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# Synthesis of 5-alkyl-2-amino-1,3,4-thiadiazoles and α,ω-bis(2-amino-1,3,4-thiadiazol-5-yl)alkanes in ionic liquids

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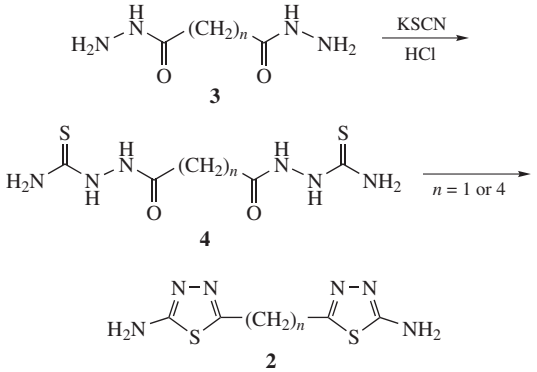
**Reaction of thiosemicarbazide with carboxylic acids, including N-substituted amino acids, in ionic liquids with $H_2SO_4$ as a catalyst affords 5-R-2-amino-1,3,4-thiadiazoles. On using alkanedicarboxylic acids, α,ω-bis(2-amino-1,3,4,-thiadiazol-5-yl)alkanes were obtained.**

1,3,4-Thiadiazole derivatives found application in medicine, agriculture and in many technological areas such as manufacturing of dyes, lubricating formulations, optically active liquid crystals, photographic materials, *etc*.[1,2] A large number of 1,3,4-thiadiazole derivatives has been patented in the agricultural field as herbicides,[3] insecticides and fungicides.[4] The 1,3,4-thiadiazole ring is moiety of biologically active compounds which possess antihypertensive, anticonvulsive[5] and antituberculosis[6] activities. 2-Amino derivatives occupy an important place in the 1,3,4-thiadiazole series. One of the best-known drugs based on 2-acetamido-5-sulfamido-1,3,4-thiadiazole, so-called 'acetazola', is a carbonic anhydrase inhibitor.[7] It is applied for therapy of many diseases such as epilepsy, glaucoma and congestive cardiac failure.[8] 2-Amino-5-mercapto-1,3,4-thiadiazole derivatives are efficient radioprotective agents.[9] 5-Alkyl-2-amino-1,3,4-thiadiazoles display spasmolytic and anti-inflammatory activities.[10]

A synthesis of 2-amino-1,3,4-thiadiazoles **1** is based on cyclocondensation of carboxylic acids with thiosemicarbazide in the acidic medium, mostly in conc. $H_2SO_4$, on heating.[11–13] In some cases, $POCl_3$,[14] $MeSO_3H$ in the presence of $P_2O_5$,[15] PPA,[16] dichlorophosphate on polyethyleneglycole and acidic aluminum oxide (with a simultaneous action of microwave radiation) are used as acidic catalysts.[17]

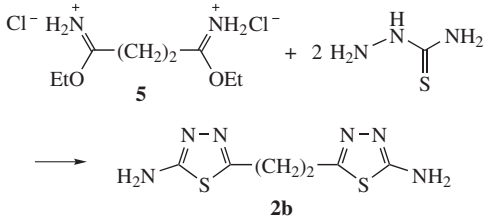
The above methods produce good results in many cases, although they have certain disadvantages, in particular, a large amount of inorganic salts is generated in neutralization of $H_2SO_4$ and other acidic catalysts, which results in adverse environmental impact and creates troubles in the isolation of the final products.




**Scheme 1**

Furthermore, these reactions are suitable only for the synthesis of monocyclic compounds. A synthesis of α,ω-bis(2-amino-1,3,4-thiadiazol-5-yl)alkanes **2** from dicarboxylic acids is based on multistep reactions, *e.g.*, on refluxing of dihydrazides **3** of corresponding diacids with KSCN in hydrochloric acid followed by cyclization of the formed α,ω-bis(thiosemicarbazid-4-yl)alkanes **4** into the target compounds **2** on treatment with an excess of conc. $H_2SO_4$,[18] compounds **2** being characterized only by melting points (Scheme 1).

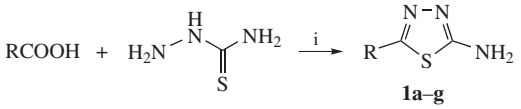
This reaction, however, is not general and is applicable for malonic and adipic acids only. 1,2-Bis(aminothiocarbamoyl)-hydrazine is produced by heating of succinic acid dihydrazide with KSCN.[18] 1,2-Bis(2-amino-1,3,4-thiadiazol-5-yl)ethane **2b** was synthesized under the action of thiosemicarbazide on bis-iminoether of succinic acid dihydrochloride **5**[19] (Scheme 2).



**Scheme 2**

The goal of this research was to develop a new general method for the preparation of both mono- (**1**) and bicyclic (**2**) 2-amino-1,3,4-thiadiazole derivatives. As an approach to the solution of that, we decided to carry out an interaction between carboxylic acids and thiosemicarbazide in ionic liquids (ILs), which over the past years have been widely employed as potential substitutes of conventional solvents for a variety of chemical processes.[20–23] From a large pool of ILs at first of choice was 1-ethyl-3-methylimidazolium hydrosulfate [emim][$HSO_4$] since it is one of the most accessible and possesses acidic properties, so it can be used both as a reaction medium and as an acidic catalyst.

Phenylacetic acid was selected as a starting object. However, its interaction with thiosemicarbazide in [emim][$HSO_4$] even at 100 °C did not bring about positive results. The target 2-amino-5-phenyl-1,3,4-thiadiazole **1a** was obtained in 87% yield after adding several drops of conc. $H_2SO_4$ to the reaction mixture and stirring at 100 °C for 5 h. These conditions proved appropriate for preparing 2-amino-1,3,4-thiadiazoles **1b–g** from other aliphatic

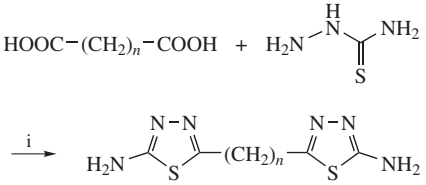


**1a–g**

**a** R = $PhCH_2$ (92%)
**b** R = Pr (73%)
**c** R = $Pr^i$ (76%)
**d** R = $CH_2NHBz$ (70%)
**e** R = $MeS(CH_2)_2CH(NHBz)$ (40%)
**f** R = MeCH(NHBz) (96%)
**g** R = $CH_2(NHTs)$ (54%)

**Scheme 3** *Reagents and conditions*: i, [emim][$HSO_4$], [hmim][$F_3P(C_2F_5)_3$] or [bmpyr][$F_3P(C_2F_5)_3$], $H_2SO_4$ (1–1.5 mol), 100 °C, 5–6 h.

monocarboxylic acids (butyric and isobutyric acids), including *N*-aroyl- or arylsulfonyl α-amino acids (Scheme 3), as well as for synthesizing α,ω-bis(2-amino-1,3,4-thiadiazol-5-yl)alkanes **2a–d** from aliphatic dicarboxylic acids – malonic, succinic, glutaric and adipic (Scheme 4).



**2a** *n* = 1 (41%)
**2b** *n* = 2 (62%)
**2c** *n* = 3 (98%)
**2d** *n* = 4 (100%)

**Scheme 4** *Reagents and conditions*: i, [emim][$HSO_4$], [hmim][$F_3P(C_2F_5)_3$] or [bmpyr][$F_3P(C_2F_5)_3$], $H_2SO_4$ (1–1.5 mol), 100 °C, 5–6 h.

† All new compounds gave satisfactory elemental analyses and their structures were confirmed by IR, MS, $^1$H and $^{13}$C NMR spectra. IR spectra were measured on a UR-20 spectrometer. $^1$H and $^{13}$C NMR spectra of compounds in DMSO-$d_6$ were recorded on a Bruker AM300 spectrometer (300 MHz for $^1$H and 75.5 MHz for $^{13}$C). MS spectra were measured on a Finnigan MAT INCOS-50 instrument. Melting points were measured on a Gallenkamp instrument (Sanyo).

*General procedure 1 for the synthesis of 5-substituted 2-amino-1,3,4-thiadiazoles* **1a–g** *and α,ω-bis(5-amino-1,3,4-thiadiazol-2-yl)alkanes* **2a–d** *in [emim][$HSO_4$]*. Thiosemicarbazide (0.25 g, 2.74 mmol) was added to 1 g of [emim][$HSO_4$] (5 mmol) and this mixture was stirred for 15 min at 50 °C. Then 3 mmol of a monocarboxylic acid or 1.5 mmol of a dicarboxylic acid and 0.5 g (4.9 mmol) of 97% $H_2SO_4$ were added, the temperature was raised to 100 °C and the reaction mixture was stirred for 5–6 h in a reaction vessel supplied with condenser and protection from moisture. The temperature was decreased to 20 °C, 2 ml of water was added, the reaction mixture was stirred for 15 min, then an aqueous solution of ammonia was added to pH 7–8, stirring was continued for 1 h, the precipitate was filtered off, washed with water and dried in air.

‡ *General procedure 2 for the synthesis of 5-substituted 2-amino-1,3,4-thiadiazoles* **1a–g** *and α,ω-bis(2-amino-1,3,4-thiadiazol-5-yl)alkanes* **2a–d** *in [hmim][$F_3P(C_2F_5)_3$] or [bmpyr][$F_3P(C_2F_5)_3$]*. The carboxylic acid (or N-protected α-amino acid) (2.2 mmol for monoacids or 1.1 mmol for diacids) and 2 mmol of thiosemicarbazide were added to 1.5–2 g of the corresponding IL and stirred for 5 min. Then 3.7 mmol of conc. $H_2SO_4$ were added, the reaction mixture was heated to 100 °C, stirred for 6 h at this temperature and cooled to 20 °C. The mixture of 5 ml of $CH_2Cl_2$:$H_2O$ (1:1 v/v) was added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (6×2 ml). The organic layer was washed with water, dried with $MgSO_4$, the solvent was evaporated, the rest was dried under $P_2O_5$ in a vacuum desiccator and the recovered IL was reused in the next runs. Aqueous ammonia was added to the aqueous layer to pH 7–8 and the reaction mixture was stirred for 1 h. Then the precipitate formed was filtered off, washed with water and dried in air.

*5-Benzyl-1,3,4-thiadiazol-2-amine* **1a**: yield 92% (procedure 1), 80% (procedure 2), 85% (procedure 2, regenerated [bmpyr][$F_3P(C_2F_5)_3$]), mp 201–203 °C (lit.,[16] 202–204 °C). $^1$H NMR, δ: 4.17 (s, 2H, $CH_2$), 7.00 (br. s, 2H, $NH_2$), 7.27 (s, 5H, Ph). $^{13}$C NMR, δ: 35.43 ($CH_2$), 126.77, 128.49, 128.57, 137.98 (Ph), 157.50 ($C_{ring}CH_2$), 168.77 (C–$NH_2$). IR (ν/cm$^{-1}$): 3320, 3104, 1632, 1612, 1520, 1504, 1452, 1424, 1368, 1328, 1216, 1148, 1076, 1048, 920, 900, 748, 700.

This procedure (see experimental, procedure 1),† however, did not allow regenerating and reuse of the IL. Therefore, we carried out the same reactions in other ILs – 1-hexyl-1-methylimidazolium and butylmethylpyrrolidinium trifluorotris(pentafluoroethyl) phosphates [hmim][$F_3P(C_2F_5)_3$] and [bmpyr][$F_3P(C_2F_5)_3$] (see experimental, procedure 2)‡ with $H_2SO_4$ as a catalyst. Thus, the target 2-amino-1,3,4-thiadiazoles **1a–g** and **2a–d** were formed in comparable yields.‡ This procedure allowed regenerating ILs, which were reused for the same reactions at least 3 times.

To conclude, a new, simple and general method was developed for the preparation of both 5-substituted 2-amino-1,3,4-thiadiazoles and α,ω-bis(5-amino-1,3,4-thiadiazol-2-yl)alkanes. This method was based on heating of mono- or dicarboxylic acids, including N-protected α-amino acids, with thiosemicarbazide at 100 °C in certain ILs with addition of $H_2SO_4$ in a catalytic amount. Some ILs have been regenerated and reused for the same reactions.

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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.2011.11.013.

*5-Benzoylaminomethyl-1,3,4-thiadiazol-2-amine* **1d**: yield 70% (procedure 1), 77% (procedure 2), 75% (regenerated [hmim][$F_3P(C_2F_5)_3$]), mp 218 °C (lit.,[24] 216 °C). $^1$H NMR, δ: 4.58 (d, 2H, $CH_2$, $^3J$ 8.4 Hz), 7.08 (br. s, 2H, $NH_2$), 7.48 (m, 3H, Ph, $^3J$ 8.2 Hz), 7.88 (d, 2H, Ph, $^3J$ 8.2 Hz), 9.27 (t, 1H, NH, $^3J$ 8.4 Hz). $^{13}$C NMR, δ: 38.59 ($CH_2$), 127.23, 128.40, 131.56, 133.59 (Ph), 156.55 ($C_{ring}CH_2$), 166.41, 169.36 (C–$NH_2$, C=O). IR (ν/cm$^{-1}$): 3312, 3120, 2932, 1628, 1600, 1580, 1528, 1512, 1484, 1424, 1344, 1312, 1264, 1180, 1152, 1068, 828, 720. MS, *m*/*z* (%): 234 ($M^+$, 52), 129 ($M^+$ – PhCO, 100), 105 (PhCO, 77), 76 ($NH_2CSNH_2$, 80).

*5-(1-Benzoylamino-3-methylthiopropyl)-1,3,4-thiadiazol-2-amine* **1e**: yield 40% (procedure 1), 35% (procedure 2), mp 198–200 °C. $^1$H NMR, δ: 2.02 (s, 3H, Me), 2.26 (m, 2H, $CH_2C$), 2.60 (m, 2H, $CH_2S$), 5.38 (q, 1H, CH, $^3J$ 8.6 Hz), 7.10 (br. s, 2H, $NH_2$), 7.52 (m, 3H, Ph, $^3J$ 8.0 Hz), 7.92 (d, 2H, Ph, $^3J$ 8.0 Hz), 9.04 (d, 1H, NH, $^3J$ 8.6 Hz). $^{13}$C NMR, δ: 14.71 (Me), 29.97 ($CH_2C$), 32.67 ($CH_2S$), 48.33 (CH), 127.47, 128.35, 131.56, 133.88 (Ph), 160.42 ($C_{ring}CH$), 166.31, 168.90 (C–$NH_2$, C=O). IR (ν/cm$^{-1}$): 3268, 1640, 1580, 1516, 1492, 1436, 1316, 1264, 1216, 1192, 1148, 1060, 968, 936, 864, 820, 804, 696. MS, *m*/*z* (%): 308 ($M^+$, 18), 247 ($M^+$ – $MeSCH_2$, 14), 234 ($HetCH_2NHCOPh$, 98), 129 ($HetCH_2NH$, 100), 105 (PhCO, 100), 77 ($NH_2CSNH_2$ + 1, 89).

*5-(Tosylaminomethyl)-1,3,4-thiadiazol-2-amine* **1g**: yield 54% (procedure 1), mp 221 °C. $^1$H NMR, δ: 2.40 (s, 3H, Me), 4.12 (d, 2H, $CH_2$, $^3J$ 8.0 Hz), 7.15 (br. s, 2H, $NH_2$), 7.42 (d, 2H, Ph, $^3J$ 7.8 Hz), 7.72 (d, 2H, Ph, $^3J$ 7.8 Hz), 8.38 (t, 1H, NH, $^3J$ 8.0 Hz). $^{13}$C NMR, δ: 20.98 (Me), 41.71 ($CH_2$), 126.56, 129.66, 137.30, 142.92 (Ph), 155.81 ($C_{ring}CH_2$), 169.60 (C–$NH_2$). IR (ν/cm$^{-1}$): 3480, 3368, 1595, 1524, 1496, 1420, 1380, 1348, 1320, 1308, 1288, 1252, 1192, 1160, 1120, 1092, 1032, 968, 836, 812, 792, 704. MS, *m*/*z* (%): 284 ($M^+$, 1), 222 (18), 218 (7), 178 (13), 154 (Ts – 1, 26), 129 ($M^+$ – Ts, 56), 114 ($M^+$ – TsNH, 50), 107 (77), 105 (99), 100 ($NH_2$Het, 77), 91 (100).

*1,2-Bis(5-amino-1,3,4-thiadiazol-2-yl)ethane* **2b**: yield 62% (procedure 1), 63% (procedure 2), mp 290–293 °C (lit.,[19] 291–293 °C). $^1$H NMR, δ: 3.36 (s, 4H, $2CH_2$), 7.15 (s, 4H, $2NH_2$). $^{13}$C NMR, δ: 28.94 ($CH_2$), 156.38 ($C_{ring}CH_2$), 168.57 (C–$NH_2$). IR (ν/cm$^{-1}$): 3240, 3096, 1656, 1556, 1444, 1424, 1400, 1372, 1360, 1224, 1172, 1152, 1052, 1016, 996, 688, 676. MS, *m*/*z* (%): 228 ($M^+$, 72), 153 (ring-$CH_2CH_2CN$ – 1, 64), 114 (ring-$CH_2$, 100).

*1,4-Bis(5-amino-1,3,4-thiadiazol-2-yl)butane* **2d**: yield 100% (procedure 1), 94% (procedure 2), mp 266–267 °C (lit.,[18] 265–267 °C). $^1$H NMR, δ: 1.68 [br. s, 4H, $CH_2(CH_2)_2CH_2$], 2.80 [br. s, 4H, $CH_2(CH_2)_2CH_2$], 7.08 (s, 4H, $2NH_2$). $^{13}$C NMR, δ: 28.16 [$CH_2(CH_2)_2CH_2$], 31.97 [$CH_2(CH_2)_2CH_2$], 157.20 ($C_{ring}CH_2$), 167.96 (C–$NH_2$). IR (ν/cm$^{-1}$): 3320, 3162, 1620, 1576, 1532, 1456, 1336, 1220, 1192, 1116, 1056, 688, 648, 632. MS, *m*/*z* (%): 256 ($M^+$, 4), 214 ($M^+$ – $NCNH_2$, 8), 199 ($M^+$ – $NCNHNH_2$, 9), 181 [ring-$(CH_2)_4CN$ – 1, 56], 141 [ring-$(CH_2)_3$ – 1, 100], 128 (ring-$CH_2CH_2$, 88), 115 (ring-Me, 62), 99 (ring – 1, 48).

For characteristics of compounds **1b**,**c**,**f** and **2a**,**c**, see Online Supplementary Materials.

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