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USE OF TETRAMETHYLTHIURAM DISULFIDE IN SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

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We have developed a method for synthesis of aryl isothiocyanates by means of thiocarbamoylation of aromatic amines by tetramethylthiuram disulfide followed by degradation of the intermediate $N_{(1)}$-aryl-N,N-dimethylthiourea by concentrated HCl. We have shown that thiocarbamoylation of 4-amino-5-ethyl-4H-1,2,4-triazole-3-thiol occurs at the 2 position of the triazole ring, while thiocarbamoylation of 4-amino-3-methyl-6-phenyl-4,5-dihydro-1,2,4-triazin-5-one leads to the dihetaryl-substituted thiourea. We consider the possibility of using $N_{(1)}$-aryl-N,N-dimethylthioureas as analogs of isothiocyanates in reactions with N-nucleophiles.

Keywords: $N_{(2)}$-(3-chloro-2-methylphenyl)-2-amino-5,6-dihydro-4H-1,3-thiazine, 4-amino-3-methyl-6-phenyl-4,5-dihydro-1,2,4-triazin-5-one, N(1)-aryl-N,N-dimethylthioureas, aryl isothiocyanates, N-aryl-$N_{(1)}$-(5-mercapto-3-methyl-4H-1,2,4-triazol-4-yl)thioureas, 6-(4-bromophenylamino)-3-methyl[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazole, tetramethylthiuram disulfide.

Aryl isothiocyanates are widely used in preparative organic synthesis, but their accessibility is limited primarily by the cost and risk of the thiophosgene method [1]. So it is important to look for alternative methods for synthesis of aryl isothiocyanates using a process that is accessible, low cost, and safe.

In reactions with aliphatic and aromatic amines, tetramethylthiuram disulfide (TMTD) forms $N_{(1)}$-alkyl(aryl)-N,N-dimethylthioureas [2-5]. The latter, when treated with excess acetic anhydride, acetyl chloride, sulfuric or hydrochloric acid, undergo degradation to form the corresponding isothiocyanates [5].

We have developed a one-pot method for obtaining the aryl isothiocyanates **3a-e** from the corresponding aromatic amines **1a-e** and 80% wettable TMTD powder. Preliminary isolation and purification of the active substance from off-grade TMTD fungicide does not result in a significant increase in the yield of the final reaction product, so thiocarbamoylation of the aromatic amines was carried out by boiling equimolar amounts of the reagents in ethanol together with the filler. The thioureas **2a-g** obtained in this case, when boiled with a three-fold excess of concentrated hydrochloric acid, form the corresponding aryl isothiocyanates **3** (Scheme 1).

We know [6] that when substituted *o*-aminophenols are boiled with TMTD, the reaction does not stop in the step of formation of the corresponding thiourea but rather further cleavage of the N,N-dimethylamino group occurs, followed by cyclization to form substituted 2-mercaptobenzoxazoles. When TMTD is reacted with 5-(2-aminophenyl)-1,3,4-oxadiazole-2-thiol, after initial formation of thiourea, the adduct undergoes a series of sequential rearrangements with formation of 2-mercapto-1,3,4-thiadiazole[2,3-*b*]quinazolin-5-one [7]. Based on

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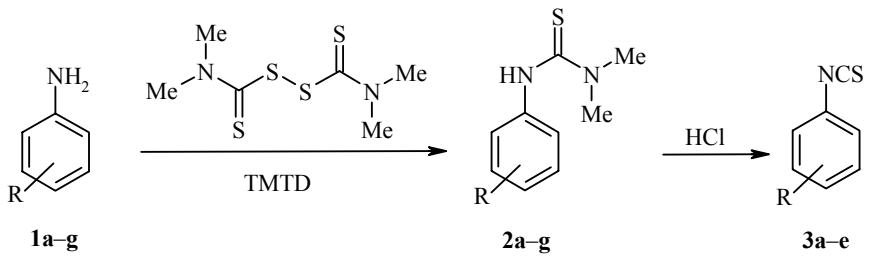
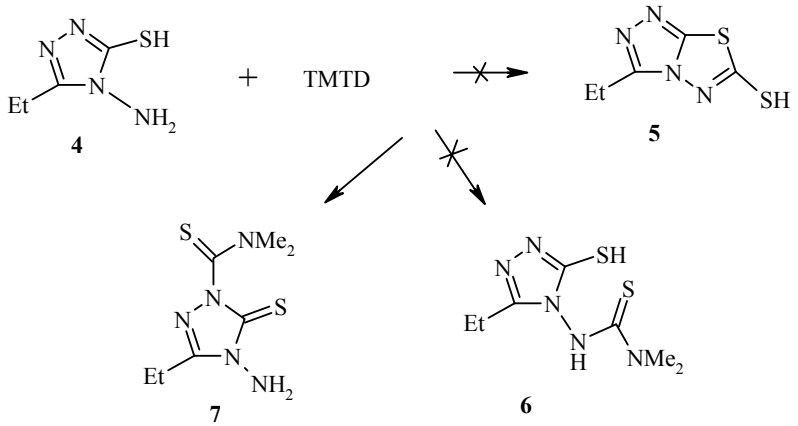
Scheme 1



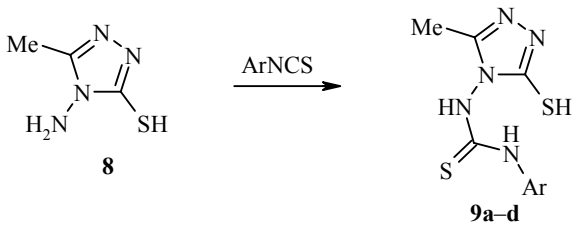
1-3 a R = H, **b** R = 2-Me, **c** R = 3-Me, **d** R = 4-Me, **e** R = 4-OMe, **f** R = 3-Cl-2-Me, **g** R = 4-Br

these data, we hypothesized that as a result of reaction of 4-amino-5-ethyl-3-mercapto-4H-1,2,4-triazole (**4**) with TMTD, either 3-ethyl-6-mercapto[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**5**) or N,N-dimethyl-N'-(3-ethyl-5-mercapto-4H-1,2,4-triazol-1-yl)thiourea (**6**) can form. Elemental analysis data for the product of reaction of compound **4** with TMTD indicate formation of compound **6**. However, according to the ^{1}H NMR spectra, instead of the expected addition of the dimethylaminomethylthione group at the exocyclic amino group of the heterocycle, addition occurs at the 2 position of the triazole ring with formation of 1-[(N,N-dimethyl)-thiocarbamoyl]-4-amino-3-ethyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazole (**7**).



Thus in the ^{1}H NMR spectrum of compound **7**, we observe a two-proton singlet for the N-amino group at 5.52 ppm and two singlets for the dimethylamino group at 3.50 ppm and 3.59 ppm, while the protons of the methyl and methylene groups of the ethyl substituent resonate at 1.86 ppm and 2.65 ppm, depending on their multiplicity.

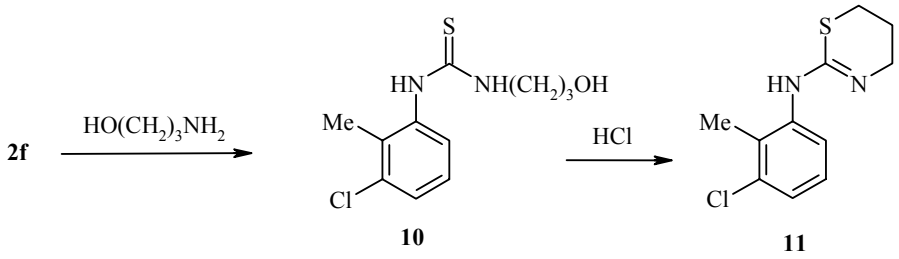
The aryl isothiocyanates **3** obtained were reacted with 4-amino-3-mercapto-5-methyl-4H-1,2,4-triazole (**8**).



9 a Ar = Ph, **b** Ar = 2-MeC$_6$H$_4$, **c** Ar = 3-MeC$_6$H$_4$, **d** Ar = 4-MeOC$_6$H$_4$

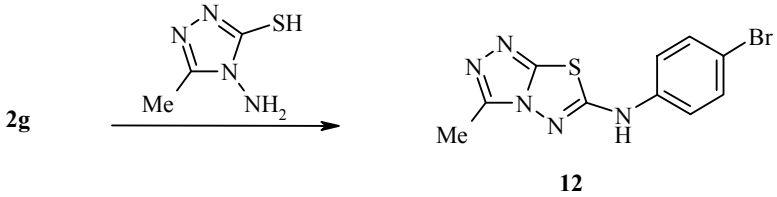
After brief heating of equimolar amounts of the corresponding starting materials in benzene, we isolated N-aryl-$N_{(1)}$-(5-mercapto-3-methyl-4H-1,2,4-triazol-4-yl)thioureas **9a-d**, in the ^{1}H NMR spectra of which signals from both NH groups were recorded in the 9.9-10.2 ppm region along with a one-proton singlet from the SH group in the 13.3-13.4 ppm region.

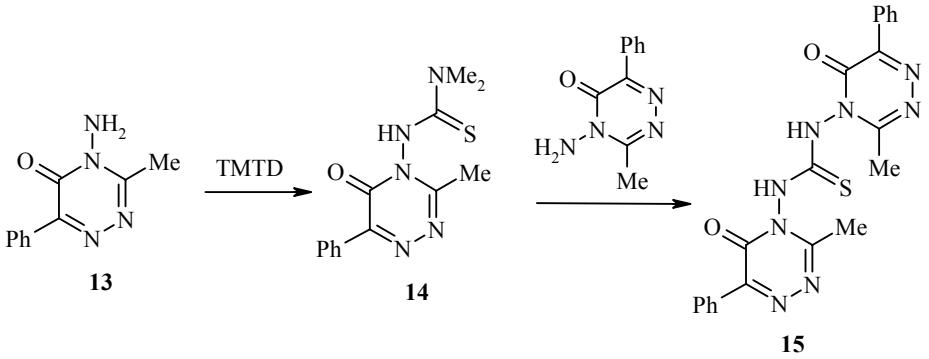
When thiourea **2f** is boiled with 3-amino-1-propanol in alcohol for 1 h, we obtain N-(3-hydroxypropyl)-$N_{(1)}$-(3-chloro-2-methylphenyl)thiourea (**10**), which when boiled in hydrochloric acid forms $N_{(2)}$-(3-chloro-2-methylphenyl)-2-amino-5,6-dihydro-4H-1,3-thiazine (**11**).



A distinguishing feature of the ^{1}H NMR spectrum of compound **11** compared with disubstituted thiourea **10** is disappearance of the one-proton singlet from the OH group at 4.15 ppm and the one-proton singlet from the NH group at 9.94 ppm. We also observe a shift of the multiplet for the three aromatic protons from the 7.13-7.22 ppm region upfield to the 6.64-6.94 ppm region.

After heating (30 h) $N_{(1)}$-(4-bromophenyl)-N,N-dimethylthiourea (**2g**) with 4-amino-3-mercapto-5-methyl-4H-1,2,4-triazole in DMF at 110°C, we isolated 6-(4-bromophenylamino)-3-methyl[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazole (**12**), completely identical to the product of reaction between 4-amino-3-mercapto-5-methyl-4H-1,2,4-triazole and 4-bromophenyl isothiocyanate under the same conditions. In the ^{1}H NMR spectrum of amidine **12**, the three-proton singlet of the methyl group appears in the 2.05 ppm region, while the amidine proton is detected in the 10.1 ppm region as a one-proton singlet.





When equimolar amounts of 4-amino-3-methyl-6-phenyl-4,5-dihydro-1,2,4-triazin-5-one (**13**) and TMTD are boiled in ethanol, instead of the expected thiourea **14** we obtained the urea **15** in satisfactory yield. A characteristic feature of the ^{1}H NMR spectrum of the latter is the disappearance of the signals from the protons of the N–NH_2 group characteristic of the starting compound **13**, and the appearance of a two-proton singlet from the two NH groups at 13.8 ppm.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker-300 (300 MHz) in DMSO-d_6, internal standard TMS.

N,N-Dimethyl-$N_{(1)}$-(3-chloro-2-methylphenyl)thiourea (2f). A mixture of 3-chloro-2-methylaniline (**1f**) (2.82 g, 0.02 mol) and 80% wettable powder of the fungicide TMTD (6 g, 0.02 mol) in ethanol (20 ml) was boiled for 5 h. The hot reaction mixture was filtered to remove the filler and insoluble impurities and then cooled down. The precipitate was filtered out and purified by crystallization from ethanol. Yield 3.71 g (81%); mp 149-151°C. ^{1}H NMR spectrum, δ, ppm: 2.24 (3H, s, CH_3), 3.32 (6H, s, $N(CH_3)_2$); 7.03-7.24 (3H, m, C_6H_3); 8.74 (1H, s, NH). Found, %: N 12.5; S 14.2. $C_{10}H_{13}ClN_2S$. Calculated, %: N 12.3; S 14.0.

$N_{(1)}$-(4-Bromophenyl)-N,N-dimethylthiourea (2g) was obtained similarly as compound **2f** from equimolar amounts of 4-bromoaniline **1g** and 80% wettable powder of the fungicide TMTD. Yield 76%; mp 165-167°C. ^{1}H NMR spectrum, δ, ppm: 2.03 (6H, s, $N(CH_3)_2$); 7.32 and 7.50 (4H, dd, C_6H_4); 9.57 (1H, s, NH). Found, %: Br 30.5; N 11.0. $C_9H_{11}BrN_2S$. Calculated, %: Br 30.8; N 11.0.

Phenyl Isothiocyanate (3a) (General Procedure). A mixture of aniline (**1a**) (93 ml, 1 mol) and 80% wettable powder of the fungicide TMTD (300 g, 1 mol) in ethanol (400 ml) was boiled for 5 h (~100°C). Then it was distilled down to 2/3 of the solvent volume and, after cooling, conc. HCl (300 ml) was added. The reaction mixture was boiled for another 5 h and, without cooling, the filler was filtered out. The filler was washed on the filter with CCl_4 (100 ml). The organic layer was separated and dried with calcined potassium carbonate. The carbon tetrachloride was driven off and the phenyl isothiocyanate was distilled under vacuum. Yield 125 g (93%); bp 109-111°C (20 mm Hg), n_D^{20} 1.6521.

The aryl isocyanates **3b-e** were obtained similarly.

2-Methylphenyl Isothiocyanate (3b). Yield 81%; bp 122-123°C (20 mm Hg), n_D^{20} 1.6365. According to the data in [8], bp 108°C (5 mm Hg).

3-Methylphenyl Isothiocyanate (3c). Yield 84%; bp 126-128°C (20 mm Hg), n_D^{20} 1.6331. According to the data in [8], bp 110°C (5 mm Hg).

4-Methylphenyl Isothiocyanate (3d). Yield 86%; bp 120-121°C (20 mm Hg), n_D^{20} 1.6349. According to the data in [8], bp 116°C (5 mm Hg).

4-Methoxyphenyl Isothiocyanate (3e). Yield 79%; bp 156-157°C (20 mm Hg), n_D^{20} 1.6485. According to the data in [8], bp 142°C (5 mm Hg).

1-[(N,N-Dimethyl)thiocarbamoyl]-4-amino-3-ethyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazole (7) was obtained as for compound **2f** from equimolar amounts (0.02 mol each) of compound **4** and 80% wettable powder of the fungicide TMTD. Yield 2.73 g (59%); mp 183-184°C. ^{1}H NMR spectrum, δ, ppm: 1.86 (3H, t, CH_3); 2.65 (2H, q, CH_2); 3.50 (3H, s, NCH_3); 3.59 (3H, s, NCH_3); 5.52 (2H, s, NH_2). Found, %: N 30.0; S 27.9. $C_7H_{13}N_5S_2$. Calculated, %: N 30.3; S 27.7.

$N_{(1)}$-(5-Mercapto-3-methyl-4H-1,2,4-triazol-4-yl)-N-phenylthiourea (9a) (General Procedure). A mixture of 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol (**8**) (1.30 g, 0.01 mol) and phenyl isothiocyanate **3a** (1.35 g, 0.01 mol) was boiled in benzene (20 ml) for 1 h and cooled. The precipitate was filtered out and crystallized from an ethanol–DMF mixture. Yield 2.20 g (83%); mp 212-213°C. ^{1}H NMR spectrum, δ, ppm: 2.28 (3H, s, CH_3); 7.17-7.63 (5H, m, C_6H_5); 10.1 (1H, s, NH); 10.2 (1H, s, NH); 13.3 (1H, s, SH). Found, %: N 26.5; S 23.9. $C_{10}H_{11}N_5S_2$. Calculated, %: N 26.4; S 24.2.

Thioureas **9b-d** were obtained similarly.

N-(2-Methylphenyl)-$N_{(1)}$-(5-mercapto-3-methyl-4H-1,2,4-triazol-4-yl)thiourea (9b). Yield 81%; mp 214-215°C. ^{1}H NMR spectrum, δ, ppm: 2.26 (3H, s, CH_3); 2.28 (3H, s, CH_3); 7.15-7.24 (4H, m, C_6H_4); 9.88 (1H, s, NH); 10.2 (1H, s, NH); 13.3 (1H, s, SH). Found, %: N 25.0; S 22.9. $C_{11}H_{13}N_5S_2$. Calculated, %: N 25.1; S 23.0.

N-(3-Methylphenyl)-$N_{(1)}$-(5-mercapto-3-methyl-4H-1,2,4-triazol-4-yl)thiourea (9c). Yield 86%; mp 229-230°C. ^{1}H NMR spectrum, δ, ppm: 2.22 (3H, s, CH_3); 2.32 (3H, s, CH_3); 7.01-7.38 (4H, m, C_6H_4); 10.2 (2H, s, NH); 13.4 (1H, s, SH). Found, %: N 25.3; S 23.1. $C_{11}H_{13}N_5S_2$. Calculated, %: N 25.1; S 23.0.

N-(4-Methoxyphenyl)-$N_{(1)}$-(5-mercapto-3-methyl-4H-1,2,4-triazol-4-yl)thiourea (9d). Yield 79%; mp 222-223°C. ^{1}H NMR spectrum, δ, ppm: 2.27 (3H, s, CH_3); 3.88 (3H, s, OCH_3); 6.83 and 7.44 (4H, dd, C_6H_4); 9.98 (1H, s, NH); 10.0 (1H, s, NH); 13.3 (1H, s, SH). Found, %: N 24.0; S 21.5. $C_{11}H_{13}N_5OS_2$. Calculated, %: N 23.7; S 21.7.

N-(3-Hydroxypropyl)-$N_{(1)}$-(3-chloro-2-methylphenyl)thiourea (10). A mixture of compound **2f** (2.29 g) and 3-amino-1-propanol (0.75 g) in ethanol (40 ml) was boiled for 3 h on a water bath and then cooled. The precipitate was filtered out and crystallized from 2-propanol. Yield 2.18 g (84%); mp 118-119°C. ^{1}H NMR spectrum, δ, ppm: 1.69 (2H, q, CH_2); 2.26 (3H, s, CH_3); 3.49 (2H, q, CH_2); 3.57 (2H, q, CH_2); 4.15 (1H, s, OH); 7.13-7.22 (3H, m, C_6H_3); 7.64 (1H, s, NH); 9.94 (1H, s, NH). Found, %: N 10.5; S 12.5. $C_{11}H_{15}ClN_2OS$. Calculated, %: N 10.8; S 12.4.

$N_{(2)}$-(3-Chloro-2-methylphenyl)-2-amino-5,6-dihydro-4H-1,3-thiazine (11). A solution of compound **10** (1.5 g) in conc. HCl (20 ml) was boiled for 5 h and then cooled down. The reaction mixture was neutralized with conc. NH_4OH to ~pH 8. The precipitate was filtered out and crystallized from 2-propanol. Yield 1.39 g (82%); mp 128-129°C. ^{1}H NMR spectrum, δ, ppm: 2.03 (2H, q, CH_2); 2.14 (3H, s, CH_3); 2.94 (2H, t, CH_2); 3.32 (2H, t, CH_2); 6.64-6.94 (3H, m, C_6H_3); 7.13 (1H, s, NH). Found, %: N 11.5; S 13.5. $C_{11}H_{13}ClN_2S$. Calculated, %: N 11.6; S 13.3.

6-(4-Bromophenylamino)-3-methyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (12). A mixture of thiourea **2g** (2.6 g), thiol **4** (1.30 g), and DMF (20 ml) was heated for 30 h at 110°C and cooled down. The reaction mixture was poured into water, the crystallized precipitate was filtered out and crystallized from an ethanol–DMF mixture. Yield 1.36 g (44%); mp 220-222°C. ^{1}H NMR spectrum, δ, ppm: 2.05 (3H, s, CH_3); 7.49 and 7.59 (4H, dd, C_6H_4); 10.1 (1H, s, NH). Found, %: N 22.5; S 10.5. $C_{10}H_8BrN_5S$. Calculated, %: N 22.6; S 10.3.

$N_{(1)}$,$N_{(2)}$-Di(3-methyl-5-oxo-6-phenyl-4,5-dihydro-1,2,4-triazin-4-yl)thiourea (15). A mixture of compound **13** (2 g, 0.01 mol) and pure TMTD (2.4 g, 0.01 mol) in ethanol (20 ml) was boiled for 5 h and cooled down. The precipitate was filtered out and recrystallized from DMF. Yield 0.83 g (37%); mp 251-252°C. ^{1}H NMR spectrum, δ, ppm: 2.32 (6H, s, CH_3); 7.43 (6H, m, C_6H_5); 8.07 (4H, d, C_6H_5); 13.8 (2H, s, NH). Found, %: N 25.3; S 7.29. $C_{21}H_{18}N_8O_2S$. Calculated, %: N 25.1; S 7.18.

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