ISOLATION, CONFORMATIONAL ANALYSIS AND X-RAY STRUCTURE DETERMINATION OF A TRIFLUOROMETHYL-STABILIZED HEXAHYDROPYRIMIDINE - AN INTERMEDIATE IN THE BIGINELLI REACTION [1]

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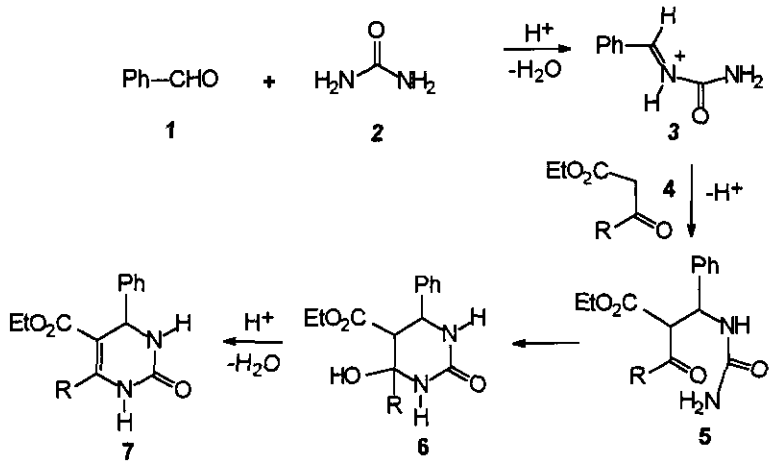
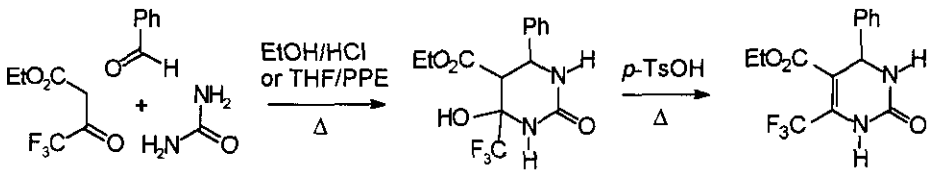
Abstract - Hexahydropyrimidine-5-carboxylic acid ethyl ester (**8**) was obtained from Biginelli-type condensation of ethyl trifluoroacetoacetate with urea and benzaldehyde. The conformational features of this hexahydropyrimidine were investigated by computational and X-Ray crystallographic studies. The geometries of the four possible diastereoisomers were fully optimized using semiempirical (AM1, AM1/MM) methods. The structure of the thermodynamically most stable diastereoisomer was further studied by *ab initio* (HF/3-21G) methods.

The cyclocondensation of benzaldehyde (**1**) with urea (**2**) and ethyl acetoacetate (**4**), known as the Biginelli reaction (Scheme 1),[2] has attracted considerable attention in recent years.[3-20] This is mainly due to the fact that this multicomponent condensation protocol provides a pyrimidine derivative (*i.e.* **7**) of proven pharmacological efficiacy.[3,4] Although alternative strategies for the synthesis of dihydropyrimidines of type (**7**) have been reported in the literature,[5-10] the classical Biginelli one-pot approach is still the most effective.[11-18] In recent years, several improved procedures for the Biginelli reaction have been published,[1,11-14] including various solid-phase modifications suitable for combinatorial chemistry.[15-18] Despite this interest, the mechanism of the Biginelli reaction itself has not been elucidated until 1997.[19] In very recent work, Hu *et al.*[14] were able to isolate an open-chain ureide of type (**5**) by using a sterically bulky acetoacetate (*i.e.* **4**, R = *tert*-butyl) in a Lewis acid-mediated Biginelli reaction. We now report the isolation of an hexahydropyrimidine intermediate of type (**6**) by employing an electron-deficient acetoacetate (*i.e.* **4**, R = CF_3) in this reaction. The relative stereochemistry and conformational properties of this hexahydropyrimidine (**6**; R = CF_3) were investigated by computational and X-Ray crystallographic studies. Note that for the sake of continuity the terms dihydropyrimidine (**7**) and hexahydropyrimidine (**6**) are used throughout this article; the IUPAC names are given in the Experimental.



Scheme 1

The original one-pot Biginelli condensation has been extended widely to include variations in all three components, making large numbers of multi-functionalized dihydropyrimidines of type (**7**) available.[3] Using ethyl trifluoroacetoacetate, urea, and benzaldehyde in the Biginelli reaction Rutter and Gustafson reported the formation of the corresponding 6-trifluoromethyldihydropyrimidine (**9**) in moderate yield (Scheme 2).[20] The structural assignment was based only on elemental (nitrogen) analysis and UV spectra. We have repeated the above Biginelli-type condensation under identical reaction conditions (EtOH/HCl) and obtained a compound that based on its melting point (162 °C) is identical with the material previously obtained by Rutter and Gustafson (lit.,[20] mp 165 °C). Using either ethanol/HCl[21] or THF/polyphosphate ester[1] as reaction medium in the Biginelli reaction this compound was obtained in 70-80 % yield. However, the ^{1}H-NMR spectrum (200 MHz, $CDCl_3$) - showing two doublets at 3.11 and 4.86 ppm ($^3J_{H5\text{-}H6}$ = 11.5 Hz) - indicated that this material is hexahydropyrimidine (**8**) rather than the expected dihydropyrimidine (**9**). This was further corroborated by ^{13}C-NMR spectroscopy, elemental analysis, and an X-Ray structure determination (see below).



8 **9**

Scheme 2

Interestingly, even under prolonged exposure to the above mentioned acidic reaction conditions transformation **8** → **9** was not observed. Only treatment with *p*-toluenesulfonic acid in refluxing toluene with azeotropic removal of water[24] led to elimination of water from **8** and to the formation of dihydropyrimidine (**9**). To our knowledge the above case is the only example where intermediates of type (**6**) (Scheme 1) have been isolated in this reaction. Undoubtedly, the strong electron-withdrawing properties of the CF_3 group - destabilizing the carbocation involved in the acid-catalyzed E1 elimination step **8** → **9** - here prevent the final sequence in the Biginelli reaction. In the related Hantzsch dihydropyridine synthesis a similar effect using trifluoroacetoacetates has been reported.[22-24]

Since the hexahydropyrimidine structure (**8**) contains three contiguous stereocenters four possible diastereoisomers (**8a-d**) (together with their four enantiomeric structures) can *a priori* be envisaged (Figure 1). Examination of the ^{1}H-NMR spectrum of **8** shows that this product is formed as a single (racemic) diastereoisomer. Furthermore, as a characteristic feature the relatively large $^3J_{H5\text{-}H6}$ coupling constant in the ^{1}H-NMR spectrum (11.5 Hz) has to be emphasized. Based on the Karplus equation such large vicinal H-H coupling constants correspond to either very small (0-20°) or very large (150-180°) dihedral angles. In order to deduce the preferred ring conformation and to get some further insight into the relative thermodynamic stabilities and geometries of these hexahydropyrimidine structures full geometry optimizations using the semiempirical AM1 method were carried out. Due to the presence of amide functionalities in **8a-d** these calculations were also performed with the force field correction method (AM1/MM). A conformational search revealed that for each diastereoisomer two conformers can be localized which differ in the conformation of the hexahydropyrimidine ring. Thus, as a result of an inversion of the hexahydropyrimidine ring (pseudoboat to pseudoboat) the C6 phenyl substituent may occupy a pseudoequatorial position as in structure (**8**) ***(eq)***, or it may be pseudoaxial as in **8** ***(ax)*** (Figure

1). At the same time the ester group at C5 undergoes a similar change in orientation (not shown). Although there are some differences in the overall geometries between the AM1 and AM1/MM optimized structures we find that in all cases the hexahydropyrimidines with equatorial C6 phenyl orientations **8a-d** ***(eq)*** are thermodynamically more stable than the corresponding **8a-d** ***(ax)*** conformers (Table 1).

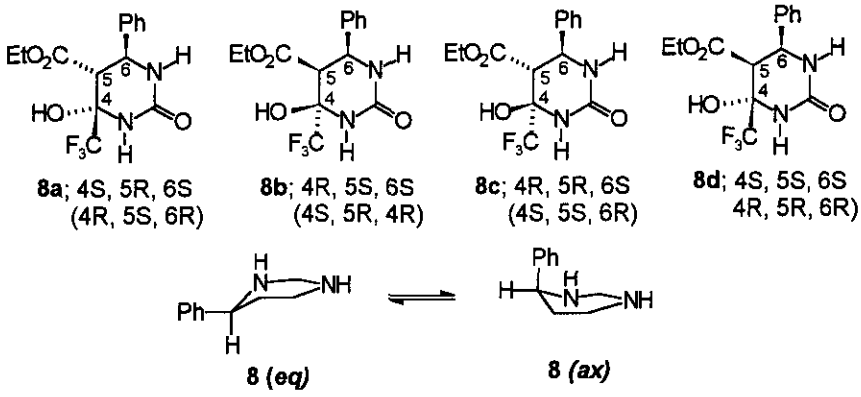


Figure 1. Possible diastereoisomeric forms of hexahydropyrimidines (**8a-d**) (only one enantiomeric form is shown), and ring inversion (schematic) of the dihydropyrimidine ring.

The relative energies for the calculated structures (**8a-d**) are summarized in Table 1. In order to correlate the observed coupling constant ($J_{H5\text{-}H6}$ = 11.5 Hz) from the ^{1}H-NMR spectrum of **8** with the calculated structures for diastereoisomers (**8a-d**) the dihedral angles for H5-C5-C6-H6 and H1-N1-C6-H6 are also given. In most cases geometry optimization leads to structures with an intramolecular O••H hydrogen bond between the C5 ester carbonyl group and the hydrogen atom of the C4 hydroxy functionality (2.08-2.55 Å). This distance is also included in Table 1.

Inspection of the relative energies given in Table 1 demonstrates that with both semiempirical methods (AM1 and AM1/MM) the thermodynamically most stable hexahydropyrimidine is the **8a** ***(eq)*** diastereoisomer. All other possible diastereoisomers (**8b-d**) are significantly higher in energy (1.34-9.43 kcal/mol for AM1; 2.20-10.06 kcal/mol for AM1/MM). The energetic differences between the corresponding **8** ***(eq)*** and **8** ***(ax)*** conformers range from 0.15 kcal/mol for **8a** to 6.14 kcal/mol for **8d** using the semiempirical AM1 or AM1/MM methods. Based on the results obtained from the calculations described above it is evident that diastereoisomer (**8a**) ***(eq)*** having the C6 phenyl substituent in equatorial position is the thermodynamically most stable of the eight possible hexahydropyrimidine diastereoisomers/conformers. Inspection of the calculated H5-C5-C6-H6 dihedral angles in Table 1 (AM1 and AM1/MM) shows that there are only two diastereoisomers that fit into the required range, namely **8a** ***(eq)*** (ϕ = 157.2° (AM1) / 162.2° (AM1/MM)) and **8c** ***(eq)*** (ϕ = 161.5° (AM1) / 168.1° (AM1/MM)). None of the **8** ***(ax)*** conformers have appropriate dihedral angles. Since the **8c** ***(eq)*** isomer is significantly higher in energy (3.19 kcal/mol with AM1; 2.87 kcal/mol with AM1/MM) than the **8a** ***(eq)*** isomer it is reasonable to assume that the thermodynamically most stable diastereoisomer/conformer corresponds to the isolated compound from the condensation reaction described in Scheme 2. Apparently, in **8a** ***(eq)*** there is no vicinal coupling between the H1 and H6 protons, which is also in agreement with the Karplus equation (a H1-N1-C6-H6 dihedral angle of ca. 90° (Table 1) corresponds to a vicinal coupling constant close to zero). However, unless there is a significant barrier to the conversion **8a** ***(eq)*** - **8a** ***(ax)*** this latter structure should also be populated.

Table 1. Relative Energies (ΔE, kcal/mol), Selected Torsional Angles (ϕ) and Intramolecular Hydrogen Bond Distances (O••H) for Hexahydropyrimidines (**8a-d**).

	AM1				AM1/MM			
	ΔE^a	$\phi_{C5\text{-}C6}{}^b$	$\phi_{N1\text{-}C6}{}^c$	$O\bullet\bullet H^d$	ΔE^a	$\phi_{C5\text{-}C6}{}^b$	$\phi_{N1\text{-}C6}{}^c$	$O\bullet\bullet H^d$
8a *(eq)*	0.00	157.7	96.4	2.29	0.00	162.2	84.3	2.33
8a *(ax)*	0.15	89.2	58.8	2.08	0.59	93.7	48.8	2.09
8b *(eq)*	1.34	55.3	129.5	2.53	2.20	48.2	90.8	2.55
8b *(ax)*	3.01	44.2	62.4	2.16	3.94	40.6	44.2	2.18
8c *(eq)*	3.19	161.5	95.1	2.21	2.87	168.1	84.1	2.21
8c *(ax)*	3.20	86.8	31.0	-	2.94	81.4	40.6	-
8d *(eq)*	3.29	55.8	124.4	-	4.63	53.7	94.8	-
8d *(ax)*	9.43	52.5	65.2	2.22	10.06	46.6	44.5	2.20

[a] Heats of formation for selected diastereoisomers: **8a** *(eq)*: -288.23 kcal/mol (AM1), -287.45 kcal/mol (AM1/MM); **8a** *(ax)*: -288.08 kcal/mol (AM1), -286.86 kcal/mol (AM1/MM)
[b] The angle reported is the H5-C5-C6-H6 dihedral angle [°]
[c] The angle reported is the H1-N1-C6-H6 dihedral angle [°].
[d] Intramolecular hydrogen bond distance between C5 ester carbonyl and C4 OH [Å].

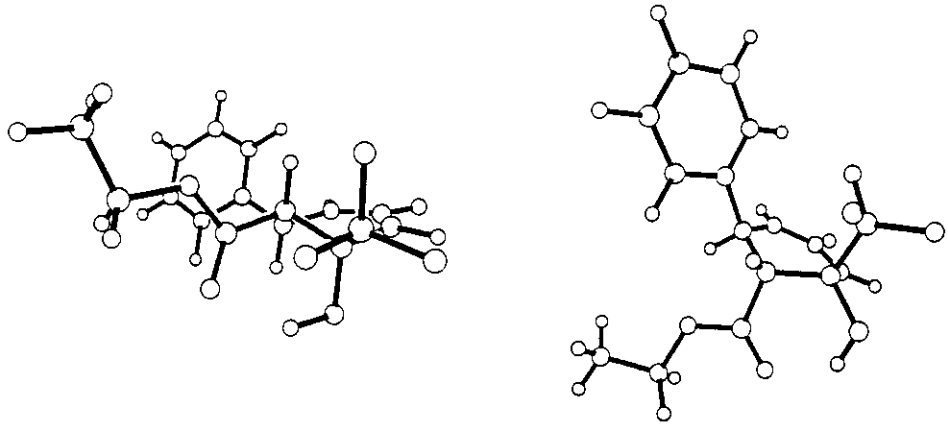


Figure 2. HF/3-21G optimized geometries for pyrimidine conformers (**8a**) *(eq)* (right) and (**8a**) *(ax)* (left).

Therefore, in order to get more reliable energy differences and geometries the structures of the thermodynamically most stable diastereoisomers (**8a**) *(eq)* and (**8a**) *(ax)* as well as **8c** *(eq)* and **8c** *(ax)* (which are also compatible with the observed ^{1}H-NMR coupling constants) were fully optimized using ab initio calculations at the HF/3-21G level (Figure 2). The energy difference of 3.02 kcal/mol between isomers (**8a**) *(eq)* (E = -1238.768219 a.u.; zero point energy correction (ZPE) = 0.313548 a.u.) and **8c**

(eq) obtained by this ab initio procedure (including ΔZPE) is essentially identical to that predicted by the semiempirical AM1 method. However, at the HF/3-21G level of theory considerably higher energies (relative to the most stable structure (**8a**) *(eq)*) for axial conformations are found (**8a** *(ax)*: 5.72 kcal/mol; **8c** *(ax)*: 7.57 kcal/mol). We have also calculated the energetical barrier for this ring inversion process (Figure 1) and find that there is a substantial barrier of 7.58 kcal/mol for inversion of the C6 aryl equatorial conformer into the C6 aryl axial isomer. Due to this large calculated interconversion barrier between the equatorial and axial conformer we assume that in solution the **8a** *(eq)* conformer predominates. Furthermore, the calculated (HF/3-21G) dipole moments of **8a** *(eq)* and **8a** *(ax)* are very similar (7.27 and 7.21 D, respectively). Therefore, no solvent induced shift in the conformer population is to be expected. Structural parameters ($\phi_{C5\text{-}C6}$, $\phi_{N1\text{-}C6}$, and O••H, respectively (see Table 1) closely match the AM1 results (**8a** *(eq)* : -177.1, 84.3, 1.90; **8a** *(ax)* : -95.2, 54.6, 1.85; **8c** *(eq)* : -170.8, 78.0, 1.96; **8c** *(ax)* : -76.4, 28.5, -). With HF/3-21G the intramolecular hydrogen bond appears to be even more pronounced than that obtained by the semiempirical methods.

Final confirmation of the relative stereochemistry in hexahydropyrimidine (**8**) was obtained by a single-crystal X-Ray analysis (Figure 3, for details see Experimental). The asymmetric unit contains four almost identical molecules (only one shown) which differ only in the degree of rotation of the C4 O-H bond and the orientation of the ester functionality at C5. The solid-state structure shown in Figure 3 corresponds well to the ab initio calculated geometry for **8a** *(eq)* shown in Figure 2. The corresponding dihedral angles are also very similar (H5-C5-C6-H6 = 177.1-178.7°).

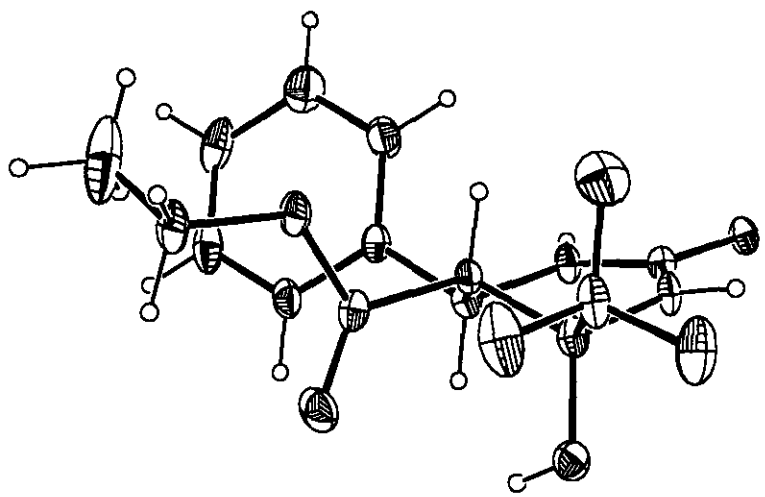
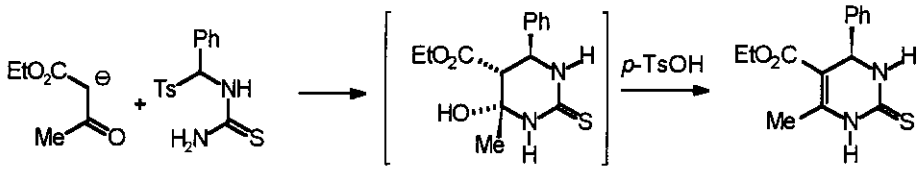


Figure 3. X-Ray structure of hexahydropyrimidine (**8a**).

Recently Shutalev and Kuksa have reported the isolation of closely related structures of type (**12**) by base-catalyzed condensation of sodium enolates of β-oxo esters (*e.g.* **10**) with α-azido or α-tosyl substituted ureas or thioureas (*e.g.* **12**, Scheme 3).[9] Based on the ^{1}H-NMR data given by the authors it can be assumed that here the same relative stereochemistry is observed as with **8a** *(eq)* ($^3J_{H5\text{-}H6}$ for **12** = 11.9 Hz)[9] although no X-Ray data for **12** are available. Here - in the absence of the electron-withdrawing CF_3 group - elimination of water is readily achieved with *p*-TsOH in refluxing acetonitrile.[9]



Scheme 3

In a recent article Nenaidenko *et al.*[25] have reported the X-Ray structure of a hexahydropyrimidine which is identical to **8** except that the ester functionality at C5 is missing. A comparison of the two solid state structures confirmed that both hexahydropyrimidines possess the same relative stereochemistry at the C4 and C6 carbons and also revealed the structural similarities between these two hexahydropyrimidines with respect to ring conformation and equatorial arrangement of the C6 phenyl groups.

In this context we have also carried out geometry optimizations (AM1 and AM1/MM) on dihydropyrimidine (**9**). In agreement with our previous calculations on dihydropyrimidines of this type[26-28] we find that - in sharp contrast to structure (**8**) - here a pseudoboat conformation for the dihydropyrimidine ring with a pseudoaxial orientation of the phenyl ring is calculated. Any attempt to locate a minimum for an equatorial phenyl arrangement failed.

In conclusion, correcting an earlier report in the literature[20] we have shown that by using ethyl trifluoroacetoacetate as a 1,3-dicarbonylcomponent in the Biginelli reaction hexahydropyrimidine (**8**) is obtained, rather than the expected dihydropyrimidine ("Biginelli compound") (**9**). Hexahydropyrimidine (**8**) corresponds to an intermediate in the Biginelli reaction that has not been isolated or observed before. Due to the strong electron-withdrawing effect of the CF_3 group, here elimination of water (**8** $\rightarrow$ **9**) is prevented which makes the isolation of this intermediate possible. The structure of hexahydropyrimidine (**8**) was confirmed by an X-Ray analysis, and the conformational features were further investigated by semiempirical and ab initio calculations. In contrast to dihydropyrimidines an arrangement where the C4 phenyl substituent occupies a pseudoequatorial position was found to be the most stable conformer.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus Mod. MFB-595 and are uncorrected. ^{1}H and ^{13}C-NMR spectra were obtained on a Varian XL-200 Gemini instrument at 200 MHz and 50 MHz, respectively. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Microanalyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. Reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-252 (Merck) plates.

*4S,5R,6S(4R,5S,6R)-4-Hydroxy-2-oxo-6-phenyl-4-trifluoromethylhexahydropyrimidine-5-carboxylic Acid Ethyl Ester (**8a**). Method A (EtOH/HCl):*[21] A mixture of benzaldehyde (212 mg, 2.0 mmol), ethyl trifluoroacetoacetate (368 mg, 2.0 mmol), urea (180 mg, 3.0 mmol), and ethanol (8 mL) containing 2 drops of conc HCl was heated under reflux for 6 h. After standing overnight at 4 °C the precipitated solid was filtered and washed with cold ethanol. Yield: 465 mg (70 %), mp 162 °C (ethanol).

Method B (THF/PPE):[1] A mixture of benzaldehyde (212 mg, 2.0 mmol), ethyl trifluoroacetoacetate (368 mg, 2.0 mmol), urea (180 mg, 3.0 mmol), and molecular sieve-dried THF (4 mL) containing 300 mg PPE[1]

was heated under reflux and stirring for 15 h. After cooling the reaction mixture was poured onto 10 g of crushed ice. The solid product was filtered, washed with ice-water and subsequently dried. Yield: 530 mg (80 %), mp 162 °C (ethanol).
IR (KBr): ν = 3420, 3370, 3220, 3100, 1740, 1725, 1675, ^{1}H-NMR ($CDCl_3$): δ = 0.84 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 3.11 (d, *J* = 11.5 Hz, 1H, H5), 3.88 (m, 2H, CH_2CH_3), 4.86 (d, *J* = 11.5 Hz, 1H, H6), 5.65 and 6.39 (2 s, 2H, 2 NH), 5.77 (s, 1H, OH), 7.36 (s, 5H, ArH); ^{1}H-NMR (DMSO-d_6): δ = 0.82 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 3.00 (d, *J* = 11.5 Hz, 1H, H5), 3.82 (m, 2H, CH_2CH_3), 4.81 (d, *J* = 11.5 Hz, 1H, H6), 7.29, 7.42 and 7.71 (3 s, 3H, 2 NH + OH), 7.39 (s, 5H, ArH); ^{13}C-NMR (DMSO-d_6): δ = 13.5, 50.8, 53.3, 60.2, 80.4 (q, $^2J_{CF}$ = 30.6 Hz), 122.9 (q, $^1J_{CF}$ = 286.2 Hz), 128.0, 128.4, 128.5, 138.4, 153.8, 167.0: Anal. Calcd for $C_{14}H_{15}N_2O_4F_3$: C, 50.61; H, 4.55; N, 8.34. Found: C, 50.73; H, 4.40; N, 8.36.

2-Oxo-4-phenyl-6-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (9). A solution of hexahydropyrimidine (**8**) (1.50 g, 4.50 mmol) in dry toluene (20 mL) containing 0.2 g of *p*-toluenesulfonic acid was refluxed for 6 h with concomitant azeotropic removal of water. After cooling to rt the mixture was filtered and evaporated *in vacuo*. The resulting oil was purified by silica gel flash chromatography (chloroform:acetone = 7:2) to yield 870 mg (62%) of dihydropyrimidine (**9**) as colorless solid, mp 156 °C (ethanol). IR (KBr): ν = 3220, 3100, 1700, 1660; ^{1}H-NMR (DMSO-d_6): δ = 1.11 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 4.09 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 5.29 (br s, 1H, H4), 7.21-7.49 (m, 5H, ArH), 8.03 and 9.81 (2 s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ = 13.5, 55.0, 81.0, 107.4, 119.5 (q, $^1J_{CF}$ = 274.2 Hz), 126.4, 128.2, 131.4 (q, $^2J_{CF}$ = 35.2 Hz), 142.0, 151.4, 163.5; Anal. Calcd for $C_{14}H_{13}N_2O_3F_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.65; H, 4.06; N, 9.00.

Computational Methods
Semiempirical AM1 [29] calculation were carried out using the PC Spartan Plus package (Version 1.0) [30] on a Pentium PC. Starting geometries were obtained using Spartans interactive building mode, and preoptimized using the SYBYL force field. Starting geometries for individual conformers were obtained by performing systematic bond rotations around the C6-phenyl and C5-ester single bonds in order to ensure that the global minimum for each conformer has been located. Geometries were completely optimized either with (AM1/MM, keyword MMOK) or without (AM1) molecular mechanics corrections for amide bonds. Convergence was achieved in all optimizations. *Ab initio* calculations were carried out at the HF/3-21G level of theory using the Gaussian 94 program package.[31] Geometries were completely optimized using redundant internal coordinates without any restrictions. The nature of the various stationary points was verified as true minima or transition states by frequency calculations.

X-Ray Analysis of Hexahydropyrimidine (8).[32]
Colorless crystals from methanol, empirical formula $C_{14}H_{15}N_2O_4F_3$ (332.28), crystal system = triclinic, space group = P1, a = 14.593(3) Å, b = 14.648(4) Å, c = 15.496(4) Å, α = 112.97(2)°, β = 94.28(2)°, γ = 99.75(2)°, V = 2969.3(13) Å^3, Z = 8. The X-Ray structure determination was performed on a modified Stoe 4-circle diffractometer, using graphite monochromatized Mo-K_α radiation (0.71069 Å) at 95 K. Cell constants were determined by a least-squares fit to the diffractometer setting angles of 37 reflections with $12.5 \le 2\theta \le 19.5°$. The structure was solved by direct methods based on 10442 unique reflections (6747 significant reflections with $I/\sigma(I) > 2$) using the SHELXS97 program. The conventional R-factor R1 was 0.0521 (873 parameters).

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32. Crystallographic data for compound (**8**) have been deposited at the Cambridge Crystallographic Data Center. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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