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Oxidative azacyclization of 1-monosubstituted thioureas in reaction with [bis(acyloxy)iodo]arenes to form 1,2,4-thiadiazole derivatives

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Abstract—For the first time, derivatives of 1,2,4-thiadiazoles have been obtained by the reaction of [bis(acyloxy)iodo]arenes with 1-monosubstituted thioureas. 1-Acetylthiourea is subject to intermolecular azacyclization to form 3,5-bis-(acetylamino)-1,2,4-thiadiazole in reaction with [bis(acyloxy)iodo]benzene. 1-Phenylthiourea forms 3,5-bis-(phenylamino)-1,2,4-thiadiazole in a single-stage reaction with (diacetoxyiodo)benzene. The reaction of 1-phenylthiourea with [bis(trifluoroacetoxy)iodo]benzene leads to the formation of 5-imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline.

1. Introduction

As structural fragments, ureas are present in many pharmaceuticals with antispasmodic, antihypoxic and other pharmacologically valuable properties. Taking into account that the search for new pharmaceuticals affecting the central nervous system has been a problem for many years, and that ureas have a wide spectrum of valuable properties,[1] the investigation of urea functionalization in reaction with [bis(acyloxy)iodo] arenes (BIA) is an area of interest. It should be mentioned that the only references on transformations of ureas in the reaction with BIA concerns their use as secondary substrates in azaheterocyclization reactions[2–7] or in dimerization processes in methanol solution.[8]

Thiourea is widely used in the production of some pharmaceuticals (sulfothiazoles, thiobarbiturates) and as an additive to some plastic materials.[9] Thiourea shows more basic properties than urea and can be protonated with strong acids at the sulfur atom. Moreover, thiourea is sensitive to the effect of strong oxidants. For instance, when the oxidation of thiourea is run in neutral (with potassium permanganate) or acid solution (or with many other oxidants), the typical oxidation product—formamidine disulfide[9] is produced. Silver, mercury, and lead oxides in water at room temperature eliminate hydrogen sulfide from the thiourea molecule giving cyanamide.[9] 1-Alkylthioureas are oxidized with mercury oxide and water under heating to form alkylcyanamides and hydrogen sulfide, while 1,3-disubstituted thioureas (R=Alk, Ar) under similar conditions are oxidized to the appropriate 1,3-disubstituted ureas.[9]

Oxidation reactions of substituted thioureas have been known for a long time. As a rule, peroxide compounds or molecular bromine are used as traditional oxidizing agents.[10–13] Among other oxidants, TsN=SO reagent has been used with acylthioureas.[14] Moreover, 2-chlorobenzothiazole,[15] *tert*-butylhypochloride,[16] dioxandibromide,[17] and others[18] are used in reactions with arylthioureas.

It should be especially noted that the data about the structures of thiadiazolidines formed from thiourea and its 1-substituted derivatives on oxidation are sufficiently inconsistent, since most of the synthesized compounds can isomerize due to interconversion in solution. Besides, the structure of thioureas oxidation products often depends on the oxidant being used. For the first time these compounds were described by the German chemists about 100 years ago[19,20] and later, these substances have been studied by various chemical and physical methods. Among the compounds mentioned, an especially great number of disputes surrounded the so-called Hector's and Dost's bases. Thus, 5-imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline was found to be oxidation product of 1-phenylthiourea with hydrogen peroxide (Hector's base—HB) in 1978.[21] The Dost's base (DB) obtained by heating the Hector's base in ammonia alcohol solution was identified as 3,5-dianilino-1,2,4-thiadiazole.[20]

Keywords: oxidation; polyvalent iodine; thioureas; 1,2,4-thiadiazoles.
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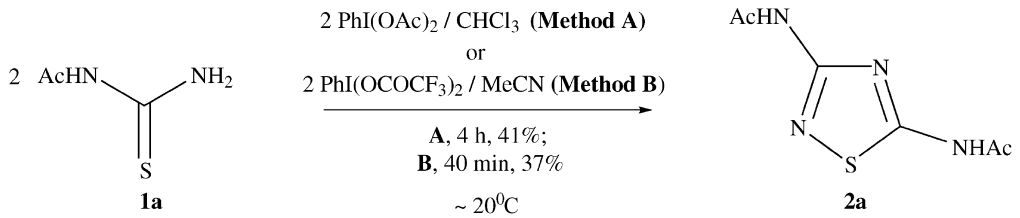


Scheme 1. Azacyclization of 1-acetylthiourea **1a** in reaction with DIB and BTI.

The appropriate 3,5-bis-(acylamino)-1,2,4-thiadiazoles were found to be the products of oxidation of 1-monoacyl derivatives thioureas.[12–14] A more complicated scheme has been observed with 1-arylthiourea.[10,11,22–24] In this case the dimeric compounds are isolated as intermediates, and then they are subject to oxidation and are cyclized with formation of HB-type bases.[10,11,23] The latter are subject to isomerization to form 3,5-diarylamino-1,2,4-thiadiazoles—DB-type bases.[22,24] We have carried out the generalization of oxidation–reduction transformations of 1-arylthioureas.[10,11,15–17,22–25]

Due to the fact that the choice of the available oxidants for such transformations is sufficiently restricted,[10–18] we took interest in the prospect of using BIA in similar azacyclization processes because of the absence of similar investigations. Taking into account the known and unique ability of BIA to oxidize organic substrates, we supposed that in reactions with 1-monosustituted thiourea, BIA would work in a more specific way than traditional oxidizers.

2. Results and discussion

Thus, 1-acetylthiourea (ATU) (**1a**) in the presence of equimolar quantities of (diacetoxyiodo)benzene (DIB) in chloroform (Method A) or in the presence of equimolar quantities of [bis(trifluoroacetoxy)iodo]benzene (BTI) in acetonitrile (Method B), was subject to oxidative cyclization to form 3,5-diacetylamino-1,2,4-thiadiazole (**2a**) in yields of 41 and 37% (Scheme 1: Methods A and B, respectively).

It should be noted that compound **2a** has been obtained earlier by the oxidation of ATU with hydrogen peroxide in alcohol solution at 0–25°C in 23% yield[12] or with 1-sulfinyl-tosylamide in 38% yield.[14] In our method the yields of compound **2a** were better using DIB or almost equal when using BTI to the literature reports.

The structure of compound **2a** was confirmed by IR-, ^{1}H NMR-spectroscopy, mass-spectrometry, and also by the comparison of the melting point of compound **2a** with the literature data.[12,14]

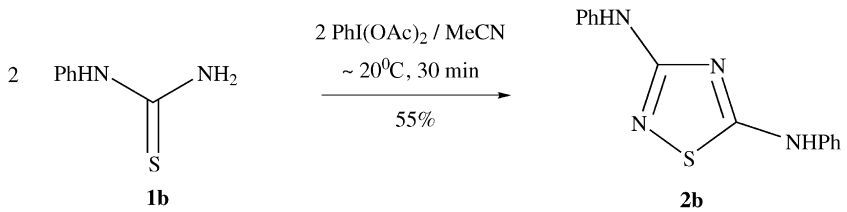
For further research we found that 1-phenylthiourea (PTU) (**1b**) was subject to azacyclization forming 3,5-dianilino-1,2,4-thiadiazole (**2b**), so-called Dost's base—DB in 55% yield only in the presence of DIB (Scheme 2).

For comparison, we considered other known ways of obtaining compound **2b**. Thus, 1,2,4-thiadiazole **2b** is obtained in 48% yield as a result of isomerization by heating a suspension of 5-imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline (HB) in ammonia alcohol solution in an autoclave at 135–140°C for 2.5 h.[24] The appropriate HB has been obtained by oxidation of 1-phenyl-1-phenylamidinothiourea bromohydrate with molecular bromine in methanol solution in 73% yield,[11] or by oxidation of PTU **1b** with hydrogen peroxide (70%),[25,26] or with *tert*-butylhypochloride (46%),[16] or with dioxandibromide (85%),[17] or with diaryltelluroxide (97%).[18] The compound **2b** has also been synthesized by the reaction of 3,5-dichloro-1,2,4-thiadiazole with aniline (boiling, 100 h) in 63% yield.[27]

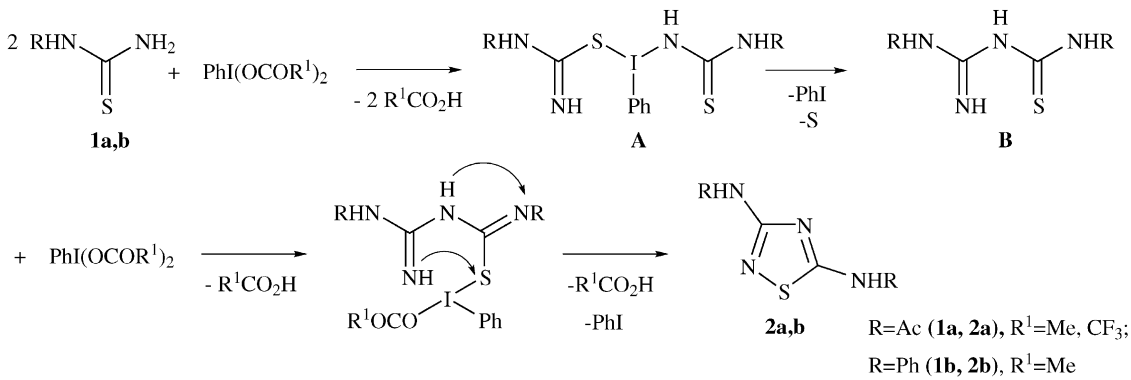
In comparison with these well-known methods of obtaining 1,2,4-thiadiazole **2b**, needing preliminary, often labour-intensive synthesis of precursors, our method produces the desired azaheterocycle **2b** starting from available PTU under normal conditions (at room temperature) by a single-stage reaction. It should be noted that direct methods for the synthesis of compound **2b** by oxidation of PTU are not known. Our process using DIB as an oxidizing reagent in reaction with PTU is a step forward in this field.

The structure of compound **2b** was confirmed by IR-, ^{1}H and ^{13}C NMR-spectroscopy, and mass-spectrometry and also by comparison of the melting point of the substance **2b** with the literature data.[24,27]

In our opinion, the 1,2,4-thiadiazoles **2a**,**b** formation using BIA proceeds according to Scheme 3. At first, 1-substituted thioureas **1a**,**b** by the reaction with BIA dimerize to form 1-*R*-3-*R*-amidinothioureas **B** via the polyvalent iodine compound **A** with elimination of the sulfur atom. Then, substances **B** are easily subject to the oxidative azacyclization initiated by BIA to form the appropriate bases **2a**,**b** of DB-type.



Scheme 2. Azacyclization of 1-phenylthiourea **1b** in reaction with DIB.



Scheme 3. Suggested scheme of synthesis of 3,5-bis-(*R*-amino)-1,2,4-thiadiazoles **2a**,**b**.

In contrast to PTU conversion in the reaction with DIB, the same reaction initiated by BTI (Scheme 4) results in trifluoroacetate formation in situ, the latter without preliminary isolation, after addition of Na_2CO_3 water solution to give 5-imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline (**3**) or HB with well-known properties.[10,11,16–18,23,28,29]

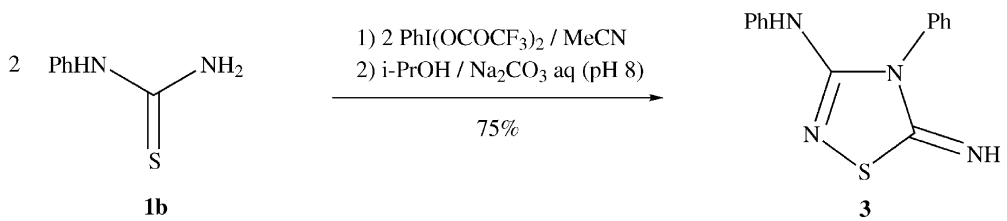
The structure of compound **3** was confirmed by IR-, ^1H and ^{13}C NMR-spectroscopy, and mass-spectrometry. Compound **3** is identical to the product of PTU oxidation with hydrogen peroxide in acidified alcoholic solution. Data about HB structure have been published.[21,30–32] It should be noted that the melting point of substance **3**, obtained by different methods (existing and suggested by us), is lower than that of HB, by about 13°C.[11]

As our contribution, we suggest the process of formation of the intermediate polyvalent iodine compound **A**, initially appearing as a result of BTI and PTU **1b** reaction (Scheme 5). The intermediate **A** after iodobenzene elimination dimerizes to form 1,6-diphenyl-dithioformamidine **B**. The latter easily converts into 1-phenyl-1-phenylamidinothiourea **C** by sulfur atom elimination, which with BTI-initiation cyclizes to form trifluoroacetate **D**. The free base **3** of HB-type is easily formed by the treatment of salt **D** solution with alkaline reagents.

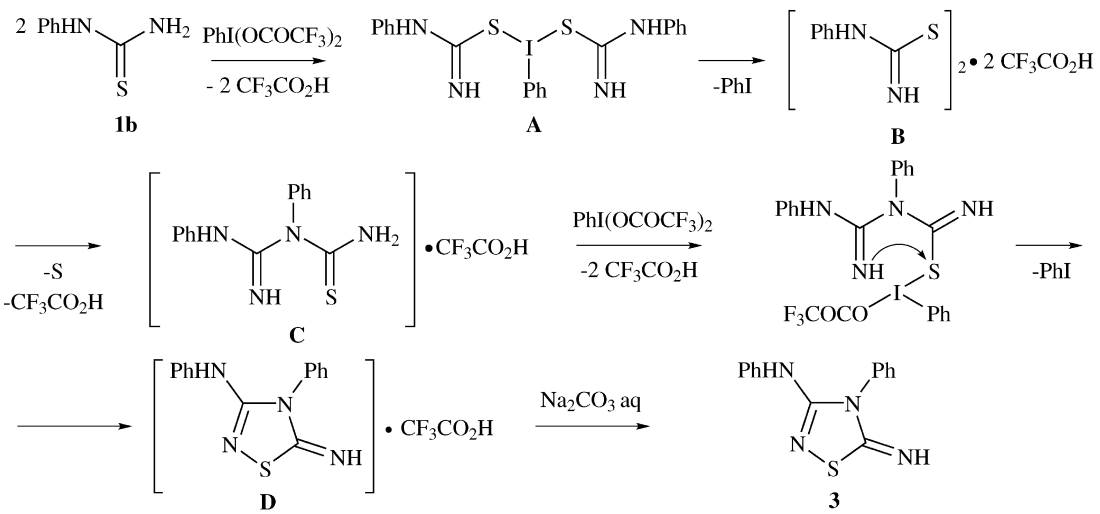
Thus, the results of our research have showed that, in comparison in the ATU **1a** conversion in reaction with BIA, the reaction of PTU **1b** with BTI finishes differently to the same reaction with DIB. In this connection the strong trifluoroacetic acid (TFA) generated gives the main effect on the formation of the final product **3**. Obviously, the TFA leads to the intermediate bases protonation, resulting in adduct **D** formation instead of its isomer **2b**. The key moment in Scheme 5 is 1-phenyl-1-phenylamidinothiourea **C** formation in the presence of TFA instead of 1-phenyl-3-phenylamidinothiourea **B** (Scheme 3). It determines the direction of the oxidation reaction. Besides, the direction of azacyclization also depends on the electrophilicity of iodosyl center of BIA molecules. When alkaline is added to trifluoroacetate **D** solution, free base **3** of HB-type is easily formed. In the case of the reaction of ATU **1a** with BTI the protonation of the appropriate base is evidently complicated due to the acetyl-groups in the structure, which decrease the electron density of the nitrogen atom of the amide group. Therefore, the presence of strong TFA in small amounts (the weak acetic acid in reaction of ATU **1a** with DIB) does not sufficiently affect the oxidation processes, which are favourable for the synthesis of compound **2a**. As follows from the above, the specific behavior of BTI in respect to PTU **1b** results from the basic properties of the intermediates, appearing during the oxidation reaction with the BTI reagent. The ability of strong TFA to protonate intermediates plays a special role, inhibiting the processes of 1,2,4-thiadiazole **2b** (isomer of compound **3**) formation. Known methods of PTU oxidation involve using the addition of strong mineral acid or acid-generating reagents. It is not make possible to earlier obtain the compounds of **2b**-type starting from 1-arylthioureas. This fact limited the application of traditional methods. Using DIB as a 'weak-acid' oxidant allows preparative possibilities of 3,5-disubstituted-1,2,4-thiadiazoles synthesis.

3. Conclusion

Summarizing the results of our research it is possible to conclude that we, using BIA as oxidizing reagents, discovered that 1-monosubstituted thioureas treated with BIA are subject to azaheterocyclization processes to form 1,2,4-thiadiazole derivatives. Analysis of the literature data has shown that our methods of desired nitrogen-containing heterocycles synthesis are more attractive both in simplicity



Scheme 4. Azacyclization of 1-phenylthiourea **1b** in reaction with BTI.



Scheme 5. Suggested scheme of synthesis of 5-imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline **3**.

of realization and in efficiency of the used oxidative agents. The difference in DIB and BTI behaviour in reactions with PTU was found. Using DIB we, for the first time, succeeded in a single-stage reaction to obtain 3,5-dianilino-1,2,4-thiadiazole starting from PTU. Taking into account that its precursor 3,5-diamino-1,2,4-thiadiazole shows hypoglycemic activity along with low toxicity,[33] the direct method of its derivatives synthesis becomes especially valuable.

4. Experimental

4.1. General

Reaction and compound identification were achieved by thin-layer chromatography (TLC) Merck DC-Alufolien Kieselgel 60 F_{254} (mobile phase: benzene–methanol=8:2).

^{1}H and ^{13}C NMR spectra were recorded on a Tesla BS-497 NMR spectrometer (at 100 and 25 MHz, respectively) in DMSO-d_6 or $CDCl_3$. Chemical shifts were registered relatively to Me_4Si (in ppm). IR-spectra were recorded on a FT-IR spectrometer (Nicolett) in KBr tablets. Accurate values of molecular ions masses were determined by high-resolution mass-spectrometry on a MAT-8200 spectrometer (from Finnigan), supplied with direct input of the sample into source, at ionizing emission energy of 70 eV.

The identification of the synthesized compounds structures and the spectral signals were made by the comparison of the chemical shifts of NMR spectra with the data obtained from computer programs Chem Office 2000 Ultra, ACDH, and ACDC.

BTI and DIB were synthesized according to the literature procedure.[34]

4.1.1. 3,5-Diacetylamino-1,2,4-thiadiazole 2a. *Method A*. A mixture of ATU **1a** (0.366 g, 3.10 mmol), DIB (1.000 g, 3.10 mmol) and chloroform (10 mL) was stirred at room temperature for 4 h. The precipitate was filtered, dried and recrystallized from ethanol to form the title compound **2a** (0.128 g, 41%).

Method B. A mixture of ATU **1a** (0.275 g, 2.33 mmol), BTI (1.000 g, 2.33 mmol) and acetonitrile (7 mL) was stirred at room temperature for 40 min. The precipitate was filtered, dried, and recrystallized from ethanol to form the title compound **2a** (0.086 g, 37%) as white crystals; mp 342–343°C (lit.,[12] mp 336–338°C; lit.,[14] mp 325–330°C (AcOH)); ν_{max}(KBr) 3449, 3201, 3109, 3000, 1693, 1665, 1579, 1545, 1529, 1332, 1289, 1237, 585 cm^{-1}; δ_H (100 MHz, DMSO-d_6) 11.00 (2H, s, 2N*H*), 2.42 (3H, s, *Me*), 2.32 (3H, s, *Me*); *m*/*z* (CI, N_2) 200 (35 M^+), 158 (87), 116 (100), 74 (17), 43 (86), 28 (7%).

4.1.2. 3,5-Dianilino-1,2,4-thiadiazole 2b. A mixture of PTU **1b** (0.472 g, 3.10 mmol), DIB (1.000 g, 3.10 mmol) and acetonitrile (10 mL) was stirred at room temperature for 30 min; the precipitated sulfur was filtered off. The filtrate after water (20 mL) addition was extracted with chloroform (60 mL). Acetonitrile (5 mL) and then water (15 mL) were added to the residue, which boiled down to get rid of solvents and PhI. The resulting precipitate was filtered off, dried, and recrystallized from acetonitrile to form the title compound **2b** (0.231 g, 55%) as white crystals; mp 200–202′C (lit.,[24,27] mp 200–202°C (EtOH)); ν_{max} (KBr) 3472, 3411, 3379, 1665, 1592, 1535, 1482, 1441, 1398, 1340, 697 cm^{-1}; δ_H (100 MHz, DMSO-d_6) 8.66 (1H, s, N*H*), 7.88–6.60 (10H, m, 2Ph), 4.98 (1H, s, N*H*); δ_C (25 MHz, DMSO-d_6) 173.2, 157.6, 144.2, 143.5, 139.5, 135.8, 128.0, 127.5, 126.0, 121.0, 117.9, 114.4; *m*/*z* (CI, N_2) 268 (100 M^+), 220 (35), 176 (7), 150 (42), 118 (48), 91 (32), 77 (45), 65 (23), 51 (22%).

4.1.3. 5-Imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline 3. A mixture of PTU **1b** (0.708 g, 4.65 mmol), BTI (2.000 g, 4.65 mmol) and acetonitrile (10 mL) was stirred at room temperature for 2 h. The resulting yellow sulfur precipitate was filtered off. Obtaining solution was left to evaporate at room temperature for one week. 1 mL of isopropyl alcohol was added to the residue, mixed up to dissolution, then water (70 mL) was added and precipitate was filtered. Aqueous Na_2CO_3 solution (10%) was added; up to pH 8. The precipitate was filtered, washed out well with water and dried to form the title compound **3** (0.468 g, 75%) as white, lightly yellowish crystals; mp 172–174°C

(C_6H_6 or acetone/spirit) (lit.,[11] mp 185–186°C; lit.,[28] mp 179–180°C; lit.,[26] mp 183–184°C; lit.,[35] mp 182°C); ν_{max} (KBr) 3472, 3411, 3379, 1665, 1592, 1535, 1482, 1441, 1398, 1340, 697 cm^{-1}; δ_H (100 MHz, DMSO-d_6) 8.22 (2H, s, 2N*H*), 8.03–7.10 (10H, m, 2Ph); δ_C (25 MHz, DMSO-d_6) 163.9, 146.3, 137.5, 132.1, 128.5–125.7, 120.5, 118.40; *m/z* (CI, N_2) 268 (100 M^+), 195 (28), 150 (49), 119 (51), 92 (21), 77 (25), 65 (17), 51 (12), 32 (8), 28 (38%).

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