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Reaction of (*S*)-(+)-4-Amino-4-aryl-5,5,5-trifluoropentan-2-ones with α-Chlorobenzyl Isocyanates. Synthesis of (*S*)-(+)-4-Aryl-6-(2-arylethenyl)- 4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-ones

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Abstract—(*S*)-(+)-4-Amino-4-aryl-5,5,5-trifluoropentan-2-ones reacted with α-chlorobenzyl isocyanates with formation of (*S*)-(+)-4-aryl-6-(2-arylethenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-ones.

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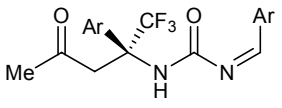
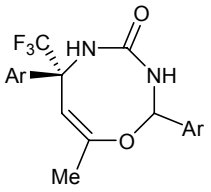
We recently [1] described (*S*)-(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-ones **Ia**–**Id** which turned out to be efficient as synthetic blocks for the preparation of chiral 4-aryl-4-trifluoromethyl-3,4-dihydroazin-2-ones [2]. In particular, it was shown that compounds **I** act as 1,4-nucleophilic–electrophilic reagents in condensations with potassium (thio)cyanate, aryl isocyanates, and aroyl isothiocyanates. On the other hand, they behaved as 1,5-binucleophiles in the reaction with triphosgene. With a view to extend the synthetic potential of compounds **I** we examined their reaction with 1,3-bielectrophilic α-chlorobenzyl isocyanates **IIa**–**IIc** [3]. Taking into account our previous results [2], we expected with some probability formation of chiral *N*-arylmethylideneureidoketones like **III** or isomeric cyclic 1,3,5-oxadiazocines **IV**.



III

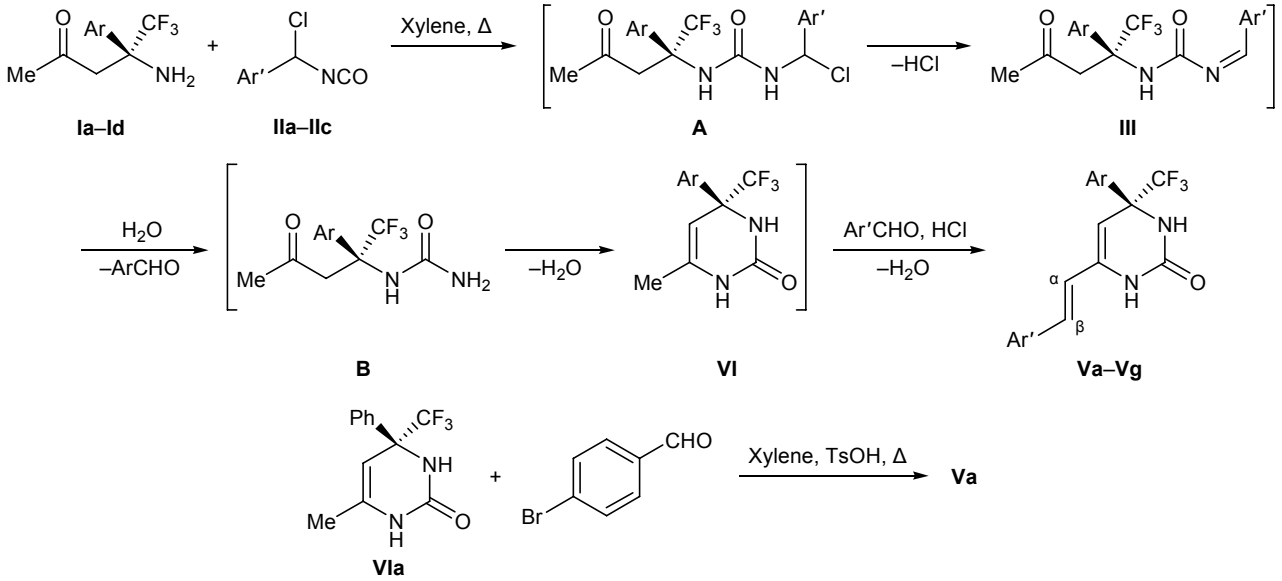


IV

However, by heating compounds **Ia**–**Id** with α-chlorobenzyl isocyanates **IIa**–**IIc** in boiling xylene over a period of 8 h we obtained (*S*)-(+)-4-aryl-6-(2-arylethenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-ones **Va**–**Vg** in 43–71% yield (Scheme 1). The process resulting in the formation of pyrimidine ring with a styryl substituent in the 6-position may involve both intra- and intermolecular transformations. Presumably, in the first step carbamoylation of the amino group in β-amino ketone **I** with α-chlorobenzyl isocyanate **II** gives *N*-(α-chlorobenzyl)ureidoketone **A** which loses hydrogen chloride at elevated temperature, yielding ureidoketone **III**. The double C=N bond in the latter is activated by the neighboring carbonyl group, and it readily undergoes hydrolysis by the action of traces of water present in the reaction mixture to produce ureidoketone **B** and aromatic aldehyde Ar′CHO. As we already noted [2], intermediate **B** is unstable under acidic conditions and is rapidly converted into dihydropyrimidinone **VI** with elimination of water molecule which ensures the next hydrolysis cycle. The subsequent condensation of pyrimidinone **VI** with aromatic aldehyde liberated as a result of hydrolysis yields final product **V**. The proposed scheme was confirmed by independent synthesis of compound **Va** by condensation of (*S*)-(–)-6-methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (**VIa**) with 4-bromobenzaldehyde in boiling xylene in the presence of *p*-toluenesulfonic acid.

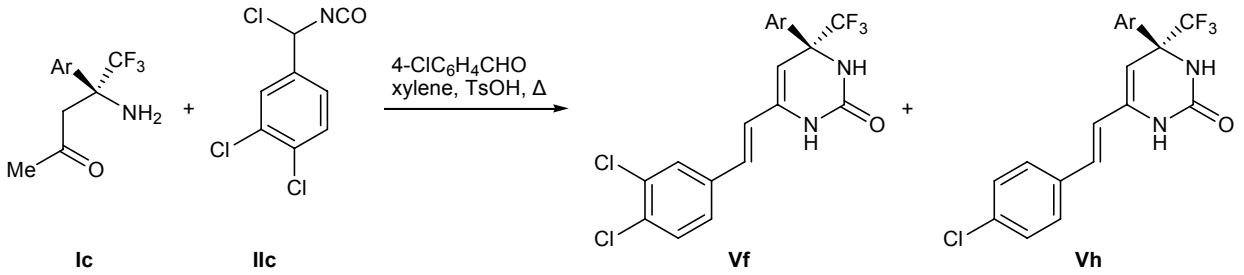
We also performed cross reaction of amino ketone **Ic** with α,3,4-trichlorobenzyl isocyanate (**IIc**) in the presence of 4-chlorobenzaldehyde and isolated a mixture of compounds **Vf** and **Vh** at a ratio of 57 : 43 (Scheme 2). The assumed structure of products **Vf** and **Vh** was consistent with their ^{1}H and ^{19}F NMR spectra and GC–MS data. Thus the above mechanism involv-

Scheme 1.



I, Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**); **II**, Ar′ = 4-BrC_6H_4 (**a**), 4-$O_2NC_6H_4$ (**b**), 3,4-$Cl_2C_6H_3$ (**c**); **V**, Ar = Ph, Ar′ = 4-BrC_6H_4 (**a**), 3,4-$Cl_2C_6H_4$ (**b**); Ar = 4-FC_6H_4, Ar′ = 4-$O_2NC_6H_4$ (**c**); Ar = 4-MeC_6H_4, Ar′ = 4-BrC_6H_4 (**d**), 4-$O_2NC_6H_4$ (**e**), 3,4-$Cl_2C_6H_3$ (**f**); Ar = 4-$MeOC_6H_4$, Ar′ = 3,4-$Cl_2C_6H_3$ (**g**); **VI**, Ar = 4-MeC_6H_4.

Scheme 2.



Ar = 4-MeC_6H_4.

ing intermolecular formation of pyrimidine ring with simultaneous functionalization of the 6-position with styryl substituent seems to be highly probable. The cyclization process does not affect the chiral carbon atom, so that compounds **Va**–**Vg** are formed with high enantiomeric purity (ee 73–82%).

Compounds **V** are optically active analogs of 6-styryl-3,4-dihydropyrimidin-2(1*H*)-ones which are generally synthesized by condensation of 6-methyl-3,4-dihydropyrimidin-2(1*H*)-ones or -thiones with aromatic aldehydes [4–6] or of cross-conjugated azatrienes with 4-toluenesulfonyl isocyanate [7]. Obviously, [4+2]-cyclocondensations of 6-styryl-3,4-dihydropyrimidin-2(1*H*)-ones with various dienophiles [6–9] may be used in the synthesis of new fused and spirocyclic pyrimidine derivatives possessing a trifluoromethyl group on chiral carbon atom.

The structure of the isolated compounds was confirmed by their IR, NMR, and mass spectra. In the IR spectra of **Va**–**Vg** we observed absorption bands due to stretching vibrations of C=O (1690–1700 cm^{-1}), conjugated C=C (1635–1640 cm^{-1}), and N–H bonds (3210–3215 cm^{-1}). Their ^1H NMR spectra contained singlets from 5-H (δ 5.44–5.61 ppm), N^3H (δ 8.33–8.50 ppm) and N^1H protons (δ 9.03–9.21 ppm) and doublets from the exocyclic α- and β-vinyl protons at δ 6.82–7.05 and 7.15–7.35 ppm, respectively. Carbon nuclei in the partially hydrogenated pyrimidine ring resonated in the ^{13}C NMR spectra at δ_C 63.12–63.60 (quartet, C^4), 89.39–99.31 (singlet, C^5), and 152.01–161.91 ppm (singlet, C^2). In most cases, the C^6 signal was overlapped by aromatic carbon signals.

Compound **Vb** displayed in the HMQC spectrum a cross peak between the proton resonating as doublet

at δ 6.91 ppm and carbon atom in position *5* of the pyrimidine ring (δ_C 97.09 ppm); therefore, that proton signal was assigned to the α-proton in the vinyl fragment. Cross peaks in the NOESY spectrum of **Vb** indicated that the 5-H proton (δ 5.48 ppm) is coupled only with the α-vinyl proton and that the N^1H proton (δ 9.09 ppm) is coupled with the β-vinyl proton (δ 7.18 ppm). These findings correspond to more stable *s-trans* conformation of 6-styrylpyrimidinones **V**.

EXPERIMENTAL

The ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer at 500.13, 470.59, and 125.75 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane (^1H, ^{13}C), or trichlorofluoromethane (^{19}F) as reference. The mass spectra were obtained on a PE SCIEX API 150 EX instrument equipped with UV (λ 254 nm) and ELSD detectors. The optical rotations were measured on a Perkin–Elmer 341 polarimeter. The optical purity was determined by ^{19}F NMR spectroscopy using tris[3-(heptafluoropropyl)hydroxymethylene-L-camphorato]europium(III) as lanthanide shift reagent.

Compounds Va–Vg (*general procedure*). A solution of 2.7 mmol of α-chlorobenzyl isocyanate **IIa**–**IIc** in 5–10 ml of anhydrous xylene was added at room temperature to a solution of 2.7 mmol of amino ketone **Ia**–**Id** in 8–10 ml of anhydrous xylene, and the mixture was heated for 8 h under reflux. The solvent was distilled off, and the residue was recrystallized from xylene–hexane (6:1).

(4*S*)-(+)-6-[(*E*)-2-(4-Bromophenyl)ethenyl]-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (Va). Yield 60%, mp 235–236°C, *ee* = 78%, $[\alpha]_D^{20}$ = +58.3° (*c* = 0.60, DMSO). IR spectrum, ν, cm^{-1}: 3225, 3220 (NH); 1690 (C=O); 1635 (C=C). ^1H NMR spectrum, δ, ppm: 5.45 s (1H, 5-H), 6.82 d (1H, α-CH, *J* = 16.5 Hz), 7.16 d (1H, β-CH, *J* = 16.5 Hz), 7.40–7.44 m (5H, H_{arom}), 7.56 d (2H, H_{arom}, *J* = 7.8 Hz), 7.62 d (2H, H_{arom}, *J* = 7.8 Hz), 8.38 s (1H, 3-H), 9.05 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 63.56 q (C^4, *J* = 28.9 Hz), 97.09 (C^5), 110.01 (α-CH), 110.94 (β-CH), 114.31 (C^6); 116.17, 116.24, 116.26, 116.42, 119.03, 122.14, 123.34, 124.86 (C_{arom}); 115.05 q (CF_3, *J* = 291.1 Hz), 152.01 (C^2). ^{19}F NMR spectrum: δ_F –77.04 ppm. Mass spectrum: *m*/*z* 424 $[M]^+$. Found, %: C 53.94; H 3.35; N 6.61. $C_{19}H_{14}BrF_3N_2O$. Calculated, %: C 53.92; H 3.33; N 6.62. *M* 423.2.

Compound **Va** was also synthesized in 74% yield by heating 0.5 g (2 mmol) of pyrimidinone **VIa** and 0.37 g (2 mmol) of 4-bromobenzaldehyde in boiling benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid over a period of 8 h.

(4*S*)-(+)-6-[(*E*)-2-(3,4-Dichlorophenyl)ethenyl]-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (Vb). Yield 49%, mp >250°C, *ee* = 77%, $[\alpha]_D^{20}$ = +53.8° (*c* = 0.97, DMSO). IR spectrum, ν, cm^{-1}: 3225, 3220 (NH); 1690 (C=O); 1640 (C=C). ^1H NMR spectrum, δ, ppm: 5.48 s (1H, 5-H), 6.91 d (1H, α-CH, *J* = 16.5 Hz), 7.18 d (1H, β-CH, *J* = 16.5 Hz), 7.40–7.47 m (5H, H_{arom}), 7.63–7.73 m (5H, H_{arom}), 8.43 s (1H, 3-H), 9.09 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 63.60 q (C^4, *J* = 27.6 Hz), 97.97 (C^5), 123.81 (α-CH), 126.22 (β-CH); 126.83, 127.41, 127.88, 128.44, 128.51, 130.37, 130.91, 131.62, 136.56, 136.96, 138.40 (C_{arom}, C^6); 115.25 q (CF_3, *J* = 291.2 Hz), 152.13 (C^2). ^{19}F NMR spectrum: δ_F –77.09 ppm. Mass spectrum: *m*/*z* 414 $[M]^+$. Found, %: C 55.22; H 3.16; N 6.80. $C_{19}H_{13}Cl_2F_3N_2O$. Calculated, %: C 55.23; H 3.17; N 6.78. *M* 413.2.

(4*S*)-(+)-4-(4-Fluorophenyl)-6-[(*E*)-2-(4-nitrophenyl)ethenyl]-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (Vc). Yield 47%, mp > 250°C, *ee* = 82%, $[\alpha]_D^{20}$ = +46.8° (*c* = 0.64, DMSO). IR spectrum, ν, cm^{-1}: 3225, 3220 (NH); 1690 (C=O); 1635 (C=C). ^1H NMR spectrum, δ, ppm: 5.61 s (1H, 5-H), 7.04 d (1H, α-CH, *J* = 16.5 Hz), 7.30–7.37 m (3H, β-CH, H_{arom}), 7.69–7.73 m (4H, H_{arom}), 8.26 d (2H, H_{arom}, *J* = 9.0 Hz), 8.50 s (1H, 3-H), 9.21 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 63.24 q (C^4, *J* = 28.9 Hz), 98.50 (C^5), 115.25 (α-CH), 115.41 (β-CH); 124.04, 127.46, 128.61, 134.54, 136.70, 142.72, 146.69, 151.88 (C_{arom}, C^6); 125.06 q (CF_3, *J* = 292.2 Hz), 152.13 d (C^2), 161.91 (C–F, *J* = 245.2 Hz). ^{19}F NMR spectrum, δ_F, ppm: –77.30, –113.92. Mass spectrum: *m*/*z* 408 $[M]^+$. Found, %: C 56.01; H 3.21; N 10.34. $C_{19}H_{13}F_4N_3O_3$. Calculated, %: C 56.03; H 3.22; N 10.32. *M* 407.3.

(4*S*)-(+)-6-[(*E*)-2-(4-Bromophenyl)ethenyl]-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (Vd). Yield 64%, mp > 250°C, *ee* = 73%, $[\alpha]_D^{20}$ = +11.14° (*c* = 1.05, DMSO). IR spectrum, ν, cm^{-1}: 3220, 3215 (NH); 1700 (C=O); 1640 (C=C). ^1H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 5.44 s (1H, 5-H), 6.82 d (1H, α-CH, *J* = 16.5 Hz), 7.17 d (1H, β-CH, *J* = 16.5 Hz), 7.26 d (2H, H_{arom}, *J* = 8.0 Hz), 7.51 d (2H, H_{arom}, *J* = 8.0 Hz), 7.42 d (2H, H_{arom}, *J* = 8.5 Hz), 7.57 d (2H, H_{arom}, *J* = 8.5 Hz), 8.33 s (1H, 3-H), 9.04 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 23.08 (CH_3), 63.45 q (C^4, *J* = 28.9 Hz), 89.39 (C^5), 109.99 (α-CH), 110.98 (β-CH), 114.24 (C^6); 121.18,

122.31, 126.05, 128.40, 128.55, 131.61, 136.56, 137.75 (C_{arom}); 125.05 q (CF_3, J = 291.1 Hz), 152.02 (C^2). ^{19}F NMR spectrum: δ_F –77.24 ppm. Mass spectrum: m/z 438 $[M]^+$. Found, %: C 54.92; H 3.67; N 6.42. $C_{20}H_{16}BrF_3N_2O$. Calculated, %: C 54.94; H 3.69; N 6.41. M 437.2.

(4*S*)-(+)-4-(4-Methylphenyl)-6-[(*E*)-2-(4-nitrophenyl)ethenyl]-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (Ve). Yield 58%, mp 225–227°C, *ee* = 73%, $[\alpha]_D^{20}$ = +16.70° (*c* = 1.20, DMSO). IR spectrum, ν, cm^{-1}: 3220, 3210 (NH); 1680 (C=O); 1640 (C=C). ^1H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 5.56 s (1H, 5-H), 7.05 d (1H, α-CH, J = 16.8 Hz), 7.26 d (2H, H_{arom}, J = 7.8 Hz), 7.31 d (1H, β-CH, J = 16.8 Hz), 7.50 d (2H, H_{arom}, J = 7.8 Hz), 7.71 d (2H, H_{arom}, J = 8.5 Hz), 8.22 d (2H, H_{arom}, J = 8.5 Hz), 8.40 s (1H, 3-H), 9.15 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 20.50 (CH_3), 63.42 q (C^4, J = 28.9 Hz), 99.31 (C^5), 125.97 (α-CH), 127.76 (β-CH); 124.12, 126.19, 127.50, 129.06, 135.38, 136.47, 137.94, 142.83, 146.66 (C_{arom}, C^6); 124.95 q (CF_3, J = 291.2 Hz), 152.06 (C^2). ^{19}F NMR spectrum: δ_F –77.16 ppm. Mass spectrum: m/z 404 $[M]^+$. Found, %: C 59.58; H 4.03; N 10.40. $C_{20}H_{16}F_3N_3O_3$. Calculated, %: C 59.55; H 4.00; N 10.42. M 403.3.

(4*S*)-(+)-6-[(*E*)-2-(3,4-Dichlorophenyl)ethenyl]-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (Vf). Yield 71%, mp 243–245°C, *ee* = 74%, $[\alpha]_D^{20}$ = +21.3° (*c* = 0.93, DMSO). IR spectrum, ν, cm^{-1}: 3225, 3215 (NH); 1670 (C=O); 1635 (C=C). ^1H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 5.44 s (1H, 5-H), 6.91 d (1H, α-CH, J = 17.0 Hz), 7.13 d (1H, β-CH, J = 17.0 Hz), 7.26 d (2H, H_{arom}, J = 7.8 Hz), 7.42 d (1H, H_{arom}, J = 8.4 Hz), 7.49 d (2H, H_{arom}, J = 7.8 Hz), 7.62 d (1H, H_{arom}, J = 8.4 Hz), 7.71 s (1H, H_{arom}), 8.34 s (1H, 3-H), 9.03 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 20.47 (CH_3), 63.38 q (C^4, J = 28.9 Hz), 98.10 (C^5), 123.87 (α-CH), 126.15 (β-CH); 126.84, 127.30, 127.86, 129.02, 130.33, 130.92, 131.60, 135.47, 136.45, 136.99, 137.86 (C_{arom}, C^6); 125.01 q (CF_3, J = 290.4 Hz), 152.10 (C^2). ^{19}F NMR spectrum: δ_F –77.20 ppm. Mass spectrum: m/z 428 $[M]^+$. Found, %: C 56.25; H 3.57; N 6.54. $C_{20}H_{15}Cl_2F_3N_2O$. Calculated, %: C 56.22; H 3.54; N 6.56. M 427.2.

(4*S*)-(+)-6-[(*E*)-2-(3,4-Dichlorophenyl)ethenyl]-4-(4-methoxyphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-one (Vg). Yield 43%, mp 215–217°C, *ee* = 76%, $[\alpha]_D^{20}$ = +93.5° (*c* = 1.39, DMSO). IR spectrum, ν, cm^{-1}: 3220, 3215 (NH); 1660 (C=O); 1640 (C=C). ^1H NMR spectrum, δ, ppm: 3.77 s (3H, CH_3O), 5.46 s (1H, 5-H), 6.91 d (1H, α-CH, J = 16.5 Hz), 7.01 d (2H, H_{arom}, J = 8.5 Hz), 7.15 d (1H, β-CH, J = 16.5 Hz), 7.43 d (2H, H_{arom}, J = 8.0 Hz), 7.53 d (2H, H_{arom}, J = 8.5 Hz), 7.63 d (1H, H_{arom}, J = 8.0 Hz), 8.35 s (1H, 3-H), 9.04 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 55.19 (CH_3O), 63.12 q (C^4, J = 28.9 Hz), 98.15 (C^5), 113.82 (α-CH), 123.90 (β-CH); 126.30, 127.26, 127.63, 127.86, 128.15, 130.33, 130.95, 131.61, 136.38, 137.01, 152.08 (C_{arom}, C^6); 125.01 q (CF_3, J = 290.9 Hz), 159.16 (C^2). ^{19}F NMR spectrum: δ_F –77.47 ppm. Mass spectrum: m/z 444 $[M]^+$. Found, %: C 54.22; H 3.43; N 6.33. $C_{20}H_{15}Cl_2F_3N_2O_2$. Calculated, %: C 54.19; H 3.41; N 6.32. M 443.2.

Reaction of (*S*)-(+)-4-amino-5,5,5-trifluoro-4-(4-methylphenyl)pentan-2-one (Ic) with α,3,4-trichlorobenzyl isocyanate (IIc) and 4-chlorobenzaldehyde. A solution of 0.64 g (2.7 mmol) of isocyanate **IIc** in 10 ml of anhydrous xylene was added at room temperature to a solution of 0.66 g (2.7 mmol) of amino ketone **Ic** and 0.4 g (2.7 mmol) of 4-chlorobenzaldehyde in 10 ml of anhydrous xylene, and the mixture was heated for 8 h under reflux. The solvent was distilled off, and the residue was recrystallized from xylene–hexane (6:1). The ^1H NMR spectrum of the product mixture contained (apart from other signals) singlets at δ 5.44 and 5.46 ppm typical of 5-H in the pyrimidine ring. Analysis of the mixture by GC–MS showed the presence of two peaks with m/z values for molecular ions of 428 (I_{rel} 57%; **Vf**) and 393 (I_{rel} 43%; **Vh**).

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