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Optically active 4-amino-4-aryl-5,5,5-trifluoropentan-2-ones: Versatile reagents for synthesis of chiral 4-trifluoromethyl-3,4-dihydroazin-2-ones

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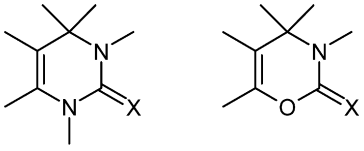
ABSTRACT

A cyclocondensation of disubstituted (thio)ureas and isocyanates derived from enantiomerically enriched 4-amino-4-aryl-5,5,5-trifluoropentan-2-ones affords a novel synthetic access to chiral 4-trifluoromethyl-substituted 3,4-dihydropyrimidin-2(1*H*)-(thi)ones and 3,4-dihydro-1,3-oxazin-2-ones, respectively.

1. Introduction

Substituted 3,4-dihydropyrimidines I and 3,4-dihydro-1,3-oxazines II are regarded as promising synthons in the design of new bioactive compounds. For instance, structural scaffold I is represented by polyfunctional 3,4-dihydropyrimidines known as Biginelli compounds [1–3] which include a number of antiviral, antibacterial, antihypertensive, and antiinflammatory agents [4]. Intensive high-throughput screening has also revealed a number of compounds I efficiently blocking calcium channels [5] and inhibiting KSP [6] and FATP4 [7]. Great pharmacological promise is also shown by fused 3,4-dihydroazinones, e.g., 3,4-dihydroquinazolones bearing a trifluoromethyl group and an alkynyl substituent at position 4 of the heterocycle which exhibit anti-HIV activity [8].



I II

X=O, S

Structures **I** and **II** contain a quaternary endocyclic chiral centre giving rise to optical isomerism. Much recent attention has been paid to enantioselective preparation of 3,4-dihydroazinones, because their bioactive derivatives in various enantiomeric forms and racemic mixtures were shown to have very different and sometimes opposite effects on the corresponding biological targets [9]. However, it was not until very recently that the first asymmetric syntheses of Biginelli compounds were reported [10] and new methods to obtain highly optically pure 4-trifluoromethyl-4-alkynyl-3,4-dihydroquinazolones (HIV RT inhibitors) were found [11]. The synthesis of chiral 1,3-oxazin-4-one derivatives can be exemplified by catalytic enantioselective Mannich reactions [12] affording highly functionalized 3,4-dihydrobenzoxazinones [12].

Lantzsch and Arlt were the first to use β-aminoketones as bifunctional reagents in the synthesis of dihydroazinones [14]. Starting from 4-methyl-4-aminopentan-2-one and phosgene, they prepared 4-methyl-4-isocyanatopentan-2-one which was further reacted with amines to give the corresponding ureas at room temperature and 1-substituted 4,4,6-trimethyl-3,4-dihydropyrimidin-2(1*H*)-ones on heating. As noted, heating the thus obtained ureas in acetic acid provides the same dihydropyrimidones, whereas the ketoisocyanate itself can thermally cyclize to 4,4,6-trimethyl-3,4-dihydro-1,3-oxazin-2-one. An alternative approach, though not studied systematically, was applied at one of the stages in the conversion of chiral β-alkoxycarbamoylketones to 1-benzyl-3,4-dihydropyrimidin-2(1*H*)-ones: it involves the initial reaction

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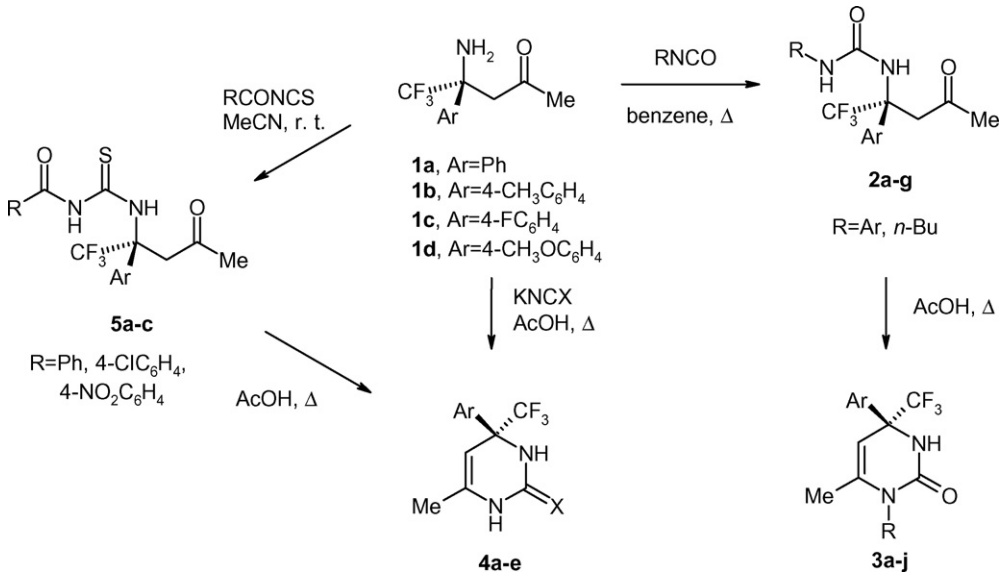


Scheme 1.

of β-aminoketones with isocyanates followed by heterocyclization of intermediately formed ureas [10b].

With regard to the fact that fluorine atoms substantially affect physical, chemical, and hence biological properties of compounds [13], it is especially challenging to find a convenient pathway to dihydroazinones I and II of high enantiopurity which would contain a trifluoromethyl group at the chiral centre. Optically active 4-amino-4-aryl-5,5,5-trifluoropentan-2-ones **1** formerly described by us are easily accessible compounds; they are conveniently obtained by the L-proline-catalyzed asymmetric reaction of aryl trifluoromethyl ketimines with acetone [15]. To explore the potentialities of **1** as building blocks in the above-mentioned synthetic schemes, we have studied their reactions with various heterocumulenes and triphosgene which furnish pharmacologically promising trifluoromethyl-substituted enantiomerically enriched 3,4-dihydroazin-2-ones with a quaternary endocyclic chiral centre.

2. Results and discussions

2.1. Reaction of S(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-ones 1 with heterocumulenes

When boiled with aryl isocyanates in dry benzene, S(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-ones **1a–c** provide, in high yields, disubstituted ureas **2a–g** (see Scheme 1 and Table 1). The latter cyclize to S(−)-4-aryl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-ones **3a–e,h,i** on boiling in glacial acetic acid. Heterocyclic products **3f,g** were isolated instead of the corresponding ureas on long boiling of the reagents in dry benzene. Likewise, compound **3j** was formed by the reaction of aminoketone **1a** with *n*-butyl isocyanate.

1-Unsubstited dihydropyrimidones **4a,b** were obtained by heating aminoketones **1** with potassium cyanate in glacial acetic acid. With potassium rhodanide, the reaction afforded 4-aryl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1*H*)-thiones **4c–e** in 75%–96% yields (see Table 2).

Though aminoketones **1** are unreactive towards alkyl(aryl) isothiocyanates, they readily react with more electrophilic aroyl isothiocyanates in dry acetonitrile at room temperature to give aroylthioureas **5a–c**. By heating compounds **5** in glacial acetic acid, dihydropyrimidinethiones **4c,d** are formed in high yields, evidently as a result of aroyl group hydrolysis from the initially formed *N*-aroyl-substituted products.

The optical purity of the heterocycles obtained has been determined by ^{19}F NMR spectroscopy using the chiral lanthanide shift reagent, *tris*(3-heptafluorobutyryl-*d*-camphorato)europium

Table 1
Analytical data of compounds **2** and **3**.

Compound	Ar	R	Yield, (%)[a]	Mp, C[b]	Ee (%)
2a	Ph	4-FC_6H_4	60	168–170	76
2b	Ph	4-ClC_6H_4	75	178–180	76
2c	Ph	3,4-$Cl_2C_6H_3$	80	165–167	75
2d	Ph	3-$CF_3C_6H_4$	81	149–151	77
2e	Ph	4-CH_3-3-ClC_6H_3	62	145–147	76
2f	4-FC_6H_4	4-CH_3-3-ClC_6H_3	75	166–168	80
2g	4-FC_6H_4	4-$^tBuC_6H_4$	70	95–97	78
3a	Ph	4-FC_6H_4	88	149–151	75
3b	Ph	4-ClC_6H_4	88	260–262	77
3c	Ph	3,4-$Cl_2C_6H_3$	81	272–275	76
3d	Ph	3-$CF_3C_6H_4$	79	132–134	76
3e	Ph	4-CH_3-3-ClC_6H_3	71	135–137	74
3f	4-$CH_3C_6H_4$	4-ClC_6H_4	78	106–108	70
3g	4-$CH_3C_6H_4$	3,4-$Cl_2C_6H_3$	75	190–192	71
3h	4-FC_6H_4	4-CH_3-3-ClC_6H_3	91	127–129	77
3i	4-FC_6H_4	4-$^tBuC_6H_4$	90	197–199	78
3j	Ph	*n*-Bu	77	69–70	75

[a] All compounds are white solids.
[b] Melting points are not corrected.

Table 2
Analytical data of compounds **4** and **5**.

Compound	Ar	R	*X*	Yield, (%)[a]	Mp, C[b]	Ee (%)
4a	Ph	–	O	73	–	75
4b	4-$CH_3C_6H_4$	–	O	71	–	70
4c	Ph	–	S	75	202–204	74
4d	4-$CH_3C_6H_4$	–	S	91	154–156	71
4e	4-FC_6H_4	–	S	96	192–194	76
5a	Ph	Ph	–	83	121–123	76
5b	Ph	4-ClC_6H_4	–	75	155–157	72
5c	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	––	74	174–176	70

[a] All compounds are white solids excepting **4a,b** which are colorless oiles.
[b] Melting points are not corrected.

(III). The analytically pure samples of compounds **3** and **4** prepared by us have much the same enantiomeric excess (*ee*) as starting aminoketones **1** (75–90%), since the chiral centre is not involved in the reactions.

2.2. Reaction of 4-amino-4-aryl-5,5,5-trifluoropentan-2-ones 1 with triphosgene

To synthesize isocyanates **6** from the corresponding β-aminoketones **1**, we studied their reactions with triphosgene [16] in inert solvents in the presence of basic catalysts. It was found that 85–90% conversion of compounds **1** afforded products **6** in satisfactory yields when we used ethyl acetate as a solvent and triethylamine as a catalyst (see Scheme 2). The by-products of the reaction, symmetric bis-ureas and 3,4-dihydro-1,3-oxazin-2-ones **7**, were difficult to remove from resulting isocyanates **6**, so that the latter were further reacted as obtained (70–80% pure). If conducted in butyl acetate, the reaction leads to a mixture of difficult-to-separate products, whereas acylation does not occur at all in toluene or chlorobenzene. At the same time, reacting β-aminoketones **1** with triphosgene in ethyl acetate in the presence of a stronger base, DBU, yields solely oxazines **7** which can thus be isolated in a pure state (Table 3). It is likely that DBU favours the intramolecular cyclization of isocyanates **6** which is intermediated by isocyanato-substituted enolates **A**.

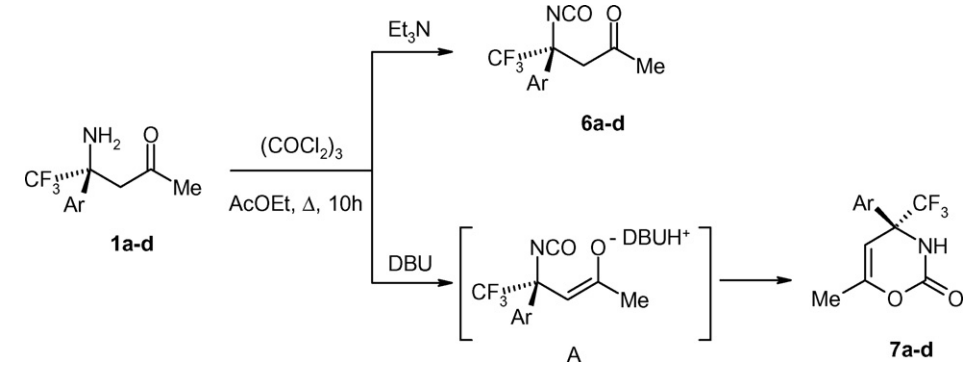
Table 3
Analytical data of compounds **7**.

Compound	Ar	Yield (%)[a]	Ee (%)
7a	Ph	48	80
7b	4-$CH_3C_6H_4$	63	75
7c	4-FC_6H_4	69	79
7d	4-$CH_3OC_6H_4$	62	75

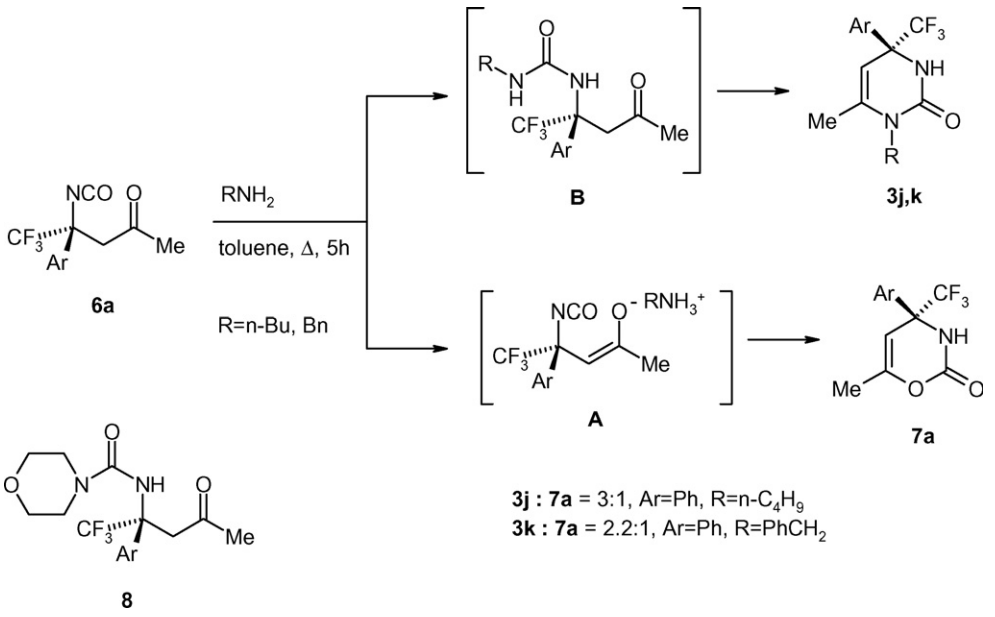
[a] All compounds are colorless oiles.

2.3. Reaction of isocyanates 6 with amines

Heating crude isocyanates **6** with primary aliphatic amines in dry toluene furnishes mixtures of 1-alkyl-substituted dihydropyrimidones **3** and dihydrooxazinones **7** in the respective ratios 2:1 to 3:1 (see Scheme 3). Importantly, compounds **3** appear to result from intramolecular cyclocondensation of intermediate ureas **B** which, as mentioned in Section 2.1, are labile under the conditions used. This conjecture about the conversion pathway is supported by the formation of urea **8** and dihydrooxazinone **7a** when isocyanate **6a** is reacted with a secondary amine (morpholine). Dihydrooxazinones **7** are probably produced by a competing



Scheme 2.



Scheme 3.

reaction, the base-catalyzed cyclization of compounds **6** (see also above in Section 2.2).

2.4. Spectral properties of compounds 2–4 and 7

The compounds synthesized have been structurally determined by a combination of physicochemical techniques. The IR spectra of solid-state ureas **2** show two types of bands in the C=O group absorption region, at 1660 and 1720 cm^{-1}, and also the band of associated NH groups at 3345 cm^{-1}. These data suggest that ureas **2** form so-called "fork" hydrogen bonds in which the carboxamide carbonyl oxygen atom of one molecule is bonded to two NH protons of another [17]. On the contrary, the ketone carbonyl group is not involved in hydrogen bonding. Pyrimidines **3** and **4**, and oxazines **7** in $CDCl_3$ solutions give rise to the ^1H NMR signals of the CH and NH groups in the respective regions 4.9–5.3 and 5.8–8.0 ppm; compounds **4** also exhibit the characteristic resonances of the protons at position 1 of the heterocycle in the region 7.9–8.1 ppm. The typical features of the ^{13}C and ^{19}F NMR spectra of the products obtained provide firm evidence for their cyclic structure. The signal from the carbon atom of the CF_3 group appears in the region 124.6–127.5 ppm as a quartet with a spin-spin coupling constant J of 285.2–287.9 Hz, whereas the quaternary endocyclic carbon atom also causes a quartet in the region 62.1–63.2 ppm with J^2_{C-F} = 26.4–30.1 Hz. Likewise, the ^{19}F NMR resonances of the CF_3 group observed in the region 79.2–79.9 ppm are characteristic of the structural moieties N–C(CF_3)(Ar)–NH and O–C(CF_3)(Ar)–NH [18].

3. Conclusion

In conclusion, we have shown experimentally that chiral β-trifluoromethyl-β-aminoketones **1** can be successfully applied in the synthesis of optically active heterocycles containing a quaternary endocyclic chiral centre, e.g., trifluoromethyl-substituted 3,4-dihydropyrimidin-2(1*H*)-(thi)ones **3–5** and 3,4-dihydro-1,3-oxazin-2-ones **7**. As found, the most convenient synthetic route to pyrimidines **3–5** involves the reaction of β-aminoketones **1** with alkyl(aryl) isocyanates or potassium cyanate (rhodanide) followed by cyclization of intermediate ureas **2**. Depending on the conditions used, the reaction of compounds **1** with triphosgene results in isocyanates **6** or dihydrooxazinones **7**. If reacted with primary aliphatic amines, isocyanates **6** produce mixtures of dihydropyrimidones **3** and dihydrooxazinones **7**.

4. Experimental part

IR spectra were measured with a UR-20 spectrometer in KBr. ^1H and ^{19}F NMR spectra were recorded on a Varian-Gemini instrument at 299.94 and 188.14 MHz, respectively, with TMS (^1H) and CCl_3F (^{19}F) as internal standards. ^{13}C NMR spectra were recorded on a Bruker Arano DRX-500 spectrometer (125.75 MHz), with TMS as internal standard. Elemental analysis was performed in the Analytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine.

4.1. General procedure for preparation of S(−)-N-aryl-N'-[(1-aryl-3-oxo-1-trifluoromethyl)butyl]ureas (2a–g) and S(−)-1,4-diaryl-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-ones (3f,g,j)

To a solution of S(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-one **1a–c** (0.02 mol) in dry benzene or toluene (40 ml), aryl(alkyl) isocyanate (0.02 mol) was added, followed by heating at 80 °C for 5 h. The resulting precipitate was filtered off and recrystallized from a benzene:hexane mixture (1:2).

4.1.1. S(−)-N-(4-Fluorophenyl)-N'-[(3-oxo-1-phenyl-1-trifluoromethyl)butyl]urea (2a)

^1H NMR ($CDCl_3$) δ: 2.18 (s, 3H), 3.48 (d, 1H, J = 17.0 Hz), 3.81 (d, 1H, J = 17.0 Hz), 6.23 (s, 1H), 6.87 (s, 1H), 6.87–6.98 (m, 2H), 7.18–7.21 (m, 2H), 7.34–7.40 (m, 5H), 7.45 (d, 2H, J = 7.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −75.45 (s, 3F). IR (KBr): υ 3345, 3420 (N–H), 1660, 1720 (C=O). $[\alpha]_D^{20}$ = −7.54 (c = 0.66; MeOH). Anal. calculated for $C_{18}H_{16}F_4N_2O_2$: C, 58.70; H, 4.38; N, 7.61%. Found: C, 58.48; H, 4.24; N, 7.77%.

4.1.2. S(−)-N-(4-Chlorophenyl)-N'-[(3-oxo-1-phenyl-1-trifluoromethyl)butyl]urea (2b)

^1H NMR ($CDCl_3$) δ: 2.19 (s, 3H), 3.51 (d, 1H, J = 17.5 Hz), 3.76 (1H, J = 17.5 Hz), 6.38 (s, 1H), 7.18 (d, 1H, J = 8.5 Hz), 7.27–7.55 (m, 7H). ^{19}F NMR ($CDCl_3$) δ: −75.43 (s, 3F). IR (KBr): υ 3340, 3440 (N–H), 1660, 1715 (C=O). $[\alpha]_D^{20}$ = −37.69 (c = 0.26; MeOH). Anal. calculated for $C_{18}H_{16}ClF_3N_2O_2$: C, 56.19; H, 4.19; N, 7.28%. Found: C, 56.47; H, 4.14; N, 7.57%.

4.1.3. S(−)-N-(4-Dichlorophenyl)-N'-[(3-oxo-1-phenyl-1-trifluoromethyl)butyl]urea (2c)

^1H NMR ($CDCl_3$) δ: 2.26 (s, 3H), 3.56 (d, 1H, J = 16.5 Hz), 3.78 (d, 1H, J = 16.5 Hz), 6.42 (s, 1H), 6.95 (d, 1H, J = 8.5 Hz), 7.18 (d, 1H, J = 8.5 Hz), 7.38–7.49 (m, 6H), 7.55 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: −75.43 (s, 3F). IR (KBr): υ 3330, 3440 (N–H), 1655, 1715 (C=O). $[\alpha]_D^{20}$ = −47.55 (c = 1.2; MeOH). Anal. calculated for $C_{18}H_{15}Cl_2F_3N_2O_2$: C, 51.57; H, 3.61; N, 6.68%. Found: C, 51.77; H, 3.49; N, 6.57%.

4.1.4. S(−)-N-[(3-Oxo-1-phenyl-1-trifluoromethyl)butyl]-N'-[3-(trifluoromethyl)phenyl]urea (2d)

^1H NMR ($CDCl_3$) δ: 2.25 (s, 3H), 3.52 (d, 1H, J = 17.5 Hz), 3.78 (d, 1H, J = 16 Hz), 6.29 (s, 1H), 7.20–7.36 (m, 7H), 7.49 (s, 3H), 7.87 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: −61.77 (s, 3F), −75.45 (s, 3F). IR (KBr): υ 3420, 3350 (N–H), 1665, 1720 (C=O). $[\alpha]_D^{20}$ = −3.28 (c = 0.10; MeOH). Anal. calculated for $C_{19}H_{16}F_6N_2O_2$: C, 54.55; H, 3.85; N, 6.69%. Found: C, 54.78; H, 3.99; N, 6.58%.

4.1.5. S(−)-N-(3-Chloro-4-methylphenyl)-N'-[(3-oxo-1-phenyl-1-trifluoromethyl)butyl]urea (2e)

^1H NMR ($CDCl_3$) δ: 2.20 (s, 3H), 2.24 (s, 3H), 3.53 (d, 1H, J = 16.5 Hz), 3.80 (d, 1H, J = 16.5 Hz), 6.30 (s, 1H), 6.90–7.06 (m, 2H), 7.20 (s, 1H), 7.27–7.47 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −75.18 (s, 3F). IR (KBr): υ 3340, 3360 (N–H), 1660, 1720 (C=O). $[\alpha]_D^{20}$ = −46.52 (c = 0.44; MeOH). Anal. calculated for $C_{19}H_{18}ClF_3N_2O_2$: C, 57.22; H, 4.55; N, 7.02%. Found: C, 57.57; H, 4.49; N, 7.09%.

4.1.6. S(−)-N-(3-Chloro-4-methylphenyl)-N'-[(1-(4-fluorophenyl)-3-oxo-1-trifluoromethyl)butyl]urea (2f)

^1H NMR (DMSO-d_6) δ: 2.12 (s, 3H), 2.24 (s, 3H), 3.65 (d, 1H, J = 16.0 Hz), 4.03 (d, 1H, J = 16.0 Hz), 6.93–7.00 (m, 2H), 7.12–7.21 (m, 3H), 7.56–7.61 (m, 3H), 8.84 (s, 1H). ^{19}F NMR (DMSO-d_6) δ: −75.87(s, 3F); −114.79 (s, 1F). IR (KBr): υ 3335, 3370 (N–H), 1660, 1720 (C=O). $[\alpha]_D^{20}$ = −18.98 (c = 0.43; MeOH). Anal. calculated for $C_{19}H_{17}ClF_4N_2O_2$. C, 54.75; H, 4.11; N, 6.72%. Found: C, 54.49; H, 4.19; N, 6.59%.

4.1.7. S(−)-N-(4-Tert-Butylphenyl)-N'-[(1-(4-fluorophenyl)-3-oxo-1-trifluoromethyl)butyl]urea (2g)

^1H NMR (DMSO-d_6) δ: 1.25 (s, 3H), 2.12 (s, 3H), 3.65 (d, 1H, J = 16.5 Hz), 4.06 (d, 1H, J = 16.5 Hz), 6.93–7.00 (m, 2H), 7.12–7.21 (m, 3H), 7.56–7.61 (m, 3H), 8.84 (s, 1H). ^{19}F NMR (DMSO-d_6) δ: −75.87 (s, 3F); −114.79 (s, 1F). IR (KBr): υ 3355, 3430 (N–H), 1663, 1723 (C = O). $[\alpha]_D^{20}$ = −10.33 (c = 0.92; MeOH). Anal. calculated for

$C_{22}H_{23}F_4N_2O_2$: C, 62.55; H, 5.25; N, 6.63%. Found: C, 62.29; H, 5.13; N, 6.51%.

*4.1.8. S(−)-1-(4-Chlorophenyl)-6-methyl-4-(methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3f**)*

^{1}H NMR (DMSO-d_6) δ: 1.63 (s, 3H), 2.38 (s, 3H), 4.99 (s, 1H), 5.71 (s, 1H), 7.16 (d, 2H, J = 7.5 Hz), 7.26 (d, 2H, J = 7.5 Hz), 7.39 (d, 2H, J = 8.0 Hz), 7.43 (d, 2H, J = 8.0 Hz). ^{19}F NMR ($CDCl_3$) δ: −79.92 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 19.74 (CH_3), 20.49 (CH_3), 62.18 (q, J_{CF} = 28.9 Hz), 95.25 (C-5), 126.24, 128.79, 128.97, 131.58, 132.41, 135.23, 136.44, 137.50 ($C_{arom.}$), 127.50 (q, J_{CF} = 285.4 Hz), 137.77 (C-6), 151.64 (C-2). IR (KBr): υ 3100, 3215 (N–H), 1674, 1697 (C=O). $[\alpha]_D^{20}$ = −124.17 (c = 1; MeOH). Anal. calculated for $C_{19}H_{16}ClF_3N_2O$: C, 59.93; H, 4.24; N, 7.36%. Found: C, 60.16; H, 4.33; N, 7.54%.

*4.1.9. S(−)-1-(3,4-Dichlorophenyl)-6-methyl-4-(methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3g**)*

^{1}H NMR (DMSO-d_6) δ: 1.62 (s, 3H), 2.32 (s, 3H), 5.30 (s, 1H), 7.20–7.27 (m, 3H), 7.55–7.68 (m, 4H), 8.73 (s, 1H). ^{19}F NMR (DMSO-d_6) δ: −77.86 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 19.65 (CH_3), 20.49 (CH_3), 62.21 (q, J_{CF} = 28.9 Hz), 95.44 (C-5), 126.25, 128.95, 130.24, 130.52, 130.78, 131.02, 131.97, 135.13, 137.15, 137.46 ($C_{arom.}$), 125.12 (q, J_{CF} = 276.6 Hz), 137.78 (C-6), 151.64 (C-2). IR (KBr): υ 3105, 3220 (N–H), 1675, 1703 (C=O). $[\alpha]_D^{20}$ = −18.12 (c = 0.46; MeOH). Anal. calculated for $C_{19}H_{15}Cl_2F_3N_2O$: C, 54.96; H, 3.64; N, 6.75%. Found: C, 55.19; H, 3.47; N, 6.54%.

*4.1.10. S(−)-1-n-Butyl-6-methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3j**)*

^{1}H NMR (DMSO-d_6) δ: 0.83 (t, 3H, J = 6.9 Hz), 1.30 (m, 4H), 1.97 (s, 3H), 2.81 (m, 2H), 3.48 (m, 2H), 5.04 (s, 1H), 7.34 (t, 1H, J = 7.5 Hz), 7.38 (t, 2H, J = 7.5 Hz), 7.57 (d, 2H, J = 7.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −79.93 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 14.00 (CH_3), 18.90 (CH_3), 31.93 (CH_2), 32.69 (CH_2), 41.75 (CH_2), 62.18 (q, J_{CF} = 28.6 Hz), 94.97 (C-5), 125.05 (q, J_{CF} = 276.6 Hz), 126.77, 128.63, 128.80, 138.28 ($C_{arom.}$), 138.73 (C-6), 152.45 (C-2). IR (KBr): υ 3100, 3215 (N–H), 1675, 1700 (C=O). $[\alpha]_D^{20}$ = −138.76 (c = 0.9; MeOH). Anal. calculated for $C_{16}H_{19}F_3N_2O$: C, 61.53; H, 6.13; N, 8.97%. Found: C, 61.50; H, 6.06; N, 9.00%.

*4.2. General procedure for preparation of S(−)-1,4-diaryl-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-ones (**3a–e,h,i**)*

A solution of S(−)-*N*-aryl-*N*′-[(1-aryl-3-oxo-1-trifluoromethyl)-butyl]urea **2a–g** (0.001 mol) in acetic acid (10 ml) was refluxed for 4 h. After evaporating the solvent, water (5 ml) was added to the residue. The solid product was filtered off, air-dried, and recrystallized from a methanol:water mixture (2:1).

*4.2.1. S(−)-1-(4-Fluorophenyl)-6-methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3a**)*

^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 3H), 5.00 (s, 1H), 5.85 (s, 1H), 7.07–7.10 (m, 2H), 7.17 (s, 1H), 7.39–7.43 (m, 3H), 7.58 (d, 2H, J = 7.0 Hz). ^{19}F NMR ($CDCl_3$) δ: −79.67 (s, 3F); −114.02 (s, 1F). ^{13}C NMR ($CDCl_3$) δ: 20.45 (CH_3), 63.16 (q, J_{CF} = 30.18 Hz), 96.28 (C-5), 116.01, 116.19, 125.93, 128.77, 128.90, 131.29, 133.17 ($C_{arom.}$), 125.13 (q, J_{CF} = 286.7 Hz), 138.23 (C-6), 152.61 (C-2), 162.27 (d, J = 248.94 Hz). IR (KBr): υ 3090, 3210 (N–H), 1680, 1695 (C=O). $[\alpha]_D^{20}$ = −151.3 (c = 1.31; MeOH). Anal. calculated for $C_{18}H_{14}F_4N_2O$: C, 61.72; H, 4.03; N, 7.80%. Found: C, 61.95; H, 4.11; N, 7.59%.

*4.2.2. S(−)-1-(4-Chlorophenyl)-6-methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3b**)*

^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 3H), 5.02 (s, 1H), 6.17 (s, 1H), 7.15 (s, 2H), 7.40–7.43 (m, 5H), 7.57 (s, 2H). ^{19}F NMR ($CDCl_3$) δ: -79.72 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 20.45 (CH_3), 63.18 (q, J_{CF} = 28.9 Hz), 96.45 (C-5), 125.11 (q, J_{CF} = 287.9 Hz), 125.92, 125.93, 128.80, 128.92, 129.40, 130.92, 134.38, 135.79 ($C_{arom.}$), 137.99 (C-6), 152.39 (C-2). IR (KBr): υ 3095, 3210 (N–H), 1675, 1695 (C=O). $[\alpha]_D^{20}$ = −101.76 (c = 0.55, MeOH). Anal. calculated for $C_{18}H_{14}F_3ClN_2O$: C, 58.95; H, 3.85; N, 7.34%. Found: C, 59.24; H, 4.01; N, 7.51%.

*4.2.3. S(−)-1-(3,4-Dichlorophenyl)-6-methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3c**)*

^{1}H NMR ($CDCl_3$) δ: 1.67 (s, 3H), 5.03 (s, 1H), 5.85 (s, 1H), 7.03-7.10 (m, 1H), 7.34–7.56 (m, 7H). ^{19}F NMR ($CDCl_3$) δ: −79.65 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 19.64 (CH_3), 62.47 (q, J_{CF} = 26.4 Hz), 125.01 (q, J_{CF} = 271.6 Hz), 126.32, 128.37, 128.42, 130.22, 130.52, 130.80, 131.08, 131.85, 137.30, 137.43 ($C_{arom.}$), 138.06 (C-6), 151.60 (C-2). IR (KBr): υ 3105, 3210 (N–H), 1675, 1700 (C=O). $[\alpha]_D^{20}$ = −158.76 (c = 0.43; MeOH). Anal. calculated for $C_{18}H_{13}F_3Cl_2N_2O$: C, 53.89; H, 3.27; N, 6.98%. Found: C, 54.14; H, 3.11; N, 6.71%.

*4.2.4. S(−)-6-Methyl-4-phenyl-4-trifluoromethyl-1-(3-trifluoromethylphenyl)-3,4-dihydropyrimidin-2(1H)-one (**3d**)*

^{1}H NMR($CDCl_3$) δ: 1.64 (s, 3H), 5.05 (s, 1H), 5.82 (s, 1H), 7.41–7.58 (m, 8H), 7.65 (d, 1H, J = 7.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −63.77 (s, 3F); −79.64 (s, 1F). ^{13}C NMR ($CDCl_3$) δ: 20.45 (CH_3), 63.12 (q, J_{CF} = 28.9 Hz), 96.91 (C-5), 125.36, 125.88, 126.66, 128.88, 128.97, 129.73, 133.17, 137.66, 137.85, 137.89 ($C_{arom.}$), 124.61 (q, J_{CF} = 245.2 Hz), 131.78 (q, J = 32.6 Hz), 125.41 (q, J = 272.8 Hz), 137.89 (C-6), 152.11 (C-2). IR (KBr): υ 3100, 3220 (N–H), 1675, 1700 (C=O). $[\alpha]_D^{20}$ = −157.6 (c = 0.15; MeOH). Anal. calculated for $C_{18}H_{13}F_3Cl_2N_2O$: C, 53.89; H, 3.27; N, 7.00%. Found: C, 57.26; H, 3.43; N, 6.88%.

*4.2.5. S(−)-1-(3-Chloro-4-methylphenyl)-6-methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3e**)*

^{1}H NMR ($CDCl_3$) δ: 1.66 (s, 3H), 2.39 (s, 3H), 5.02 (s, 1H), 6.49 (s, 1H), 7.36 (s, 1H), 7.22–7.28 (m, 2H), 7.39–7.46 (m, 3H), 7.57 (d, 2H, J = 7.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −79.75 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 19.75 (CH_3), 20.75 (CH_3), 63.20 (q, J_{CF} = 28.9 Hz), 96.35 (C-5), 125.90, 127.82, 128.77, 128.91, 130.10, 131.19, 134.62, 135.79, 136.73, 138.01 ($C_{arom.}$), 125.07 (q, J_{CF} = 286.7 Hz), 138.06 (C-6), 152.73(C-2). IR (KBr): υ 3090, 3220 (N–H), 1680, 1700 (C=O). $[\alpha]_D^{20}$ = −90.73 (c = 0.23; MeOH). Anal. calculated for $C_{19}H_{15}F_4ClN_2O$: C, 57.23; H, 3.79; N, 7.03%. Found: C, 57.46; H, 3.53; N, 6.84%.

*4.2.6. S(−)-1-(3-Chloro-4-methylphenyl)-4-(4-fluorophenyl)-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3h**)*

^{1}H NMR ($CDCl_3$) δ: 1.66 (s, 3H), 2.38 (s, 3H), 5.01 (s, 1H), 5.89 (s, 1H), 7.09 (d, 1H, J = 8.4 Hz), 7.26 (d, 3H, J = 7.5 Hz), 7.44 (d, 2H, J = 7.5 Hz), 7.50 (d, 1H, J = 8.4 Hz). ^{19}F NMR ($CDCl_3$) δ: −79.96 (s, 3F), −114.10 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 19.68 (CH_3), 20.39 (CH_3), 62.84 (q, J_{CF} = 28.9 Hz), 95.97 (C-5), 115.80, 127.80, 128.05, 130.07, 131.17, 134.01, 134.59, 135.74, 136.74 ($C_{arom.}$), 124.98 (q, J_{CF} = 286.7 Hz), 138.30 (C-6), 152.48 (C-2), 162.73 (q, J = 248.9 Hz). IR (KBr): υ 3115, 3240 (N–H), 1675, 1698 (C=O). $[\alpha]_D^{20}$ = −106.6 (c = 0.36; MeOH). Anal. calculated for $C_{22}H_{21}F_4N_2O$: C, 65.18; H, 5.22; N, 6.91%. Found: C, 65.39; H, 5.47; N, 6.74%.

*4.2.7. S(−)-1-(4-Tert-Buthylphenyl)-6-methyl-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**3i**)*

^{1}H NMR ($CDCl_3$) δ: 1.32 c (s, 9H), 1.63 (s, 3H), 4.93 (s, 1H), 5.72 (s, 1H), 7.09–7.15 (m, 4H), 7.40 (d, 2H, J = 8.1 Hz), 7.56 (d, 3H). ^{19}F NMR($CDCl_3$) δ: −79.91 (s, 3F); −114.24 (s, 1F). ^{13}C NMR ($CDCl_3$) δ: 20.45 (CH_3), 31.34 ($3CH_3$), 34.69 ($C(CH_3)$), 62.83 (q, J_{CF} = 31.4 Hz), 95.48 (C-5), 115.64, 115.82, 126.09, 128.07, 128.84, 134.22, 134.40

($C_{arom.}$), 125.09 (q, J_{CF} = 286.7 Hz), 138.99 (C-6), 151.36 (C-2), 162.69 (q, C_{arom}, J = 248.9 Hz). IR (KBr): υ 3130, 3265 (N–H), 1680, 1695 (C=O). $[\alpha]_D^{20}$ = −103.3 (c = 0.32; MeOH). Anal. calculated for $C_{19}H_{15}F_4N_2ClO$: C, 57.23; H, 3.79; N, 7.02%. Found: C, 57.45; H, 3.67; N, 6.84%.

4.3. General procedure for preparation of S(−)-4-aryl-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-(thi)ones (**4a-e**)

To a solution of S(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-one **1a–d** (0.001 mol) in acetic acid (10 ml), potassium cyanate or rhodanide (0.003 mol) was added and the reaction mixture was boiled for 2 h. After evaporating the solvent, a 10% solution of sodium hydrocarbonate (5 ml) was added to the residue, followed by extracting with dichloromethane (2 × 20 ml). The organic layer was dried over sodium sulfate and evaporated. Solid products were recrystallized from a methanol:water mixture (1:3) and oily products were chromatographed on a silica gel column eluted with an ethyl acetate-hexane mixture (2:1).

4.3.1. S(−)-6-Methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**4a**)

^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 3H), 5.05 (s, 1H), 5.82 (s, 1H), 7.41–7.58 (m, 8H), 7.65 (d, 1H, J = 7.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −79.64 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 20.45 (CH_3), 63.12 (q, J_{CF} = 28.9 Hz), 96.91 (C-5), 125.36, 125.88, 126.66, 128.88, 128.97, 129.73, 133.17, 137.66, 137.85, 137.89 ($C_{arom.}$), 124.61 (q, J_{CF} = 245.2 Hz), 131.78 (q, J = 32.6 Hz), 125.41 (q, J_{CF} = 272.8 Hz), 137.89 (C-6), 152.11 (C-2). IR (KBr): υ 2950, 3210 (N–H) 1700 (C = O). $[\alpha]_D^{20}$ = −108.93 (c = 0.5; MeOH). Anal. calculated for $C_{12}H_{11}F_3N_2O$: C, 56.25; H, 4.33; N, 10.93%. Found: C, 56.40; H, 4.26; N, 10.89%.

4.3.2. S(−)-6-Methyl-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-one (**4b**)

^{1}H NMR (DMSO/CCl_4, 2:1) δ: 1.76 (s, 3H), 2.31 (s, 3H), 4.71 (s, 1H), 7.18 (d, 2H, J = 7.5 Hz), 7.40 (d, 2H, J = 7.5 Hz), 7.96 (s, 1H), 8.70 (s, 1H). ^{19}F NMR (DMSO/CCl_4, 2:1) δ: −79.62 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 18.27 (CH_3), 20.61 (CH_3), 64.38 (q, J_{CF} = 28.9 Hz), 93.31 (C-5), 125.75, 128.25, 128.97, 129.44 ($C_{arom.}$), 124.65 (q, J_{CF} = 247.7 Hz), 135.26 (C-6), 138.54 (C-5), 153.28 (C = S). IR (KBr): υ 2950, 3200 (N–H) 1705 (C=O). $[\alpha]_D^{20}$ = −157.26 (c = 0.26; MeOH). Anal. calculated for $C_{13}H_{13}F_3N_2O$: C, 57.78; H, 4.85; N, 10.37%. Found: C, 57.70; H, 4.87; N, 10.30%.

4.3.3. S(−)-6-Methyl-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-thione (**4c**)

^{1}H NMR (DMSO/CCl_4, 2:1) δ: 1.81 (s, 3H), 4.95 (s, 1H), 7.34–7.42 (m, 4H), 7.52 (d, 2H, J = 8.0 Hz), 9.58 (s, 1H), 10.19 (s, 1H). ^{19}F NMR (DMSO/CCl_4, 2:1) δ: −77.03 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 17.47 (CH_3), 63.34 (q, J_{CF} = 27.7 Hz), 94.16 (C-5), 125.63, 126.18, 128.30, 128.39 ($C_{arom.}$), 129.2 (q, J_{CF} = 285.4 Hz), 134.24 (C-6), 138.53 (C-5), 175.00 (C=S). IR (KBr): υ 2900, 3200 (N–H) 1655 (C=S). $[\alpha]_D^{20}$ = −23.33 (c = 0.40; MeOH). Anal. calculated for $C_{12}H_{11}F_3N_2S$: C, 52.93; H, 4.07; N, 10.29%. Found: C, 52.83; H, 4.01; N, 10.30%.

4.3.4. S(−)-6-Methyl-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-thione (**4d**)

^{1}H NMR (DMSO/CCl_4, 2:1) δ: 1.80 (s, 3H), 2.31 (s, 3H), 4.91 (s, 1H), 7.20 (d, 2H, J = 7.5 Hz), 7.39 (d, 2H, J = 7.5 Hz), 9.51 (s, 1H), 10.16 (s, 1H). ^{19}F NMR (DMSO/CCl_4, 2:1) δ: −77.04 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 17.47 (CH_3), 20.37 (CH_3), 63.10 (q, J_{CF} = 28.9 Hz), 94.18 (C-5), 125.94, 127.91, 128.61, 133.92 ($C_{arom.}$), 126.7 (q, J_{CF} = 286.7 Hz), 135.62 (C-6), 137.44 (C-5), 174.80 (C=S). IR (KBr): υ 2995, 3200 (N–H) 1665 (C=S). $[\alpha]_D^{20}$ = −76.77 (c = 0.33; MeOH). Anal. calculated for $C_{13}H_{13}F_3N_2S$: C, 54.53; H, 4.58; N, 9.78%. Found: C, 54.66; H, 4.54; N, 9.72%.

4.3.5. S(−)-4-(4-Fluorophenyl)-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidin-2(1H)-thione (**4e**)

^{1}H NMR (DMSO/CCl_4, 2:1) δ: 1.81 (s, 3H), 4.97 (s, 1H), 7.16–7.33 (m, 2H), 7.56–7.59 (m, 2H), 9.58 (s, 1H), 10.22 (s, 1H). ^{19}F NMR (DMSO/CCl_4, 2:1) δ: −77.17 (s, 3F), −114.31 (s, 1F). ^{13}C NMR (DMSO-d_6) δ: 17.55 (CH_3), 62.85 (q, J_{CF} = 28.9 Hz), 93.76 (C-5), 115.06, 128.01, 128.54, 134.31 ($C_{arom.}$), 124.4 (q, J_{CF} = 287.9 Hz), 134.66 (C-6), 162.76 (C-5), 174.83 (C=S). IR (KBr): υ 2998, 3210 (N–H) 1655 (C=S). $[\alpha]_D^{20}$ = −31.38 (c = 0.29; MeOH). Anal. calculated for $C_{12}H_{10}F_4N_2S$: C, 49.65; H, 3.47; N, 9.65%. Found: C, 49.64; H, 3.50; N, 9.65%.

4.4. General procedure for preparation of S(−)-N-aroyl-N'-[(1-aryl-3-oxo-1-trifluoromethyl)butyl]thioureas (**5a–c**)

To a solution of S(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-one **1a–b** (0.02 mol) in dry acetonitrile (40 ml), aroyl isothiocyanate (0.02 mol) was added, followed by stirring the mixture at room temperature for 6 h. The resulting precipitate was filtered off, washed with acetonitrile, and dried.

4.4.1. S(−)-N-Benzoyl-N'-[(3-oxo-1-phenyl-1-trifluoromethyl)butyl]thiourea (**5a**)

^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3H), 3.79 (d, 1H, J = 16.5 Hz), 4.50 (s, 1H, J = 16.5 Hz), 7.26–7.65 (m, 8H), 7.90 (d, 2H, J = 12 Hz), 9.07(s, 1H), 12.23 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: -77.07 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 31.30 (CH_3), 41.76 (CH_2), 65.65 (q, J_{CF} = 27.6 Hz), 126.23 (q, J_{CF} = 245.9 Hz), 127.13, 127.67, 128.57, 128.96, 129.16, 131.37, 133.81, 134.40 ($C_{arom.}$), 167.33 (C=O), 179.87 (C=O), 201.50 (C=O). IR (KBr): υ 3400, 3010 (N–H) 1665, 1710 (C=O), 1555 (C=S). $[\alpha]_D^{20}$ = −66.84 (c = 0.75; MeOH). Anal. calculated for $C_{19}H_{17}F_3N_2O_2S$: C, 57.86; H, 4.34; N, 7.10%. Found: C, 57.81; H, 4.32; N, 7.13%.

4.4.2. S(−)-N-(4-Chlorobenzoyl)-N'-[(3-oxo-1-phenyl-1-trifluoromethyl)butyl]thiourea (**5b**)

^{1}H NMR (DMSO-d_6) δ: 2.21 (s, 3H), 3.96 (d, 1H, J = 17.4 Hz), 4.45 (d, 1H, J = 17.4 Hz), 7.37–7.57 (m, 7H), 8.04 (d, 2H, J = 8.4 Hz), 11.60 (s, 1H), 12.42 (s, 1H). ^{19}F NMR (DMSO-d_6) δ: −75.73 (s, 3F). ^{13}C NMR (DMSO-d_6) δ: 30.71 (CH_3), 41.52 (CH_2), 64.67 (q, J = 27.2 Hz), 126.30 (J_{CF} = 245.9 Hz), 127.15, 128.28, 128.49, 128.57, 128.62, 130.72, 134.54, 138.21 ($C_{arom.}$), 168.29 (C=O), 180.00 (C=O), 201.91 (C=O). IR (KBr): υ 3400, 3015 (N–H) 1665, 1705 (C=O), 1565 (C = S). $[\alpha]_D^{20}$ = −49.76 (c = 0.15; MeOH). Anal. calculated for $C_{19}H_{16}ClF_3N_2O_2S$: C, 53.21; H, 3.76; N, 6.53%. Found: C, 53.10; H, 3.75; N, 6.60%.

4.4.3. S(−)-N-(4-Nitrobenzoyl)-N'-[(1-(4-methylphenyl)-3-oxo-1-trifluoromethyl)butyl]thiourea (**5c**)

^{1}H NMR (DMSO-d_6) δ: 2.21 (s, 3H), 2.34 (s, 3H), 3.95 (d, 1H, J = 17.0 Hz), 4.41 (d, 1H, J = 17.0 Hz), 7.19 (d, 2H, J = 9.0 Hz), 7.33 (d, 2H, J = 9.0 Hz), 8.23 (d, 2H, J = 8.8 Hz), 8.32 (d, 2H, J = 8.8 Hz), 11.89 (s,1H), 12.24 (s, 1H). ^{19}F NMR (DMSO-d_6) δ: −75.89 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: ^{13}C NMR (DMSO-d_6) δ: 20.50 (CH_3), 30.49 (CH_3), 41.52 (CH_2), 64.57 (q, J = 27.2 Hz), 126.24 (J_{CF} = 245.9 Hz), 123.08, 126.88, 128.68, 130.26, 131.39, 137.73, 149.80, 167.46 ($C_{arom.}$), 174.80 (C=O), 179.66 (C=O), 201.34 (C=O) IR (KBr): υ 3400, 3010 (N–H) 1665, 1705 (C=O), 1560 (C=S). $[\alpha]_D^{20}$ = −82.44 (c = 0.44; MeOH). Anal. calculated for $C_{19}H_{16}F_3N_3O_4S$: C, 51.94; H, 3.67; N, 9.56%. Found: C, 52.13; H, 3.64; N, 9.49%.

*4.5. General procedure for preparation of 4-aryl-4-isocyanato-5,5,5-trifluoropentan-2-ones (**6a–d**)*

To a solution of S(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-one **1a–d** (2.02 mmol) in dry ethyl acetate (10 ml), triphosgene (2.78 g, 1.02 mmol), along with three drops of dry triethylamine, was added. The reaction mixture was boiled for 15–20 h and the solvent was evaporated. The dry residue of the product (yield 85–90%) was converted further without additional purification.

*4.6. General procedure for preparation of S(−)-4-aryl-6-methyl-4-trifluoromethyl-3,4-dihydro-1,3-oxazin-2-ones (**7a–d**)*

To a solution of S(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-one **1a–d** (2.02 mmol) in dry ethyl acetate (10 ml), triphosgene (2.78 g, 1.02 mmol), along with three drops of DBU, was added. The reaction mixture was boiled for 8–10 h and the solvent was evaporated. The residue was chromatographed on a silica gel column eluted with an ethyl acetate-hexane mixture (1:1).

*4.6.1. S(−)-6-Methyl-4-phenyl-4-trifluoromethyl-3,4-dihydro-1,3-oxazin-2-one (**7a**)*

^{1}H NMR ($CDCl_3$) δ: 2.00 (s, 3H), 5.19 (s, 1H), 7.04 (s, 1H), 7.26–7.41 (m, 5H). ^{19}F NMR ($CDCl_3$) δ: −79.25 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 18.72 (CH_3), 63.20 (q, J_{CF} = 30.1 Hz), 95.25 (C-5), 124.33 (q, J_{CF} = 286.7 Hz), 125.90, 129.05, 129.19 ($C_{arom.}$), 136.43 (C-6), 149.92 ($C_{arom.}$), 150.62 (C-2). $[\alpha]_D^{20}$ = −105.23 (c = 1.85; MeOH). Anal. calculated for $C_{12}H_{10}F_3NO_2$: C, 56.04; H, 3.92; N, 5.45%. Found: C, 55.92; H, 3.88; N, 5.50%.

*4.6.2. S(−)-6-Methyl-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydro-1,3-oxazin-2-one (**7b**)*

^{1}H NMR ($CDCl_3$) δ: 1.99 (s, 3H), 2.36 (s, 3H), 5.18 (s, 1H), 6.95 (s, 1H), 7.23 (d, 2H, J = 8.0 Hz), 7.38 (d, 2H, J = 8.0 Hz). ^{19}F NMR ($CDCl_3$) δ: −79.27 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 18.68 (CH_3), 20.99 (CH_3), 63.10 (q, J = 30.2 Hz), 95.37 (C-5), 124.42 (q, J_{CF} = 285.4 Hz), 125.80, 129.69, 133.54 ($C_{arom.}$), 139.18 (C-6), 149.93 ($C_{arom.}$), 150.47 (C-2). $[\alpha]_D^{20}$ = −108.1 (c = 0.64; MeOH). Anal. calculated for $C_{13}H_{12}F_3NO_2$: C, 57.57; H, 4.46; N, 5.16%. Found: C, 57.58; H, 4.49; N, 5.11%.

*4.6.3. S(−)-4-(4-Fluorophenyl)-6-methyl-4-trifluoromethyl-3,4-dihydro-1,3-oxazin-2-one (**7c**)*

^{1}H NMR ($CDCl_3$) δ: 2.01 (s, 3H), 5.20 (s, 1H), 6.93 (s, 1H), 7.08–7.15 (m, 2H), 7.50–7.56 (m, 2H), 7.95 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: −79.48 (s, 3F), −113.31 (s, 1F). ^{13}C NMR ($CDCl_3$) δ: 18.71 (CH_3), 63.00 (q, J_{CF} = 30.1 Hz), 95.03 (C-5), 116.11 ($C_{arom.}$), 124.40 (q, J_{CF} = 285.6 Hz), 128.12, 132.33, 149.90 ($C_{arom.}$), 150.86 (C-6), 161.93 (C-2). $[\alpha]_D^{20}$ = −112.766 (c = 1.0; MeOH). Anal. calculated for $C_{12}H_9F_4NO_2$: C, 52.37; H, 3.30; N, 5.09. Found: C, 52.50; H, 3.26; N, 5.09%.

*4.6.4. S(−)-6-Methyl-4-(4-methoxylphenyl)-4-trifluoromethyl-3,4-dihydro-1,3-oxazin-2-one (**7d**)*

^{1}H NMR ($CDCl_3$) δ: 1.99 (s, 3H), 3.81 (s, 3H), 5.18 (s, 1H), 6.93 (s, 1H), 6.93 (d, 2H, J = 9.0 Hz), 7.35 (d, 2H, J = 9.0 Hz), 7.47 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: −79.45 (s, 3F). ^{13}C NMR ($CDCl_3$) δ: 18.61 (CH_3), 55.31 (CH_3), 62.97 (q, J_{CF} = 28.92 Hz), 95.41 (C-5), 114.33 ($C_{arom.}$), 124.44 (q, J_{CF} = 285.5 Hz), 127.68, 128.47, 149.95 ($C_{arom.}$), 150.42 (C-6), 160.03 (C-2). $[\alpha]_D^{20}$ = −106.1 (c = 0.40; MeOH). Anal. calculated for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88%. Found: C, 54.33; H, 4.18; N, 4.96%.

*4.7. Reaction of 4-aryl-4-isocyanato-5,5,5-trifluoropentan-2-ones **6a,b** with amines*

To a solution of 4-aryl-4-isocyanato-5,5,5-trifluoropentan-2-one **6a,b** (0.002 mol) in dry toluene (10 ml), an amine, e.g., butylamine, benzylamine, or morpholine (0.002 mol) was added. The reaction mixture was boiled for 5 h and the solvent was evaporated to obtain a mixture of dihydropyrimidone **3j,k** and dihydrooxazinone **7a,b**. In the reaction with morpholine, the residue was chromatographed on a silica gel column eluted with an ethyl acetate-hexane mixture (2:1) to yield urea **8**.

*4.7.1. S(−)-N-[(3-Oxo-1-phenyl-1-trifluoromethyl)butyl]morpholinecarboxamide (**8**)*

^{1}H NMR ($CDCl_3$) δ: 2.22 c (s, 3H), 3.42–3.55 (m, 6H), 3.71 (m, 4H), 5.94 c (s, 1H), 7.06 (m, 2H), 7.43 (m, 2H). ^{19}F NMR ($CDCl_3$) δ: −74.58 (s, 3F), −114.98 (s, 1F). ^{13}C NMR ($CDCl_3$) δ: 32.13 (CH_3), 44.16, 44.41 (CH_2), 63.20 (q, J_{CF} = 27.6 Hz), 66.51 (CH_2), 115.38 (C_{arom}), 125.42 (q, J_{CF} = 286.7 Hz), 127.88, 132.85 ($C_{arom.}$), 156.14 (C═O), 162.47 (q, J = 247.7 Hz), 205.68 (C═O). $[\alpha]_D^{20}$ = −33.65 (c = 0.95; MeOH).Anal. calculated for $C_{16}H_{19}F_3N_2O_3$: C, 55.81; H, 5.56; N, 8.14%. Found: C, 55.77; H, 5.58; N, 8.19%.

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