ISSN 1070-4280, Russian Journal of Organic Chemistry, 2012, Vol. 48, No. 3, pp. 430–433. © Pleiades Publishing, Ltd., 2012.
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Synthesis of (*S*)-(–)-1,4-Diaryl-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thiones

N. M. Golovach, V. A. Sukach, and M. V. Vovk

Institute of Organic Chemistry, National Academy of Sciences of Ukraine,
ul. Murmanskaya 5, Kiev, 02660 Ukraine
e-mail: mvovk@i.com.ua

Received June 3, 2011

Abstract—(*S*)-(+)-4-Amino-4-aryl-5,5,5-trifluoropentan-2-one reacted with aryl isothiocyanates containing electron-withdrawing substituents to give (*S*)-(–)-1,4-diaryl-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thiones.

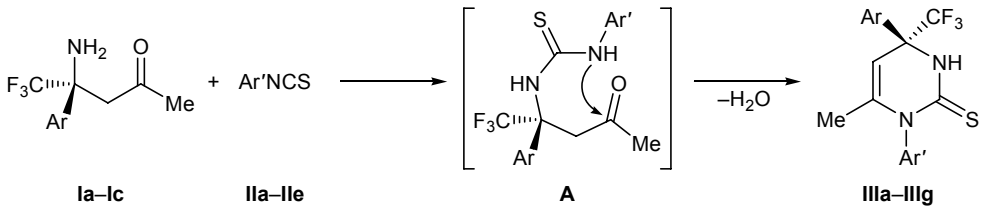
DOI: 10.1134/S1070428012030165

3,4-Dihydropyrimidine-2(1*H*)-thiones are biologically important pyrimidine derivatives. For example, monastrol [ethyl 4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate] is an effective allosteric inhibitor of the mitotic kinesin Eg5 [1, 2]. Most partly hydrogenated pyrimidine-2-thiones synthesized so far are 4-monosubstituted derivatives. Their 4,4-disubstituted analogs have been studied to a much lesser extent, though some of these were found to exhibit strong anti-inflammatory and analgesic activity [2–5]. Unlike 4-monosubstituted 3,4-dihydropyrimidine-2(1*H*)-thiones which are generally synthesized by the Biginelli reaction [6], 4,4-disubstituted derivatives are obtained by condensation of α,β-unsaturated ketones with ammonium thiocyanate [7, 8] or of β-isothiocyanato carbonyl compounds with amines [9–12]. The reaction of β-amino ketones with aryl isothiocyanates was less successful, for it was accompanied by side formation of 6-hydroxy-3,4,5,6-tetrahydropyrimidine-2(1*H*)-thiones [13].

Introduction of a trifluoromethyl group into molecules of organic compounds endows them with qualitatively new chemical and biological properties [14, 15]; of particular interest are structures in which trifluoromethyl group is attached to an asymmetric carbon atom [16, 17]. We previously synthesized optically active 4-aryl-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thiones having no substituent on N^1 by condensation of chiral β-trifluoromethyl-β-amino ketones with potassium thiocyanate or acyl isothiocyanates [18]. Our attempts to involve in analogous reaction ethyl or phenyl isothiocyanate as electrophile were unsuccessful.

We succeeded in synthesizing the target compounds with the use of more electrophilic aromatic isothiocyanates. Preparatively accessible [19] (*S*)-(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-ones **Ia**–**Id** with high optical purity reacted with aryl isothiocyanates **IIa**–**IIe** having electron-withdrawing substituents in the benzene ring to give (*S*)-(–)-1,4-diaryl-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thiones **IIIa**–**IIIg** in 58–87% yield with an optical purity of 88–96% (Scheme 1). Most probably, the reaction involves intermediate formation of thioureas **A** which,

Scheme 1.



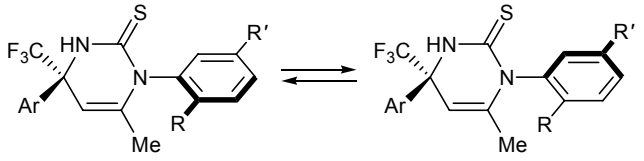
Ia–Ic **IIa–IIe** **A** **IIIa–IIIg**

I, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-FC_6H_4 (**c**); **II**, Ar′ = 2-FC_6H_4 (**a**), 2-$F_3CC_6H_4$ (**b**), 4-$O_2NC_6H_4$ (**c**), 2-Cl-5-$F_3CC_6H_3$ (**d**), 3,5-$(F_3C)_2C_6H_3$ (**e**); **III**, Ar = Ph, Ar′ = 2-$F_3CC_6H_4$ (**a**), 4-$O_2NC_6H_4$ (**b**); Ar = 4-MeC_6H_4, Ar′ = 2-FC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), 2-Cl-5-$F_3CC_6H_3$ (**e**), 3,5-$(F_3C)_2C_6H_3$ (**f**); Ar = 4-FC_6H_4, Ar′ = 4-$O_2NC_6H_4$ (**g**).

unlike analogous ureas [18], undergo intramolecular cyclization under neutral rather than acid conditions. Stepwise transformation of β-amino ketones **Ia**–**Id** does not affect the chiral center, and its absolute configuration is retained in the cyclization products.

The ^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds **IIIa**–**IIIg** unambiguously indicate their dihydropyrimidinethione structure. Pyrimidinethiones **IIIa**, **IIIc**, and **IIIe** having an *ortho*-substituted phenyl ring on N^1 displayed in almost all NMR spectra a double set of signals with an intensity ratio of ~0.6:0.4. Presumably, this is the result of atropisomerism arising from restricted rotation of the *ortho*-substituted benzene ring about the C–N bond due to the presence of methyl group in position *6* of the pyrimidine ring (Scheme 2).

Scheme 2.



IIIa, **IIIc**, **IIIe**

R = F_3C, R′ = H (**a**); R = F, R′ = H (**c**); R = Cl, R′ = F_3C (**e**).

The presence in the ^{19}F NMR spectra of **IIIc** and **IIIe** of two nearby signals from the CF_3 group made it difficult to perform NMR experiments with the use of shift reagents; so that we failed to determine optical purity of these compounds.

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were measured on a Bruker Avance DRX-500 instrument at 500.13, 470.59, and 125.75 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) as internal reference. The mass spectra were obtained on a PE Sciex API 150EX LC–MS system (Perkin Elmer) equipped with UV (λ 254 nm) and ELSD detectors. The optical rotations were measured on an Anton Paar polarimeter. The optical purity of compounds **IIIa**, **IIIb**, **IIId**, **IIIf**, and **IIIg** was determined by ^{19}F NMR spectroscopy using tris[3-(heptafluorobutyryl)-L-camphorato]europium(III) as lanthanide shift reagent.

(*S*)-(–)-1,4-Diaryl-6-methyl-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thiones IIIa–IIIg (*general procedure*). Aryl isothiocyanate **IIa**–**IIe**, 3.6 mmol, was added to a solution of 3.3 mmol of amino ketone **Ia**–**Ic** in 1 ml of anhydrous acetonitrile, and the mixture was heated for 10 h under reflux. In the synthesis of compounds **IIIb** and **IIId**, the precipitate was filtered off and washed with hexane. In the other cases, the mixture was evaporated, the oily residue was dissolved in 15 ml of methylene chloride, the solution was washed with a solution of sodium carbonate, and the organic phase was separated, dried over anhydrous sodium sulfate, and evaporated. The products were recrystallized from 60% aqueous methanol.

(*S*)-(–)-6-Methyl-4-trifluoromethyl-1-[2-(trifluoromethyl)phenyl]-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (IIIa). Yield 65%, mp 157–158°C, *ee* 93%, $[\alpha]_D^{20}$ = –10.91° (*c* = 1.0, MeOH). IR spectrum (KBr), ν, cm^{-1}: 3165 (NH), 1705 [NHC(S)]. ^{1}H NMR spectrum, δ, ppm: 1.63 s and 1.65 s (3H, CH_3), 5.17 s and 5.34 s (1H, 5-H), 7.19–7.81 m (10H, H_{arom}, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.64, 20.82 (CH_3); 63.08 q, 63.16 q (C^4, *J* = 28.9 Hz); 98.93, 99.18 (C^5); 124.60 q, 126.71 q (CF_3, *J* = 286.5 Hz); 125.99, 126.01, 126.08, 127.36, 127.40, 127.44, 127.48, 128.94, 129.05, 129.09, 129.18, 129.46, 132.60, 132.63, 132.67, 132.75, 136.54, 136.71, 137.71, 137.82, 137.93, 138.14 (C_{arom}, C^6); 178.29, 178.55 (C=C). ^{19}F NMR spectrum, δ_F, ppm: –78.56 s (CF_3), –63.07 s and –62.66 s (CF_3). Mass spectrum: *m*/*z* 417 $[M]^+$. Found, %: C 54.83; H 3.37; N 6.72; S 7.69. $C_{19}H_{14}F_6N_2S$. Calculated, %: C 54.81; H 3.39; N 6.73; S 7.70. *M* 416.4.

(*S*)-(–)-6-Methyl-1-(4-nitrophenyl)-4-phenyl-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thione (IIIb). Yield 70%, mp 171–172°C, *ee* 96%, $[\alpha]_D^{20}$ = –2.99° (*c* = 1.0, MeOH). IR spectrum (KBr), ν, cm^{-1}: 3175 (NH), 1700 [NHC(S)]. ^{1}H NMR spectrum, δ, ppm: 1.65 s (3H, CH_3), 5.27 s (1H, 5-H), 7.16 s (1H, NH), 7.27–7.55 m (7H, H_{arom}), 8.29 d (2H, H_{arom}, *J* = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.05 (CH_3), 63.07 q (C^4, *J* = 28.9 Hz), 100.23 (C^5), 124.45 q (CF_3, *J* = 286.5 Hz); 124.56, 125.96, 129.26, 129.32, 131.00, 135.93, 137.19, 145.92, 147.66 (C_{arom}, C^6); 178.12 (C=S). ^{19}F NMR spectrum: δ_F –78.78 ppm, s (CF_3). Mass spectrum: *m*/*z* 394 $[M]^+$. Found, %: C 54.98; H 3.57; N 10.69; S 8.14 $C_{18}H_{14}F_3N_3O_2S$. Calculated, %: C 54.96; H 3.59; N 10.68; S 8.15. *M* 393.4.

(*S*)-(–)-1-(2-Fluorophenyl)-6-methyl-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thione (IIIc). Yield 77%, mp 118–119°C, $[\alpha]_D^{20}$ = –30.51° (*c* = 1.00, MeOH). IR spectrum (KBr), ν, cm^{-1}: 3198 (NH), 1695 [NHC(S)]. ^{1}H NMR spectrum, δ, ppm: 1.62 s and 1.66 s (3H, CH_3), 2.36 s and

2.38 s (3H, CH_3), 5.14 s and 5.22 s (1H, 5-H), 7.19–7.67 m (9H, H_{arom}, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.30, 20.47 (CH_3); 21.06 (CH_3); 62.92 q, 62.97 q (C^4, J = 28.9 Hz); 99.31, 99.39 (C^5); 125.83 q, 125.91 q (CF_3, J = 286.4 Hz); 116.37, 116.52, 124.37, 124.40, 124.68, 124.72, 125.85, 125.95, 128.03, 128.17, 128.27, 129.01, 129.23, 129.51, 129.80, 130.90, 131.44, 131.52, 134.66, 136.52, 139.14, 158.40 d (J = 251.5 Hz), 158.53 d (J = 251.5 Hz), 159.53 d (J = 16.3 Hz) (C_{arom}, C^6); 178.31, 178.46 (C=S). ^{19}F NMR spectrum, δ_F, ppm: –120.99 s, 121.84 s (2′-F); –78.67 s, –79.05 s (CF_3). Mass spectrum: m/z 381 $[M]^+$. Found, %: C 59.97; H 4.25; N 7.38; S 8.45. $C_{19}H_{16}F_4N_2S$. Calculated, %: C 59.99; H 4.24; N 7.36; S 8.43. M 380.4.

(*S*)-(–)-6-Methyl-4-(4-methylphenyl)-1-(4-nitrophenyl)-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thione (IIId). Yield 87%, mp 177–178°C, *ee* 95%, $[\alpha]_D^{20}$ = –20.93° (c = 1.00, MeOH). IR spectrum (KBr), ν, cm^{-1}: 3200 (NH), 1695 [NHC(S)]. ^1H NMR spectrum, δ, ppm: 1.65 s (3H, CH_3), 2.39 s (3H, CH_3), 5.25 s (1H, 5-H), 7.16 s (1H, NH), 7.25–7.46 m (6H, H_{arom}), 8.29 d (2H, H_{arom}, J = 8.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.31 (CH_3), 21.06 (CH_3), 63.09 q (C^4, J = 28.9 Hz), 100.37 (C^5), 124.36 q (CF_3, J = 285.4 Hz); 124.54, 125.80, 129.91, 131.00, 134.26, 135.76, 139.41, 145.96, 147.64 (C_{arom}, C^6); 178.08 (C=S). ^{19}F NMR spectrum: δ_F –78.99 ppm, s (CF_3). Mass spectrum: m/z 408 $[M]^+$. Found, %: C 55.98; H 3.95; N 10.33; S 7.85. $C_{19}H_{16}F_3N_3O_2S$. Calculated, %: C 56.01; H 3.96; N 10.31; S 7.87. M 407.4.

(*S*)-(–)-1-[2-Chloro-5-(trifluoromethyl)phenyl]-6-methyl-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thione (IIIe). Yield 58%, oily substance, $[\alpha]_D^{20}$ = –43.78° (c = 1.00, MeOH). IR spectrum (KBr), ν, cm^{-1}: 3168 (NH), 1700 [NHC(S)]. ^1H NMR spectrum, δ, ppm: 1.65 s and 1.67 s (3H, CH_3), 2.32 s and 2.34 s (3H, CH_3), 5.25 s (1H, 5-H), 6.99–7.02 m (1H, H_{arom}), 7.18–7.27 m (1H, H_{arom}), 7.28–7.32 m (2H, H_{arom}), 7.44–7.47 m (2H, H_{arom}), 7.59–7.66 m (2H, H_{arom}, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.30, 20.54 (CH_3); 21.05, 21.39 (CH_3); 63.17 q, 63.21 q (C^4, J = 28.9 Hz); 99.98, 100.23 (C^5); 124.61 q, 124.77 q (CF_3, J = 285.4 Hz); 125.77, 125.78, 125.95, 125.96, 126.97, 127.00, 128.15, 128.97, 129.89, 129.90, 130.81, 130.96, 134.63, 134.70, 135.40, 135.52, 137.79, 137.99, 138.53, 138.60, 139.22, 139.29 (C_{arom}, C^6); 177.45, 177.51 (C=S). ^{19}F NMR spectrum, δ_F, ppm: –78.48 s, –78.64 s (CF_3); –63.60 s, –63.64 s (CF_3). Mass spectrum: m/z 465 $[M]^+$. Found, %: C 51.65; H 3.27; N 6.05; S 6.89. $C_{20}H_{15}ClF_6N_2S$. Calculated, %: C 51.67; H 3.25; N 6.03; S 6.90. M 464.9.

(*S*)-(–)-1-[3,5-Bis(trifluoromethyl)phenyl]-6-methyl-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thione (IIIf). Yield 80%, mp 151–152°C, *ee* 96%, $[\alpha]_D^{20}$ = –15.26° (c = 1.00, MeOH). IR spectrum (KBr), ν, cm^{-1}: 3195 (NH), 1695 [NHC(S)]. ^1H NMR spectrum, δ, ppm: 1.64 s (3H, CH_3), 2.39 s (3H, CH_3), 5.27 s (1H, 5-H), 7.18–7.49 m (5H, H_{arom}, NH), 7.64–7.70 m (2H, H_{arom}), 7.91 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.04 (CH_3), 21.27 (CH_3), 62.91 q (C^4, J = 28.9 Hz), 100.64 (C^5), 122.70 q (CF_3, J = 285.8 Hz); 125.84, 126.32, 129.91, 130.38, 132.62, 134.15, 135.53, 139.43, 141.83 (C_{arom}, C^6); 178.23 (C=S). ^{19}F NMR spectrum, δ_F, ppm: –78.94 s, –64.00 s (CF_3). Mass spectrum: m/z 499 $[M]^+$. Found, %: C 50.59; H 3.06; N 5.59; S 6.45. $C_{21}H_{15}F_9N_2S$. Calculated, %: C 50.61; H 3.03; N 5.62; S 6.43. M 498.4.

(*S*)-(–)-4-(4-Fluorophenyl)-6-methyl-1-(4-nitrophenyl)-4-trifluoromethyl-3,4-dihydropyrimidine-2(1*H*)-thione (IIIg). Yield 67%, oily substance, *ee* 88%, $[\alpha]_D^{20}$ = –130.90° (c = 1.0, MeOH). IR spectrum (KBr), ν, cm^{-1}: 3170 (NH), 1695 [NHC(S)]. ^1H NMR spectrum, δ, ppm: 1.68 s (3H, CH_3), 5.26 s (3H, 5-H), 6.23 s (1H, H_{arom}), 7.17–7.43 m (4H, H_{arom}, NH), 7.55–7.57 m (2H, H_{arom}), 8.31 d (2H, H_{arom}, J = 8.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.31 (CH_3), 63.05 q (C^4, J = 28.9 Hz), 99.31 (C^5), 126.34 q (CF_3, J = 285.4 Hz); 124.41, 126.58, 128.21, 130.94, 131.42, 136.54, 139.02, 157.46, 159.46, 158.40 d (J = 251.5 Hz) (C_{arom}, C^6); 178.40 (C=S). ^{19}F NMR spectrum, δ_F, ppm: –112.88 s (4′-F), –78.96 s (CF_3). Mass spectrum: m/z 412 $[M]^+$. Found, %: C 52.53; H 3.21; N 10.19; S 7.77. $C_{18}H_{13}F_4N_3O_2S$. Calculated, %: C 52.55; H 3.19; N 10.21; S 7.79. M 411.4.

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