Aniline Exchange of 2-Aryl-4,5-diphenyl-substituted Isothiazolium Salts

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Dedicated to Professor Dr. Klaus Hafner on the occasion of his 80th birthday

4,5-Diphenyl-substituted N-(R1-aryl)-isothiazolium salts 4 react with anilines 2 (R2) to form 4,5-disubstituted N-(R2-aryl)-isothiazolium salts 4. The influence of donor and acceptor substituents in the N-aryl ring of 4 and in the anilines 2 on the course of the exchange was studied. The structure of the salts 4 was confirmed by a crystal structure determination of 4i.

Key words: 4,5-Diphenyl-isothiazolium Salts, Aniline Exchange

Introduction

The reactivity of isothiazolium salts toward nucleophiles is higher than that of isothiazoles. As a consequence, the tendency of nucleophilic ring cleavage by quaternization of isothiazoles increases [1].

Isothiazolium salts are characterized by a high synthetic potential [1]. Therefore, they react with N-nucleophiles like ammonia, primary amines, hydrazines and hydroxylamines by ring transformation and with retention of the ring size to isothiazoles, pyrazoles and oxazoles [2,3]. The synthesis of 3-aminopyrroles by ring transformation of substituted 5-aminoisothiazolium salts has been investigated [4]. N-Aryl-isothiazolium salts with an active methyl or methylene group in 5-position of the isothiazole ring rearrange in a base-induced reaction with secondary amines such as DCHA by deprotonation and oxidative dimerization to thieno-annulated N-aryl-6aλ4-thia-1,6-diazapentalenes [5 – 9], spirocyclic isothiazolium salts [10,11] and thianthrene derivatives [10]. In contrast, weaker bases, such as substituted anilines, compete due to their basicity and nucleophilicity in the reaction with N-aryl-4,5-dialkyl-isothiazolium salts. Thus, ring transformation occurs by nucleophilic attack of aniline at the 5-position inducing virtually a migration of the sulfur atom to the 3-position of the ring and elimination of aniline. The reaction of 5-methyl- or methylene-substituted salts 1 with anilines 2 (R2) thus gives rearranged, 3,4-disubstituted salts 3 (R1) (Scheme 1) [1,12].

Here, we report on our studies of the reaction of 5-phenyl-isothiazolium salts 4 (R1) with substituted anilines 2 (R2).

Results and Discussion

The isothiazolium salts 4 were conveniently synthesized by intramolecular cyclocondensation of β-thiocyanatovinyl aldehydes and anilines 2 in the presence of perchloric and glacial acetic acid [8]. The substituents of the 2-aryl ring (R2/R2) were graded according to the pKa value of the corresponding anilinium ions.

We have investigated the reaction of these 4,5-diphenyl-isothiazolium salts 4 (R1) with various substituted anilines 2 (R2) in the presence of methanol (50 °C, 22 h). After purification and isolation the new isothiazolium salts 4 (R2) were received. Interestingly,
all 5-phenyl-isothiazolium salts 4 (R^1) react exclusively by aniline exchange to give salts 4 with R^2 in the N-aryl ring and in no case by ring transformation and exchange of aniline to 3,4-diphenylisothiazolium salts 5 (Scheme 2), observed previously for 5-methyl- or methylen-substituted salts (see Scheme 1) [12].

Further, we studied the influence of substituents in the N-aryl ring of salts 4. In previous studies, Noack [13] found that the reaction of acceptor-substituted salts 1 (R = CH_3, R^1 = 4-Cl, 4-Br) with donor-substituted anilines 2 (R^2 = 4-CH_3, 4-OCH_3) always yields salts 3 bearing an electron-donating substituent R^2 after ring transformation and exchange of the aniline moiety. Similar results could also be expected for the aniline exchange of 4,5-diphenyl-isothiazolium salts 4.

Therefore, the acceptor-substituted salts 4a [14], b [15] and 4d [16] (R^1) were reacted with donor-substituted anilines 2f, g, i in alcohol (Table 1). Not surprisingly, the salts 4a, b, c (R^1) were converted by exchange of aniline to isothiazolium salts 4f, g and 4i [17] (R^2) in good yields (55 – 73 %). Compared to the conventional synthesis of the donor-substituted salts 4f, g and 4i [17] (31 – 42 %) by intramolecular cyclocondensation of β-thiocyanatovinyl aldehydes with anilines 2, the transformation of acceptor-substituted salts 4 by aniline exchange is a good alternative method to receive salts 4f, g and 4i in improved yields.

It should be noted that in all transformations reported here, in salt 4, e.g. 4a [14] (R^1 = 2-NO_2), the aniline group present in the precursor was displaced by a more strongly basic aniline 2, e.g. 2g (R^2 = 2-OCH_3), to form the salt 4g (R^2).

The mechanism of aniline exchange could be explained by the nucleophilic attack of the aniline 2 (R^2) at the C-3 carbon atom of the isothiazolium ring to form the intermediate 6, followed by S–N ring cleavage resulting in the acyclic species 7. After elimination of aniline 2 (R^1) and nucleophilic N→S cyclization the aniline exchanged salt 4 (R^2) is obtained (Scheme 3) [3]. In another possible pathway of this transformation, the aniline 2 (R^2) undergoes nucleophilic attack at the sulfur atom of salt 4 (R^1) to form 7 by ring cleavage. After cyclization to give the intermediate 6 and elimination of aniline 2 (R^1) from the C-3 position of the isothiazole the salt 4 (R^2) is obtained [2].

Further, we studied the reaction of acceptor-substituted salts 4a [14], b [15], c, d [16], e with the unsubstituted aniline 2h (R^2 = H). The results are presented in Table 2. In all of these cases, the transformation by aniline exchange gave the unsubstituted salt 4h [17] in good to high yields (62 – 93 %).

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**Scheme 2. Reaction of 4,5-diphenyl-isothiazolium salts 4 with anilines 2.**

**Table 1. Aniline exchange of salts 4a, b, d.**

<table>
<thead>
<tr>
<th>Educt 4</th>
<th>Aniline 2</th>
<th>Product 4 (R^1)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a [14]</td>
<td>g R^2 = 2-OCH_3</td>
<td>4g</td>
<td>73</td>
</tr>
<tr>
<td>b [15]</td>
<td>i R^2 = 4-OCH_3</td>
<td>4i [17]</td>
<td>58</td>
</tr>
<tr>
<td>d [16]</td>
<td>f R^2 = 3-OCH_3</td>
<td>4f</td>
<td>55</td>
</tr>
</tbody>
</table>

**Table 2. Aniline exchange of salts 4a–e.**

<table>
<thead>
<tr>
<th>Educt 4</th>
<th>Aniline 2</th>
<th>Product 4</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a [14]</td>
<td>h R^2 = H</td>
<td>h [17] R^2 = H</td>
<td>89</td>
</tr>
<tr>
<td>b [15]</td>
<td>h R^2 = H</td>
<td>h [17] R^2 = H</td>
<td>91</td>
</tr>
<tr>
<td>e [16]</td>
<td>h R^2 = H</td>
<td>h [17] R^2 = H</td>
<td>91</td>
</tr>
<tr>
<td>e [16]</td>
<td>h R^2 = H</td>
<td>h [17] R^2 = H</td>
<td>93</td>
</tr>
</tbody>
</table>
We also investigated the conversion of isothiazolium salt 4h [17] (R1 = H) with substituted anilines 2a–e (R2). As expected, in no cases an aniline-exchanged salts 4a–e (R2) could be obtained, and the starting salt 4h (R1 = H) was recovered.

All synthesized isothiazolium salts were characterized after the ring transformation by 1H, 13C and IR spectroscopy as well as mass spectrometry (see Experimental Section). The structure of the aniline-exchanged isothiazolium salt 4i (R2 = 4-CH3) was confirmed by a crystal structure determination. The structure of the cation of 4i is presented in Fig. 1, and the crystallographic data are given in the Experimental Section.

In summary, the reaction of 4,5-diphenyl-isothiazolium salts 4 (R1) with various substituted anilines 2 (R2) gives the salts 4 with R2 by exchange and elimination of aniline 2 (R1). We have developed an useful method for the synthesis of donor-substituted salts 4f, g and 4i [17]. The aniline exchange proposed for the 3,4-diphenyl salts 5, was confirmed by an X-ray structure determination of 4i. This rules out any ring transformation which was encountered with 4,5-dialkyl-isothiazolium salts 1.
Experimental Section

General

M.p.: Boetius micro melting point apparatus; corrected. IR spectra: Genesis FTIR Unicum Analytical System (ATI Mattson); KBr pellets. 1H and 13C NMR spectra: Varian Gemini-300 and Bruker Avance DRX-400; δ in ppm rel. to Si(CH3)4 as internal standard. MS: Quadrupole-MS VG 12-250; 70 eV. Elemental analyses: Heraeus CHNO Rapid Analyzer.

General procedure for the preparation of salts 4

The new salts 4c, e, f, g were prepared according to a literature procedure [8]. Compounds 4a [14], 4b [15], 4d [16], 4h [17] and 4i [17] have been described elsewhere.

2-(4-Methylsulfonylphenyl)-4,5-diphenylisothiazolium perchlorate (4e)

Yield: 59 %, m. p. 219 – 223 °C. – IR (KBr): ν = 1083 s (ClO4), 1226 s (SO2CH3), 1358 s (ClO4), 1431 s (SO2CH3), 1582 s (SO2CH3). – 1H NMR ([D6]DMSO): δ = 3.36 (s, 3H, OCH3), 7.24 – 7.62 (m, 14H, arom. H), 7.69 – 7.73 (m, 10H, arom. H), 7.64 (d, J = 6.8 Hz, 1H, arom. H). – 13C NMR ([D6]DMSO): δ = 52.7 (CO2CH3), 123.3, 125.8 (C-4), 128.3, 129.1, 129.4, 129.6, 131.3, 132.0, 132.3 (C-4CO2CH3), 135.5, 139.9, 157.7 (C-3), 165.0 (CO2CH3), 166.3 (C-5). – ESI-MS: m/z = 372.1 [M+ClO4]+. – C22H18ClNO5S (471.92): calcd. C 56.76, H 3.90, N 3.26, S 7.24; found C 56.76, H 3.97, N 3.26, S 7.22.

2-(3-Methoxyphenyl)-4,5-diphenylisothiazolium perchlorate (4f)


2-(2-Methoxyphenyl)-4,5-diphenylisothiazolium perchlorate (4g)

Yield: 32 %, m. p. 164 – 168 °C. – IR (KBr): ν = 1093 s (ClO4), 1226 s (SO2CH3), 1358 s (ClO4), 1431 s (SO2CH3), 1582 s (SO2CH3). – 1H NMR ([D6]DMSO): δ = 4.03 (s, 3H, OCH3), 7.28 – 7.31 (t, 1H, arom. H), 7.48 – 7.58 (m, 10H, arom. H), 7.64 (d, J = 6.8 Hz, 1H, arom. H). – 13C NMR ([D6]DMSO): δ = 56.8 (OCH3), 113.7, 121.4, 125.2 (C-4), 125.8, 126.4, 128.7, 129.1, 129.4, 129.6, 129.9, 129.6, 132.1, 133.0, 134.1, 151.8 (C-OCH3), 159.0 (C-3), 166.4 (C-5). – ESI-MS: m/z = 344.1 [M+ClO4]+. – C22H18ClNO5S (443.91): calcd. C 59.63, H 4.09, N 3.16, S 7.22; found C 59.88, H 3.95, N 3.17, S 6.99.

Crystal structure determination of 4i

C22H18ClNO5S, Mw = 443.88, T = 213(2) K. Suitable single crystals were obtained from ethanol. Crystal size: 0.20 × 0.20 × 0.10 mm3; monoclinic crystal system, space group P21/c, a = 11.567(2), b = 21.210(4), c = 16.877(3) Å, β = 91.51(2)°, V = 4139.1(13) Å3, Z = 8, ρcalc = 1.425 g cm−3, μ(MoKα) = 0.32 mm−1. The intensities were measured on a Stoe IPDS1 diffractometer with graphite-monochromatized MoKα radiation (λ = 0.71073 Å). θ range for data collection: 2.27 – 27.94°, index ranges −15 ≤ h ≤ 15, −27 ≤ k ≤ 26, −22 ≤ l ≤ 22. Reflections collected: 32992, independent reflections: 9824 [R(int) = 0.090], transmission (max./min.): 0.997/0.939. The structure was solved with Direct Methods and refined with full-matrix least-squares on F2 (SHELXS/L-97 [18]). Data/parameters: 9824/541. Final R1/wR2 [I ≥ 2σ(I)]: 0.074/0.187, Final R1/wR2 (all data): 0.163/0.211; largest peak/holes in final difference map: 0.62/−0.53 e Å−3.

CCDC 678529 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.


