# A Novel Route to 1-Benzyl-1,2,4-triazole Derivatives through Disproportionation of Isothiosemicarbazones [1]



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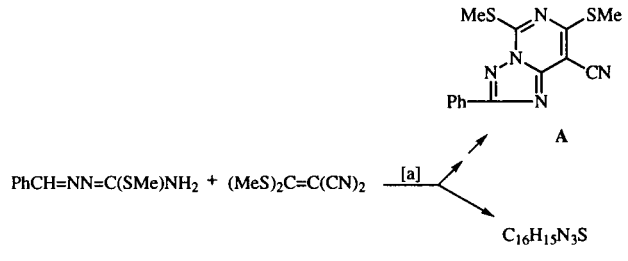
Received October 28, 1996

Aromatic isothiosemicarbazones **1-4** underwent disproportionation at elevated temperature in the presence of a thiol or a thiol-releasing substance to give 1-arylmethylene-3-alkylthio-5-aryl-1*H*-1,2,4-triazole derivatives **6-9** in moderate yields. An isothiosemicarbazone of aliphatic aldehyde with no α-hydrogen did not give rise to the corresponding disproportionation under the similar conditions. Cross reaction occurred between two different isothiosemicarbazones but the cross compound could be isolated only in a poor yield. Any inert solvent markedly inhibited the disproportionation reaction even only with a slight dilution. A tentative reaction mechanism, in which it might involve a potential nitrene-sulfonium ion pair as a key step, is presented.

*J. Heterocyclic Chem.*, **34**, 733 (1997).

In the course of a study on the selective nucleophilic substitution of the methylthio groups in 5,7-bis(methylthio)[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitrile (**A**) by a hard base, a benzyl-containing compound was found in the reaction mixture starting with benzaldehyde *S*-methylisothiosemicarbazone **1**, bis(methylthio)methylenemalononitrile and *N*-methylpiperidine for preparation of the substrate **A** (Scheme 1). We were much interested in the formation of the benzyl-containing compound because of the apparent reduction of the benzylidene moiety of the starting isothiosemicarbazone. After analytical and spectral study, it was found that the benzyl compound was 1-benzyl-3-methylthio-5-phenyl-1*H*-1,2,4-triazole (**6**), which had a novel substitution pattern on the 1,2,4-triazole ring and thus had not yet been reported previously. The present paper deals with a novel route to 1-benzyl-1,2,4-triazole derivatives through disproportionation of isothiosemicarbazones.

Scheme 1




[a] In *N*-methylpiperidine at 140° (bath temperature).

The *N*-benzyl structure of the compound **6** was supported by the observations of the signals δ 5.36 (2H, s) and δ 52.7 (tt, $^1J_{CH}$ = 140.0 Hz and $^3J_{CH}$ = 5.6 Hz) in the $^1H$ and $^{13}C$ nmr spectra, respectively, as well as a base peak m/z 91 (100%) which may probably be a tropylium ion in the mass spectrum. The appearance of the resonance peak at δ 52.7 as a triple triplet which is assignable to the methylene carbon is attributed to the long-range coupling with the two *ortho* protons on the phenyl group to which it is attached. This is supported by the $^{13}C$ nmr spectrum of triazole **9** which showed the corresponding signal as a simple triplet at δ 48.5 ($^1J_{CH}$ = 143.4 Hz) because the triazole has no *ortho* proton on the benzene ring. The magnitude of the chemical shift value 5.36 for the methylene protons strongly suggest that the methylene group should be linked to a nitrogen and not to a carbon atom.

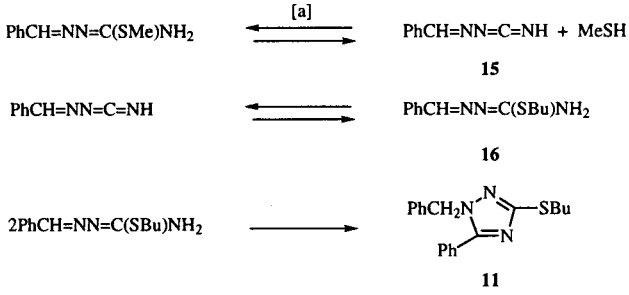
Subtraction of the easily assignable groups, *i.e.*, the benzyl, phenyl and methylthio groups from the molecular composition leaves a trivalent unit ($C_2N_3$). Taking into account the original arrangement of atoms in the isothiosemicarbazone **1**, the unit should be a 1,2,4-triazole ring and thus the trisubstituted triazole indicated above can be obtained.

The oxidation level [2] of each carbon which carries the phenyl group is -1 for benzyl group and +3 for C-5. Because the benzylidene carbon of the isothiosemicarbazone has the oxidation level of +1, the formation of triazole **6** might be the result of hydride transfer between the benzylidene carbons of two isothiosemicarbazone molecules. The hydride transfer was confirmed by the reaction of monodeuteriated isothiosemicarbazone **5** which gave the corresponding triazole-$d_2$ **10** as shown by the molecular ion $M^+$ (m/z 283) and the dideuteriotropylium ion (m/z 93, 100%). Both signals assigned to the methylene protons at δ 5.36 and the methylene carbon at δ 52.7 were disappeared in the dideuteriated triazole **10**. Consequently, the formation of triazole **6** can be interpreted as the result of a special disproportionation in which both oxidation and reduction species from the starting isothiosemicarbazone are incorporated together into a single molecule of the product.

Although the disproportionation product did not contain any structures originating from bis(methylthio)methylenemalononitrile, exclusion of bis(methylthio)methylenemalononitrile from the reaction mixture resulted in the marked reduction of the yield of the product. The initial reaction between isothiosemicarbazone and bis(methylthio)methylenemalononitrile might be a nucleophilic attack of the terminal amino group on the bis(methylthio)methylene carbon in the ketenedithioacetal [3] to generate methanethiol. It can be deduced from the above discussion that the thiol was the essential factor that actually stimulate the disproportionation reaction rather than bis(methylthio)methylenemalononitrile itself. In order to demonstrate this idea, *S*-methylisothiourea which has been known to generate easily methanethiol was incorporated into the reaction mixture consisting of isothiosemicarbazone **1** and *N*-methylpiperidine in place of bis(methylthio)methylenemalononitrile. The yield [4] of triazole **6** significantly increased to 43% compared with the yield 4.3% obtained in the absence of any thiol source.

Butanethiol was not suitable as a catalyst for disproportionation in spite of its favorable low-volatility which made it possible to maintain a higher concentration than that of the low-boiling methanethiol. Presumably the bulky alkyl group was an obstacle to the nucleophilic attack on the benzylidene carbon of isothiosemicarbazone and thus required prolonged heating periods of time which, in turn, promoted the alkyl-exchange reaction on the sulfur atom and resulted in extensive contamination of product **6** with 3-butylthiotriazole **11**. The formation of compound **11** may be interpreted as the result of participation of *S*-butylisothiosemicarbazone (**16**) in the disproportionation reaction, which may probably be produced by the addition of butanethiol to the carbodiimide **15** formed by the elimination of methanethiol from isothiosemicarbazone **1** (Scheme 2).

Scheme 2

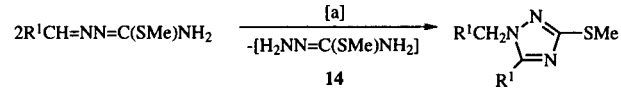


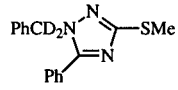

[a] At 140° (bath temperature) in the presence of butanethiol.

Consequently bis(methylthio)methylenemalononitrile functions as a good thiol source by sustained release of methanethiol under the reaction conditions. A strong base, such as tetrabutylammonium hydroxide, did not catalyze the present disproportionation and gave total recovery of the starting isothiosemicarbazone.

The disproportionation reaction was highly sensitive to the presence of a solvent or diluent. For example, addition of one ml of chlorobenzene to two mmoles of isothiosemicarbazone completely inhibited the reaction. Although it is conventional practice to use ketene dithioacetals in combination with bases [3], even *N*-methylpiperidine added as a base could act as a diluent and thus inhibit the reaction. Thus, the present reaction was best carried out by heating a mixture of isothiosemicarbazone and bis(methylthio)methylenemalononitrile in the molar ratio of 2:1 at 140° (bath temperature) under a hood for 2 hours (Scheme 3). Extraction of the product and the unreacted isothiosemicarbazone with hot diisopropyl ether, followed by chromatographic purification gave the disproportionation product in about 50% yield. No attempt was made to improve further the yield of 1-benzyltriazoles.

Scheme 3



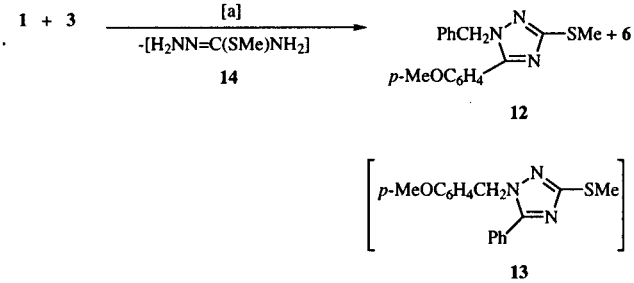

| No. | $R^1$ | No. | $R^1$ |
|---|---|---|---|
| **1** | Ph | **6** | Ph |
| **2** | 4-$ClC_6H_4$ | **7** | 4-$ClC_6H_4$ |
| **3** | 4-$MeOC_6H_4$ | **8** | 4-$MeOC_6H_4$ |
| **4** | 2,6-$Cl_2C_6H_3$ | **9** | 2,6-$Cl_2C_6H_3$ |
| **5** | $PhCD=NN=C(SMe)NH_2$ | **10** |  |



[a] At 140° (bath temperature) in the presence of bis(methylthio)methylenemalononitrile.

A cross reaction was performed by subjecting an equimolar mixture of two isothiosemicarbazones to similar reaction conditions (Scheme 4). Only a few percent of the cross compound **12** could be isolated and identified. The structure of the cross product thus obtained can safely be

Scheme 4

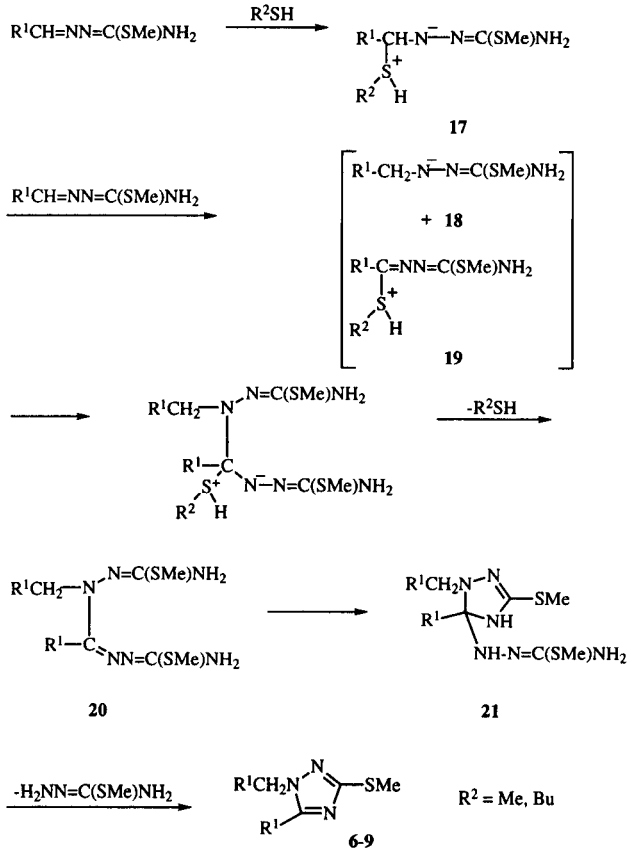



[a] At 140° (bath temperature) in the presence of bis(methylthio)methylenemalononitrile.

assigned as compound **12** and not to the alternative structure **13** on the basis of its mass spectrum which showed a prominent peak at m/z 91 due to the tropylium ion.

The first step of the disproportionation reaction may be the nucleophilic attack of a thiol on the benzylidene carbon of isothiosemicarbazone to generate an adduct **17** (Scheme 5). When the negatively charged nitrogen in **17** restores its carbon-nitrogen double bond, the hydride can transfer to the benzylidene carbon of another isothiosemicarbazone molecule to produce an ion pair consisting of a nitrene **18** and a sulfonium ion **19**. The ion pair could keep a sufficiently close proximity to each other to induce nucleophilic addition of **18** to **19** to form a bond between them. Loss of the thiol to produce a neutral species **20**, followed by intramolecular cyclization to a triazoline precursor **21** can furnish the disproportionation product with loss of *S*-methylisothiosemicarbazide **14**. The liberated *S*-methylisothiosemicarbazide **14** should be unstable and easily decompose under the reaction conditions. The proposed mechanism could explain why addition of a diluent seriously inhibits the present reaction.

Scheme 5




## EXPERIMENTAL

Melting points are uncorrected. Microanalyses were performed with a Yanaco CHN CORDER MT-5 analyser at the Microanalytical Laboratory of Kitasato University. The uv and mass spectra were recorded on JASCO UVIDEC 610 and JMS-AX 505 HA instruments, respectively. The $^1H$ and $^{13}C$ nmr spectra were obtained with a JNM EX-400 spectrometer operating at 400 and 100 MHz, respectively. Tetramethylsilane was used as an internal standard and J values are given in Hz. Preparative high-pressure liquid chromatography (hplc) was carried out on a Kusano Kagaku KHLC-201 instrument with a 100 x 22 or a 300 x 15 mm glass column packed with silica gel.

Isothiosemicarbazones.

Isothiosemicarbazones **1-5** were prepared according to the literature method [5].

Disproportionation Reaction of Isothiosemicarbazone **1** in the Presence of Bis(methylthio)methylenemalononitrile. Formation of 1-Benzyl-3-methylthio-5-phenyl-1*H*-1,2,4-triazole **6**.

A mixture of benzaldehyde *S*-methylisothiosemicarbazone **1** (0.97 g, 5 mmoles) and bis(methylthio)methylenemalononitrile (0.43 g, 2.5 mmoles) was heated at 140° (bath temperature) for 2 hours under a hood with occasional agitation. The sticky amorphous mass was mixed with sufficient silica gel (Wakogel C-300) to spread the tarry mass over the surface of the particles and to form a free-flowing powder. The powder was triturated repeatedly with hot isopropyl ether (5 x 10 ml) to separate the product from the dark-red tarry materials. The extracts, which contained the disproportionation product **6** and unreacted isothiosemicarbazone, were made acidic with concentrated hydrochloric acid to *p*H 2 and evaporated under reduced pressure. After removal of any water by azeotropic distillation with benzene (3 x 2 ml), the residue was mixed with silica gel (5.0 g) and extracted with hot isopropyl ether (10 x 8 ml). Evaporation of the solvent gave substantially pure triazole **6** (0.42 g, 60%) which was further purified by column chromatography on silica gel (Wakogel C-300, 40 g) with chloroform as the eluent followed by recrystallization from hexane-isopropyl ether (1:1) with active carbon to give the desired product as white fiber-like crystals, mp 77-78°; ms: m/z (relative intensity): 281 ($M^+$, 36), 190 (16) and 91 (100).

*Anal.* Calcd. for $C_{16}H_{15}N_3S$: C, 68.31; H, 5.38; N, 14.94; S, 11.38. Found: C, 68.14; H, 5.59; N, 14.86; S, 11.45.

The corresponding dideuteriated analog **10** was prepared in the same manner as described above starting with isothiosemicarbazone **5** and showed ms: (relative intensity): 283 ($M^+$, 76), 190 (31) and 93 (100).

Triazoles **7-9** were obtained similarly with appropriate modifications (Tables 1-3).

Disproportionation of Isothiosemicarbazone **1** in the Presence of *S*-Methylisothiuronium Hydriodide.

Finely divided thiourea (0.3 g, 4 mmoles) and iodomethane (0.6 g, 4 mmoles) were heated under reflux in methanol (3 ml) to dissolve any solid material and then the solution was boiled for 30 minutes. After the solvent was removed by evaporation, isothiosemicarbazone **1** (0.77 g, 4 mmoles) and *N*-methylpiperidine (0.4 ml) were added to the residue (0.90 g, quantitative) and

Table 1
Analytical and Physical Data for 1,3,5-Trisubstituted 1,2,4-Triazoles

| Compound No. | Yield (%) | Mp°C [Solvent] | Formula | Calcd./Found C | H | N | M+ (Relative Intensity) | Base Peak |
|---|---|---|---|---|---|---|---|---|
| **7** | 49.6 | 139-139.5 [a] | $C_{16}H_{13}Cl_2N_3S$ | 54.86<br>55.03 | 3.74<br>3.87 | 12.00<br>11.97 | 349(18) | 125 |
| **8** | 32.3 | 83-84 [b] | $C_{18}H_{19}N_3O_2S$ | 63.33<br>63.12 | 5.61<br>5.68 | 12.31<br>12.30 | 341(7) | 83 |
| **9** | 30.0 | 158-159 [b] | $C_{16}H_{11}Cl_4N_3S$ | 45.85<br>46.01 | 2.65<br>2.74 | 10.03<br>10.08 | 419(14) | 110 |
| **11** | 10.2 | Oil | $C_{19}H_{21}N_3S$ | 70.56<br>70.48 | 6.55<br>6.63 | 13.00<br>12.84 | 323(19) | 91 |
| **12** | 6.0 | 104-105 [c] | $C_{17}H_{17}N_3OS$ | 65.58<br>65.69 | 5.50<br>5.51 | 13.50<br>13.41 | 311(69) | 91 |

[a] Benzene; [b] 1:1 Benzene-hexane; [c] 1:5 Benzene-hexane.

Table 2
UV and $^1H$ NMR Spectral Data for 1,3,5-Trisubstituted 1,2,4-Triazoles

| Compound No. | UV [a] | $^1H$ NMR [b] |
|---|---|---|
| **6** | 203 (4.50), 237 sh (4.08), 264 (3.68) | 2.64 (s, 3H, Me), 5.36 (s, 2H, $CH_2$) and 7.17-7.57 (m, 10H, aromatic) |
| **7** | 204 (4.58), 223 (4.42), 2.42 sh (4.26), 275 sh (3.78) | 2.63 (s, 3H, Me), 5.30 (s, 2H, $CH_2$), 7.11, 7.32, 7.43 and 7.47 (each doublet, 2H, J = 8.3 Hz, aromatic) |
| **8** | 204 (4.58), 229 (4.31), 2.42 sh (4.25), 276 sh (4.01) | 2.63 (s, 3H, SMe), 3.78 and 3.83 (each singlet, 3H, OMe), 5.27 (s, 2H, $CH_2$), 6.86, 6.95, 7.12 and 7.50 (each doublet, 2H, J = 8.8 Hz, aromatic) |
| **9** | 205 (4.54), 227 sh (4.33), 245 sh (3.64) | 2.59 (s, 3H, Me), 5.44 (s, 2H, $CH_2$), 7.16-7.27 (m, 3H, aromatic) and 7.37 (s, 3H, aromatic) |
| **11** | 204 (4.51), 237 sh (4.11), 270 sh (3.61) | 0.93 (t, 3H, J = 7.3 Hz, Me), 1.47 (sex, 2H, J = 7.3 Hz, $CH_2$), 1.74 (quin, 2H, J = 7.3 Hz, $CH_2$), 3.18 (t, 2H, J = 7.3 Hz, $SCH_2$), 5.35 (s, 2H, $NCH_2$), 7.16-7.57 (m, 10H, aromatic) |
| **12** | 205 (4.58), 244 (4.21), 273 sh (3.99) | 2.63 (s, 3H, SMe), 3.83 (s, 3H, OMe), 5.35 (s, 2H, $CH_2$), 6.94 (d, 2H, J = 8.8 Hz, aromatic), 7.17-7.37 (m, 5H, aromatic) and 7.50 (d, 2H, J = 8.8 Hz, aromatic) |

[a] λ max (nm) (log ε) in ethanol; [b] δ, J (Hz) in deuteriochloroform.

Table 3
Chemical Shift Values of Triazole Ring Carbons [a]

| Compound No. | C-3 [b] | C-5 [c] |
|---|---|---|
| **6** | 161.1 | 156.3 |
| **7** | 161.6 | 155.3 |
| **8** | 160.7 | 156.0 |
| **9** | 160.7 | 150.7 |
| **10** | 161.1 | 156.3 |
| **11** | 160.4 | 156.2 |
| **12** | 160.9 | 156.3 |

[a] δ, ppm in deuteriochloroform; [b] q, $^3J_{CH}$ = 4.9 Hz, except for **11** which appeared as a triplet, $^3J_{CH}$ = 4.6 Hz; [c] appeared as a singlet.

the mixture was heated at 140° (bath temperature) for 2 hours. The *N*-methylpiperidine was evaporated under reduced pressure and the residue was subjected to the extraction procedure with hot isopropyl ether in the similar manner as described above to give substantially pure product **5** (0.24 g, 43%) as yellowish crystalline solid. The $^1H$ nmr spectrum was identical with that of the compound obtained in the presence of bis(methylthio)methylenemalononitrile.

Disproportionation of Isothiosemicarbazone **1** in the Presence of Butanethiol.

A mixture of isothiosemicarbazone **1** (0.97 g, 5 mmoles) and butanethiol (0.45 g, 5 mmoles) was heated at 140° (bath temperature) for 8 hours and the resulting amorphous material was worked up by the same procedure as above. Chromatographic separation of the products on silica gel (Wakogel C-300, 35 g) with chloroform gave triazoles **6** (0.086 g, 12%) and **11** (0.083 g, 10%).

Cross Reaction between Isothiosemicarbazones **1** and **3** in the Presence of Bis(methylthio)methylenemalononitrile.

A mixture of bis(methylthio)methylenemalononitrile (0.43 g, 2.5 mmoles), isothiosemicarbazones **1** (0.48 g, 2.5 mmoles) and **3** (0.56 g, 2.5 mmoles) was heated at 140° (bath temperature) for 2 hours under a hood with occasional agitation. After pretreatment of the reaction mixture to separate the disproportionation products from a tarry material and unreacted isothiosemicarbazones in the same manner as described above, the crude product was subjected to column chromatography on silica gel (Wakogel C-300, 40 g) with chloroform as the eluent to collect any fractions showing resonances at about δ 5.3 ppm. The frac-

tions, after removal of the solvent, were subjected to further chromatographic separation by hplc on silica gel eluting with dichloromethane to give triazole **6** (0.058 g, 17%) and the cross reaction product **12** (0.05 g, 6%). The cross compound was recrystallized from benzene-hexane (1:5) to give analytically pure compound as fiber-like crystals.

## REFERENCES AND NOTES

[1] For a previous report entitled Cyclization of Isothiosemicarbazones **10**, see C. Yamazaki, Y. Miyamoto and H. Sakima, *J. Chem. Soc., Perkin Trans. I*, 825 (1994).

[2] The oxidation level was estimated according to the definition described by G. M. Loudon, Organic Chemistry, II Ed, The Benjamin/Cummings Publishing Company, Inc., Menlo Park, California, 1988, pp 386-387.

[3] A. Kakehi, S. Ito and B. Wada, *Bull. Chem. Soc. Japan*, **57**, 893 (1984); G. E. H. Elgemeie, S. E. El-Ezbawy, H. A. Ali and Abdel-Kader Mansour, *Bull. Chem. Soc. Japan*, **67**, 738 (1994); Y. Tominaga, J.-K. Luo and R. N. Castle, *J. Heterocyclic Chem.*, **31**, 771 (1994).

[4] Throughout the text, the yields of the products were determined for the isolated compounds.

[5] C. Yamazaki, *Can. J. Chem.*, **53**, 610 (1975); *Bull. Chem. Soc. Japan*, **54**, 1767 (1981).