroform–methanol (9:1) or petroleum ether–EtOAc (7:3). Kieselgel 60 Macherey-Nagel (140–270 mesh) was used for column chromatography (gradient elution with chloroform–methanol from 0 to 10% of the latter or petroleum ether–EtOAc from 0 to 30% of the latter). All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated.

Reaction of trifluoromethyl 1,3-dicarbonyl compounds with formaldehyde and α -amino esters; General Procedure. To a solution of the appropriate amino ester hydrochloride 2a–f (5.4 mmol) in acetate buffer (pH 5.9) (1.5 mL) trifluoromethyl 1,3-dicarbonyl compound 1a–c (2.7 mmol) and formaldehyde 33% aqueous solution (11 or 40 mmol) were added. The resulting mixture was stirred for 24 h at room temperature, then it was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The product was purified by column chromatography on Kieselgel 60 (chloroform–MeOH 10:0→9:1 or hexane–EtOAc 10:0→7:3).

Ethyl 1,3-bis(2-ethoxy-2-oxoethyl)hexahydropyrimidine-5-carboxylate (3a). Yield 0.55 g (62%); colorless oil; $R_f = 0.38$ (CH_2Cl_2 –EtOAc, 7:3). ^1H NMR (500 MHz, CDCl_3): $\delta = 1.25$ (t, J 7.1 Hz, 3H, CH_3), 1.28 (t, J 7.1 Hz, 6H, CH_3), 2.88 (dd, J 12.5 and 10.8 Hz, 2H, $\text{CH}_2^{(a)}\text{N}$), 3.05 (tt, J 10.8 and 4.2 Hz, 1H, CH), 3.31 (ddd, J 12.5, 4.2 and 1.5 Hz, 2H, $\text{CH}_2^{(e)}\text{N}$), 3.43 (d, J 17.1 Hz, 2H, NCH_2CO_2), 3.58 (d, J 17.1 Hz, 2H, NCH_2CO_2), 3.63 (d, J 10.8 Hz, 1H, $\text{NCH}_2^{(a)}\text{N}$), 3.96 (dt, J 10.8 Hz and 1.5 Hz, 1H, $\text{NCH}_2^{(e)}\text{N}$), 4.14 (q, J 7.1 Hz, 2H, CHCO_2CH_2), 4.19 (q, J 7.1 Hz, 4H, OCH_2). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 14.15, 14.16, 36.96, 52.68, 54.68, 60.98, 61.04, 72.55, 169.71, 171.36$. ^{15}N NMR (50 MHz, CDCl_3): $\delta = 36.65$. MS (ESI): m/z 331 [$\text{M} + \text{H}$] $^+$ ($\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_6$), 353 [$\text{M} + \text{Na}$] $^+$ ($\text{C}_{15}\text{H}_{26}\text{N}_2\text{NaO}_6$). Anal. Calcd. for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.48; H, 7.87; N, 8.47 %.

Ethyl 1,3-bis(2-methoxy-1-methyl-2-oxoethyl)hexahydropyrimidine-5-carboxylate (3b). Yield 0.50 g (56%); colorless oil; $R_f = 0.4$ (CH_2Cl_2 –EtOAc, 7:3); $[\alpha]_{\text{D}}^{20} -34.1 \pm 0.1$ (c 1, CHCl_3). ^1H NMR (500 MHz, CDCl_3): $\delta = 1.26$ (t, J 7.1 Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.34 (d, J 7.1 Hz, 6H, CHCH_3), 2.68 (dd, J 11.8 and 10.8 Hz, 1H, $\text{CH}_2^{(a)}\text{N}$), 2.75 (dd, J 11.8 and 10.8 Hz, 1H, $\text{CH}_2^{(a)}\text{N}$), 2.86 (tt, J 10.8 and 4.3 Hz, 1H, CH), 3.14 (ddt, J 11.8, 4.3 Hz and 1.5 Hz, 1H, $\text{CH}_2^{(e)}\text{N}$), 3.26 (ddt, J 11.8, 4.3 and 1.5 Hz, 1H, $\text{CH}_2^{(e)}\text{N}$), 3.41 (d, J 10.7 Hz, 1H, $\text{NCH}_2^{(a)}\text{N}$), 3.50 (q, J 7.1 Hz, 1H, CHCH_3), 3.58 (q, J 7.1 Hz, 1H, CHCH_3), 3.71 (s, 6H, OCH_3), 3.76 (dt, J 10.7, and 1.5 Hz, 1H, $\text{NCH}_2^{(e)}\text{N}$), 4.13 (q, J 7.1 Hz, 2H, OCH_2). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 14.19, 15.25, 15.43, 38.76, 48.88, 51.59, 51.63, 59.26, 59.85, 60.65, 68.55, 172.15, 173.44, 173.66$. ^{15}N NMR (50 MHz, CDCl_3): $\delta = 46.64, 47.81$. MS (ESI): m/z 331 [$\text{M} + \text{H}$] $^+$ ($\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_6$). Anal. Calcd. for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.51; H, 7.87; N, 8.48 %.

Ethyl 1,3-bis[1-(methoxycarbonyl)-2-methylpropyl]hexahydropyrimidine-5-carboxylate (3c). Yield 0.13 g (10%); colorless oil; $R_f = 0.56$ (hexane–EtOAc, 7:3). ^1H NMR (500 MHz, CDCl_3): $\delta = 0.86$ (d, J 6.5 Hz, 3H, CHCH_3), 0.87 (d, J 6.5 Hz, 3H, CHCH_3), 0.96 (d, J 6.5 Hz, 3H, CHCH_3), 0.98 (d, J 6.5 Hz, 3H, CHCH_3), 1.25 (t, J 7.1 Hz, 3H, OCH_2CH_3), 2.02 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.07 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.55 (m, 1H, $\text{CH}_2^{(a)}\text{N}$), 2.79 (m, 1H, $\text{CH}_2^{(a)}\text{N}$), 2.80 (m, 1H, $\text{CHCO}_2\text{CH}_2\text{CH}_3$), 2.86 (d, J 14.2 Hz, 1H, $\text{CHCH}(\text{CH}_3)_2$), 2.93 (d, J 9.9 Hz, 1H, $\text{CHCH}(\text{CH}_3)_2$), 2.99 (m, 1H, $\text{CH}_2^{(e)}\text{N}$), 3.07 (m, 1H, $\text{CH}_2^{(e)}\text{N}$), 3.27 (d, J 10.4 Hz, 1H, $\text{NCH}_2^{(a)}\text{N}$), 3.51 (dt, J 10.4 and 1.5 Hz, 1H, $\text{NCH}_2^{(e)}\text{N}$), 3.72 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.12 (q, J 7.1 Hz, 2H, OCH_2). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 14.21, 19.07, 19.30, 19.43, 19.49, 26.94, 27.23, 39.45, 49.22, 50.84, 50.99, 51.03, 60.50, 70.46, 71.77, 72.07, 171.83, 172.45, 172.68$. ^{15}N NMR (50 MHz, CDCl_3): $\delta = 43.60$. MS (ESI): m/z 385 [$\text{M} + \text{H}$] $^+$ ($\text{C}_{19}\text{H}_{35}\text{N}_2\text{O}_6$), 409 [$\text{M} + \text{Na}$] $^+$ ($\text{C}_{19}\text{H}_{34}\text{N}_2\text{NaO}_6$). Anal. Calcd. for $\text{C}_{19}\text{H}_{34}\text{N}_2\text{O}_6$: C, 59.05; H, 8.87; N, 7.25. Found: C, 58.98; H, 8.79; N, 7.24, 44.62 %.

Ethyl 1,3-bis[1-(methoxycarbonyl)-2-methylpropyl]-5-(trifluoroacetyl)hexahydropyrimidine-5-carboxylate (4c). Yield 0.62 g (48%); colorless oil; $[\alpha]_{\text{D}}^{20} -34.6 \pm 0.1$ (c 1, CHCl_3); $R_f = 0.36$ (hexane–EtOAc, 7:3). ^1H NMR (500 MHz, CDCl_3): $\delta = 0.85$ (d, 3H, J 6.5 Hz, CHCH_3), 0.86 (d, J 6.5 Hz, 3H, CHCH_3), 0.88 (d, J 6.5 Hz, 3H, CHCH_3), 1.06 (d, J 6.5 Hz, 3H, CHCH_3), 1.23 (t, J 7.1 Hz, 3H, OCH_2CH_3), 2.03 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.09 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.66 (d, J 11.8 Hz, 1H, $\text{CH}_2^{(a)}\text{N}$), 2.75 (d, J 14.2 Hz, 1H, NCH), 2.77 (d, J 14.2 Hz, 1H, NCH), 3.01 (d, J 12.7 Hz, 1H, $\text{CH}_2^{(a)}\text{N}$), 3.07 (d, J 9.2 Hz, 1H, $\text{NCH}_2^{(a)}\text{N}$), 3.46 (dt, J 12.7 and 1.5 Hz, 1H, $\text{CH}_2^{(e)}\text{N}$), 3.59 (dt, J 9.2 and 1.5 Hz, 1H, $\text{NCH}_2^{(e)}\text{N}$), 3.62 (dt, J 11.8 and 1.5 Hz, 1H, $\text{CH}_2^{(e)}\text{N}$), 3.69 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.15 (q, J 7.1 Hz, 2H, OCH_2). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 13.80, 18.68, 19.54, 19.61, 19.80, 27.13, 27.14, 50.38, 50.90, 51.07, 54.74, 57.64$.

62.48, 69.36, 72.66, 72.83, 115.70 (q, $^1J_{C,F} = 294.2$ Hz, CF₃), 166.78, 171.49, 173.65, 185.76 (q, $^2J_{C,F} = 33.8$ Hz, $\underline{C}OCF_3$). ^{15}N NMR (50 MHz, CDCl₃): $\delta = 41.02, 43.12$. ^{19}F NMR (470 MHz, CDCl₃): $\delta = -73.05$. MS (ESI): m/z 505 [M + Na]⁺ (C₂₁H₃₃F₃N₂NaO₇). Anal. Calcd. for C₂₁H₃₃F₃N₂O₇: C, 52.28; H, 6.89; N, 5.81. Found: C, 52.22; H, 6.83; N, 5.80 %.

Ethyl 1,3-bis[1-(methoxycarbonyl)-2-methylbutyl]hexahydropyrimidine-5-carboxylate (3d). Yield 0.36 g (26%); colorless oil; $R_f = 0.65$ (hexane–EtOAc, 7:3). 1H NMR (300 MHz, CDCl₃): $\delta = 0.89$ (d, J 6.0 Hz, 6H, CHCH₃), 0.94 (d, J 6.0 Hz, 6H, CHCH₃), 1.22 (t, J 7.1 Hz, 3H, OCH₂CH₃), 1.57 (m, 2H, NCHCH₂), 1.64 (m, 2H, NCHCH₂), 1.64 (m, 2H, CH(CH₃)₂), 2.83 (d, J 10.9 Hz, 1H, CH₂N), 3.10 (d, J 12.3 Hz, 1H, CH₂N), 3.28 (d, J 9.0 Hz, 1H, NCH₂N), 3.32 (t, J 7.1 Hz, 1H, NCH), 3.37 (t, J 7.1, 1H, NCH), 3.41 (m, 1H, CH), 3.50 (m, 1H, CH₂N), 3.64 (d, J 12.4 Hz, 1H, CH₂N), 3.66 (d, J 9.0 Hz, 1H, NCH₂N), 3.70 (s, 6H, CO₂CH₃), 4.18 (q, J 7.1, 2H, OCH₂). ^{13}C NMR (125 MHz, CDCl₃): $\delta = 14.09, 21.94, 22.14, 22.47, 22.80, 24.78, 25.00, 38.09, 38.53, 39.34, 48.80, 51.09, 51.21, 51.66, 60.46, 62.85, 63.33, 69.21, 172.20, 172.77, 173.16$. MS (ESI): m/z 413.3 [M – H]⁺ (C₂₁H₃₇N₂O₆). Anal. Calcd. for C₂₃H₃₈N₂O₇: C, 60.85; H, 9.24; N, 6.76. Found: C, 60.97; H, 9.22; N, 6.81 %.

Ethyl 1,3-bis[1-(methoxycarbonyl)-2-methylbutyl]-5-(trifluoroacetyl)hexahydropyrimidine-5-carboxylate (4d). Yield 0.55 g (40%); colorless oil; $[\alpha]_D^{20} -28.5 \pm 0.1$ (c 1, CHCl₃); $R_f = 0.78$ (hexane–EtOAc, 7:3). 1H NMR (500 MHz, CDCl₃): $\delta = 0.88$ (d, J 6.4 Hz, 3H, CHCH₃), 0.88 (d, J 6.4 Hz, 3H, CHCH₃), 0.89 (d, J 6.4 Hz, 3H, CHCH₃), 0.94 (d, J 6.4 Hz, 3H, CHCH₃), 1.24 (t, J 7.1 Hz, 3H, OCH₂CH₃), 1.55 (m, 2H, NCHCH₂), 1.61 (m, 2H, NCHCH₂), 1.65 (m, 1H, CH(CH₃)₂), 1.67 (m, 1H, CH(CH₃)₂), 2.82 (d, J 12.0 Hz, 1H, CH₂^(a)N), 3.11 (d, J 12.3 Hz, 1H, CH₂^(a)N), 3.27 (d, J 8.8 Hz, 1H, NCH₂^(a)N), 3.33 (t, J 7.6 Hz, 1H, NCH), 3.35 (t, J 7.6 Hz, 1H, NCH), 3.50 (d, J 12.3 Hz, 1H, CH₂^(e)N), 3.64 (d, J 12.0 Hz, 1H, CH₂^(e)N), 3.65 (d, J 8.8 Hz, 1H, NCH₂^(e)N), 3.69 (s, 6H, CO₂CH₃), 4.20 (q, J 7.1 Hz, 2H, OCH₂). ^{13}C NMR (125 MHz, CDCl₃): $\delta = 13.80, 22.04, 22.33, 22.53, 22.71, 24.45, 24.76, 37.88, 37.95, 50.03, 51.26, 51.34, 54.23, 57.67, 62.48, 63.56, 63.67, 68.67, 115.68$ (q, $^1J_{C,F} = 293.7$ Hz, CF₃), 166.83, 172.51, 172.57, 186.06 (q, $J_{C,F} = 33.9$ Hz, $\underline{C}OCF_3$). MS (ESI): m/z 511 [M + H]⁺ (C₂₁H₃₈F₃N₂O₆). Anal. Calcd. for C₂₃H₃₇F₃N₂O₇: C, 54.11; H, 7.30; N, 5.49. Found: C, 54.05; H, 7.22; N, 5.46 %.

Ethyl 1,3-bis(1-benzyl-2-ethoxy-2-oxoethyl)-5-(trifluoroacetyl)hexahydropyrimidine-5-carboxylate (4e). Yield 0.76 g (46%); colorless oil; $[\alpha]_D^{20} -30.8 \pm 0.1$ (c 1, CHCl₃); $R_f = 0.71$ (hexane–EtOAc, 7:3). 1H NMR (300 MHz, CDCl₃): $\delta = 1.17$ (t, J 7.1 Hz, 3H, CO₂CH₂CH₃), 1.24 (t, J 7.1 Hz, 6H, CHCO₂CH₂CH₃), 2.92 (d, J 13.4 Hz, 2H, CH₂Ph), 3.06 (dd, J 13.4 and 3.1 Hz, 2H, CH₂Ph), 3.15 (d, J 11.8 Hz, 1H, CH₂^(a)N), 3.30 (d, J 9.1 Hz, 1H, NCH₂^(a)N), 3.47 (d, J 10.2 Hz, 1H, CH₂^(a)N), 3.56 (d, J 10.2 Hz, 1H, CH₂^(e)N), 3.81 (d, J 11.8 Hz, 1H, CH₂^(e)N), 3.89 (d, J 9.1 Hz, 1H, NCH₂^(e)N), 4.09 (q, J 7.1 Hz, 2H, OCH₂), 4.02 (m, 2H, NCH), 4.18 (t, J 7.1 Hz, 4H, CHCO₂CH₂), 7.12–7.31 (m, 10H, CH(Ar)). ^{13}C NMR (75 MHz, CDCl₃): $\delta = 13.77, 14.25, 35.64, 35.75, 50.61, 54.38, 57.68, 60.34, 60.49, 62.52, 67.46, 67.77, 69.33, 115.52$ (q, $^1J_{C,F} = 294.1$ Hz, CF₃), 126.56, 128.34, 128.40, 137.47, 137.60, 166.62, 170.57, 170.67, 185.80 (q, $\underline{C}OCF_3$, $^2J_{C,F} = 33.7$ Hz). MS (ESI): m/z 607 [M + H]⁺ (C₃₁H₃₈F₃N₂O₇). Anal. Calcd. for C₃₁H₃₇F₃N₂O₇: C, 61.38; H, 6.15; N, 4.62. Found: C, 61.33; H, 6.11; N, 4.62 %.

Diethyl 5-acetylhexahydropyrimidine-1,3-diacetate (3f). Yield 0.34 g (42%); dark orange oil; $R_f = 0.3$ (hexane–EtOAc, 7:3). 1H NMR (300 MHz, CDCl₃): $\delta = 1.26$ (t, J 7.0 Hz, 6H, OCH₂CH₃), 2.03 (s, 3H, OCH₃), 3.09 (t, J 11.3 Hz, 2H, CH₂N), 2.97 (td, J 10.4 and 3.5 Hz, 1H, CH), 3.14 (d, J 12.3 Hz, 2H, CH₂N), 3.28 (d, J 17.0 Hz, 2H, NCH₂CO₂), 3.43 (d, J 17.0 Hz, 2H, NCH₂CO₂), 3.71 (d, J 10.5 Hz, 2H, NCH₂N), 4.12 (q, J 7.1 Hz, 4H, COCH₂). ^{13}C NMR (125 MHz, CDCl₃): $\delta = 14.08, 28.58, 44.94, 52.69, 55.06, 60.70, 72.95, 170.15, 207.83$. Anal. Calcd. for C₁₆H₂₄N₂O₆: C, 55.98; H, 8.05; N, 9.33. Found: C, 56.04; H, 8.06; N, 9.35 %.

Diethyl 5-acetyl-5-trifluoroacetylhexahydropyrimidine-1,3-diacetate (4f). Yield 0.75 g (70%); red oil; $R_f = 0.2$ (hexane–EtOAc, 7:3). 1H NMR (500 MHz, CDCl₃): $\delta = 1.27$ (t, J 7.1 Hz, 3H, OCH₂CH₃), 1.28 (t, J 7.1 Hz, 3H, OCH₂CH₃), 2.07 (s, 3H, OCH₃), 3.09 (dd, J 12.5 and 3.6 Hz, 2H, CH₂N), 3.44 (dd, J 12.8 and 3.6 Hz, 2H, CH₂N),

3.61 (d, *J* 17.2 Hz, 2H, NCH₂CO₂), 3.73 (d, *J* 17.2 Hz, 2H, NCH₂CO₂), 3.85 (d, *J* 10.4 Hz, 1H, NCH₂^(a)N), 3.92 (d, *J* 10.4 Hz, 1H, NCH₂^(e)N), 4.19 (q, *J* 7.1 Hz, 2H, OCH₂), 4.20 (q, *J* 7.1 Hz, 2H, OCH₂). ¹³C NMR (125 MHz, CDCl₃): δ = 14.10, 14.16, 24.96, 44.35, 51.48, 53.69, 62.05, 76.58, 118.12 (q, ¹J_{C,F} = 290 Hz, CF₃), 168.23 (CO₂), 175.92 (q, *J*_{C,F} = 33.7 Hz, C₂OCF₃), 207.55. MS (ESI): *m/z* 397 [M + H]⁺ (C₁₆H₂₄F₃N₂O₆). Anal. Calcd. for C₁₆H₂₃F₃N₂O₆: C, 48.48; H, 5.85; N, 7.07. Found: C, 48.55; H, 5.82; N, 7.08 %.

5-Acetyl-1,3-bis[(2-ethoxy-1-(4-hydroxybenzyl)-2-oxoethyl)]hexahydropyrimidine (3g). Yield 0.64 g (46%); red-orange solid; mp 60–61 °C (decomp.); [α]_D²⁰ –28.7±0.1 (c 1, CHCl₃); *R*_f = 0.67 (CH₂Cl₂–MeOH, 9:1). ¹H NMR (500 MHz, CDCl₃): δ = 1.15 (t, *J* 7.1 Hz, 3H, CH₃), 1.18 (t, *J* 7.1 Hz, 3H, CH₃), 2.07 (s, 3H, OCH₃), 2.61 (t, *J* 10.8 Hz, 1H, CH₂N), 2.81 (d, *J* 8.4 Hz, 4H, CH₂Ar), 2.89 (m, 1H, CH), 2.92 (m, 1H, CH₂N), 3.02 (d, *J* 9.2 Hz, 1H, CH₂N), 3.29 (d, *J* 9.2 Hz, 1H, CH₂N), 3.48 (d, *J* 10.4 Hz, 1H, NCH₂^(a)N), 3.55 (t, *J* 7.8 Hz, 2H, NCH₂CO₂), 3.49 (t, *J* 7.8 Hz, 2H, NCH₂CO₂), 3.79 (d, *J* 10.4 Hz, 1H, NCH₂^(e)N), 4.08 (q, *J* 7.1 Hz, 2H, OCH₂), 4.12 (q, *J* 7.1 Hz, 2H, OCH₂), 6.62–7.05 (m, 10H, CH(Ar)). ¹³C NMR (125 MHz, CDCl₃): δ = 14.25, 14.40, 28.66, 34.47, 35.27, 46.40, 49.15, 51.61, 60.70, 60.79, 66.89, 67.16, 69.79, 115.45, 128.85, 129.47, 130.31, 154.81, 171.65, 172.25, 209.17. HRMS-ESI: *m/z* [M + H]⁺ calcd for C₂₈H₃₆N₂O₇: 513.2595; found 513.2604.

1,3-Bis(2-ethoxy-2-oxoethyl)-5-(trifluoroacetyl)hexahydropyrimidine (5a). Yield 144 mg (15%); colorless solid; mp 93–95 °C; *R*_f = 0.24 (hexane–EtOAc, 7:3). ¹H NMR (500 MHz, CDCl₃): δ = 1.28 (t, *J* 7.1 Hz, 6H, CH₃), 2.84 (m, 2H, CH₂N), 3.21 (m, 2H, CH₂N), 3.33 (d, *J* 17.0 Hz, 2H, CH₂CO₂), 3.38 (d, *J* 8.0 Hz, 1H, NCH₂N), 3.48 (d, *J* 17.0 Hz, 2H, CH₂CO₂), 3.49 (m, 1H, CH), 3.75 (d, *J* 8.0 Hz, 1H, NCH₂N), 4.19 (q, *J* 7.1 Hz, 4H, OCH₂). ¹³C NMR (125 MHz, CDCl₃): δ = 14.22, 40.08, 52.23, 52.57, 54.88, 60.89, 72.64, 115.39 (q, ¹J_{C,F} = 292 Hz, CF₃), 170.28, 190.84 (q, ²J_{C,F} = 34 Hz, C₂OCF₃). ¹⁹F NMR (470 MHz, CDCl₃): δ = –78.10. HRMS-ESI: *m/z* [M + H]⁺ calcd for C₁₄H₂₂F₃N₂O₅: 355.1475; found 355.1472.

1,3-Bis(2-ethoxy-2-oxoethyl)-5-(2,2,2-trifluoro-1,1-dihydroxy)hexahydropyrimidine (6). Yield 0.13 g (12%); white solid; Mp 61–62 °C; *R*_f = 0.22 (hexane–EtOAc, 7:3). ¹H NMR (500 MHz, CDCl₃): δ = 1.28 (t, *J* 7.1 Hz, 6H, CH₃), 2.22 (m, 1H, CH), 2.50 (m, 2H, CH₂N), 3.18 (d, *J* 17.0 Hz, 2H, NCH₂CO₂), 3.24 (d, *J* 8.0 Hz, 1H, NCH₂N), 3.30 (d, *J* 17.0 Hz, 2H, NCH₂CO₂), 3.36 (m, 2H, CH₂N), 3.76 (d, *J* 8.0 Hz, 1H, NCH₂N), 4.20 (q, *J* 7.1 Hz, 4H, OCH₂), 6.80 (br.s 2H, OH). ¹³C NMR (125 MHz, CDCl₃): δ = 14.15, 35.51, 52.30, 52.59, 55.63, 61.36, 74.36, 94.71 (q, ²J_{C,F} = 28 Hz, CF₃C(OH)₂), 123.89 (q, ¹J_{C,F} = 287 Hz, CF₃), 170.03. ¹⁹F NMR (470 MHz, CDCl₃): δ = –85.59. HRMS-ESI: *m/z* [M + H]⁺ calcd for C₁₄H₂₄F₃N₂O₆: 373.1581; found 373.1578.

1,3-Bis[2-ethoxy-1-(4-hydroxybenzyl)-2-oxoethyl]-5-(trifluoroacetyl)hexahydropyrimidine (5f). Yield 0.69 g (45%); colorless solid; mp 63–65 °C; *R*_f = 0.78 (CH₂Cl₂–MeOH, 9:1). ¹H NMR (500 MHz, CDCl₃): δ = 1.12 (t, *J* 7.0 Hz, 3H, CH₃), 1.15 (t, *J* 7.0 Hz, 3H, CH₃), 2.73–2.79 (m, 1H, CH₂N), 2.79–2.98 (m, 4H, CH₂Ar), 2.85–2.94 (m, 1H, CH₂N), 3.12–3.18 (m, 1H, CH₂N), 3.35–3.45 (m, 1H, CH₂N), 3.39–3.46 (m, 1H, CH), 3.42–3.59 (m, 2H, NCHCO₂), 3.54–3.59 (m, 1H, NCH₂N), 3.89 (d, *J* 10.8 Hz, 1H, NCH₂N), 4.02 (q, *J* 7.0 Hz, 2H, OCH₂), 4.09 (q, *J* 7.0 Hz, 2H, OCH₂), 6.61–6.75 (m, 4H, *o*-Ar), 6.81–7.05 (m, 4H, *m*-Ar). ¹³C NMR (125 MHz, CDCl₃): δ = 14.17, 14.27, 34.54, 40.86, 48.24, 51.28, 61.15, 66.82, 69.39, 115.57 (q, ¹J_{C,F} = 292 Hz, CF₃), 129.09, 130.20, 130.45, 154.75, 171.63, 172.23, 189.23 (q, ²J_{C,F} = 35.3 Hz, C₂OCF₃). MS (ESI): *m/z* 567 [M + H]⁺ (C₂₈H₃₄F₃N₂O₇).

5-Ethoxycarbonyl-1,3-bis[2-ethoxy-1-(4-hydroxybenzyl)-2-oxoethyl]-3,4,5,6-tetrahydropyrimidin-1-ium trifluoroacetate (7). Yield 1.12 g (63%); pale yellow solid; mp 77–78 °C; *R*_f = 0.22 (CH₂Cl₂–MeOH, 9.5:0.5). ¹H NMR (500 MHz, CDCl₃): δ = 1.24 (t, *J* 7.1 Hz, 3H, CCO₂CH₂CH₃), 1.27 (t, *J* 7.1 Hz, 3H, CO₂CH₂CH₃), 1.30 (t, *J* 7.1 Hz, 3H, CO₂CH₂CH₃), 2.88 (quintet, *J* 7.5 Hz, 1H, CH), 2.97 (dd, *J* 14.5 Hz, *J* 10.6 Hz, 1H, CH₂^AAr), 3.08 (dd, *J* 14.9 and 11.1 Hz, 1H, CH₂^BAr), 3.34 (ddd, *J* 14.1, 5.0 and 1.5 Hz, 1H, CH₂N), 3.34 (dd, *J* 14.5 and 5.4 Hz, 1H, CH₂^BAr), 3.35 (dd, *J* 14.9 and 5.1 Hz, 1H, CH₂^BAr), 3.45 (dd, *J* 14.1 and 7.5 Hz, 1H, CH₂^(a)N), 3.46 (dd, *J* 14.1 and 7.5 Hz, 1H, CH₂^(a)N), 3.64 (ddd, *J* 14.1, 5.0 and 1.5 Hz, 1H, CH₂^(e)N), 4.13 (q, *J* 7.1 Hz, 2H, CCO₂CH₂), 4.24 and 4.26 (both

q, J 7.1 Hz, 2x2H, OCH₂), 4.67 (dd, J 10.6 and 5.4 Hz, 1H, NCH), 4.79 (dd, J 11.1 and 5.1 Hz, 1H, NCH), 6.76 (d, J 8.5 Hz, 2H, *m*-Ar), 6.79 (d, J 8.5 Hz, 2H, *m*-Ar'), 7.00 (d, J 8.5 Hz, 2H, *o*-Ar), 7.06 (d, J 8.5 Hz, 2H, *m*-Ar'), 8.46 (s, 1H, NCHN). ¹³C NMR (125 MHz, CDCl₃): δ = 14.27, 14.38, 35.41, 36.19, 36.39, 45.13, 46.40, 63.15, 63.02, 63.74, 68.98, 69.24, 116.93, 117.03, 126.78, 126.96, 131.15, 131.18, 156.78, 158.02, 158.04, 169.44, 169.59, 169.85. ¹⁵N NMR (50 MHz, CDCl₃): δ = 120.25. ¹⁹F NMR (470 MHz, CDCl₃): δ = -76.04. HRMS-ESI: m/z [M - CF₃CO₂]⁺ calcd for C₂₉H₃₈N₂O₈: 541.2544; found 541.2550.

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