Dithiocarbamates as an Efficient Intermediate for the Synthesis of Symmetrical Substituted 2,5-Diamino-1,3,4-thiadiazoles in Water

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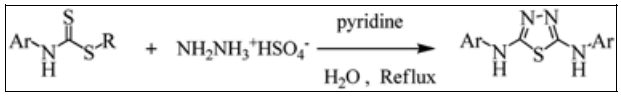

Synthesis of symmetrical substituted 2,5-diamino-1,3,4-thiadiazoles is described. Reaction of easily prepared dithiocarbamates with hydrazine gives the corresponding thiadiazoles in moderate to good yields. This method is new, efficient, and simple especially in the work-up procedure.

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INTRODUCTION

Heterocyclic compounds constitute a large family of organic compounds, which include many biological materials in life. Especially five-membered ring heterocyclic compounds serve as the core compound of a large number of substances that have interesting biological activities [1]. One class of this family is 1,3,4-thiadiazoles, which due to its heteroaromatic characters and biological properties have been of special interested in recent years. 1,3,4-thiadiazoles have been used in numerous therapeutic areas such as antimicrobial [2,3], antitumor [2], antibacterial [4,5], anticonvulsant and antiangiogenic [6], antihypertensive [7], hypoglycemic activity [8], and are key intermediates in the preparation of various biologically active compounds such as megazol [9], acetazolamide [10], antitubercular [11], antifungal [12], anti-inflammatory [13], analgesic activity, and lower ulcerogenic potential [14]. Substituted 1, 3, 4-thiadiazoles are also useful compounds in agriculture (as herbicides, fungicides, bactericides, and plant growth regulator) [15] and in many other fields of technology such as dyes, lubricating compositions, optically active liquid crystals, and photographic materials [16].

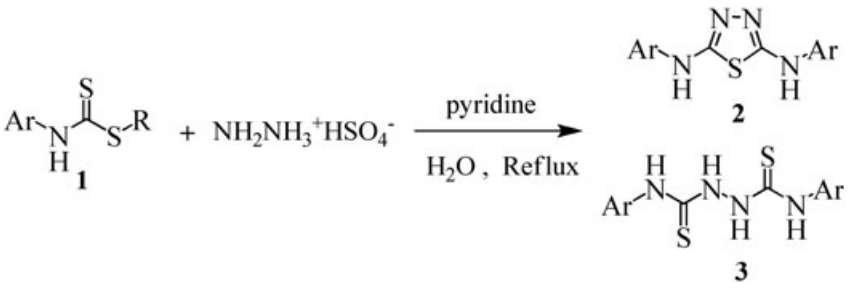
Synthesis of 1,3,4-thiadiazoles usually involves multistep procedures such as cyclization of thiosemicarbazide with di-(2-pyridyl)thionocarbonate (DPT), dicyclohexylcarbodiimide (DCC), [17] or concentrated strong mineral acids [18], or cyclodehydration reaction of acylthiosemicarbazate bounded to a resin with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC), TMSCl, PPh_3, $SOCl_2$, PCl_5, and diphenylchlorophosphate [1,19]. A few publications have reported the synthesis of these compounds under milder conditions, such as oxidative cyclization of thiosemicarbazone with $FeCl_3$ [16], or reaction of thiosemicarbazide, and CS_2 under reflux condition [20].

Although there are many reports for the synthesis of thiadiazoles, few reports are available for the synthesis of symmetrical 2,5-disubstituted amino-1,3,4-thiadiazoles in the literatures. Okuma *et al.* reported synthesis of the symmetrical 2,5-di (*p*-tolyl)-1,3,4-thiadiazole by the reaction of disulfur dichloride and *p*-tolylaldehyde hydrazone in the presence of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) [21]. Thompson and coworkers also have synthesized symmetrical thiadiazoles and used these compounds as ligand in the coordination chemistry [22]. Hassan *et al.* have found the 2,5-disubstituted amino-1,3,4-thiadiazoles as byproduct [23].

RESULTS AND DISSCUSION

Recently, we have reported a one-pot procedure for the synthesis of 2-amino-5-substituted-1,3,4-thiadiazoles in water by using dithiocarbamates and acid hydrazides [24]. As the biological activity of thiadiazoles are depending on the type of modification in the ring, and in continuation of our research on dithiocarbamates, we were interested in the synthesis of a range of symmetrical 2,5-disubstituted amino-1,3,4- thiadiazoles under mild reaction conditions with the reaction of dithiocarbamates with hydrazine salt (Scheme 1). For this purpose, we have synthesized the starting materials by the reaction of aromatic amines, carbon disulfide, alkyl halide or acrylonitrile in the presence of triethylamine [25]. After synthesizing of the starting materials, we focused on the optimization of the reaction conditions by varying the ratio of the starting materials, pyridine or triethyl amine as promoter, temperature, and the solvent. We have found that the best condition was when two equivalents of dithiocarbamate, one equivalent of hydrazine sulfate, and 2-3 equiv. of pyridine were used in

Scheme 1. Reaction of dithiocarbamates with hydrazine salt to prepare thiadiazole rings.



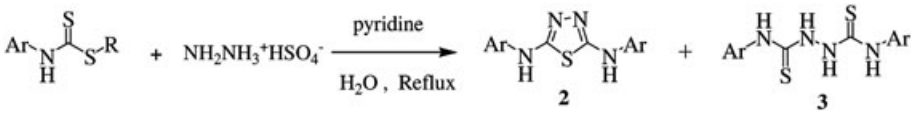
water under reflux condition. Under these optimal conditions 2,5-disubstituted amino-1,3,4-thiadiazoles **2** were obtained as the major products.

As shown in Table 1, dithiocarbamates prepared with ethyl iodide, allyl chloride, and acrylonitrile gave the thiadiazole ring as the only product in good yields. Although the reaction of benzyl dithiocarbamates with hydrazine sulfate gave the uncyclized product **3** under the same conditions, but by using the 1:1 ratio of water and dimethyl sulfoxide (DMSO) as solvent, the thiadiazole rings were obtained in moderate yields. Electron-donating and withdrawing groups on the aromatic ring of amine did not affect the reaction condition. This reaction condition is not efficient for primary and secondary aliphatic amines. The structure of the products was elucidated by their ^{1}H and ^{13}C nuclear magnetic resonance (NMR), and carbon-hydrogen-nitrogen analysis (CHN) elemental analysis. The ^{1}H NMR of the products show a broad peaks at 8.5–11 ppm in DMSO as NMR solvent, whereas the uncyclized products show two broad peaks at 8–12 ppm for the N—H groups. The carbon NMR shows a peak at 155–165 ppm, which is related to the thiadiazole ring.

Proposed mechanism for the synthesis of substituted 2, 5-diamino-1,3,4-thiadiazoles is shown in Scheme 2. Mixture of pyridine and water give a mild basic media in which the hydrazine sulfate was converted to hydrazine.

Table 1

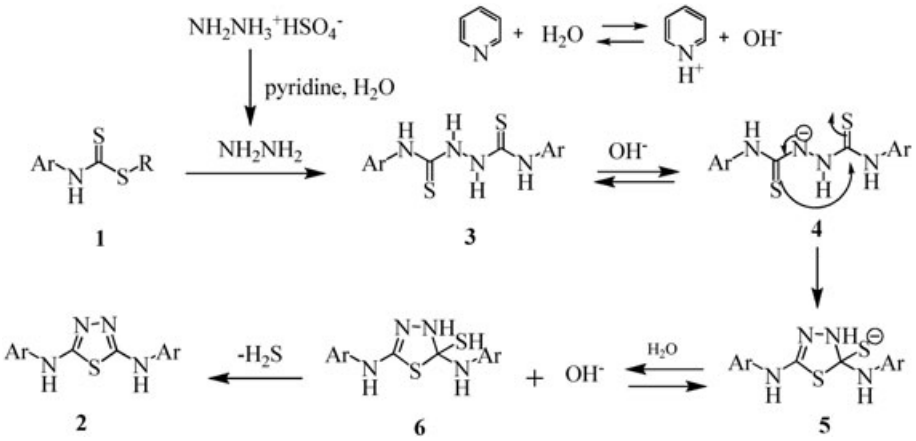
Synthesis of substituted 2, 5-diamino-1,3,4-thiadiazoles using dithiocarbamates and hydrazine sulfate in water.[a]



Entry	Ar	R	Product-2[b] (Mp)	Product-3[b]
1	Ph	—CH_2CH_2CN	62 (244–7)[26][c]	–
2	4-ClC_6H_4	—CH_2CH_2CN	82 (256–8)[27]	–
3	4-BrC_6H_4	—CH_2CH_2CN	95 (251–3)[28]	–
4	$C_{10}H_7$	—CH_2CH_2CN	66 (263–5)	–
5	Ph	—CH_2CH_3	42	–
6	4-ClC_6H_4	—CH_2CH_3	61	–
7	4-BrC_6H_4	—CH_2CH_3	45	–
8	$C_{10}H_7$	—CH_2CH_3	84	–
9	4-$MeOC_6H_4$	—CH_2CH_3	60 [27]	–
10	4-MeC_6H_4	—CH_2CH_3	61 (252–6)[27b]	–
11	3,4-$Cl_2C_6H_3$	—CH_2CH_3	62 (260—3)	–
12	Ph	—$CH_2CH{=}CH_2$	50	–
13	4-ClC_6H_4	—$CH_2CH{=}CH_2$	28	–
14	4-BrC_6H_4	—$CH_2CH{=}CH_2$	40	–
15	$C_{10}H_7$	—$CH_2CH{=}CH_2$	75	–
16	Ph	—$CH_2C_6H_5$	25[d]	25[29]
17	4-ClC_6H_4	—$CH_2C_6H_5$	50[d]	10[27]
18	4-BrC_6H_4	—$CH_2C_6H_5$	29[d]	40[28]
19	$C_{10}H_7$	—$CH_2C_6H_5$	66[d]	–

[a]Reaction conditions: dithiocarbamate (2 mmole), hydrazine sulfate (1 mmol), pyridine (2–3 mmol), and water (5 mL) for 20 h at reflux.
[b]Isolated yields.
[c]References for the known compounds.
[d]The reaction was carried out in 1:1 portion of water and DMSO at reflux.

Scheme 2. Proposed mechanism for synthesis of thiadiazole ring.



So it can attack dithiocarbamate **1** to prepare compound **3**. In basic media, compound **3** was converted to the anion **4**. Cyclization via nucleophilic attack of sulfur on the thiocarbonyl group produced anion **5**, which was converted to **6** by absorbing a proton from water. Aromatization of **5** proceeded by elimination of H_2S [24].

CONCLUSIONS

In conclusion, we have shown a new protocol for the synthesis of 2,5-disubstituted amino-1,3,4-thiadiazoles with the reaction of dithiocarbamates prepared with aromatic amines and hydrazine sulfate in water. The procedure is mild, efficient, and gives good yields. It avoids hazardous organic solvents and toxic catalysts, especially in the cyclization step. The work-up is simple and the products were obtained by simple filtration.

EXPERIMENTAL

Genaral. All reactions were carried out in an atmosphere of air. Chemicals and solvents were purchased from Merck and Fluka and used as received. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300-MHz spectrometer. Chemical shifts are reported in (ppm) relative to tetramethylsilane (TMS) or $CDCl_3$ as internal. Dithiocarbamates were prepared according to the reported procedures.

General procedure for the preparation of 2,5- disubstituted amino-1,3,4-thiadiazole. 2 mmol of dithiocarbamate, 1 mmol of hydrazine sulfate salt, and 2–3 mmol pyridine were added to 5-mL water. The mixture was heated under reflux condition for 20 h with vigorous stirring until reaction was complete. Then, the mixture was cooled to room temperature, and the product was filtered and washed with water and petroleum ether to obtain the pure 2,5-disubstituted amino-1,3,4-thiadiazoles. In the case of entries 16–18, the filtrate was extracted with ethyl acetate to give the uncyclized products. The organic layer was washed with water (three times) and then treated with sodium sulfate. Evaporation of the solvent gives the crude product that was purified by recryctalization in ethanol. Structure of the products characterized with their IR, ^{1}HNMR, ^{13}CNMR, and CHN analysis. spectroscopic data for selected compounds: N^2,N^5-bis (4-chlorophenyl)-1,3,4-thiadiazole-2,5-diamine: **(Table** 1, **Entries 2, 6, 13, and 17)** mp 256–258°C; IR (KBr) υ_{max} 3212, 3112, 1598, 1546, 1482, 1444, 1189, 746, 693 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 7.35 (d, J = 8.8 Hz, 4H), 7.59 (d, J = 8.8 Hz, 4H), 10.05 (s, 2H, —NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) = 119.2, 125.3, 129.6, 140.8, 156.5. Anal. Calcd. for $C_{14}H_{10}Cl_2N_4S$: C, 49.85; H, 2.96; N, 16.61. Found: C, 49.52; H, 2.91; N, 16.27. N^2,N^5-bis (naphthalen-2-yl)-1,3,4-thiadiazole-2,5-diamine **(Table** 1, **entries 4, 8, 15, 19)**: mp 263–265°C; IR (KBr) υ_{max} 3196, 1581, 1541, 1469, 1396, 1251, 790, 765, 619 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.49-7.60 (m, 8H), 7.83 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 7.9 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 9.79 (s, 2H, —NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) = 114.9, 121.9, 122.4, 125.1, 125.6, 126.1, 128.3, 133.8, 136.8, 143.6, 157.9. Anal. Calcd. for $C_{22}H_{16}N_4S$: C, 71.73; H, 4.35; N, 15.21. Found: C, 71.06; H, 4.17; N, 15.01. N^2,N^5-bis(3,4-dichlorophenyl)-1,3,4-thiadiazole-2,5-diamine **(Table** 1, **entry 11)**: mp 260–263°C; IR (KBr) υ_{max} 3391, 3248, 1625, 1596, 1536, 1475, 1131, 810 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 7.37 (dd, J = 8.8 and 2.2 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 2.2 Hz, 2H), 10.3 (s, 2H, —NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) = 117.1, 117.9, 122.3, 130.7, 131.2, 140.7, 155.6. Anal. Calcd. for $C_{14}H_8Cl_4N_4S$: C, 41.37; H, 1.97; N, 13.38. Found: C, 41.43; H, 1.96; N, 13.93.

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REFERENCES AND NOTES

[1] Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Gong, Y.-D. J Comb Chem 2005, 7, 816.

[2] Swamy, S. N.; Priya, B. B. S.; Doreswamy, P. B. H.; Prasad, J. S.; Rangappa, K. S. Eur J Med Chem 2006, 41, 531.

[3] Kaleta, Z.; Makowski, B. T.; Sos, T.; Dembinski, R. Org Lett 2006, 8, 1625.

[4] Jazayeri, S.; Moshafi, M. H.; Firoozpour, L.; Emami, S.; Rajabalian, S.; Haddad, M.; Pahlavanzadeh, F.; Esnaashari, M.; Shafiee, A.; Foroumadi, A. Eur J Med Chem 2009, 44, 1205.

[5] Rozen, M. H.; Blatter, H. M. U.S. Pat. 3,624,098, 1971; Chem Abstr 1982, 96, 142833e.

[6] Rzeski, W.; Matysiakb, J.; Kandefer-Szerszen, M. Bioorg Med Chem 2007, 15, 3201.

[7] Turner, S.; Myers, M.; Gadie, B.; Nelson, A. J.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. J Med Chem 1988, 31, 902.

[8] Hanna, M. A.; Girges, M. M.; Rasala, D.; Gawinecki, R. Drug Res 1995, 45, 1074.

[9] Carvalho, S. A.; Lopes, F. A. S.; Salomão, K.; Romeiro, N. C.; Wardell, S. M. S. V.; de Castro, S. L; da Silva, E. F.; Fraga, C. A. M. Bioorg Med Chem 2008, 16, 413.

[10] Almajan, G. L.; Innocenti, A.; Puccetti, L.; Manole, G.; Barbuceanu, S.; Saramet, I.; Scozzafava, A.; Supuran, C. T. Bioorg Med Chem Lett 2005, 15, 2347.

[11] Kolavi, G.; Hegde, V.; Khazi, I. A.; Gadad, P. Bioorg Med Chem 2006, 14, 3069.

[12] Chen, C.-J.; Song, B.-A.; Yang, S.; Xu, G.-F.; Bhadury, P. S.; Jin, L.-H.; Hu, D.-Y.; Li, Q.-Z.; Liu, F.; Xue, W.; Lu, P.; Chen, Z. Bioorg Med Chem 2007, 15, 3981.

[13] Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. J Med Chem 1993, 36, 1802.

[14] Kumar, H.; Javed, S. A.; Khan, S. A.; Amir, M. Eur J Med Chem 2008, 43, 2688.

[15] Dong, H.-S.; Quan, B.; Zhu, D.-W.; Li, W.-D. J Mol Struct 2002, 613, 1.

[16] Kilburn, J. P.; Lau, J.; Jones, R. C. F. Tetrahedron Lett 2003, 44, 7825.

[17] Severinsen, R.; Kilburn, J. P.; Lau, J. F. Tetrahedron 2005, 61, 5565.

[18] Oru, E. E.; Rollas, S.; Kandemirli, F.; Shvets, N.; Dimoglo, A. S. J Med Chem 2004, 47, 6760.

[19] Tu, G.-G.; Li, S.-H.; Huang, H.-M.; Li, G.; Xiong, F.; Mai, X.; Zhu, H.-W.; Kuang, B.-H.; Xu, W. F. Bioorg Med Chem 2008, 16, 6663.

[20] Talath, S.; Gadad, A. K. Eur. J Med Chem 2006, 41, 918.

[21] Okuma, K.; Nagakura, K.; Nakamija, Y.; Kubo, K.; Shioji, K. Synthesis 2004, 1929.

[22] Tandon, S. S.; Chen, L.; Thompson, L. K.; Bridson, J. N. Inorg Chem 1994, 33, 490.

[23] Hassan, A. A.; Mourad, A. F. E.; El-shaieb, K. M.; Abou-Zied, A. H. Molecules 2005, 10, 822.

[24] Aryanasab, F.; Ziyaei-Halimehjani, A.; Saidi, M. R., Tetrahedron Lett 2010, 51, 790.

[25] (a) Ziyaei-Halimehjani, A.; Maleki, H.; Saidi, M. R. Tetrahedron Lett 2009, 50, 2747; (b) Ziyaei-Halimehjani, A.; Pourshojaei, Y.; Saidi, M. R. Tetrahedron Lett 2009, 50, 32; (c) Ziyaei-Halimehjani, A.; Marjani, K.; Ashouri, A. Green Chem, 2010, 12, 1306; (d) Azizi, N.; Aryanasab, F.; Torkian, L.; Ziyaei-Halimehjani, A.; Saidi, M. R. J Org Chem 2006, 71, 3634.

[26] Hassan, A. A.; Mourad, A. E.; El-Shaieb, K. M.; Abou-Zied, A. H. Molecules 2005, 10, 822.

[27] (a) Joshua, C. P.; Annie, V. J. Ind Chem Soc 1990, 67, 759; (b) Konher, M. V. Ind J Chem 1973, 11, 321.

[28] Guha, P. C. J Am Chem Soc 1923, 45, 1036.

[29] (a) Baird, W.; Burns, R.; Wilson, F. J. J Chem Soc 1927, 2527; (b) Stanovnik, B.; Tisler, M. J Org Chem 1961, 26, 5200.