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Heterocyclization of thiocarbonohydrazides: Facile synthesis of 5-unsubstituted-1,3,4-thiadiazoles

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ABSTRACT

2-(Hydrazinecarbothioyl)-*N*-substituted hydrazinecarbothioamides react with 2,3,5,6-tetra-chloro-1,4-benzoquinone in high yields in a novel fast and facile method to give 5-unsubstituted-1,3,4-thiadiazole-2-amine derivatives. The synthesized compounds were characterized by spectroscopic methods and confirmed by using X-ray crystallography. A rationale for the formation of the products is presented.

1. Introduction

Thiadiazole is a prevalent and important five-membered heterocyclic system. There are several isomers of thiadiazole. A glance at standard reference works shows that 1,3,4-thiadiazole has been investigated more than other isomers [1].

The most familiar thiadiazole containing compound could be acetazolamide, the famous carbonic anhydrase inhibitor currently used in treatment of glaucoma [2], high-altitude illness [3], cancer [4,5], HIV [4], seizures [6], diabetes [7], and hypertension [8]. Synthesis of 1,3,4-thiadiazoles usually involves multi-step procedures such as cyclization of thiosemicarbazide with di-(2-pyridyl)thionocarbonate (DPT), dicyclohexylcarbodimide (DCC) [9]. Oxidative cyclization of thiosemicarbazides with $FeCl_3$ [10] or reaction of thiosemicarbazides and CS_2 under reflux [11] have been reported. Treatment of isothiocyanates with pure lithiated (trimethylsilyl)diazomethane (Me_3SiCN_2Li) in Et_2O afforded 2-amino substituted-1,3,4-thiadiazoles [12,13].

Although, there are many reports for the synthesis of 1,3,4-thiadiazoles [14,15], few reports are available for the synthesis of 5-unsubstituted 1,3,4-thiadiazoles. Diethyl chlorophosphate in DMF was proposed as a cyclizing agent for the synthesis of 5-unsubstituted 1,3,4-thiadiazoles [16]. The latter were formed in moderate yields by cyclization of thiohydrazides. 5-Unsubstituted 1,3,4-thiadiazoles are of interest as biologically active compounds [17,18]. Further, they are used in the synthesis of various heterocyclic compounds [19,20].

2. Experimental

2.1. General experimental procedure

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra (KBr discs) were recorded on a Bruker FT-IR and Shimadzu 408 instruments. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker AM 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) with tetramethylsilane as the internal standard; the chemical shifts are expressed in δ and coupling constants in Hz. The ^{13}C NMR assignments (q = quaternary carbon atoms) were made with the aid of DEPT 135/90 spectra. Mass spectra (70 eV, electron impact mode) were recorded on a Finnigan MAT 312 instrument. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt. Preparative layer chromatography (plc) used air-dried 1.0 mm thick layer of slurry

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applied silica gel (Merck Pf_{254}) on 48 cm wide and 20 cm high glass plates using the solvent listed.

2.2. Starting materials

2,3,5,6-Tetrachloro-1,4-benzoquinone (CHL-*p*, **2**) was purchased from Fluka. 2-(Hydrazinecarbonothioyl)-*N*-aryl/alkyl hydrazinecarbo-thioamides **1a–d** were prepared according to published procedures for preparation compounds **1a** [21] and **1b–d** [22].

2.3. Reaction of *1a–d* with 2,3,5,6-tetrachloro-1,4-benzoquinone (*2*)

2-(Hydrazinecarbonothioyl)-*N*-substituted hydrazinecarbothioamides **1a–d** (1 mmol) in 20 mL dry ethyl acetate was added to 246 mg (1 mmol) (CHL-*p*, **2**) in 20 mL dry ethyl acetate at room temperature. The reaction mixture was stirred for 3 h. After standing for 24 h, the precipitate was filtered, washed with cold ethyl acetate and identified as 2,3,5,6-tetrachloro-*p*-benzohydroquinone **4** [23]. The filtrate was pre-concentrated, then applied to 3 plc plates and developed using toluene/ethyl acetate (ϕr = 10:2 for **1a**, **1b**, and ϕr = 10:4 for **1c**, **1d**) to give *N*-substituted-1,3,4-thiadiazol-2-amines **3a–d**, extracted by acetone and recrystallized from listed solvents.

N-Phenyl-1,3,4-thiadiazol-2-amine (**3a**): red crystals (acetonitrile), yield 87% (0.154 g), mp: 173 °C (lit. 171–172 °C) [16,20].

N-Benzyl-1,3,4-thiazol-2-amine (**3b**): red crystals (acetonitrile), yield 89% (0.170 g), mp: 109–110 °C (lit. 108 °C) [19]. IR (KBr, cm^{-1}): υ 3421–3380 (NH str.), 1611 (C=N str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (br, 1H, NH–CH_2Ph), 8.20 (s, 1H, CH=N), 7.36–7.31 (m, 3H, Ar–H), 7.29–7.28 (m, 2H, Ar–H), 4.51 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5 (C=N), 142.3 (CH=N), 138.7 (Ar–C), 128.3, 127.5, 127.0 (Ar–CH), 48.3 (CH_2–Ph). MS *m/z* (%) 191 (M^+, 70), 163 (11), 86 (100), 91 (13), 76 (10).

N-Allyl-1,3,4-thiazol-2-amine (**3c**): red crystals (acetonitrile), yield 85% (0.112 g), mp: 74–75 °C (lit. 73 °C) [19]. IR (KBr, cm^{-1}): υ 3426–3384 (NH str.), 1600 (C=N str.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (br, 1H, NH-allyl), 7.90 (s, 1H, CH=N), 5.90–5.89 (m, 1H, allyl-CH=), 5.15–5.11 (m, 2H, allyl-CH_2=), 3.92–3.90 (m, 2H, allyl-CH_2N). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6 (C=N), 142.4 (CH=N), 135.00 (allyl-CH), 115.45 (allyl-CH_2=), 46.05 (allyl-CH_2N). MS *m/z* (%) 141 (M^+, 30), 113(28), 86 (100), 55 (40), 41 (75).

N-Ethyl-1,3,4-thiazol-2-amine (**3d**): red crystals (acetonitrile), yield 84% (0.108 g), mp: 71–72 °C (lit. 70 °C) [24]. IR (KBr, cm^{-1}): υ 3424–3372 (NH str.), 1601 (C=N str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (br, 1H, NH–C_2H_5), 7.96 (s, 1H, CH=N), 3.49 (q, 2H, CH_2, *J* = 7.50 Hz), 1.19 (t, 3H, *J* = 7.50 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8 (C=N), 143.1 (CH=N), 40.1 (CH_2), 14.3 (CH_3). MS *m/z* (%) 129 (M^+, 55), 101 (40), 86 (100), 43 (50), 29 (80).

2,3,5,6-Tetrachlorobenzene-1,4-diol (**4**) [23]: mp: 230–232 °C (lit. 232 °C).

2.4. Single crystal X-ray structure determination of *3a*

Single crystals were obtained by recrystallization from acetonitrile. The single crystal X-ray diffraction study was carried out on an Agilent SuperNova diffractometer with EOS detector at 173 K using Mo kα radiation (λ = 0.71073 Å). Direct methods (SHELXS-98) [25] were used for structure solution and refinement was carried out using SHELXL-2013 [25] (full-matrix least-squares on F^2). Hydrogen atoms were localized by different Fourier synthesis map and refined using a riding model [H(N) free]. A semi-empirical absorption correction was applied.

3a: $C_8H_7N_3S$, M = 177.23 g mol^{-1}, red crystal, size 0.40 mm × 0.06 mm × 0.06 mm, monoclinic space group $P2_1/n$ (no. 14), a = 11.3811(5) Å, b = 5.3161(2) Å, c = 14.3650(6) Å, β = 112.249(5) Å, V = 798.82(6) $Å^3$, Z = 4, D_{calcd} = 1.474 mg m^{-3}, $F(000)$ = 368, μ = 0.344 mm^{-1}, T = 173 K, 3093 measured reflection ($2\theta_{max}$ = 58.8°), 1978 independent [R_{int} = 0.015], 112 parameters, 1 restraint, R_1 [for 1604 $I > 2\sigma(1)$] = 0.043, wR^2 (for all data) = 0.097, S = 1.07, largest diff. peak and hole = 0.232 $eÅ^{-3}$/−0.218 $eÅ^{-3}$.

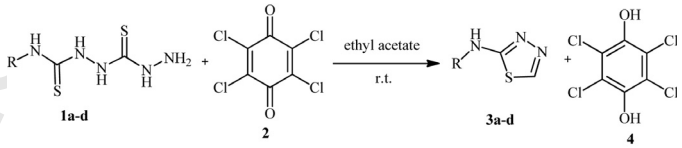
Crystallographic data (excluding structure factors) for the structure reported in this work has been deposited with Cambridge crystallographic Data Center on supplementary publication no. CCDC-1046364. Copies of the data can be obtained free of charge on application to the director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44 1223 3360333; e-mail: deposit@ccdc.cam.ac.uk).

3. Results and discussion

For the synthesis of 5-unsubstituted 1,3,4-thiadiazoles as will be outlined in detail below, we report the heterocyclization of thiocarbonohydrazides **1a–d** using 2,3,5,6-tetrachloro-1,4-benzoquinones (CHL-*p*, **2**) as a reaction mediator.

After adding ethyl acetate solutions of **1a–d** to an equimolar quantity of 2,3,5,6-tetrachloro-1,4-bezoquinone (CHL-*p*, **2**), in ethyl acetate and letting it stand for 24 h at room temperature, the initial green colored turned to violet, which gradually changed to reddish brown. The isolated compounds **3a–d** (Scheme 1) were characterized by their IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and single X-ray crystallography.

The IR spectrum of **3c** as an example was characterized by the presence of broad NH at 3426–3384, the band at 1600 was assigned to C=N stretching. The bands attributed to C=S stretching vibrations were not observed in the IR spectra of **3a–d**.



1 and **3**: R, **a** = C_6H_5; **b** = C_6H_4-CH_2; **c** = CH_2=CH-CH_2; **d** = C_2H_5

Scheme 1. Reaction of **1a–d** with CHL-*p* (**2**).

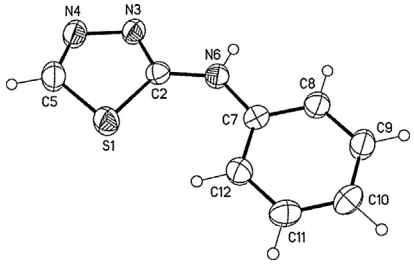


Fig. 1. Molecular structure of **3a** in the crystal (one crystallographic independent molecule is shown; displacement parameters are drawn at 50% probability level).

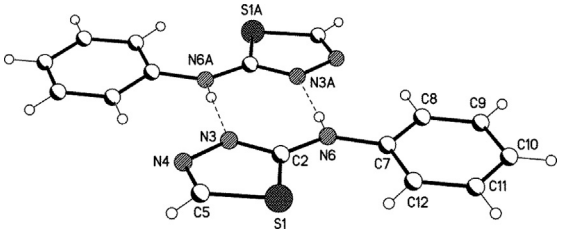


Fig. 2. Asymmetric unit of **3a** with intermolecular hydrogen bonds shown as dotted lines.

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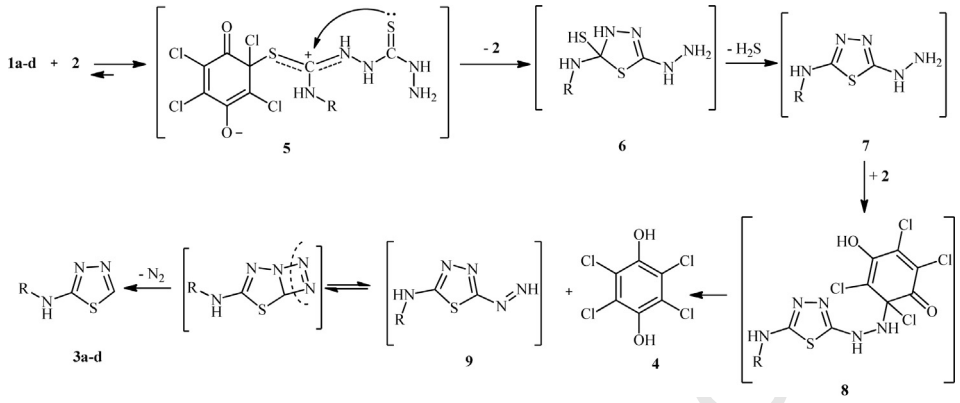

Scheme 2. The mechanism of formation 5-unsubstituted-1,3,4-thiadiazoles.

The chemical shifts obtained from ^{1}H NMR spectrum of **3c** supported the proposed structure. Resonance assigned to allyl group was detected at 3.92–3.90 (allyl-CH_2N), 5.15–5.11(allyl-CH_2=) and 5.90–5.89 (allyl-CH=). The ^{1}H NMR clearly showed singlet signal at 7.90 due to CH=N, whereas a broad band with D_2O exchangeable observed at 8.10 for NH-allyl.

^{13}C NMR data of representative compounds **3a–d** which were obtained using DEPT technique at 100 MHz, also support the carbon framework by discrimination of CH_2, CH and quaternary carbons. The ^{13}C NMR of **3c** showed downfield signals at 167.60, 142.40, 135.00 and 115.45 attributed to C=N, CH=N, allyl-CH= and allyl-CH_2= respectively. The upfield signal resonated at 46.05 due to (allyl-CH_2N).

N-Phenyl-1,3,4-thiadiazol-2-amine (**3a**) was confirmed unambiguously by single crystal X-ray structure analysis (Fig. 1 and Tables S1–S7 in Supporting information) (note that the crystallographic numbering does not correspond to systematic IUPAC numbering rules).

The S(1)–C(5) bond length of 1.726(2) Å and S(1)–C(2) 1.7323(19) has single bond character, whereas bond lengths C(2)–N(3) 1.318(2) Å, C(5)–N(4) 1.285(3) Å suggest that these bonds have double bond character, as they comparable to C=N bond. The 2-phenyl amino-1,3,4-thiadiazole molecule (**3a**) is planar (mean deviation from the L.S. plane through all non hydrogen atoms 0.042 Å, angle between the L.S: planes of the 1,3,4-thiadiazole ring and the phenyl ring 3.0°). Intermolecular hydrogen bonding between N6A, N3A from one molecule to N3 and N6 of another forms a dimer with C_i-symmetry (Fig. 2).

Since the aforementioned reactions do not take place when no **2** is added to the solution of **1a–d** in ethyl acetate, the presence of (CHL-*p*, **2**), is definitely required for the transformation observed. Charge-transfer complexes may (but not necessarily have to) play an intermediate role. Since the cyclization involves intramolecular attacks on the thiocarbonyl group, it is conceivable that (CHL-*p*, **2**) accelerates the process as a proton or a Lewis acid, possibly through intermediate **5** (Scheme 2), activating the respective C=S bond toward nucleophilic addition. This behavior may well be supported by the polar nature of the solvent stabilizing Zwitter-ionic adducts.

4. Conclusion

An efficient and fast reaction between thiocarbonohydrazides **1a–d** and CHL-*p*, **2** was observed to give 1,3,4-thiadiazoles. These oxidative cyclization reactions of **1a–d** using CHL-*p*, which react as a mediator, provide the products in higher yields with lower costs. This environmentally benign procedure will be explored for other substrates.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2015.05.034.

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