One-pot regioselective synthesis of new 5-(arylsulfonylamino)imidazo[2,1-b]thiazoles

Valery Y. Serykh, Gulnur N. Chernysheva, Evgeniy V. Kondrashov, Aleksandr V. Vashchenko, Vladimir I. Smirnov, and Igor B. Rozentsveig*

A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Street, Irkutsk 664033, Russia
E-mail: i_roz@irioch.irk.ru

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.380

Abstract

N-(2,2-Dichloro-2-phenylethylidene)-4-chlorobenzenesulfonamide reacts with 2-aminothiazoles to give products of nucleophilic addition in good yields. The adducts are cyclized into the unexpected 5-(arylsulfonyl)amino-6-phenylimidazo[2,1-b]thiazoles in 70-75% yield; whereas the anticipated isomeric 6-(arylsulfonyl)amino-5-phenylimidazo[2,1-b]thiazoles were not observed.

Keywords: Imines, nucleophilic addition, cyclization, imidazo[2,1-b]thiazoles, sulfonamides

Introduction

Owing to the activated electron-deficient azomethine group in their structures, N-acyl- and N-sulfonyl α-halo imines react efficiently with O-, N-, S-nucleophiles, aromatics and heteroaromatics to afford various functionalized acyclic and heterocyclic amide and sulfonamide derivatives.1-12 Moreover, besides the carbon atom of azomethine group, α-haloimines contain another electrophilic reactive site, namely the carbon atom of the polyhalomethyl group. Thus, these compounds are promising dielectrophiles that can be used as key reagents in the preparation of amidines,7 biologically active amino acids,9 and heterocycles.8,10-12

N-Sulfonyl-substituted phenyldichloroacetaldehydines of the type 1 are key representatives of activated electrophilic imines, that are available through previously developed methods based on free-radical reaction of N,N-dichlorosulfonamides with phenylacetylene (Scheme 1).13,14 Until now, no alternative syntheses to N-(2,2-dichloro-2-phenylethylidene)arenesulfonamides of type 1 have been developed.

The formation of imine 1 is a one-pot free-radical process proceeding via unstable intermediate N-chloro-N-vinyl adducts (see Scheme 1). The reaction is performed under argon in CCl₄. Reagent addition order is important: when N,N-dichloroamide is added to a solution of phenylacetylene, the yields of imines are substantially higher than when the reagents are mixed in the reverse order (90–95 vs. 40–64%). The reaction has an induction period after which it proceeds with notable self-heating. It is important that the reaction mixture is cooled during the exotherm and is heated for 3 h after the exothermic process has been complete. Imine 1 is precipitated upon cooling of the reaction mixture and can be readily separated and used for further synthetic transformations without additional purification.

Imine 1 reacts with nucleophiles on the carbon atom of the activated azomethine groups, and also can act as a dielectrophile, successively involving the azomethine moiety and polyhalomethyl fragment in the process. Based on these reactions, the synthesis of heterocycles, containing the arylsulfonylamide pharmacophore, has been developed. In the present work we have studied the reaction of imine 1 with a range of 2-amino-4,5-diaryl-thiazoles to elaborate a method for the synthesis of sulfonylamino-substituted imidazo[2,1-b]thiazoles.

Worthy of note is that imidazo[2,1-b]thiazoles exhibit a wide range of biological activity. For example, imidazo[2,1-b]thiazoles are inhibitors of acetylcholine esterase and other enzymes, as well as receptor inhibitors. They also demonstrate diuretic, antitumour, antimicrobial, fungicidal and antihelmintic activity.

The most efficient method to obtain imidazo[2,1-b]thiazoles is the conversion of 2-aminothiazole with α-halocarbonyl compounds or propargylbromide (Scheme 2). Imidazo[2,1-b]thiazoles can also be prepared via the reaction of α-halocarbonyl compounds with 2-mercaptoimidazoles. The most promising approach to amino-substituted imidazo[2,1-b]thiazoles is based on multicomponent reactions of 2-aminothiazole, isocyanides, and aldehydes or 2-bromoacetophenone derivatives, aromatic aldehydes, thiourea, and isocyanides (Scheme 2).
Scheme 2. Methods for the preparation of imidazo[2,1-b]thiazoles.\textsuperscript{28,29}

However, with the exception of our previous report,\textsuperscript{11} the literature contains no information on the preparation of N-sulfonylamino-substituted derivatives of imidazo[2,1-b]thiazole.

Results and Discussion

4,5-Diaryl-substituted 2-aminothiazoles 3a and 3b, required for the directed synthesis of the target imidazothiazole derivatives, were prepared according to Scheme 3. The first step was the synthesis of sulfonylimine 1 followed by C-amidoalkylation of anisole or thioanisole. Next, the amidoalkylation products 2a and 2b were reacted with thiourea (Scheme 3). Anisole derivatives 2a and 3a were previously prepared according to this protocol.\textsuperscript{30} The corresponding thioanisole derivatives 2b and 3b were synthesized during the present work and have not been previously described.

C-Amidoalkylation of thioanisole was more difficult than the analogous reaction of anisole. Anisole reacts with imine 1 in the presence of boron trifluoride etherate.\textsuperscript{1} Unfortunately, under the same conditions thioanisole gave no C-amidoalkylation product 2b. Apparently, BF\textsubscript{3} affords a stable, poorly nucleophilic and non-reactive complex with thioanisole.
We have found that compounds 2a and 2b are produced in satisfactory yield in the presence of H$_2$SO$_4$/P$_4$O$_{10}$ mixture. When H$_2$SO$_4$ is employed without P$_4$O$_{10}$ or oleum as a strong acid, the yield of amidooalkylated derivatives 2a and 2b was significantly lower.

The reaction proceeded at room temperature under vigorous stirring. An excess of aromatic substrate contributes to an increased yield of amidooalkylated products 2a and 2b. Substitution was directed to the para-position and the ortho- or meta-isomeric products were not observed.

It can be assumed that, in the presence of H$_2$SO$_4$ or oleum, anisole and thioanisole are deactivated due to sulfonation. However, the H$_2$SO$_4$/P$_4$O$_{10}$ combination was an effective protonating medium that readily promoted the formation for sulfonamidoalkyl cations, key intermediates of C-amidoalkylation; whereas the sulfonation side reaction was probably less favourable in the H$_2$SO$_4$/P$_4$O$_{10}$ mixture.

\[
\begin{align*}
\text{Cl} & \quad \text{SO}_2 \quad \text{N} \quad \text{Ph} \\
& \quad \underset{+}{\text{XMe}}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{SO}_2 \quad \text{H} \quad \text{N} \quad \text{Ph} \\
& \quad \underset{\text{XMe}}{\text{XMe}}
\end{align*}
\]

\[\text{H}_2\text{SO}_4, \text{P}_4\text{O}_{10} \quad \text{CCl}_4, 3-5 \text{h} \]

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{H} & \quad \text{N} \quad \text{S} \quad \text{O}_2 \quad \text{Ph} \\
& \quad \underset{-}{\text{XMe}}
\end{align*}
\]

\[\text{ClCl} \quad \text{XMe} \]

Scheme 3. Synthesis of compounds 2a and 2b, and aminothiazoles 3a and 3b.

4,5-Diaryl-2-aminothiazoles 3a and 3b are probably formed via intermediate chloroaziridines A, followed by the ring-opening accompanied by chlorine migration to furnish isomeric imines B. The latter can exist as the tautomeric enamide C. They are able to give intermediate adduct D with thiourea and heterocyclic derivative E followed by aromatization owing to elimination of the sulfonamide moiety, as shown in Scheme 4.

In the present investigation, we did not isolate intermediate structures A, B, and C. However, the proposed pathway for formation of aminothiazoles 3a and 3b is in agreement with previously published results regarding formation of the similar chloroaziridine from N-[1-(4-methylphenyl)-2-phenyl-2,2-dichloroethyl]-4-chlorobenzenesulfonamide$^7$ and synthesis of enamide C from anisole derivative 2a occurs in the absence of thiourea at room temperature.$^8$
Synthesized compounds 3a and 3b were further investigated in the reaction with imine 1. It has been found that the process results in the formation of previously unknown adducts 4a and 4b (Scheme 5).

Scheme 4. A possible route to the formation of the 2-amino-4,5-diarylthiazoles 3a and 3b.

Scheme 5. Formation of adducts 4a and 4b in the reaction of sulfonylimine 1 with aminothiazoles 3a and 3b, respectively.

Maximum yields of adducts 4a and 4b have been achieved in dioxane. The formation of these adducts occurs without heating in the absence of catalysts and this was tentatively attributed to the high electrophilicity of the activated azomethine group of imine 1.
The formation of adducts 4a and 4b was confirmed by spectroscopic analysis. The $^1$H and $^{13}$C NMR spectra of compounds 4a and 4b were in agreement with the proposed structures. The resonances due to the NH-CH-NH fragment, the double doublet at 6.46-6.48 ppm, corresponding to the CH group, as well as two doublets at 8.17-8.24 and 8.93-8.95 ppm, corresponding to NH groups with a coupling constant of 9.5-9.8 Hz, are symptomatic for these adducts.

Further heterocyclization of compounds 4a and 4b was carried out in the presence of base, but this reaction unexpectedly gave 5-(arylsulfonyl)amino-6-phenylimidazo[2,1-b]thiazoles 5a and 5b, respectively; whereas the anticipated isomeric derivatives, 6-(arylsulphonyl)amino-5-phenylimidazo[2,1-b]thiazoles 6a and 6b, were not observed (Scheme 6).

NaOH in dioxane was the most efficient combination for the preparation of compounds 5a and 5b via a two-stage one-pot method without isolation of intermediate adducts 4a and 4b (Scheme 7).

**Scheme 6.** Heterocyclization of adducts 4 into 5-sulfonylaminoimidazo[2,1-b]thiazoles 5.

**Scheme 7.** Two-stage one-pot synthesis of imidazo[2,1-b]thiazoles 5a and 5b.
A possible reaction pathway leading to the formation of compounds 5 involves heterocyclization of adducts 4 into intermediate imidazothiazoles 6, which undergo further isomerization into the final compounds according to the Dimroth rearrangement (Scheme 8).


To rationalize the selective formation of the 5-amino-substituted derivatives 5, ab initio and DFT methods were used to model the structures 5 and 6 (Table 1 and 2), and the relative energies of the 5- and 6-amino-substituted derivatives was estimated.

With an unsubstituted amino group in the imidazothiazole structure (Table 1, entries 1 and 4), the 6-amino isomer was energetically preferred by 2.8-3.2 kcal/mol. However, with a strong electron-withdrawing substituent at the exocyclic nitrogen atom, the energy difference between the isomers either disappeared (according to MP2, Table 1, entries 2 and 3) or was inversed (according to B3LYP, Table 1, entries 5 and 6).

Bearing in mind that N-sulfonyl-substituted aminoimidazothiazoles are potent NH-acids, and the reaction was carried out in the presence of strong base (NaOH), it was logical to suggest that in the reaction mixtures the products existed as their corresponding anions. Modeling the corresponding anions (Table 2) showed that 5-sulfonylamino-substituted imidazothiazoles were significantly preferred (6-8 kcal/mol), compared to 6-substituted isomers.
Table 1. Relative energies of neutral molecules in gas phase at completely optimized geometries, kcal/mol

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R^1</th>
<th>R^2</th>
<th>6-amino isomer</th>
<th>5-amino isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R-S-N=N-NHR^1</td>
<td>R-S-N=NHR^1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

MP2/6-311+G(d,p)^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R^1</th>
<th>R^2</th>
<th>6-amino isomer</th>
<th>5-amino isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>0</td>
<td>2.81</td>
</tr>
<tr>
<td>2</td>
<td>4-OMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>Ph</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4-SMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>Ph</td>
<td>0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

B3LYP/6-311+G(d,p) + ZPE^b

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R^1</th>
<th>R^2</th>
<th>6-amino isomer</th>
<th>5-amino isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>0</td>
<td>3.26</td>
</tr>
<tr>
<td>5</td>
<td>4-OMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>Ph</td>
<td>2.56</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>4-SMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>Ph</td>
<td>2.55</td>
<td>0</td>
</tr>
</tbody>
</table>

^a MP2 calculations were performed using the Firefly QC package\(^{31}\) which is partially based on Gamess US source code.\(^{32}\)

^b DFT calculations were performed using the Gaussian 09 program package.\(^{33}\)

Table 2. Relative energies of anions in gas phase at completely optimized geometries, kcal/mol

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R^2</th>
<th>6-amino isomer</th>
<th>5-amino isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>R-S-N=N-NR^1</td>
<td>R-S-N=NNR^1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

MP2/6-311+G(d,p)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R^2</th>
<th>6-amino isomer</th>
<th>5-amino isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-OMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>7.92</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4-SMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>8.11</td>
<td>0</td>
</tr>
</tbody>
</table>

B3LYP/6-311+G(d,p) + ZPE

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R^2</th>
<th>6-amino isomer</th>
<th>5-amino isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4-OMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>5.71</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>4-SMeC_6H_4</td>
<td>4-ClC_6H_4SO_2</td>
<td>5.68</td>
<td>0</td>
</tr>
</tbody>
</table>

Taking into account the structures of 5a and 5b obtained by MP2 calculations, one can see that sulfonamide aryl group and the 6-aryl substituent of the imidazothiazole are positioned one
above the other in almost parallel planes with a distance of 3.1-3.2 Å between them, resulting from intramolecular \( \pi \) stacking. We analysed structure 5a by AIMALL program\(^{34} \) according to Bader’s quantum theory of atoms in molecules.\(^{35} \) The wavefunction for the AIM analysis was obtained using a Gaussian\(^{33} \) program at the MP2/6-311++G** level. Fortuitously, we were able to identify 7 critical points located between the benzene rings (2 bond-critical points with electronic density \( \rho(r) = 7.8*10^{-3} \) and \( 1.0*10^{-2} \); 3 ring-critical points \( \rho(r) = 6.1*10^{-3}, 5.4*10^{-3}, 5.1*10^{-3} \) and 2 cage-critical points \( \rho(r) = 4.7*10^{-3} \) and \( 5.0*10^{-3} \)). The electronic density \( \rho(r) \) values suggested the presence of orienting intramolecular bonding and corresponded to typical aromatic non-covalent interactions.\(^{36,37} \) These conclusions were experimentally supported by XRD analysis (Figure 1).

It should be noted that the structure of 5a, derived by the MP2 method, corresponded best with the SAR data.

![Figure 1. Thermal ellipsoid plot for compound 5a (50% probability contours).](image)

The structure of imidazo[2,1-b]thiazole 5a was unequivocally supported by single crystal X-ray crystallographic analysis (Fig. 1) and confirmed our conclusions from the spectroscopic data. In the crystal structure of 5a, the molecule associated with a solvent molecule. The benzene ring in the position 6 and the aromatic ring of arylsulfonyl group were substantially parallel, and the distance between them at 3.53 Å indicated intramolecular \( \pi \)-stacking between the aromatic fragments.

For molecules of 5 and 6 or their amide anions, the calculation of charge distribution obtained by AIM showed that C-3 carbon atom has a moderate positive charge (~+0.4 and ~+0.5 for neutral molecules and sulfonamide anions, correspondingly). This data could suggest the reaction path including possible nucleophilic attack of hydroxyl anion on C-3 atom of imidazothiazole ring followed by the Dimroth rearrangement (Scheme 8). At the same time, the
reaction path, presented in the scheme 8, is not proved to the full extent. Although Dimroth type isomerization is described for a range of heterocyclic compounds, similar transformations are not typical for 1,3-thiazole fragments. Therefore, further investigation of a possible reaction path is needed.

Experimental Section

**General.** Compound 3a was synthesized according to the previously developed method. 1H, 13C NMR spectra were recorded on a Bruker DPX-400 spectrometer (400.61, 100.13 MHz, respectively) with TMS as an internal standard. IR spectra were recorded on a Bruker IFS-25 instrument on KBr discs. Crystal data were collected on a Bruker D8 Venture diffractometer with MoKα radiation (λ = 0.71073) using the θ and ω scans. The structure was solved and refined by direct methods using the SHELX program. Data were corrected for absorption effects using the multi-scan method (SADABS). Non-hydrogen atoms were refined anisotropically using SHELX. For details of the data collection and the structure solution and refinement, see Supplementary data. CCDC 996956 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

**4-Chloro-N-[2,2-dichloro-1-[4-(methoxy)phenyl]-2-phenylethyl]benzenesulfonamide (2a).** Imine 1 (3.63 g, 10 mmol), anisole (5 mL), and CHCl₃ (15 mL) were stirred in the presence of concentrated sulfuric acid (0.3 mL) and P₄O₁₀ (0.36 g) for 3 h. The excess of anisole and CHCl₃ was evaporated. Then aqueous ammonia solution (30%, 15 mL) was carefully added to the acidic residue. The reaction mass was mixed and the precipitate obtained was filtered off, washed with water, dried and recrystallized. Colorless plates, yield 4.38 g, 93%, mp 91-92 °C (from benzene); IR (νmax, cm⁻¹): 1160, 1320 (SO₂), 3240 (NH) cm⁻¹. 1H NMR (400.61 MHz, DMSO-d₆): δ 3.69 (3H, s), 5.45 (1H, d 3JCHNH 9.5 Hz), 6.68-6.74 (2H, m), 6.94-6.97 (4H, m), 7.03-7.07 (2H, m), 7.10-7.14 (1H, m), 7.34-7.40 (2H, m), 7.55-7.61 (2H, m), 8.89 (1H, d, 3JCHNH 9.5 Hz). 13C NMR (100.13 MHz, DMSO-d₆): δ 55.1, 79.9, 91.1 113.7, 126.8, 128.1, 128.4, 129.1, 130.2, 130.3, 131.1, 131.9, 135.5, 140.0, 159.1. Anal. Calcd. for C₂₁H₁₈Cl₃NO₃S (471): C, 53.58; H, 3.85; N, 2.98; S 6.81%. Found: C, 52.96; H, 3.83; N, 2.91; S, 6.78%.

**4-Chloro-N-[2,2-dichloro-1-[4-(methylsulfanyl)phenyl]-2-phenylethyl]benzenesulfonamide (2b).** Compound 2b was obtained according to the above method from imine 1 (3.63 g, 10 mmol) and thioanisole (5 mL). The reaction time was 5 h. Colorless plates, yield 4.48 g, 92%, mp 115-117 °C (from benzene); IR (νmax, cm⁻¹): 1167, 1344 (SO₂), 3200 (NH) cm⁻¹. 1H NMR (400.61 MHz, DMSO-d₆): δ 2.37 (3H, s), 5.16 (1H, d 3JCHNH 9.6 Hz), 6.81-6.85 (2H, m), 6.95-6.96 (2H, m), 7.25-7.28 (2H, m), 7.30-7.33 (1H, m), 7.35-7.39 (2H, m), 7.42-7.46 (2H, m), 7.58-7.64 (2H, m), 8.86 (1H, d, 3JCHNH 9.6 Hz). 13C NMR (100.13 MHz, DMSO-d₆): δ 15.8, 72.4, 98.4, 126.0, 127.3, 128.2, 128.5, 128.7, 129.7, 129.9, 130.3, 131.5, 137.25 137.33, 138.4. Anal.
Calcd. for C_{21}H_{18}Cl_{3}NO_{2}S_{2} (487): C, 51.81; H, 3.73; N, 2.88; S 13.17%. Found: C, 52.06; H, 3.75; N, 2.71; S, 13.48%.

**Synthesis of 5-[4-(methylsulfanyl)phenyl]-4-phenyl-1,3-thiazol-2-amine (3b).** The compound 2b (0.97 g, 2 mmol), thiourea (0.76 g, 10 mmol) and Na_{2}CO_{3} (0.85 g, 8 mmol) were stirred at 100 °C for 5 h in DMF (15 mL). The reaction mixture was poured into water (30-40 mL), the precipitate was separated, dried, washed with 10% aqueous ammonia solution (50 mL). Colorless powder, yield 0.51 g, 87%, mp 93-94 °C (precipitate); IR (ν_{max}, cm^{-1}): 1631 (C=N), 3409-3275 (NH) cm^{-1}. 1H NMR (400.61 MHz, DMSO-d_{6}): δ 2.44 (3H, s), 7.11-7.17 (6H, m), 7.22-7.28 (3H, m), 7.37-7.41 (2H, m). 13C NMR (100.13 MHz, DMSO-d_{6}): δ 14.4, 118.6, 125.9, 127.2, 128.0, 128.4, 129.1, 129.3, 135.4, 136.9, 144.8, 165.9. Anal. Calcd. for C_{16}H_{14}N_{2}S_{2} (298): C, 64.39; H, 4.73; N, 9.39; S 21.49%. Found: C, 63.72; H, 4.62; N, 9.41; S, 21.58%.

**General procedure for the synthesis of adducts 4a,b.** Imine 1 (0.72 g, 2 mmol) and aminothiazole 2a (0.50 g, 2 mmol) were stirred in 1,4-dioxane (10 mL) at r.t. for 4 h. Then the reaction mass was mixed with water (50 mL), the precipitate was filtered off, washed with ether and dried.

**4-Chloro-N-{2,2-dichloro-1-[5-(4-methoxyphenyl)-4-phenyl-1,3-thiazol-2-ylamino]-2-phenylethyl}benzenesulfonamide (4a).** Colorless powder, yield 1.00 g, 86%, mp 142-144 °C (precipitate); IR (ν_{max}, cm^{-1}): 1163, 1339 (SO_{2}), 1610 (C=N), 3382-3238 (NH) cm^{-1}. 1H NMR (400.61 MHz, DMSO-d_{6}): δ 3.74 (3H, s), 6.48 (1H, dd, 3J_{CHNH} 9.5 Hz, 3J_{CHNH} 9.6 Hz), 6.81-6.94 (2H, m), 7.03-7.15 (2H, m), 7.15-7.44 (10H, m), 7.60-7.68 (2H, m), 7.73-7.83 (2H, m), 8.17 (1H, d, 3J_{CHNH} 9.5 Hz), 8.93 (1H, d, 3J_{CHNH} 9.6 Hz). 13C NMR (100.13 MHz, DMSO-d_{6}): δ 55.0, 71.2, 94.5, 102.7, 114.1, 124.2, 126.9, 127.0, 127.9, 128.0, 128.1, 128.2, 129.1, 129.3, 130.4, 135.1, 136.8, 139.1, 140.0, 142.4, 158.6, 162.8. Anal. Calcd. for C_{30}H_{24}Cl_{3}N_{3}O_{3}S_{2} (645): C, 55.86; H, 3.75; N, 6.51; S, 9.94%. Found: C, 54.56; H, 3.69; N, 6.58; S, 9.52%.

**4-Chloro-N-{2,2-dichloro-1-[5-(4-(methylsulfanyl)phenyl)-4-phenyl-1,3-thiazol-2-ylamino]-2-phenylethyl}benzenesulfonamide (4b).** Yellow powder, yield 0.97 g, 82%, mp 91-93 °C (precipitate); IR (ν_{max}, cm^{-1}): 1168, 1342 (SO_{2}), 1586 (C=N), 3247-3292 (NH) cm^{-1}. 1H NMR (400.61 MHz, DMSO-d_{6}): δ 2.45 (3H, s), 6.46 (1H, dd, 3J_{CHNH} 9.5 Hz, 3J_{CHNH} 9.6 Hz), 6.70-6.78 (2H, m), 7.37-7.41 (2H, m), 7.73-7.83 (2H, m), 8.17 (1H, d, 3J_{CHNH} 9.5 Hz), 8.93 (1H, d, 3J_{CHNH} 9.6 Hz). 13C NMR (100.13 MHz, DMSO-d_{6}): δ 14.4, 118.6, 125.8, 126.9, 127.3, 127.6, 128.0, 128.1, 128.2, 128.3, 128.6, 129.0, 129.5, 134.9, 136.9, 137.5, 139.1, 140.0, 143.1, 163.2. Anal. Calcd. for C_{30}H_{24}Cl_{3}N_{3}O_{3}S_{3} (661): C, 54.5; H, 3.66; N, 6.36; S, 14.55%. Found: C, 53.6; H, 3.59; N, 6.28; S, 14.63%.

**General procedure for the synthesis of imidazo[2,1-b][1,3]thiazols 5a,b.**

**Method A.** Compound 4a or 4b (1 mmol) and NaOH (0.15 g, 3.5 mmol) were stirred in 1,4-dioxane (10 mL) for 5 h. The reaction mass was mixed with water (30 mL) and 10% hydrochloric acid was added to neutralize it. The precipitate was filtered off, dried and washed with ether.
Method B. Imine 1 (0.72 g, 2 mmol), aminothiazole 3a or 3b (2 mmol) were stirred in 1,4-dioxane (10 mL) for 4 h. Then NaOH (0.29 g, 7.2 mmol) and 1.4-dioxane (10 mL) were added and the reaction mixture was stirred for 5 h. The reaction mass was mixed with water (50 mL) and 10% hydrochloric acid was added to neutralize it. The precipitate was filtered off, dried and washed with ether.

4-Chloro-N-[2-(4-methoxyphenyl)-3,6-diphenylimidazo[2,1-b][1,3]thiazol-5-yl]benzenesulfonamide (5a). Coloured powder, yield 0.43 g, 75% (method A) and 0.65 g, 63% (method B), mp 194-196 °C (precipitate); IR (νmax, cm⁻¹): 1172, 1342 (SO₂), 1601 (C=N) cm⁻¹. ¹H NMR (400.61 MHz, DMSO-d₆): δ 3.73 (3H, s), 6.84-6.90 (2H, m), 7.15-7.20 (4H, m), 7.38-7.46 (7H, m), 6.99-7.08 (5H, m), 10.08 (1H, s). ¹³C NMR (100.13 MHz, DMSO-d₆): δ 56.5, 114.4, 115.8, 115.9, 123.2, 125.3, 126.6, 127.8, 128.1, 128.27, 128.29, 128.4, 128.7, 129.3, 130.5, 131.6, 132.7, 137.6, 139.4, 141.9, 145.3 159.5. Anal. Calcd. for C₃₀H₂₂ClN₃O₃S₂ (572): C, 62.98; H, 3.88; N, 7.34; S, 11.21%. Found: C, 61.30; H, 3.81; N, 7.23; S, 11.32%.

4-Chloro-N-[2-[4-(methylsulfanyl)phenyl]-3,6-diphenylimidazo[2,1-b][1,3]thiazol-5-yl]benzenesulfonamide (5b). Yellow powder, yield 0.41 g, 70% (method A) and 0.65 g, 61% (method B), mp 188-190 °C (precipitate); IR (νmax, cm⁻¹): 1162, 1339 (SO₂), 1596 (C=N) cm⁻¹. ¹H NMR (400.61 MHz, DMSO-d₆): δ 2.44 (3H, s), 6.99-7.08 (5H, m), 7.13-7.20 (7H, m), 7.35-7.40 (2H, m), 7.44-7.52 (4H, m), 10.10 (1H, s). ¹³C NMR (100.13 MHz, DMSO-d₆): δ 14.2, 114.2, 115.9, 124.9, 125.7, 126.6, 127.2, 127.8, 127.9, 128.1, 128.3, 128.7, 128.8, 129.4, 131.45, 131.47, 132.6, 137.5, 139.3, 139.4, 141.9, 145.2. Anal. Calcd. for C₃₀H₂₂ClN₃O₂S₃ (588): C, 61.26; H, 3.77; N, 7.14; S 16.36%. Found: C, 60.06; H, 3.72; N, 7.09; S, 16.45%.

Acknowledgements

Spectroscopic and analytical data were obtained using instrumentation in the Baykal Analytical Center for Collective Use SB RAS.

References


http://dx.doi.org/10.1002/jcc.540141112


34. Keith, T. A. AIMAll (Version 15.05.18). TK Gristmill Software, Overland Park KS, USA, 2015 (aim.tkgristmill.com)


http://dx.doi.org/10.1016/j.comptc.2012.06.004

http://dx.doi.org/10.1002/jcc.21162

http://dx.doi.org/10.1016/S0065-2725(10)01005-6

http://dx.doi.org/10.1107/S0108767707043930