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

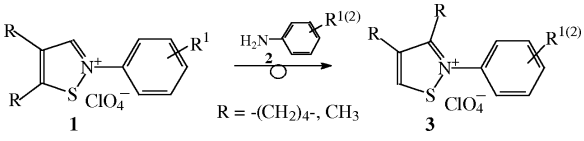
4,5-Diphenyl-substituted *N*-(R^1-aryl)-isothiazolium salts **4** react with anilines **2** (R^2) to form 4,5-disubstituted *N*-(R^2-aryl)-isothiazolium salts **4**. The influence of donor and acceptor substituents in the *N*-aryl ring of **4** and in the anilines **2** on the course of the exchange 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 substiuted 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-6aλ^4-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 methylen-substituted salts **1** with anilines **2** (R^1) thus gives rearranged 3,4-disubstituted salts **3** (R^1) (Scheme 1) [1, 12].



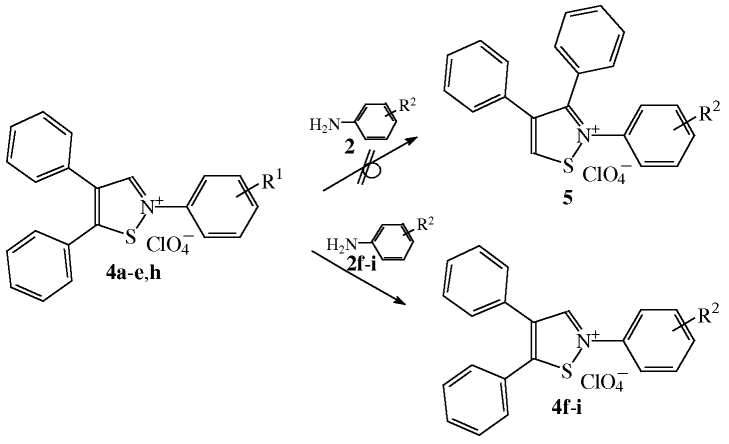
Scheme 1. Reaction of 4,5-dialkyl-isothiazolium salts **1** with anilines **2**.

Here, we report on our studies of the reaction of 5-phenyl-isothiazolium salts **4** (R^1) with substituted anilines **2** (R^2).

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 (R^1/R^2) were graded according to the pK_a value of the corresponding anilinium ions.

We have investigated the reaction of these 4,5-diphenyl-isothiazolium salts **4** (R^1) with various substituted anilines **2** (R^2) in the presence of methanol (50 °C, 22 h). After purification and isolation the new isothiazolium salts **4** (R^2) were received. Interestingly,



2/4/5	R^1/R^2
a	2-NO_2
b	4-NO_2
c	4-SO_2CH_3
d	3-NO_2
e	4-CO_2CH_3
f	3-OCH_3
g	2-OCH_3
h	H
i	4-OCH_3

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

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).

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

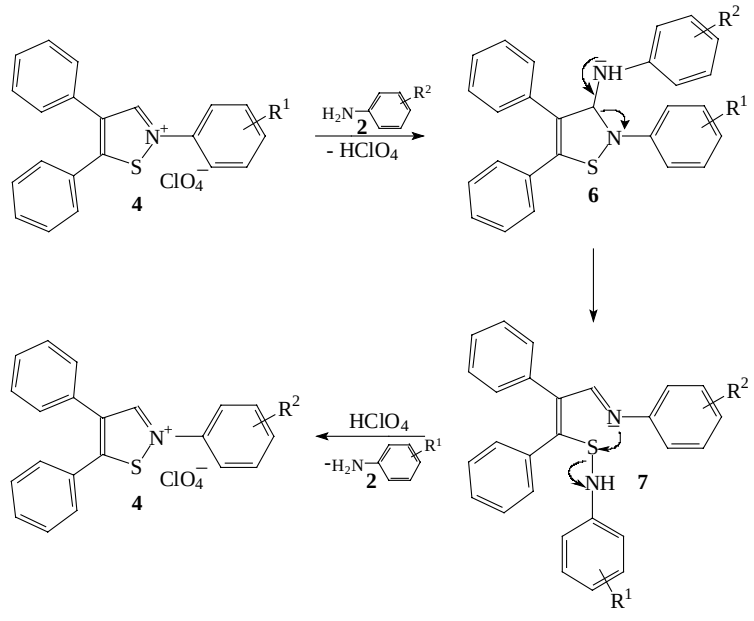
Educt **4**	Aniline **2**	Product **4** (R^2)	Yield (%)
a [14] (R^1 = 2-NO_2)	**g** (R^2 = 2-OCH_3)	**4g**	73
b [15] (R^1 = 4-NO_2)	**i** (R^2 = 4-OCH_3)	**4i** [17]	58
d [16] (R^1 = 3-NO_2)	**f** (R^2 = 3-OCH_3)	**4f**	55

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

Educt **4**	Aniline **2**	Product **4**	Yield [%]
a [14] (R^1 = 2-NO_2)	**h** (R^2 = H)	**h** [17] (R^2 = H)	89
b [15] (R^1 = 4-NO_2)	**h** (R^2 = H)	**h** [17] (R^2 = H)	91
c (R^1 = 4-SO_2CH_3)	**h** (R^2 = H)	**h** [17] (R^2 = H)	62
d [16] (R^1 = 3-NO_2)	**h** (R^2 = H)	**h** [17] (R^2 = H)	91
e (R^1 = 4-CO_2CH_3)	**h** (R^2 = H)	**h** [17] (R^2 = H)	93

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 %).



Scheme 3. Proposed mechanism of aniline exchange of 4,5-diphenyl-isothiazolium salts **4**.

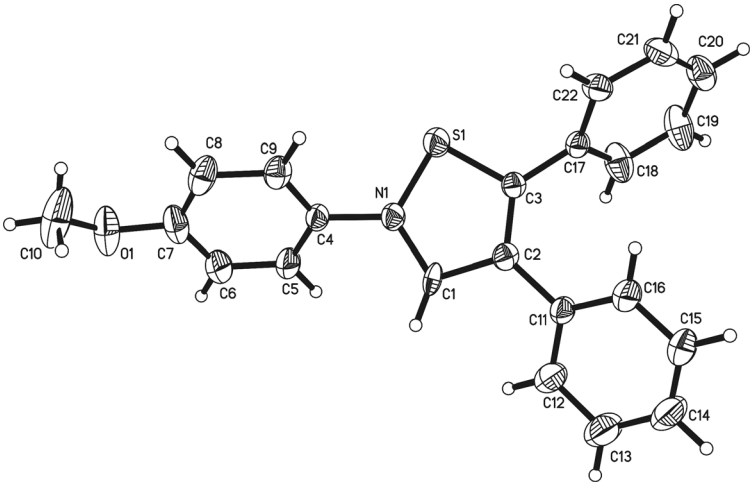


Fig. 1. Molecular structure of the 2-(4-methoxyphenyl)-4,5-diphenylisothiazolium cation of **4i** in the crystal.

We also investigated the conversion of isothiazolium salt **4h** [17] (R^1 = H) with substituted anilines **2a – e** (R^2). As expected, in no cases an aniline-exchanged salts **4a – e** (R^2) could be obtained, and the starting salt **4h** (R^1 = H) was recovered.

All synthesized isothiazolium salts were characterized after the ring transformation by ^{1}H, ^{13}C and IR spectroscopy as well as mass spectrometry (see Experimetal Section). The structure of the aniline-exchanged isothiazolium salt **4i** (R^2 = 4-OCH_3) 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** (R^1) with various substituted anilines **2** (R^2) gives the salts **4** with R^2 by exchange and elimination of aniline **2** (R^1). 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 Unicam Analytical System (ATI Mattson); KBr pellets. ^{1}H and ^{13}C NMR spectra: Varian Gemini-300 and Bruker Avance DRX-400; δ in ppm rel. to $Si(CH_3)_4$ 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 (**4c**)*

Yield: 59 %, m. p. 219 – 223 °C. – IR (KBr): ν = 1089 s (ClO_4), 1152 s (SO_2CH_3), 1299 s (SO_2CH_3) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.36 (s, 3H, SO_2CH_3), 7.44 – 7.64 (m, 10H, arom. H), 8.26 – 8.33 (m, 4H, arom. H), 10.08 (s, 1H, 3-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 43.2 (SO_2CH_3), 124.5, 125.8 (C-4), 128.7, 128.8, 129.2, 129.4, 129.4, 129.6, 129.7, 132.3, 135.5, 140.1 (*C*-SO_2CH_3), 143.1, 158.0 (C-3), 166.7 (C-5). – ESI-MS: *m/z* = 392.1 [M–ClO_4]$^+$. – $C_{22}H_{18}ClNO_6S_2$ (491.97): calcd. C 53.71, H 3.69, N 2.85, S 13.04; found C 53.66, H 3.63, N 2.99, S 13.25.

*2-(4-Methoxycarbonylphenyl)-4,5-diphenylisothiazolium perchlorate (**4e**)*

Yield: 49 %, m. p. 199 – 203 °C. – IR (KBr): ν = 1087 s (ClO_4), 1286 s (CO_2CH_3), 1720 s (C=O) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.93 (s, 3H, CO_2CH_3), 7.46 – 7.66 (m, 10H, arom. H), 8.19, 8.31 (2 d, *J* = 8.7 Hz, 4H, arom. H), 10.10 (s, 1H, 3-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 52.7 (CO_2CH_3), 123.3, 125.8 (C-4), 128.8, 129.1, 129.4, 129.6, 129.6, 131.3, 132.0, 132.3 (*C*-CO_2CH_3), 135.5, 139.9, 157.7 (C-3), 165.0 (CO_2CH_3), 166.3 (C-5). – ESI-MS: *m/z* = 372.1 [M–ClO_4]$^+$. – $C_{23}H_{18}ClNO_6S$ (471.92): calcd. C 58.54, H 3.84, N 2.97, S 6.79; found C 58.04, H 3.77, N 2.95, S 6.99.

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

Yield: 31 %, m. p. 139 – 144 °C. – IR (KBr): ν = 1083 s (ClO_4) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.86 (s, 3H, OCH_3), 7.24 – 7.62 (m, 14H, arom. H), 9.97 (s, 1H, 3-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 56.0 (OCH_3), 109.0, 115.0, 117.4, 125.9 (C-4), 128.9, 129.1, 129.4, 129.5, 129.6, 131.5, 132.2, 135.2, 137.5, 157.4 (*C*-OCH_3), 160.4 (C-3), 165.4 (C-5). – ESI-MS: *m/z* = 344.1 [M–ClO_4]$^+$. – $C_{22}H_{18}ClNO_5S$ (443.91): calcd. C 59.63, H 4.09, N 3.16, S 7.22; found C 59.67, H 4.28, N 3.26, S 7.31.

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

Yield: 32 %, m. p. 164 – 168 °C. – IR (KBr): ν = 1093 s (ClO_4) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 4.03 (s, 3H, OCH_3), 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), 7.69 – 7.73 (t, 1H, arom. H), 7.99 (d, *J* = 7.6 Hz, 1H, arom. H), 9.90 (s, 1H, 3-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 56.8 (OCH_3), 113.7, 121.4, 125.2 (C-4), 125.8, 126.4, 128.7, 129.1, 129.4, 129.5, 129.6, 132.1, 133.0, 134.1, 151.8 (*C*-OCH_3), 159.0 (C-3), 166.4 (C-5). – ESI-MS: *m/z* = 344.1 [M–ClO_4]$^+$. – $C_{22}H_{18}ClNO_5S$ (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***

$C_{22}H_{18}ClNO_5S$, M_r = 443.88, T = 213(2) K. Suitable single crystals were obtained from ethanol. Crystal size: 0.20 × 0.20 × 0.10 mm^3; monoclinic crystal system, space group $P2_1/c$, a = 11.567(2), b = 21.210(4), c = 16.877(3) Å, β = 91.51(2)°, V = 4139.1(13) Å^3, Z = 8, ρ_{calcd} = 1.425 g cm^{-3}, μ(MoK_α) = 0.32 mm^{-1}. The intensities were measured on a Stoe IPDS1 diffractometer with graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). θ range for data collection: 2.27 – 27.94°, index ranges $-15 \le h \le 15$, $-27 \le k \le 26$, $-22 \le l \le 22$. 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 F^2 (SHELXS/L-97 [18]). Data/parameters = 9824/541. Final R_1/wR_2 [$I \ge 2\sigma(I)$]: 0.074/0.187, Final R_1/wR_2 (all data): 0.163/0.211; largest peak/hole 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.

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