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Spirorhodanines

Diversity-Oriented Approach to Spirorhodanines via a [2+2+2] Cyclotrimerization

Sambasivarao Kotha*[a] and Gaddamedi Sreevani[a]

Abstract: Spirocyclic compounds have been increasingly utilized in drug discovery due to their inherent three-dimensional structural complexity. Here, we report a diversity oriented approach to spirorhodanines via a [2+2+2] cyclotrimerization reaction with propargyl halides as co-partners. In another sequence, we employed *o*-xylylene dibromide as a coupling partner to assemble spirorhodanines.

Introduction

Rhodanines are five membered heterocyclic compounds useful in drug design and discovery.[1] Rhodanine ring allows hydrogen bonding, hydrophobic interactions and metal ion interactions at the ligand binding sites of proteins with amino acids.[2] Therefore, rhodanines exhibit interesting biological activities.[3] Rhodanine derivatives show numerous categories of activities and these include antibacterial,[3a–3c] antidiabetic,[3d] anticancer,[3e] antifungal,[3f] anti-hepatitis C virus activity,[3g] anti-inflammatory agent, c-Jun *N*-terminal kinase (JNK) stimulating phosphatase-1 (JSP-1) inhibitors,[3h] HIV inhibitors,[3i,j,3k] aldose reductase inhibitors (ARI),[3l] inhibitors of dengue virus protease[3m] and chikungunya virus[3n] etc. Due to these applications, rhodanines have become as indispensable tools for development of new therapeutic agents. Currently, epalrestat (**1**) is the only available ARI used for curing diabetes in the market and it is sold by the name ONO-2235.[4] Some of the therapeutically active compounds containing rhodanine motif as core unit are shown in Figure 1. Classical methods for the synthesis of rhodanine derivatives involve the assembly of rhodanine moiety **13** followed by a Knoevenagel condensation with aldehyde derivative (Scheme 1).[5] Unfortunately, very limited reports are available for the synthesis of spirorhodanine derivatives and they rely on condensation of rhodanines with carbonyl compounds followed by [3+2] cycloaddition reaction.[6]

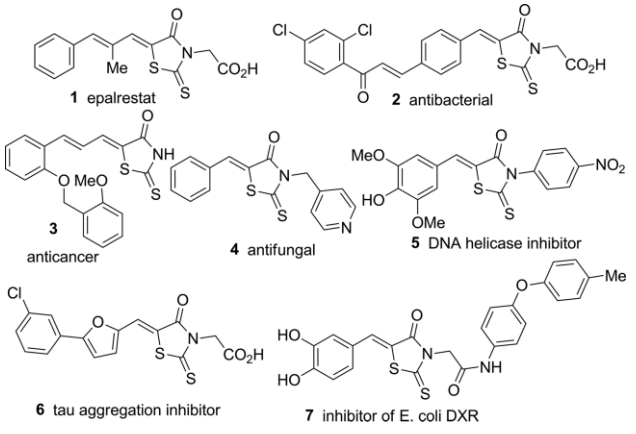
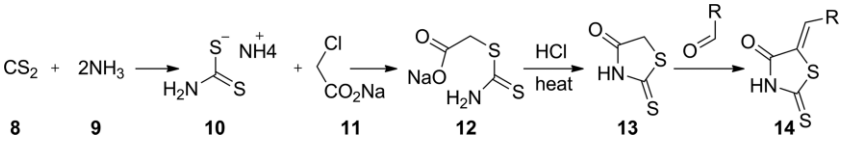


Figure 1. Biologically active compounds containing rhodanine as a core unit.

Transition metal-catalysed [2+2+2] cycloaddition reaction appears to be an atom economical route to design various heterocycles. This protocol enables the formation of multiple C–C bonds in a single step and tolerates a variety of functional groups and thus provides an easy access to complex heterocyclic and carbocyclic systems.[7] Since, there are no reports available for the synthesis of spiro derivatives of rhodanines via [2+2+2] cycloaddition reaction, we conceived a cycloaddition approach involving diyne precursors and here we disclose our efforts in this direction.



Scheme 1. Classical method of synthesis of rhodanine derivatives.

Results and Discussion

To prepare spirorhodanine derivatives, initially we protected nitrogen atom of rhodanine by treating rhodanine (**13**) with MeI using Et_3N as a base to deliver *N*-methyl rhodanine (**16**),

[a] *Department of Chemistry, Indian Institute of Technology Bombay, Powai Mumbai 400076, India.*
E-mail: srk@chem.iitb.ac.in
http://ether.chem.iitb.ac.in/~srk/

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800775.

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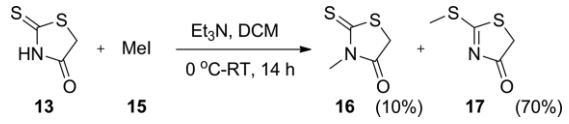
however, we observed *S*-methylated product **17** as a major compound (Scheme 2). Compounds **16** and **17** were differentiated on the basis of distinct chemical shift of *S*-methyl protons (singlet) at 2.7 ppm and *N*-methyl protons at 3.36 ppm in ^{1}H NMR spectrum (Figure 2).[8]



Scheme 2. Methylation of rhodanine (**13**).

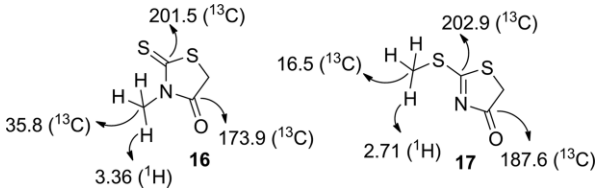
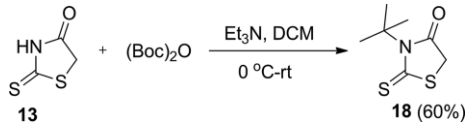


Figure 2. Comparison of ^{1}H and ^{13}C NMR values of methylated rhodanine.

Later, we intended to protect with *tert*-butyloxy carbonyl group. In this regard, rhodanine (**13**) was treated with $(Boc)_2O$ and Et_3N in DCM and under these conditions didn't get the desired Boc protected product, surprisingly, *N-tert*-butyl rhodanine (**18**) was formed as fluorescent yellow oil in 60 % yield rather than the expected Boc protected rhodanine (Scheme 3). The structure of the compound **18** was confirmed on the basis of spectroscopic data. For example, ^{13}C NMR spectrum showed two peaks in the carbonyl region and the third carbonyl peak was absent i.e., singlets, C=S at 175.25 ppm, carbonyl carbon C=O at 203.68 ppm and *tert*-butyl carbon attached to nitrogen appeared at 65.64 ppm. Finally, the presence of molecular ion peak at *m/z* 212.0175 $[M + Na]^+$ supported the molecular formula of the compound **18** (Figure 3).



Scheme 3. Protection of NH of rhodanine with $(Boc)_2O$.

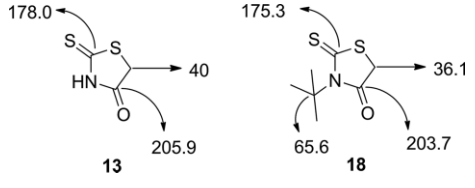


Figure 3. Comparison of ^{13}C NMR values of rhodanines **13** and **18**.

Subsequently, *N*-protected rhodanine **18** was treated with *o*-xylylene dibromide (**19**) and the corresponding spiro derivative **20** was isolated in good yields (Scheme 4). The spiro derivative **20** was confirmed by single-crystal X-ray diffraction data and it clearly indicated the presence of *N*-*t*Bu group (Figure 4).

Scheme 4. Synthesis of spiro derivative **20** using *o*-xylylene dibromide (**19**).

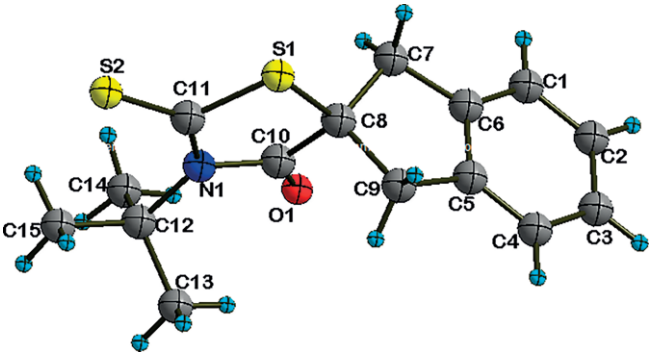
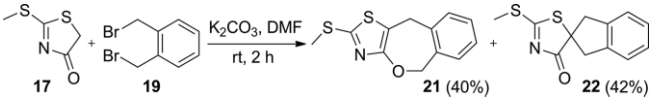


Figure 4. ORTEP diagram of **20** showing thermal ellipsoids at 50 % probability level (CCDC no. 1835689).

Interestingly, when the compound **17** was treated with *o*-xylylene dibromide (**19**) in DMF and K_2CO_3 as a base, the oxepine derivative **21** was formed along with the expected spiro compound **22** (Scheme 5). Further, the structure of compound **21** was confirmed by single-crystal X-ray diffraction data (Figure 5).



Scheme 5. Reaction of *o*-xylylene dibromide (**19**) with rhodanine compound **17**.

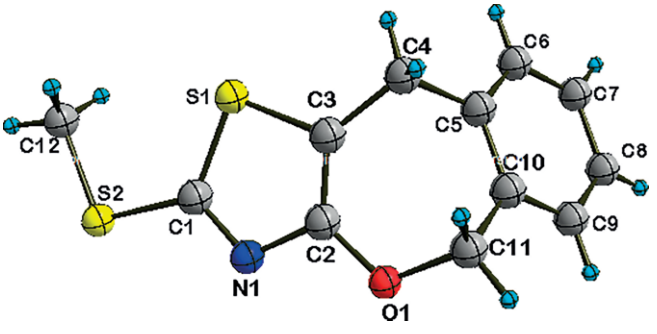


Figure 5. ORTEP diagram of **21** showing thermal ellipsoids at 50 % probability level (CCDC no. 1835688).

Next, *N*-protected rhodanines **16** and **18** were dipropargylated with propargyl bromide in the presence of K_2CO_3 in DMF and the corresponding diyne derivatives **24a** and **24b**, respectively were obtained in good yields (Scheme 6).

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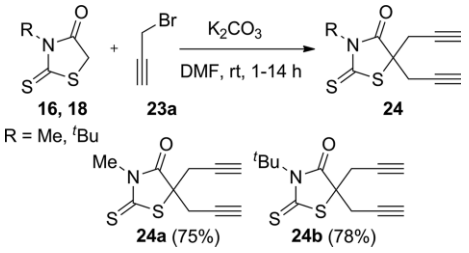
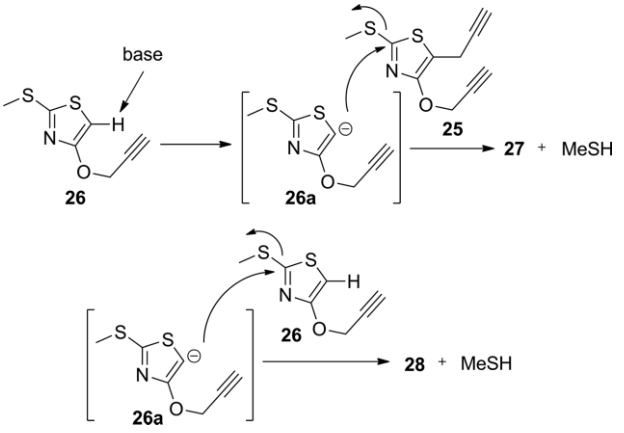


Scheme 6. Dipropargylation of rhodanine.

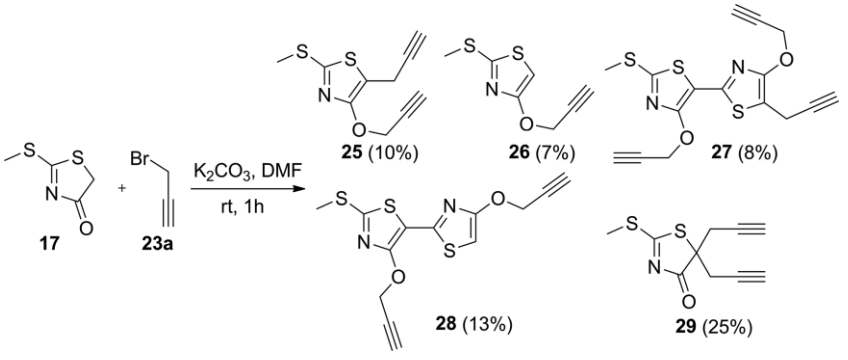
To synthesize the diyne precursor of *S*-methylated rhodanine **17** suitable for [2+2+2] cyclotrimerization,[7] we treated rhodanine **17** with propargyl bromide and K_2CO_3 in DMF at room temp. Surprisingly, we obtained unwanted side products **25**–**28** along with the desired dipropargyl rhodanine derivative **29** (Scheme 7). Structures of these products were confirmed by ^1H NMR and ^{13}C NMR spectroscopic data. HRMS data further supported their molecular formula. Moreover, single-crystal X-ray diffraction data unambiguously established the structure of the dimeric compound **28** (Figure 6).

The formation of the products **27** and **28** can be explained by the attack of intermediate anion **26a** which is generated from compound **26** by removing a proton with base, on the same compound **26** or on the compound **25** by eliminating SMe group instead reacting with propargyl bromide (Scheme 8).



Scheme 8. Mechanism of formation of compounds **27** and **28**.

The dipropargyl derivatives **24a**, **24b** and **29** have been used as synthons for [2+2+2] cyclotrimerization reaction with propargyl halides as partners using $Mo(CO)_6$ in MeCN under microwave irradiation (MWI) conditions. The corresponding spiro de-



Scheme 7. Reaction of propargyl bromide with rhodanine derivative **17**.

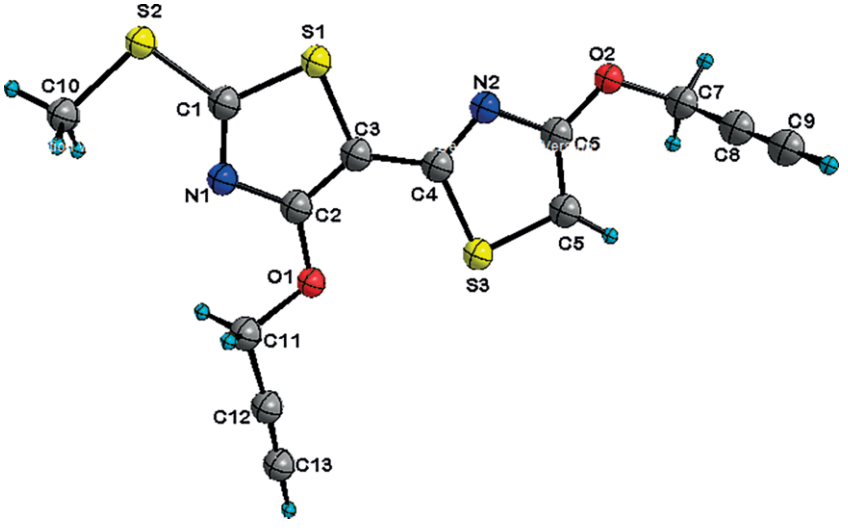


Figure 6. Scheme ORTEP diagram of **28** showing thermal ellipsoids at 50 % probability level (CCDC no. 1835686).

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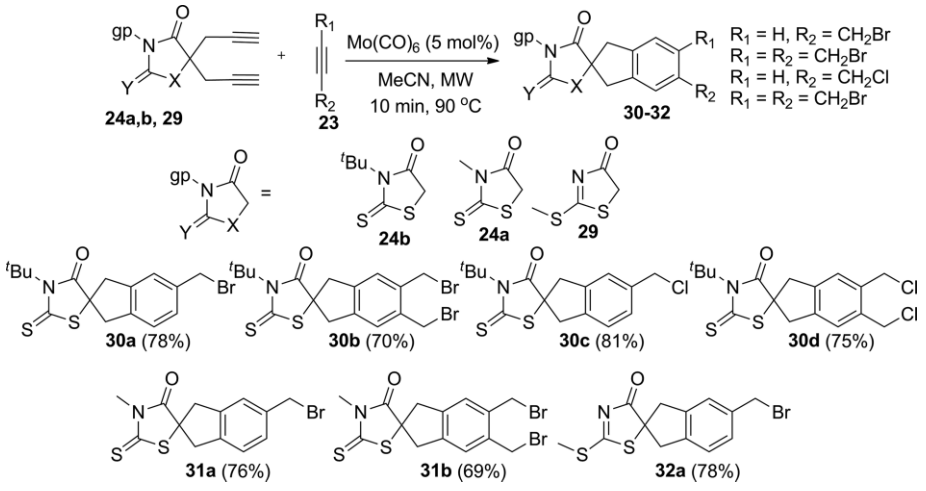

Scheme 9. [2+2+2] Cyclotrimerization of dipropargyl derivatives with propargyl halides.

rivatives **30**–**32** were isolated in good yields under the MWI conditions (Scheme 9).

Conclusions

In summary, we have demonstrated a useful synthetic approach to spirorhodanine derivatives via a [2+2+2] cyclotrimerization strategy for the first time. We have also shown the synthesis of simple spirorhodanine derivatives using *o*-xylylene dibromide. In case of *S*-methyl rhodanine, we have observed dihydrooxepine derivative, and its structure was unambiguously established by single-crystal X-ray diffraction data. The methodology reported here and the compounds prepared in this study may find useful applications in drug design and medicinal chemistry.

Experimental Section

General: All reactions were performed under an argon or nitrogen atmosphere using well-dried reaction flask. All products available commercially, were used as received without further purification. All the solvents used as reaction media were dried with predried molecular sieves (4 Å) in oven. Column chromatography was performed with silica gel (100–200 mesh) using mixture of petroleum ether and EtOAc as eluent. ^{1}H NMR and ^{13}C NMR spectroscopic data were recorded on 400 MHz and 100 MHz or 500 MHz and 125 MHz spectrometers using tetramethylsilane (TMS) as an internal standard and [D]chloroform as a solvent. The high resolution mass spectroscopy (HRMS) was performed using Bruker (Maxis Impact) or Micromass Q-ToF spectrometer. The microwave reactor used was Discover® SP by CEM Corporation and all the microwave reactions were performed under the standard method, where time and temperature can be monitored manually.

General Procedure for the Preparation of *N*-Protected Rhodanines: $(Boc)_2O$ or MeI (2 equiv.) was added to a solution of rhodanine (**13**) (1 equiv.) and Et_3N (2 equiv.) in CH_2Cl_2 (0.7 M) at 0 °C. Then the reaction mixture was brought to room temp. and stirred for 7 to 10 h at room temp. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated. Then the crude residue was purified by column chromatography on silica gel using appropriate mixture of EtOAc/petroleum ether (1:99 to 20:80) to provide *N*-protected rhodanines.

***N*-Alkylation of Rhodanine:** According to the general procedure, rhodanine (**13**) (1.0 g, 7.5 mmol), MeI (0.94 mL, 15.0 mmol), Et_3N (2.1 mL, 15.0 mmol) were stirred in dry CH_2Cl_2 (5 mL/1 mmol) at room temp. for 7 h. The crude residue was purified by column chromatography on silica gel with 5 % EtOAc-petroleum ether gave *N*-methyl rhodanine (**16**) (110 mg, 10 % yield) as a white solid and further continuation of column with 15 % EtOAc-petroleum ether afforded *S*-methylated compound **17** (860 mg, 78 % yield) as a light brown solid. The NMR spectra matched with the lit reports.[8a]

***N*-Methylrhodanine (16):**[8a] White crystalline solid, 10 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.36 (s, 3 H), 4.0 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.4, 35.8, 173.9, 201.5 ppm. DEPT135 (125 MHz, $CDCl_3$): δ = 31.4, 35.8 ppm.

2-(Methylthio)thiazol-4(5*H*)-one (17):[8b] Light brown solid, 78 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.70 (s, 3 H), 4.0 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.5, 39.9, 187.6, 202.9 ppm. DEPT135 (125 MHz, $CDCl_3$): δ = 16.5, 39.9 ppm.

***N*-(*tert*-Butyl)rhodanine (18):** According to the general procedure, rhodanine (**13**) (1.0 g, 7.5 mmol), $(Boc)_2O$ (0.94 mL, 15.0 mmol), Et_3N (2.1 mL, 15.0 mmol) were stirred in dry CH_2Cl_2 (5 mL/1 mmol) at room temp. for 7 h. The crude residue was purified by column chromatography on silica gel with petroleum ether to 1 % EtOAc-petroleum ether gave *N*-*tert*-butyl rhodanine (**18**) (852.63 mg, 60 % yield) as a fluorescent yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (s, 9 H), 3.81 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.0, 36.1, 65.6, 175.3, 203.7 ppm. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + Na]^+$ $C_7H_{11}NNaOS_2$ 212.0174, found 212.0175.

General Procedure for the C-Alkylation of *N*-Protected Rhodanines: To a suspension of *N*-protected rhodanine (1 equiv.) and K_2CO_3 (5 equiv.) in dry DMF (0.5 M) was added *o*-xylylene dibromide (**19**) or propargyl bromide (**23a**) (1.5 or 3 equiv.). The resulting mixture was stirred at room temp. for 1 h to 18 h. After completion of the reaction (TLC monitoring), the reaction was quenched by adding water and then the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated. Then the crude residue was purified by column chromatography on silica gel with EtOAc–hexane (1:99 to 10:95) to give compound.

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Compound 20: According to the general procedure, 3-(*tert*-butyl)rhodanine (**18**) (100 mg, 0.53 mmol), *o*-xylylene dibromide (**19**) (209.5 mg, 0.79 mmol), K_2CO_3 (365 mg, 2.65 mmol) were stirred in dry DMF (0.5 M) at room temp. for 1 h. The crude residue was purified by column chromatography on silica gel with petroleum ether to 1 % EtOAc-petroleum ether gave compound **20** (104.7 mg, 68 % yield) as a fluorescent yellow green crystalline solid. MP: 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 9 H), 3.36 (d, J = 16.25 Hz, 2 H), 3.81 (d, J = 16.25 Hz, 2 H), 7.22 (s, 4 H) ppm. ^{13}C NMR (100MHz, $CDCl_3$): δ = 29.2, 46.0, 62.6, 65.5, 124.5, 127.7, 139.1, 179.8, 201.7 ppm. DEPT135 NMR (100 MHz, $CDCl_3$): δ = 29.2, 46.0, 124.5, 127.7 ppm. IR: $\tilde{\nu}$ = 990, 1049, 1165, 1183, 1263, 1299, 1362, 1402, 1419, 1456, 1484, 1729, 2927, 2979 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + Na]^+$ $C_{15}H_{17}NNaOS_2$ 314.0644, found 314.0643.

Synthesis of Compound 21 and 22: According to the general procedure, compound **17** (300 mg, 2.04 mmol), *o*-xylylene dibromide (**19**) (808.16 mg, 3.06 mmol), K_2CO_3 (1.4 g, 10.2 mmol) were stirred in dry DMF (0.5 M) at room temp. for 1 h. The crude residue was purified by column chromatography on silica gel with petroleum ether to 1 % EtOAc-petroleum ether gave compound **21** as a solid and further continuation of column afforded compound **22** as a brown liquid.

Compound 21: Crystalline solid, 40 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.59 (s, 3 H), 4.05 (s, 2 H), 5.23 (s, 2 H), 7.18–7.20 (m, 1 H), 7.28–7.33 (m, 2 H), 7.36–7.38 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4, 29.6, 70.9, 101.9, 127.8, 128.1, 129.5, 130.3, 135.0, 139.9, 158.3, 159.7 ppm. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + Na]^+$ $C_{12}H_{11}NNaOS_2$ 272.0174, found 272.0173.

Compound 22: Brown sticky liquid, 42 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (s, 3 H), 3.34 (d, J = 16.44 Hz, 2 H), 3.84 (d, J = 16.41 Hz, 2 H), 7.23 (s, 4 H) ppm. ^{13}C NMR (100MHz, $CDCl_3$): δ = 16.4, 47.4, 72.2, 124.4, 127.6, 140.1, 191.1, 201.6 ppm. IR: $\tilde{\nu}$ = 3071, 3023, 2927, 2849, 1716, 1522, 1451, 1313, 1274, 1220, 1179, 1025, 991, 971 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + Na]^+$ $C_{12}H_{11}NNaOS_2$ 272.0174, found 272.0173.

***N*-Methyl-5,5-di(2-propynyl)rhodanine (24a):** According to the general procedure, *N*-methylrhodanine (**16**) (100 mg, 0.68 mmol), propargyl bromide (**23a**) (0.18 mL, 2.04 mmol), K_2CO_3 (469.38 mg, 3.40 mmol) were stirred in dry DMF (3 mL) at room temp. for 4 h. The crude residue was purified by column chromatography on silica gel with 5 % EtOAc-petroleum ether gave diyne compound **24a** (113.77 mg, 75 % yield) as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.12 (t, J = 2.60 Hz, 2 H), 2.86–2.99 (dq, J_1 = 2.60, J_2 = 16.95 Hz, 4 H), 3.41 (s, 3 H) ppm. ^{13}C NMR (125MHz, $CDCl_3$): δ = 29.5, 31.5, 61.8, 73.1, 77.1, 176.6, 199.7 ppm. DEPT135 NMR (100 MHz, $CDCl_3$): δ = 29.5, 31.5, 73.1, 77.1 ppm. IR: $\tilde{\nu}_{max}$ = 3289, 2941, 2918, 2123, 1726, 1688, 1456, 1422, 1349, 1322, 1301, 1127, 1037, 1012, 966 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + H]^+$ $C_{10}H_{10}NOS_2$ 224.0198, found 224.0198.

***N*-(*tert*-Butyl)-5,5-di(2-propynyl)rhodanine (24b):** According to the general procedure, *N*-*tert*-butylrhodanine (**18**) (300 mg, 1.58 mmol), propargyl bromide (**23a**) (0.42 mL, 4.76 mmol), K_2CO_3 (1.1 g, 7.93 mmol) were stirred in dry DMF (5 mL) at room temp. for 5 h. The crude residue was purified by column chromatography on silica gel with 1 % EtOAc-petroleum ether gave diyne compound **24b** (328.1 mg, 78 % yield) as a fluorescent liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.81 (s, 9 H), 2.12 (t, J = 2.65 Hz, 2 H), 2.79–2.83 (dd, J_1 = 2.65, J_2 = 16.95 Hz, 2 H), 2.86–2.90 (dd, J_1 = 2.65, J_2 = 16.95 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.4, 29.1, 59.3, 66.1, 72.9, 77.6, 178.0, 201.6 ppm. IR: $\tilde{\nu}_{max}$ = 3291, 2977, 2932, 1729, 1480, 1423, 1401, 1368, 1285, 1266, 1190, 1176, 1053, 1034, 1009 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + K]^+$ $C_{13}H_{15}KNOS_2$ 304.0227, found 304.0227.

Reaction of Compound 17 with Propargyl Bromide (23a): According to the general procedure, compound **17** (300 mg, 2.04 mmol), propargyl bromide (**23a**) (0.6 mL, 6.12 mmol), K_2CO_3 (1.4 g, 10.20 mmol) were stirred in dry DMF (5 mL) at room temp. for 1.5 h. The crude residue was purified by column chromatography on silica gel with petroleum ether gave compound **25**, continuing the column delivered compound **26**. Further elution gave compound **27** and continuing the column with 1 % EtOAc-petroleum ether afforded compound **28** and compound **29**.

Compound 25: Colourless liquid, 10 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.11 (t, J = 2.75 Hz, 1 H), 2.47 (t, J = 2.40 Hz, 1 H), 2.62 (s, 3 H), 3.59 (d, J = 2.75 Hz, 2 H), 4.90 (d, J = 2.40 Hz, 2 H) ppm. ^{13}C NMR (125MHz, $CDCl_3$): δ = 14.7, 16.7, 58.3, 69.8, 75.1, 79.2, 81.2, 107.4, 156.6, 161.1 ppm. IR: $\tilde{\nu}_{max}$ = 3294, 2924, 2854, 2125, 1726, 1565, 1422, 1379, 1331, 1232, 1168, 1087, 1044, 1032, 960 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + H]^+$ $C_{10}H_{10}NOS_2$ 224.0198, found 224.0196.

Compound 26: Colourless liquid, 7 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.51 (t, J = 2.40 Hz, 1 H), 2.65 (s, 3 H), 4.80 (d, J = 2.40 Hz, 2 H), 6.13 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.6, 57.7, 75.7, 78.3, 90.7, 161.8, 164.4 ppm. IR: $\tilde{\nu}_{max}$ = 3294, 2925, 2850, 1658, 1554, 1527, 1451, 1337, 1312, 1160, 1045 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + H]^+$ $C_7H_8NOS_2$ 186.0042, found 186.0045.

Compound 27: Colourless liquid, 8 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.13 (t, J = 2.70 Hz, 1 H), 2.46 (t, J = 2.40 Hz, 1 H), 2.52 (t, J = 2.40 Hz, 1 H), 2.68 (s, 3 H), 3.64 (d, J = 2.75 Hz, 2 H), 4.92 (d, J = 2.40 Hz, 2 H), 5.12 (d, J = 2.40 Hz, 2 H) ppm. ^{13}C NMR (125MHz, $CDCl_3$): δ = 14.6, 16.4, 58.1, 58.3, 69.8, 75.0, 75.6, 78.6, 79.3, 81.4, 106.8, 107.6, 151.7, 156.8, 158.1, 165.2 ppm. IR: $\tilde{\nu}_{max}$ = 3288, 2926, 1561, 1448, 1363, 1343, 1111, 1080, 1048 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + Na]^+$ $C_{16}H_{12}N_2NaO_2S_3$ 382.9953, found 382.9953.

Compound 28: Brown solid, 13 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (t, J = 2.38 Hz, 1 H), 2.53 (t, J = 2.40 Hz, 1 H), 2.68 (s, 3 H), 4.82 (d, J = 2.40 Hz, 2 H), 5.12 (d, J = 2.40 Hz, 2 H), 6.20 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4, 29.9, 57.7, 58.4, 75.6, 78.4, 78.5, 90.5, 154.7, 158.6, 161.9, 165.9 ppm. IR: $\tilde{\nu}_{max}$ = 3289, 2917, 2849, 2122, 1660, 1558, 1521, 1451, 1366, 1345, 1326, 1159, 1108, 1054, 1029, 888 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + H]^+$ $C_{13}H_{11}N_2O_2S_3$ 322.9977, found 322.9977.

Compound 29: Light brown solid, 25 %. M.p. 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 (t, J = 2.60 Hz, 2 H), 2.75 (s, 3 H), 2.77–2.82 (dd, J_1 = 2.60, J_2 = 17.0 Hz, 2 H), 2.95–2.99 (dd, J_1 = 2.60, J_2 = 17.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 28.5, 68.3, 72.4, 78.0, 188.5, 202 ppm. IR: $\tilde{\nu}_{max}$ = 3289, 3013, 2928, 2850, 2122, 1715, 1447, 1422, 1314, 1272, 1250, 1221, 1178, 1076, 1033, 1019, 993, 970 cm^{-1}. HRMS (ESI, Q-ToF) *m/z*: calculated for $[M + H]^+$ $C_{10}H_{10}NOS_2$ 224.0198, found 224.0197.

General Procedure for [2+2+2] Cycloaddition Under MWI Conditions: To a solution of diyne (1 equiv.) and propargyl halide (2 equiv.) in dry acetonitrile (5 mL), $Mo(CO)_6$ (5 mol-%) was added and the reaction mixture was reacted under microwave irradiation (MWI) conditions for 15 min. After the completion of reaction (TLC monitoring), the solvent was concentrated at reduced pressure and the crude product was purified by silica gel column chromatography using EtOAc/petroleum ether (5:95 to 30:70) to give [2+2+2] cyclotrimerized compound.

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Compound 30a: Yellow liquid, 78 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 9 H), 3.34 (d, J = 16.48 Hz, 2 H), 3.79 (dd, J_1 = 3.25, J_2 = 16.75 Hz, 2 H), 4.48 (s, 2 H), 7.17–7.26 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1, 33.6, 45.78, 45.84, 62.5, 65.6, 124.9, 125.2, 128.7, 137.6, 139.6, 139.9, 179.6, 201.4 ppm. IR: $\tilde{\nu}_{max}$ = 3015, 2959, 2923, 2856, 1738, 1699, 1491, 1434, 1369, 1311, 1258, 1218, 1187, 1143, 1074, 1007 cm^{-1}.

Compound 30b: Yellow solid, 70 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.83 (s, 9 H), 3.34 (d, J = 16.70 Hz, 2 H), 3.78 (d, J = 16.70 Hz, 2 H), 4.64 (s, 4 H), 7.23 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1, 30.1, 45.8, 62.2, 65.7, 127.1, 136.4, 140.8, 179.6, 201.1 ppm. IR: $\tilde{\nu}_{max}$ = 2975, 2935, 1732, 1657, 1446, 1367, 1286, 1266, 1215, 1173, 1049, 992 cm^{-1}. HRMS (ESI, Q-ToF) m/z: calculated for $[M + Na]^+$ $C_{17}H_{19}Br_2NNaOS_2$ 497.9167, found 497.9168 and other isotopic peaks are 499.9138 and 501.9139.

Compound 30c: Fluorescent yellow liquid, 81 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84 (s, 9 H), 3.35 (d, J = 16.45 Hz, 2 H), 3.79 (dd, J_1 = 5.70, J_2 = 16.45 Hz, 2 H), 4.57 (s, 2 H), 7.19–7.26 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1, 45.8, 46.3, 62.6, 65.6, 124.8, 128.3, 137.3, 139.5, 139.9, 179.6, 201.4 ppm. IR: $\tilde{\nu}$ = ($_{max}$3018), 2976, 2931, 1737, 1492, 1435, 1400, 1368, 1286, 1265, 1175, 1117, 1085, 1049, 993 cm^{-1}. HRMS (ESI, Q-ToF) m/z: calculated for $[M + Na]^+$ $C_{16}H_{18}ClNNaOS_2$ 362.0411, found 362.0412.

Compound 30d: Yellow solid, 75 %. M.p. 136–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.83 (s, 9 H), 3.35 (d, J = 16.60 Hz, 2 H), 3.79 (d, J = 16.60 Hz, 2 H), 4.72 (s, 4 H), 7.26 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1, 43.4, 45.8, 62.3, 65.7, 126.8, 136.0, 140.6, 179.5, 201.1 ppm. IR: $\tilde{\nu}_{max}$ = 3018, 2976, 2933, 1732, 1449, 1426, 1400, 1368, 1293, 1272, 1174, 1085, 1050, 993 cm^{-1}. HRMS (ESI, Q-ToF) m/z: calculated for $[M + Na]^+$ $C_{17}H_{19}Cl_2NNaOS_2$ 410.0177, found 410.0176.

Compound 31a: Light brown liquid, 76 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.40 (d, J = 16.40 Hz, 2 H), 3.46 (s, 3 H), 3.84–3.88 (dd, J_1 = 4.20, J_2 = 16.40 Hz, 2 H), 4.49 (s, 2 H), 7.21 (d, J = 8.20 Hz, 1 H), 7.28 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.9, 33.5, 46.80, 46.81, 64.9, 124.9, 125.3, 128.9, 137.8, 139.5, 139.8, 178.6, 200.0 ppm. IR: $\tilde{\nu}_{max}$ = 932, 1004, 1122, 1213, 1275, 1303, 1345, 1421, 1492, 1682, 1725, 2851, 2922, 3016 cm^{-1}. HRMS (ESI, Q-ToF) m/z: calculated for $[M + Na]^+$ $C_{13}H_{12}BrNNaOS_2$ 363.9436, found 363.9436 and other isotopic peak is 365.9421.

Compound 31b: Light brown solid, 69 %. M.p. 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (d, J = 16.65 Hz, 2 H), 3.46 (s, 3 H), 3.86 (d, J = 16.60 Hz, 2 H), 4.65 (s, 4 H), 7.26 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1, 31.9, 46.8, 64.6, 127.2, 136.5, 140.6, 178.5, 199.7 ppm. IR: $\tilde{\nu}_{max}$ = 2917, 2854, 1730, 1426, 1350, 1306, 1276, 1215, 1134, 1123, 1014, 932 cm^{-1}. HRMS (ESI, Q-ToF) m/z: calculated for $[M + Na]^+$ $C_{14}H_{13}Br_2NNaOS_2$ 455.8698, found 455.8698 and other isotopic peaks are 457.8689 and 459.8654.

Compound 32a: Brown high density liquid, 78 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.75 (s, 3 H), 3.33 (d, J = 16.55 Hz, 2 H), 3.80 (dd, J_1 = 3.20, J_2 = 16.55 Hz, 2 H), 4.49 (s, 2 H), 7.19–7.27 (m, 3 H) ppm. ^{13}C NMR (125MHz, $CDCl_3$): δ = 16.4, 33.6, 47.1, 72.0, 124.7, 125.1, 128.6, 137.4, 140.6, 140.9, 190.9, 201.6 ppm. IR: $\tilde{\nu}_{max}$ = 932, 1004, 1122, 1213, 1275, 1303, 1345, 1421, 1492, 1682, 1725, 2851, 2922, 3016 cm^{-1}. HRMS (ESI, Q-ToF) m/z: calculated for $[M + H]^+$ $C_{13}H_{13}BrNOS_2$ 341.9616, found 341.9615 and other isotopic peak is 343.9598.

CCDC 1835689 (for **20**), 1835688 (for **21**), 1835686 (for **28**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: [2+2+2] Cyclotrimerization · $Mo(CO)_6$ · *O*-Xylylene dibromide · Propargyl halides · Spirorhodanine

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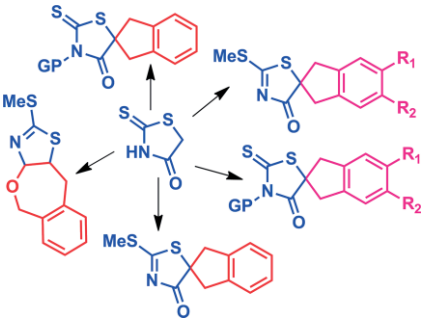
Spirorhodanines



$Mo(CO)_6$ was used as a catalyst for the synthesis of spirorhodanine derivatives with propargyl halides as co-partners, via a [2+2+2] cyclotrimerization reaction. Synthesis of spirorhodanines by utilizing *o*-xylylene dibromide was also developed.

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