Monatshefte für Chemie 136, 2045–2049 (2005)
DOI 10.1007/s00706-005-0372-1

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

A Coupling Reaction of 4-Amino-5-mercapto-3-substituted-1,2,4-triazoles to Generate Symmetrically Substituted Hydrazines

Ming Li[1,*], **Guilong Zhao**[1], **Lirong Wen**[1], **Xiao Wang**[1], **Xiaomao Zou**[2], and **Huazheng Yang**[2]

[1] College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P.R. China
[2] State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P.R. China

Received March 11, 2005; accepted (revised) March 29, 2005
Published online November 14, 2005

Summary. A novel coupling reaction of 4-amino-5-mercapto-3-substituted-1,2,4-triazoles to generate symmetrically substituted hydrazines, *N*,*N*′-bis(5-mercapto-3-substituted-1,2,4-triazol-4-yl)hydrazines was unexpectedly observed. Five examples are presented to demonstrate this reaction. All isolated products were unambiguously characterized.

Keywords. Triazole; Coupling reaction; Acetal; Synthesis.

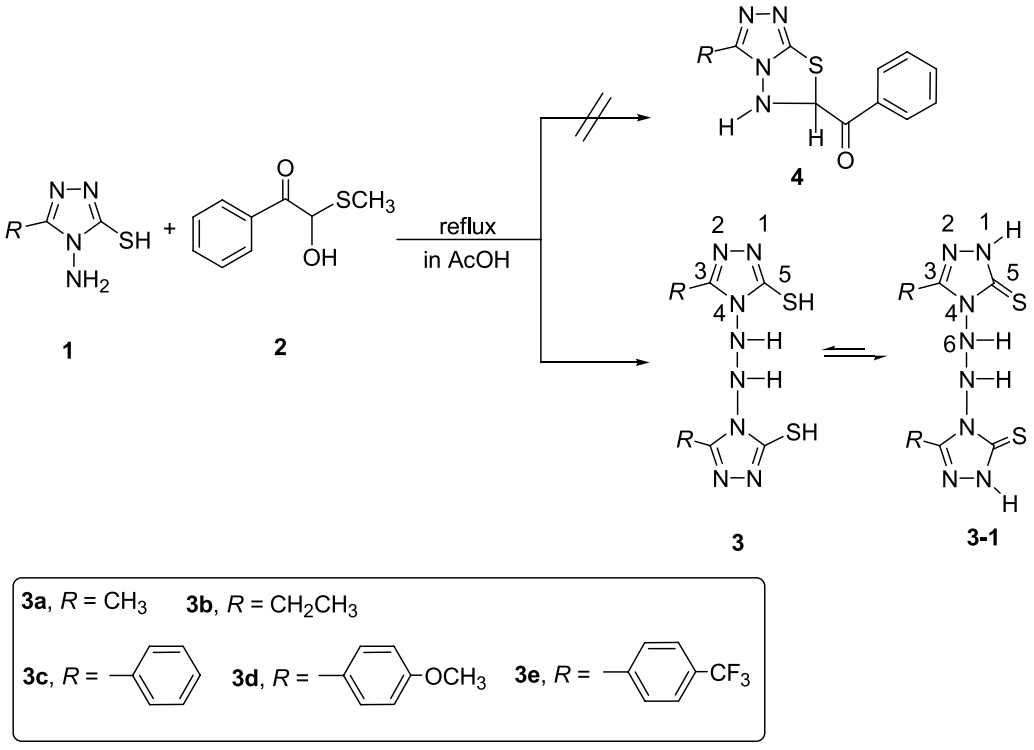
Introduction

Triazole derivatives have been reported as a class of useful heterocyclic compounds, and have found widespread applications in the fields of agrochemicals and pharmaceuticals [1–3]. During the course of our investigation directed towards the synthesis of biologically active triazole compounds, we have unexpectedly discovered a novel coupling reaction of 4-amino-5-mercapto-3-substituted-1,2,4-triazoles **1** [4] to give rise to *N*,*N*′-bis(5-mercapto-3-substituted-1,2,4-triazol-4-yl)hydrazines **3**. Thus, the reaction of **1** with α-hydroxy-α-methylthioacetophenone **2** [5] in refluxing glacial acetic acid or pyridine did not produce the anticipated compounds **4**; instead, it yielded the novel coupling products **3** in satisfactory isolated yields (Scheme 1).

Results and Discussion

This novel coupling reaction was first observed in the case of **1a**. Initially, the reaction of **1a** with the acetophenone **2** was carried out in refluxing dry ethanol

* Corresponding author. E-mail: liming928@263.net



Scheme 1

with several drops of concentrated hydrochloric acid. However, **2** was readily transformed into a new compound, while **1a** was not consumed at all. The new compound was isolated and identified as the hemiacetal, α-ethoxy-α-hydroxyacetophenone **5**, resulting from the substitution of the methylthio group in **2** by the ethoxyl group ethanol. In fact, the hemiacetal was observed when **2** was recrystallized from absolute ethanol.

The reaction of **1a** with **2** was subsequently performed in refluxing glacial acetic acid, and the coupling product **3a** was unexpectedly isolated in a satisfactory yield. This reaction was also performed in refluxing pyridine, where we expected to obtain the initially anticipated product **4** ($R = CH_3$), only to find that the reaction also gave rise to the coupling product **3a** in a lower yield than that obtained in refluxing glacial acetic acid. This reaction might well be extended to develop other similar protocols for the synthesis of such symmetrically substituted hydrazines starting from other commonly encountered amines, such as aliphatic amines and aniline derivatives. Encouraged by the novel structure of **3a** and especially the above-mentioned great potential, we thus tested the generality of the reaction of **1a** with **2**. The substituents at C-3 of the triazole ring were extended to both aliphatic and aromatic moieties with both electron-withdrawing and electron-donating groups attached to them (Scheme 1). To our surprise, all these substrates **1** gave satisfactory results, and the ready isolation of the coupling products **3** proved the expected generality of this reaction. Further extension of the generality of this reaction is now in progress in our laboratory, with great expectation to develop a more general procedure for the coupling reaction of commonly encountered

amines, such as aliphatic amines and other aromatic amines. Preliminary results have shown that the reactions involving aromatic amines, such as aniline, did not proceed chemoselectively under the above-mentioned reaction conditions and a large number of products was generated. Therefore, the optimization of the reaction conditions for these unsatisfactory reactions is now under investigation. It is also worth noting that when $R = H$, the coupling reaction of **1** was not observed under the aforementioned reaction conditions, and this reaction may require more vigorous conditions.

It is obvious that the reaction mechanism is considerably interesting and challenging. Also, the role played by **2** in this reaction is not very clear; nonetheless, it is clear that **2** does not function as a catalyst, since a catalytic amount of **2** in this reaction has proved useless to the transformation of **1** to **3** and one equivalent of **2** is required in each case. The investigation into this mechanism is now under way.

The work-up procedure was also optimized. The use of chloroform in the procedure was remarkably effective in the simplification of the work-up, since it could dissolve practically all the other components in the residue except the coupling product **3a**, due to the poor solubility of **3a** in chloroform. However, in the case of **3d**, acetonitrile was employed instead of chloroform. An attempt to use column chromatography to purify the product was successful but considerably tedious, owing to the existence of impurities that possess similar polarity to that of the target molecule.

Compound **3** actually exists as a tautomeric form, 1,2,4-triazol-5-thione **3-1** (Scheme 1), with the H atom in the mercapto group having been transferred to the N-1 position. The absence of the absorption band of S–H (usually at 2550–2600 cm^{-1}) in the IR spectrum of **3** provided proof for the thione form [6].

In conclusion, we have discovered a novel coupling reaction of 4-amino-5-mercapto-3-substituted-1,2,4-triazoles **1** to generate the symmetrically substituted hydrazines **3** providing great potential to extend this reaction to other substrates, such as aliphatic and aromatic amines.

Experimental

Melting points were determined on a RY-1 apparatus and are uncorrected. H NMR spectra were recorded on a JEOL JNM-ECP 600 M spectrometer at 600 MHz and ^{13}C NMR spectra were at 150 MHz, with *DMSO*-d_6 as solvent and *TMS* as internal standard. IR spectra were obtained on a Nicolet 501P FT-IR spectrophotometer from KBr discs. Mass spectra were recorded on a VG ZAB-HS mass spectrometer at 8 KV using fast-atom bombardment technique. Elemental analyses were carried out with an ELEMENTO EL-III CHNS analyzer and gave satisfactory results.

In a typical procedure for the synthesis of **3**, 0.547 g **2** (3 mmol) and 0.391 g **1a** (3 mmol) were dissolved in 20 cm^3 glacial acetic acid, and the resulting solution was then refluxed for ~6 h. On cooling, the solvent was evaporated to dryness on a rotary evaporator to furnish a solid residue, which was transferred into a flask containing 40 cm^3 $CHCl_3$. The obtained suspension solution was subsequently stirred for ~5 h and the solid was collected, which upon recrystallization from absolute ethanol yielded **3a** as colorless needles.

N,N′-Bis(5-mercapto-3-methyl-1,2,4-triazol-4-yl)hydrazine (**3a**, $C_6H_{10}N_8S_2$)
Yield 65%; mp 273–275°C; ^1H NMR: $\delta = 2.17$ (s, 3H×2, CH_3×2), 13.05 (br, s, 1H×2, NH×2, NH-1 or NH-6), 13.17 (br, s, 1H×2, NH×2, NH-6 or NH-1) ppm; ^{13}C NMR: $\delta = 10.85$ (CH_3), 148.87 (C-3),

165.88 (C-5) ppm; IR (KBr): $\bar{\nu} = 3119$ (N-H), 1462, 1548, 1608 (aromatic skeleton), 1249 (C=S), 1391 (CH_3) cm^{-1}; FAB-MS (8 kV): $m/z = 259$ (M + 1).

*N,N′-Bis(3-ethyl-5-mercapto-1,2,4-triazol-4-yl)hydrazine (***3b**, $C_8H_{14}N_8S_2$)
Colorless needles; yield 70%; mp 254–256°C; ^{1}H NMR: $\delta = 1.14$–1.70 (t, 3H×2, CH_3×2, $J = 7.7$ Hz), 2.51–2.55 (q, 2H×2, CH_2, $J = 7.7$ Hz), 13.10 (br, s, 1H×2, NH×2, NH-1 or NH-6), 13.19 (br, s, 1H×2, NH×2, NH-6 or NH-1) ppm; ^{13}C NMR: $\delta = 10.12$ (CH_3), 15.74 (CH_2), 148.87 (C-3), 165.88 (C-5) ppm; IR (KBr): $\bar{\nu} = 3125$ (N-H), 1464, 1552, 1602 (aromatic skeleton), 1248 (C=S), 1389 (CH_3) cm^{-1}; FAB-MS (8 kV): $m/z = 287$ (M + 1).

N,N′-Bis(5-mercapto-3-phenyl-1,2,4-triazol-4-yl)hydrazine (**3c**, $C_{16}H_{14}N_8S_2$)
Colorless needles; yield: 59%; mp 259–260°C; ^{1}H NMR: $\delta = 7.51$–7.53, 7.90–7.92 (mm, (3H + 2H)×2, Ph-H), 13.70 (br, s, 1H×2, NH×2, NH-1 or NH-6), 13.87 (br, s, 1H×2, NH×2, NH-6 or NH-1) ppm; ^{13}C NMR: $\delta = 125.42$, 125.62, 129.10, 130.60 (C of Ph), 150.16 (C-3), 166.97 (C-5) ppm; IR (KBr): $\bar{\nu} = 3123$ (N-H), 1464, 1550, 1600 (aromatic skeleton), 1249 (C=S), 1380 (CH_3) cm^{-1}; FAB-MS (8 kV): $m/z = 383$ (M + 1).

N,N′-Bis[5-mercapto-3-(p-methoxyphenyl)-1,2,4-triazol-4-yl]hydrazine (**3d**, $C_{18}H_{18}N_8O_2S_2$)
Colorless needles; yield: 68%; mp 253–255°C; ^{1}H NMR: $\delta = 3.82$ (s, 3H, CH_3), 7.06–7.08, 7.84–7.86 (dd, 2H×2 each, $J = 9.2$ Hz), 13.57 (br, s, 1H×2, NH×2, NH-1 or NH-6), 13.71 (br, s, 1H×2, NH×2, NH-6 or NH-1) ppm; ^{13}C NMR: $\delta = 55.37$ (CH_3), 114.53, 117.85, 127.30, 160.98 (C of Ph), 150.10 (C-3), 166.60 (C-5) ppm; IR (KBr): $\bar{\nu} = 3129$ (N-H), 1450, 1568, 1599 (aromatic skeleton), 1257 (C=S), 1384 (CH_3) cm^{-1}; FAB-MS (8 kV): $m/z = 443$ (M + 1).

N,N′-Bis[5-mercapto-3-(p-trifluoromethylphenyl)-1,2,4-triazol-4-yl]hydrazine
(**3e**, $C_{18}H_{12}F_6N_8S_2$)
Colorless needles; yield: 73%; mp 273–274°C; ^{1}H NMR: $\delta = 7.91$–7.92, 8.12–8.14 (dd, 2H×2 each, $J = 8.3$ Hz), 13.89 (br, s, 2H×2, NH×2, NH-1 and NH-6) ppm; ^{13}C NMR: $\delta = 122.97$, 124.77, 126.11, 126.42 (C of Ph), 129.30 (CF_3), 149.08 (C-3), 167.49 (C-5) ppm; IR (KBr): $\bar{\nu} = 3134$ (N-H), 1460, 1545, 1601 (aromatic skeleton), 1245 (C=S), 1380 (CH_3) cm^{-1}; FAB-MS (8 kV): $m/z = 519$ (M + 1).

The Preparation of Hemiacetal ***5***
In the above-mentioned procedure for the synthesis of **3**, the solvent was displaced by dry ethanol with several drops of conc HCL. The mixture was then stirred while refluxing for 3–4 h. The new compound as monitored by TLC was isolated using column chromatography as a colorless oil. ^{1}H NMR: $\delta = 8.06$–8.07, 7.64–7.66, 7.52–7.55 (m each, 2H + 1H + 2H, Ph–H), 6.99 (br, s, 1H, OH), 5.53 (s, 1H, CH), 3.79–3.84, 3.60–3.65 (q + q each, 1H each, CH_2, $^2J = 9.8$ Hz, $^3J = 7.0$ Hz), 1.15–1.17 (t, 3H, $J = 7.0$ Hz) ppm. The prochirality of the CH_2 group can be observed from the above spectral data, owing to the existence of the chiral center at the α-C; IR (neat): $\bar{\nu} = 3423$ (OH), 1692 (C=O), 1227, 1283 (C–O) cm^{-1}.

Acknowledgements

The authors express sincere gratitude to the Natural Science Foundation of China (No. 20572057) and the Natural Science Foundation of Shandong Province (No. Y2003B01) for financial support.

References

[1] Maxwell JR, Wasdahl DA, Wolfson AC, Stenberg V (1984) J Med Chem **27**: 1565
[2] Chiara BV, Maurizio M, Augusto CA, Mario G (1998) J Heterocyclic Chem **35**: 29

[3] Couderchet M, Schmalfub J, Boger P (1998) Pestic Sci **52**: 381
[4] Triazoles **1** were readily prepared according to the earlier reports, Sasaki T, Ito E (1981) J Heterocyclic Chem **18**: 1353; Reid JR, Heindel ND (1976) J Heterocyclic Chem **13**: 925
[5] Compound **2** was readily prepared by the well-known *Pummerer* rearrangement according to Russell GA, Mikol GJ (1966) J Am Chem Soc **88**: 5498
[6] This conclusion has been verified unambiguously by X-ray diffraction method. Please see our previous research result concerning a similar tautomerism for reference, Wen LR, Li GQ, Li M, Jing SX, Zhang SS (2003) Chinese J Structural Chem **22**: 529