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Synthesis of 5-methyl-4-polyfluoroaryl-1,3-thiazol-2-amines

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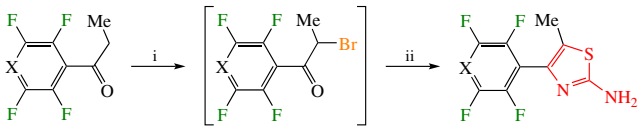
1-(Polyfluoroaryl)propan-1-ones were transformed into 5-methyl-4-polyfluoroaryl-1,3-thiazol-2-amines by a two-step reaction sequence involving formation of 2-bromo-1-(polyfluoroaryl)propan-1-ones under the acidic bromination conditions followed by heterocyclization with thiourea to finally afford new 5-methyl-4-polyfluoroaryl-1,3-thiazol-2-amines in high yields. 1,1′-(2,3,5,6-Tetrafluoro-1,4-phenylene)-dipropan-1-one was involved in the similar reaction to give a derivative containing two thiazole moieties.



X = CF, CCF_3, CCN, CCO_2Et, CH, N; yields up to 94%
i, Br_2, AcOH (cat.), $CHCl_3$, 25 °C, 2 days
ii, $(NH_2)_2CS$, EtOH, 80 °C, 1 h

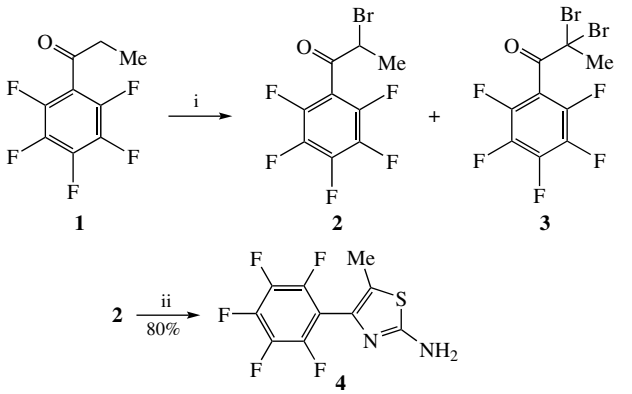
Keywords: thiazoles, α-bromo ketones, organofluorine compounds, bromination, thiourea, X-ray diffraction analysis.

Thiazole derivatives find application in agricultural chemistry as fungicides[1,2] and insecticides.[3] The introduction of thiazole moiety into organic molecules can be responsible for the occurrence of anticancer effect[4–6] as well as anti-inflammatory,[7,8] antimicrobial,[9,10] antiviral[11] and anticonvulsant[12] activities. Coordination polymers derived from thiazoles were shown to exhibit luminescence;[13] metal–organic frameworks based on thiazole-containing ligands were reported to possess an ability to absorb CO_2.[14,15] On the other hand, introducing fluorine atoms into organic compounds may improve their useful properties or give new ones, such as lipophilicity, improved stability and bioactivity.[16] Fluorine-containing thiazole derivatives are poorly studied, so the development of methods for their preparation is of interest.

One of the most common methods for the preparation of 2-aminothiazoles is the Hantzsch thiazole synthesis, which involves, for example, the reaction of α-halo ketones with thiourea. The synthesis of 4-aryl-1,3-thiazoles bearing two fluorine atoms or CF_3 group in the aryl moiety was conducted by the reaction of aromatic α-halo ketones with thioamides.[17] 4-Aryl-1,3-thiazoles containing poly- or perfluorinated aryl groups have not been studied yet.

In this article, we report on the bromination of 1-(polyfluoroaryl)propan-1-ones for producing polyfluoroaromatic α-bromo ketones and their further reaction with thiourea to synthesize 5-methyl-4-polyfluoroaryl-1,3-thiazol-2-amines. It was reported[18] that bromination of methyl pentafluorophenyl ketone in diethyl ether led to the corresponding α-bromo derivative in a high yield. We carried out the reaction of homologous 1-(pentafluorophenyl)propan-1-one **1** with bromine in diethyl ether at room temperature for 5 days and obtained a mixture of the starting ketone **1** and 2-bromo-1-(pentafluorophenyl)propan-1-one **2** in the 50:50 ratio (Scheme 1, Table 1). The reaction of ketone **1** with bromine in acetic acid at room temperature for 2 days provided bromo ketone **2** along with a small amount of 2,2-dibromo-1-(pentafluorophenyl)-propan-1-one **3**. The treatment of ketone **1** with bromine in chloroform in the presence of a catalytic amount of acetic acid at room temperature for 2 days afforded the only target monobromo ketone **2**, which was isolated in 82% yield (see Scheme 1 and Table 1).

Heating of bromo ketone **2** with thiourea in ethanol gave 5-methyl-4-pentafluorophenyl-1,3-thiazol-2-amine **4** in 80% yield (see Scheme 1). To our delight, thiazole **4** can be obtained by the two-step reaction without isolating intermediate bromo ketone **2**. Thus, the interaction of ketone **1** with bromine followed by evaporating volatile substances and subsequent heating the reaction product with thiourea in ethanol led to thiazole **4** in a similar yield (Scheme 2). In the same manner,

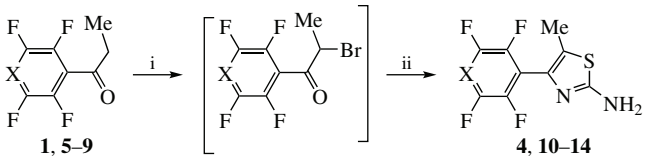


Scheme 1 *Reagents and conditions*: i, Br_2, solvent, 25 °C, 2–5 days (see Table 1); ii, $(NH_2)_2CS$, EtOH, 80 °C, 1 h.

Table 1 Optimization of monobromination of 1-(pentafluorophenyl)-propan-1-one **1**.

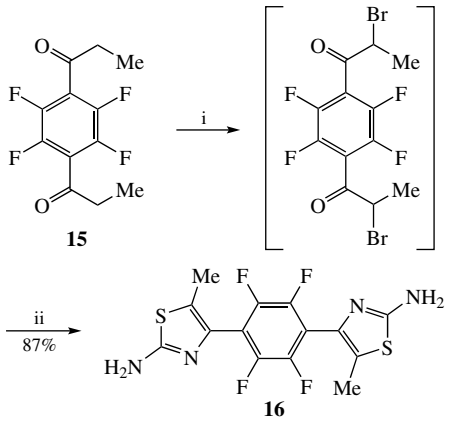
Entry	Solvent	*t*/days	**1/2/3** ratio[a]
1	Et_2O	5	50:50:0
2	AcOH	2	0:94:6
3	$CHCl_3$/AcOH (cat.)	2	0:100:0

[a] From ^{19}F NMR.



1, **4** X = CF, 84% **7**, **12** X = CCO_2Et, 93%
5, **10** X = CCF_3, 92% **8**, **13** X = CH, 94%
6, **11** X = CCN, 90% **9**, **14** X = N, 86%

Scheme 2 *Reagents and conditions*: i, Br_2, AcOH (cat.), $CHCl_3$, 25 °C, 2 days; ii, $(NH_2)_2CS$, EtOH, 80 °C, 1 h.



Scheme 3 *Reagents and conditions*: i, Br_2, AcOH (cat.), $CHCl_3$, 25 °C, 2 days; ii, $(NH_2)_2CS$, EtOH, 80 °C, 1 h.

analogs **10**–**14** were readily prepared form the corresponding precursors **5**–**9**. Analogously, 1,1′-(2,3,5,6-tetrafluoro-1,4-phenylene)dipropan-1-one **15** was converted into derivative **16** containing two thiazole moieties (Scheme 3).

The structure of bis(thiazole) **16** (solvate with DMF) has been established by the single-crystal X-ray analysis (Figure 1).† The unit cell contains one crystallographically independent half of a molecule of **16** and one molecule of DMF. According to the X-ray diffraction data, the thiazole ring and the phenylene ring of **16** are perfectly planar in the crystal, the standard deviations

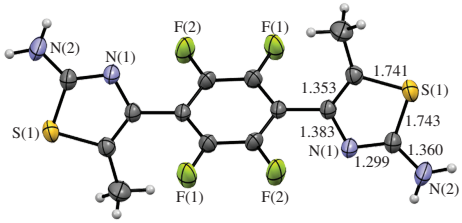


Figure 1 Molecular structure of compound **16** and the selective bond lengths in Å (the molecule is located at the symmetry center).

† *Crystal data for bis(thiazole)* **16** *(solvate with DMF)*. $C_{20}H_{24}F_4N_6O_2S_2$ (M = 520.57), triclinic, space group $P\bar{1}$, a = 6.1778(4), b = 7.2790(4) and c = 14.9148(8) Å, α = 81.614(2), β = 88.460(2) and γ = 70.306(3)°, V = 624.53(6) Å^3, Z = 1, d_{calc} = 1.384 g cm^{-3}, μ = 0.272 mm^{-1}, $F(000)$ = 270, independent reflections 2884 (R_{int} = 0.037), wR_2 = 0.1438, S = 1.03 for all reflections (R = 0.0436 for 2351 reflections $F > 4\sigma$). Crystallographic data were obtained on a Bruker Kappa Apex II CCD diffractometer using φ, ω scans of narrow (0.5°) frames with MoK_α radiation (λ = 0.71073 Å) and a graphite monochromator. The structures were solved by direct methods and refined by full-matrix least-squares method against all F^2 in anisotropic approximation using the SHELX-97 programs set.[19] The hydrogen atoms positions were calculated with the riding model.

CCDC 2308048 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

from the mean plane being 0.001 Å for both. The plane of the thiazole ring is turned out of the phenylene plane by 59.4(1)°.

The starting 1-(polyfluoroaryl)propan-1-ones **1**, **5**–**9**, and **15** are available compounds and can be prepared as reported.[20,21]

In conclusion, an efficient two-step synthesis of 5-methyl-4-polyfluoroaryl-1,3-thiazol-2-amines from 1-(polyfluoroaryl)-propan-1-ones has been developed. The process was carried out without isolating intermediate 2-bromo-1-(polyfluoroaryl)-propan-1-ones. A series of new 5-methyl-4-polyfluoroaryl-1,3-thiazol-2-amines was obtained by this method in high yields. These compounds may be promising ligands for synthesizing new metal–organic frameworks.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.038.

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