

Condensation of 2-Amino-1,3-thiazole Salts and Benzo Analogs with Trifluoroacetylacetone

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Abstract—The condensation of 2-amino-1,3-thiazolium perchlorates and their benzo analogs with trifluoroacetylacetone in acetic acid afforded the corresponding [1,3]thiazolo[3,2-*a*]pyrimidinium, pyrimido[2,1-*b*][1,3]benzothiazolium, and naphtho[2',1':4,5][1,3]thiazolo[3,2-*a*]pyrimidinium salts as a single isomer in which the trifluoromethyl group is located in the γ -position with respect to the bridgehead nitrogen atom. The structure of the synthesized compounds was confirmed by ¹H NMR spectra and elemental analyses.

Keywords: 2-amino-1,3-thiazole, benzo derivatives, trifluoroacetylacetone, [1,3]thiazolo[3,2-*a*]pyrimidine, ¹H NMR spectra, bridgehead nitrogen

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INTRODUCTION

Polycyclic compounds with a bridgehead nitrogen atom constitute a large group of fused heterocycles, and chemistry of these compounds continues to develop extensively. Thiazole and pyrimidine rings are structural fragments of many important natural and synthetic biologically active molecules. These fragments occur both separately (as in nucleic acids, coenzymes, penicillin) and in combination with each other as isolated moieties (vitamin B₁) or fused thiazolo[3,2-*a*]pyrimidine system (thiochrom). Derivatives of thiazolo[3,2-*a*]pyrimidine and its benzo analogs are of practical significance, in particular as promising pharmaceuticals. Compounds exhibiting antitumor, analgesic, hypotensive, and bactericidal activities have been found in this series [1], and their substantial advantage is low toxicity. The use of β -diketones in the synthesis of pyrimidine derivatives has long been known. As early as the late 19th century, it has been found that guanidine, urea, thiourea, and amidines react with β -diketones to give monocyclic pyrimidines. Fused pyrimidines with a bridgehead nitrogen atom have been synthesized in the early 20th century.

Pyrimidine derivatives were synthesized [2, 3] from α -amino heterocycles with an endocyclic NH group, i.e., imidazoles, triazoles, tetrazoles, and indoles. Chuiguk [4] proposed to obtain fused pyrimidines with

a bridgehead nitrogen atom by condensation of a protonated α -amino NH-heterocycle with β -diketones, β -diketo aldehydes, and other 1,3-difunctional carbonyl compounds. This universal method makes it possible to synthesize pyrimidinium salts by fusion of a pyrimidine ring to any nitrogen heterocycle.

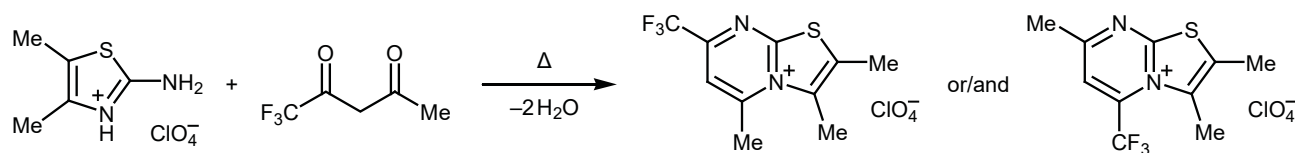
The goal of the present work was to synthesize [1,3]thiazolo[3,2-*a*]pyrimidinium, pyrimido[2,1-*b*]-[1,3]benzothiazolium, and naphtho[2',1':4,5][1,3]thiazolo[3,2-*a*]pyrimidinium salts.

RESULTS AND DISCUSSION

In this study, trifluoroacetylacetone (1,1,1-trifluoropentane-2,4-dione) was selected as β -dicarbonyl component. Condensation of trifluoroacetylacetone with 2-aminothiazolium and 2-aminobenzothiazolium perchlorates gave [1,3]thiazolo[3,2-*a*]pyrimidinium, pyrimido[2,1-*b*][1,3]benzothiazolium, and naphtho[2',1':4,5][1,3]thiazolo[3,2-*a*]pyrimidinium salts with a trifluoromethyl group in the pyrimidine ring. However, this condensation could lead to the formation of isomeric products (Scheme 1). As a rule, reactions with unsymmetrical β -diketones gave rise to mixtures of isomeric salts, though in some cases only one isomer was detected in the crude product.

The reaction direction is determined by steric and electronic factors, as well as by the basicity of the corresponding aminothiazole. In our case, the reactions

Scheme 1.



were regioselective, and only one of the possible isomers was present in the reaction mixture. This result is not unexpected since the trifluoromethyl group exerts a strong electron-withdrawing inductive effect, thus reducing the partial negative charge on the nearest carbonyl group. Therefore, the distant γ -carbonyl group becomes more electrophilic, and it reacts more rapidly at the endocyclic nitrogen atom to give that isomer in which the methyl group is located in the α -position with respect to the bridgehead nitrogen.

The product structure was determined by ^1H NMR spectroscopy [5] on the basis of the chemical shifts of protons of the methyl groups at the α - and γ -positions relative to the bridgehead nitrogen atom (Fig. 1). Thiazolopyrimidinium salts synthesized previously by reactions of 2-aminothiazole and its benzo analogs with a symmetrical β -diketone, namely acetylacetone [6], were used as model compounds for which chemical shifts of protons in the α - and γ -methyl groups are known.

It is seen from Fig. 1 that the chemical shifts of the α -methyl protons of **1** and **2a** are almost similar (δ 2.73 and 2.76 ppm, respectively), which confirms the formation of isomer with the methyl group in the α -position with respect to the bridgehead nitrogen atom in the condensation of 2-aminothiazole with trifluoroacetylacetone. Furthermore, the ^1H NMR spectrum of **1** showed two doublets at δ 8.03 and 8.15 ppm (δ 8.01 and 8.15 ppm in the spectrum of **2a**) with a coupling constant of 5.0 Hz. In the spectra of compounds **2a–2j**, the α -methyl protons resonated at δ 2.04, 2.06, 2.05, 2.05, 2.06, 2.05, and 1.97 ppm, respectively. The upfield position of these signals is determined by

shielding effect of the phenyl ring in the 3-position, which provides an additional evidence for the α -position of the methyl group with respect to the bridgehead nitrogen atom. Thus, the ^1H NMR data clearly and reliably confirm the structure of the synthesized salts.

The obtained thiazolo[3,2-*a*]pyrimidinium salts and their benzo analogs readily undergo condensations at the α -methyl group to give cyanine dyes.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian 300 spectrometer (300 MHz) using $\text{DMSO-}d_6$ as solvent and tetramethylsilane as internal standard. The structures of the synthesized compounds are shown in Fig. 2. Initial 2-aminothiazoles were prepared according to reported procedures. In particular, 1,3-thiazol-2-amine was synthesized from thiourea and ethanol chlorination product [7], and 4-methyl-, 4,5-dimethyl-, and 4-phenyl-1,3-thiazol-2-amines were synthesized from thiourea and the corresponding ketones according to Dodson and King [8]. 4-Aryl-1,3-thiazol-2-amines ($\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{Br}, \text{Cl}, \text{Me}, \text{Et}, \text{OMe}$) were prepared from thiourea and appropriately substituted acetophenones [11], and 4,5-diphenyl-1,3-thiazol-2-amine was synthesized as described in [10]. 1,3-Benzothiazol-2-amine and its 6-bromo derivative were obtained by cyclization of *N*-phenylthiourea by the action of bromine [11]. The other 6-substituted 1,3-benzothiazol-2-amines ($\text{Cl}, \text{Me}, \text{MeO}, \text{NO}_2$) were synthesized from *para*-substituted anilines and ammonium thiocyanate in the presence of copper(II) chloride [12]. Naphtho[2,1-*d*][1,3]thiazol-2-amine was synthesized

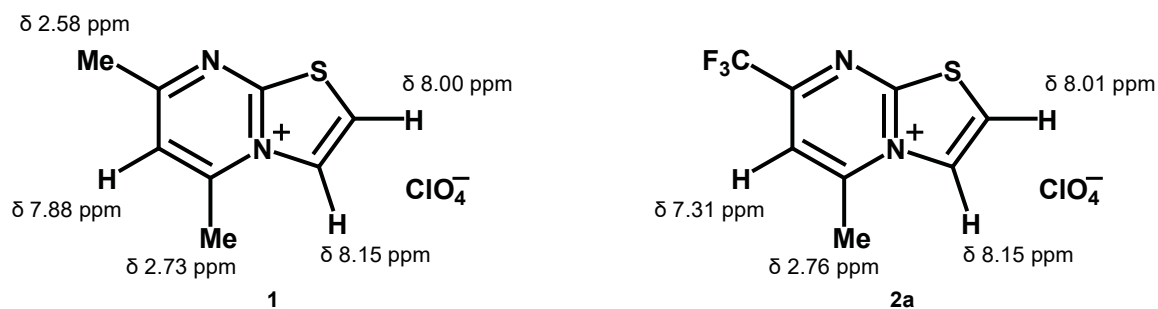


Fig. 1. ^1H NMR chemical shifts of model compounds **1** and **2a**.

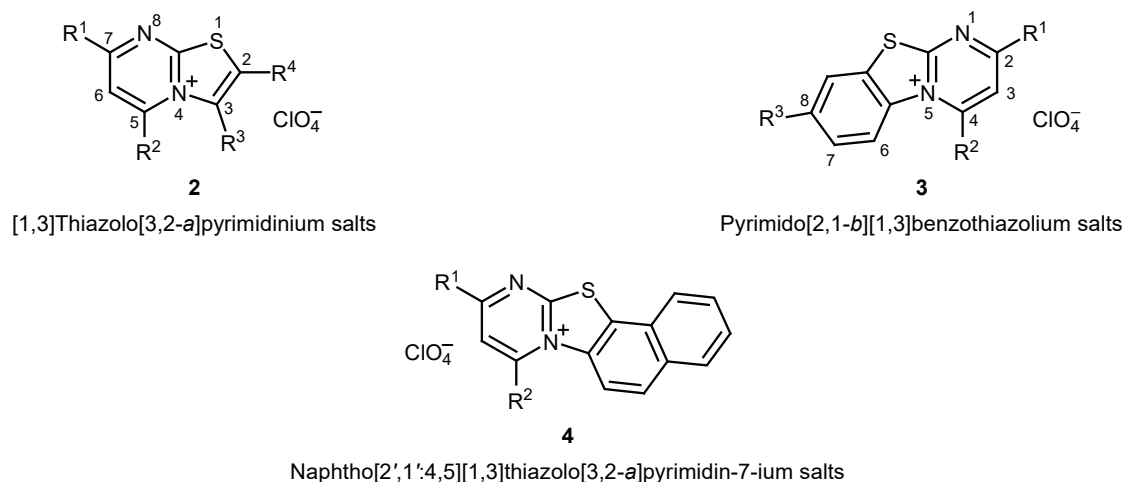


Fig. 2. Structures of compounds 2–4.

from naphthalen-2-amine according to [12]. The two-step synthesis of trifluoroacetylacetone was described in [13].

5-Methyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-a]pyrimidin-4-ium perchlorate (2a). A mixture of 3.99 g (0.02 mol) of 2-amino-1,3-thiazolium perchlorate and 3.85 g (0.025 mol) of trifluoroacetylacetone was heated at 135–140°C for 1.5–2 h. The mixture was cooled to room temperature, and the precipitate was filtered off, washed with ethanol and diethyl ether, and recrystallized from ethanol. Yield 4.90 g (77%), mp 222–223°C. ¹H NMR spectrum, δ, ppm: 2.76 s (3H, CH₃), 7.51 s (1H, 6-H), 8.01 d and 8.15 d (1H each, 2-H, 3-H, *J* = 5.0 Hz). Found, %: C 30.23; H 2.03; S 10.23. C₈H₆ClF₃N₂O₄S. Calculated, %: C 30.14; H 1.88; S 10.05.

3,5-Dimethyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-a]pyrimidin-4-ium perchlorate (2b) was synthesized in a similar way from 4.27 g (0.02 mol) of 2-amino-4-methyl-1,3-thiazolium perchlorate and 3.85 g (0.025 mol) of trifluoroacetylacetone. Yield 6.22 g (93%), mp 219–220°C. ¹H NMR spectrum, δ, ppm: 2.66 s (3H, 3-CH₃), 2.83 s (3H, 5-CH₃), 7.24 s (1H, 6-H), 7.38 s (1H, 2-H). Found, %: C 32.63; H 2.32; S 9.77. C₉H₈ClF₃N₂O₄S. Calculated, %: C 32.48; H 2.40; S 9.62.

5-Methyl-3-phenyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-a]pyrimidin-4-ium perchlorate (2c) was synthesized in a similar way from 5.51 g (0.02 mol) of 2-amino-4-phenyl-1,3-thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 6.82 g (87%), mp 267°C. ¹H NMR spectrum, δ, ppm: 2.04 s (3H, 5-CH₃), 7.25 s (5H, C₆H₅), 7.37 s (1H, 6-H), 7.54 s (1H, 2-H). Found, %: C 42.67; H 2.73;

S 8.33. C₁₄H₁₀ClF₃N₂O₄S. Calculated, %: C 42.58; H 2.59; S 8.83.

3-(4-Chlorophenyl)-5-methyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-a]pyrimidin-4-ium perchlorate (2d) was synthesized in a similar way from 6.2 g (0.02 mol) of 2-amino-4-(4-chlorophenyl)-1,3-thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 6.54 g (84%), mp 234–235°C. ¹H NMR spectrum, δ, ppm: 2.06 s (3H, CH₃), 7.23 s (4H, C₆H₄), 7.38 s (1H, 6-H), 7.65 s (1H, 2-H). Found, %: C 39.70; H 2.37; S 7.78. C₁₄H₉Cl₂F₃N₂O₄S. Calculated, %: C 39.53; H 2.12; S 7.53.

3-(4-Bromophenyl)-5-methyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-a]pyrimidin-4-ium perchlorate (2e) was synthesized in a similar way from 7.09 g (0.02 mol) of 2-amino-4-(4-bromophenyl)-1,3-thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 8.05 g (85%), mp > 305°C. ¹H NMR spectrum, δ, ppm: 2.05 s (3H, CH₃), 7.21 s (4H, C₆H₄), 7.36 s (1H, 6-H), 7.62 s (1H, 2-H). Found, %: C 35.68; H 2.07; S 6.93. C₁₄H₉BrClF₃N₂O₄S. Calculated, %: C 35.48; H 1.90; S 6.76.

5-Methyl-3-(4-methylphenyl)-7-(trifluoromethyl)[1,3]thiazolo[3,2-a]pyrimidin-4-ium perchlorate (2f) was synthesized in a similar way from 5.79 g (0.02 mol) of 2-amino-4-(4-methylphenyl)-1,3-thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 7.60 g (93%), mp 276°C. ¹H NMR spectrum, δ, ppm: 2.05 s (3H, 5-CH₃), 2.12 s (3H, CH₃C₆H₄), 7.10 s (4H, CH₃C₆H₄), 7.18 s (1H, 6-H), 7.56 s (1H, 2-H). Found, %: C 44.23; H 3.17; S 8.01. C₁₅H₁₂ClF₃N₂O₄S. Calculated, %: C 44.06; H 2.94; S 7.83.

3-(4-Methoxyphenyl)-5-methyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium perchlorate (2g) was synthesized in a similar way from 6.11 g (0.02 mol) of 2-amino-4-(4-methoxyphenyl)-1,3-thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 7.39 g (87%), mp 276–267°C. ¹H NMR spectrum, δ, ppm: 2.06 s (3H, 5-CH₃), 3.57 s (3H, OCH₃), 6.35 s (4H, C₆H₄), 7.31 s (1H, 6-H), 7.55 s (1H, 2-H). Found, %: C 42.27; H 2.93; S 7.41. C₁₅H₁₂ClF₃N₂O₅S. Calculated, %: C 42.40; H 2.82; S 7.57.

3-(4-Ethylphenyl)-5-methyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium perchlorate (2h) was synthesized in a similar way from 6.07 g (0.02 mol) of 2-amino-4-(4-ethylphenyl)-1,3-thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 7.01 g (83%), mp 248–249°C. ¹H NMR spectrum, δ, ppm: 0.95 t (3H, CH₃, *J* = 7.0 Hz), 2.05 s (3H, CH₃), 2.43 q (2H, *J* = 7.0 Hz), 7.11 s (4H, C₆H₄), 7.15 s (1H, 6-H), 7.53 s (1H, 2-H). Found, %: C 45.61; H 3.20; S 7.43. C₁₆H₁₄ClF₃N₃O₄S. Calculated, %: C 45.44; H 3.31; S 7.57.

2,3,5-Trimethyl-7-(trifluoromethyl)[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium perchlorate (2i) was synthesized in a similar way from 4.55 g (0.02 mol) of 2-amino-4,5-dimethyl-1,3-thiazolium perchlorate and 3.85 g (0.025 mol) of trifluoroacetylacetone. Yield 4.50 g (65%), mp 251–252°C. ¹H NMR spectrum, δ, ppm: 2.25 s and 2.57 s (3H each, 2-CH₃, 3-CH₃), 2.85 s (3H, 5-CH₃), 7.22 s (1H, 6-H). Found, %: C 34.52; H 2.97; S 8.14. C₁₀H₁₀ClF₃N₂O₄S. Calculated, %: C 34.65; H 2.90; S 9.23.

5-Methyl-2,3-diphenyl-7-(trifluoromethyl)-[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium perchlorate (2j) was synthesized in a similar way from 7.03 g (0.02 mol) of 2-amino-4,5-diphenyl-1,3-thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 8.09 g (86%), mp 261–262°C. ¹H NMR spectrum, δ, ppm: 1.97 s (3H, CH₃), 6.87 s (5H, C₆H₅), 7.10 s (5H, C₆H₅), 7.27 s (1H, 6-H). Found, %: C 51.14; H 2.82; S 6.97. C₂₀H₁₄ClF₃N₂O₄S. Calculated, %: C 51.00; H 2.97; S 6.80.

4-Methyl-2-(trifluoromethyl)pyrimido[2,1-*b*]-[1,3]benzothiazol-5-ium perchlorate (3a). A mixture of an ethanolic solution of 4.99 g (0.02 mol) of 2-amino-1,3-benzothiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone was refluxed for 2.5–3 h. The mixture was cooled to room temperature, and the precipitate was filtered off and washed with ethanol and diethyl ether. An additional amount of the

product was isolated from the filtrate by reprecipitation with diethyl ether. The product was recrystallized from ethanol. Yield 6.48 g (95%), mp 248–249°C. ¹H NMR spectrum, δ, ppm: 3.05 s (3H, CH₃), 6.55 d (2H, *J* = 9.0 Hz), 7.27 q (2H, *J* = 9.0 Hz), 7.44 s (1H, 3-H). Found, %: C 38.89; H 2.37; S 8.53. C₁₂H₈ClF₃N₂O₄S. Calculated, %: C 39.07; H 2.17; S 8.69.

8-Bromo-4-methyl-2-(trifluoromethyl)pyrimido[2,1-*b*][1,3]benzothiazol-5-ium perchlorate (3b) was synthesized in a similar way from 6.57 g (0.02 mol) of 2-amino-6-bromo-1,3-benzothiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 8.50 g (95%), mp 297°C. ¹H NMR spectrum, δ, ppm: 3.03 s (3H, CH₃), 7.46 s (1H, 3-H), 7.69 q (1H, *J* = 9.0 Hz), 8.03 s (1H, 9-H), 8.16 d (1H, *J* = 9.0 Hz). Found, %: C 32.03; H 1.70; S 7.02. C₁₂H₇BrClF₃N₂O₄S. Calculated, %: C 32.18; H 1.56; S 7.15.

8-Methoxy-4-methyl-2-(trifluoromethyl)pyrimido[2,1-*b*][1,3]benzothiazol-5-ium perchlorate (3c) was synthesized in a similar way from 5.59 g (0.02 mol) of 2-amino-6-methoxy-1,3-benzothiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 7.79 g (97%), mp 288°C. ¹H NMR spectrum, δ, ppm: 2.97 s (3H, CH₃), 3.65 s (3H, OCH₃), 7.13 q (1H, *J* = 9.0 Hz), 7.27 s (1H, 3-H), 7.36 d (1H, *J* = 2.0 Hz), 8.14 (1H, *J* = 9.0 Hz). Found, %: C 39.02; H 2.32; S 8.21. C₁₃H₁₀ClF₃N₂O₅S. Calculated, %: C 39.14; H 2.51; S 8.03.

8-Chloro-4-methyl-2-(trifluoromethyl)pyrimido[2,1-*b*][1,3]benzothiazol-5-ium perchlorate (3d) was synthesized in a similar way from 5.68 g (0.02 mol) of 2-amino-6-chloro-1,3-benzothiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 7.74 g (96%), mp 284°C. ¹H NMR spectrum, δ, ppm: 3.02 s (3H, CH₃), 7.37 s (1H, 3-H), 7.47 q (1H, *J* = 9.0 Hz), 7.76 d (1H, *J* = 3.0 Hz), 8.17 d (1H, *J* = 9.0 Hz). Found, %: C 35.62; H 1.82; S 7.83. C₁₂H₇Cl₂F₃N₂O₄S. Calculated, %: C 35.73; H 1.74; S 7.94.

4,8-Dimethyl-2-(trifluoromethyl)pyrimido[2,1-*b*][1,3]benzothiazol-5-ium perchlorate (3e) was synthesized in a similar way from 5.27 g (0.02 mol) of 2-amino-6-methyl-1,3-benzothiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 7.41 g (97%), mp 278°C. ¹H NMR spectrum, δ, ppm: 2.28 s (3H, 8-CH₃), 3.05 s (3H, 4-CH₃), 7.41 q (1H, *J* = 9.0 Hz), 7.42 s (1H, 3-H), 7.67 d (1H, *J* = 3.0 Hz), 8.19 d (1H, *J* = 10.0 Hz). Found, %: C 40.92; H 2.50; S 8.21. C₁₃H₁₀ClF₃N₂O₄S. Calculated, %: C 40.78; H 2.61; S 8.21.

4-Methyl-8-nitro-2-(trifluoromethyl)pyrimido-[2,1-*b*][1,3]benzothiazol-5-ium perchlorate (3f) was synthesized in a similar way from 5.89 g (0.02 mol) of 2-amino-6-nitro-1,3-benzothiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 6.37 g (77%), mp 293°C. ¹H NMR spectrum, δ, ppm: 3.06 s (3H, CH₃), 7.17 q (1H, *J* = 9.0 Hz), 7.45 s (1H, 3-H), 7.72 d (1H, *J* = 3.0 Hz), 8.15 d (1H, *J* = 9.0 Hz). Found, %: C 34.65; H 1.80; S 7.83. C₁₂H₇ClF₃N₃O₄S. Calculated, %: C 34.82; H 1.69; S 7.83.

8-Methyl-10-(trifluoromethyl)naphtho[2',1':4,5]-[1,3]thiazolo[3,2-*a*]pyrimidin-7-ium perchlorate (4a) was synthesized in a similar way from 5.99 g (0.02 mol) of 2-aminonaphtho[2,1-*d*][1,3]thiazolium perchlorate and 4.62 g (0.03 mol) of trifluoroacetylacetone. Yield 8.11 g (97%), mp 271°C. ¹H NMR spectrum, δ, ppm: 3.09 s (3H, CH₃), 7.38 s (1H, 9-H), 8.19 d (6H, H_{arom}, *J* = 9.0 Hz). Found, %: C 45.77; H 2.31; S 7.77. C₁₆H₁₀ClF₃N₂O₄S. Calculated, %: C 45.88; H 2.39; S 7.71.

CONCLUSIONS

The condensation of 2-amino-1,3-thiazolium perchlorates and their benzo analogs with trifluoroacetylacetone afforded previously unknown thiazolo[3,2-*a*]pyrimidinium salts with the trifluoromethyl group located in the γ-position with respect to the bridgehead nitrogen atom. The synthesized compounds attract interest due to their potential biological activity and possible use as precursors to cyanine dyes.

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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