HETEROCYCLES, Vol. 100, No. 7, 2020, pp. 1072 - 1083. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 23rd March, 2020, Accepted, 14th May, 2020, Published online, 25th May, 2020
DOI: 10.3987/COM-20-14262

SYNTHESIS OF LESINURAD VIA A MULTICOMPONENT REACTION WITH ISOCYANIDES AND DISULFIDES

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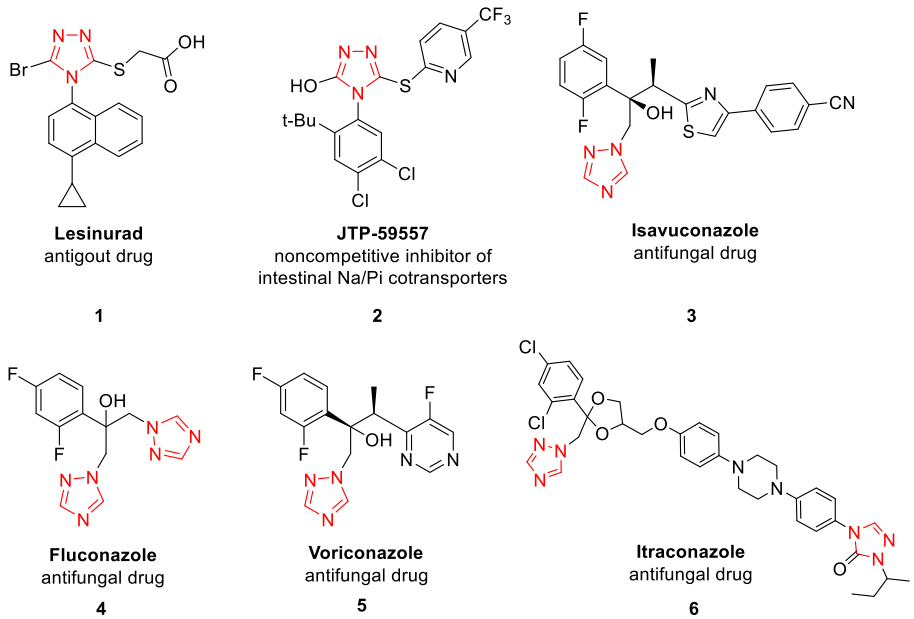
Abstract – An efficient synthesis of Lesinurad, a selective uric acid reabsorption (URAT1) inhibitor, is described in this article. The route to synthesis of Lesinurad avoids the use of thiophosgene and the formation of thiols. The key reaction in this synthesis is construction of the 1,2,4-triazole ring in 72% yield. The title product is obtained in 45% yield over 5 steps.

1,2,4-Triazole is a five-membered heterocyclic organic compound which with a molecular formula of $C_2H_3N_3$ and consisting of two carbon atoms and three nitrogen atoms. The 1,2,4-triazole moiety is an important feature present in many small molecules used in drug and biological applications. Scheme 1 shows selected examples of molecules (compounds **1**–**6**) that contain the 1,2,4-triazole moiety in various forms as approved drugs,[1] as potent inhibitors of biological targets/pathways.[2]

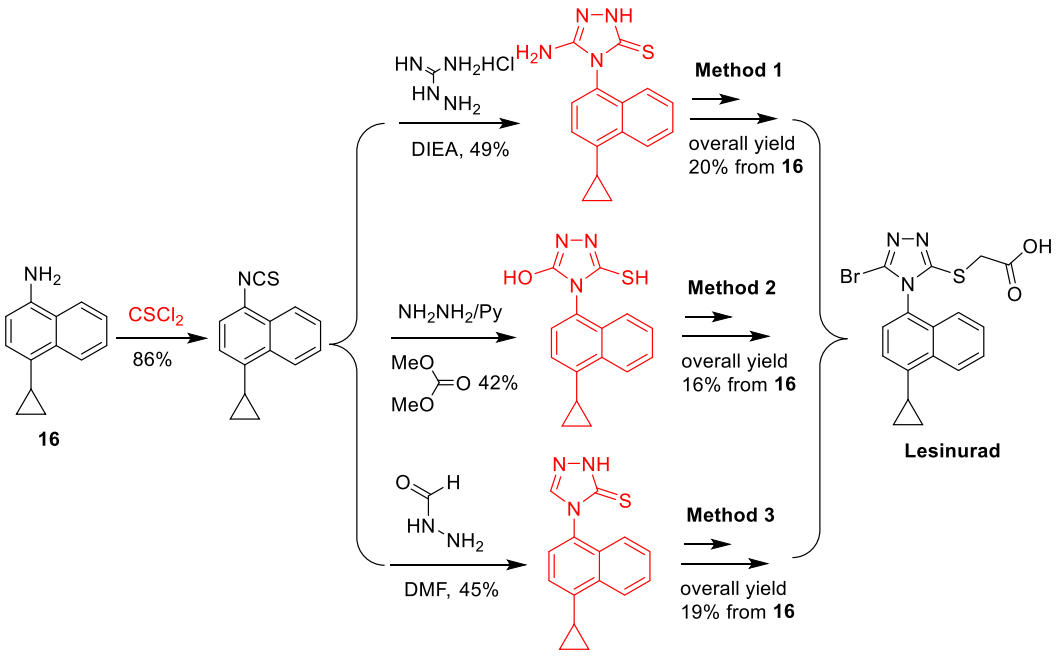


Scheme 1. Selected examples of molecules that contain the 1,2,4-triazole moiety

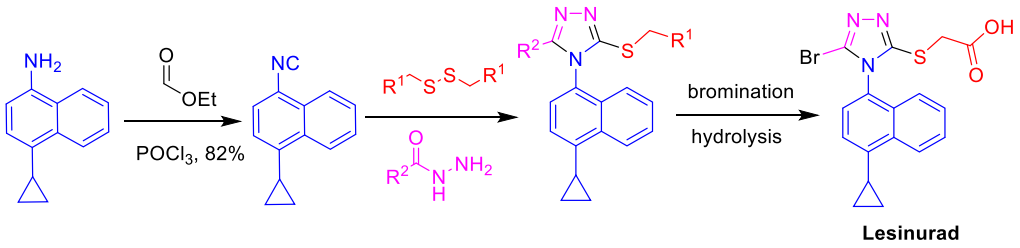
Thereinto, Lesinurad is a selective uric acid reabsorption (URAT1) inhibitor (marketed by AstraZeneca as Zurampic) approved for use in combination with xanthine oxidase inhibitors for the treatment of hyperuricemia associated with gout.[3] URAT1 is a major transporter enzyme that is responsible for the reuptake of uric acid from the renal tubules; inhibition of URAT1 function therefore increases excretion of uric acid.[4] It is therefore very desirable to develop an efficient synthetic methodology for the construction of Lesinurad.

Until now, many methods were reported for Lesinurad in the literature (Scheme 2).[5-7] Although many approaches toward Lesinurad have been developed, the majority of strategies to give the product have some limiting factors. For example, almost all methods synthesize isothiocyanates as the key intermediate. Thiophosgene is used in the process of synthesis, which is toxic and inconvenient to operate. Inhalation causes the irritation of respiratory system and delayed pulmonary edema. Vapor irritates eyes. Liquid burns skin and eyes. Ingestion causes irritation of the mouth and stomach. The introduction of the bromine atom is carried out by a diazotization reaction of an amino group, which is complicated in operation and expensive in raw materials and is not easy to reduce cost. Large-scale synthesis of Lesinurad requires the handling of 4-aryl-[1,2,4]triazole-3-thiol-related intermediates, which was reported to have toxic effects on skin, eyes, and the respiratory tract. In spite of the fact that many synthetic processes have been described already, there is still a need for new and improved processes for the production of Lesinurad characterized by easier workup, more cost-effective syntheses, utilization of less toxic reagents and higher overall yield.

Reported synthetic routes for Lesinurad



This study



Scheme 2. Synthesis of Lesinurad

Our synthetic plan was inspired from previous work by our group on the synthesis of the generation of isothioureas and related molecular moieties.[8] The ester precursor to Lesinurad can be synthesized in one step from the corresponding isocyanide and disulfide using the three-component protocol. We found that the same effect can be achieved without using TEMPO in this step. Then we explored the feasibility of our strategy with the synthesis of corresponding hydrazines and disulfides to get the optimal condition. Compared with the yield of 52% in previous work by our group, the yield of this key step reached 72% in this study. Herein, we describe in full the evolution of our synthetic toward Lesinurad.

We first used the model reaction shown in Table 1 for the synthesis of **8** to identify the optimal conditions for the multicomponent reaction. Our study involved changing the reagent ratio and temperature, choice of oxidant and solvent. As summarized in Table 1, reagent ratio (**a:b:c:d:e**=1:0.2:2:1:4) was found necessary for complete activation to occur to achieve a high reaction yield (entry 4 vs entries 1, 2, 3 and 5). With regard to the oxidant used, NBS was better than NCS in promoting the reaction (entry 4 vs entry 6). In our previous work, the yield is 0% if without adding TEMPO in room temperature. TEMPO was used as an initiator to oxidize disulfide and generate sulfur free radicals. Sulfenyl halide was generated through this radical pathway by reacting with NBS. The reaction can be performed without TEMPO and has no effect on the experiment (entry 7 vs entry 4). It seems that heating causes NBS to produce free radicals so that the reaction can proceed down. Lower temperature (such as entries 8, 9, 10 and 11) was also tested and gave unsatisfactory results when compared to the 70 °C (entry 4). Among the solvents tested, DCE seemed to be the best while THF, DMF, DCM or toluene, all produced much worse yields (entry 4 vs entries 12, 13, 14 and 15).

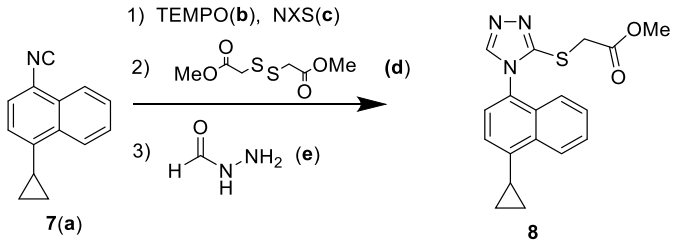
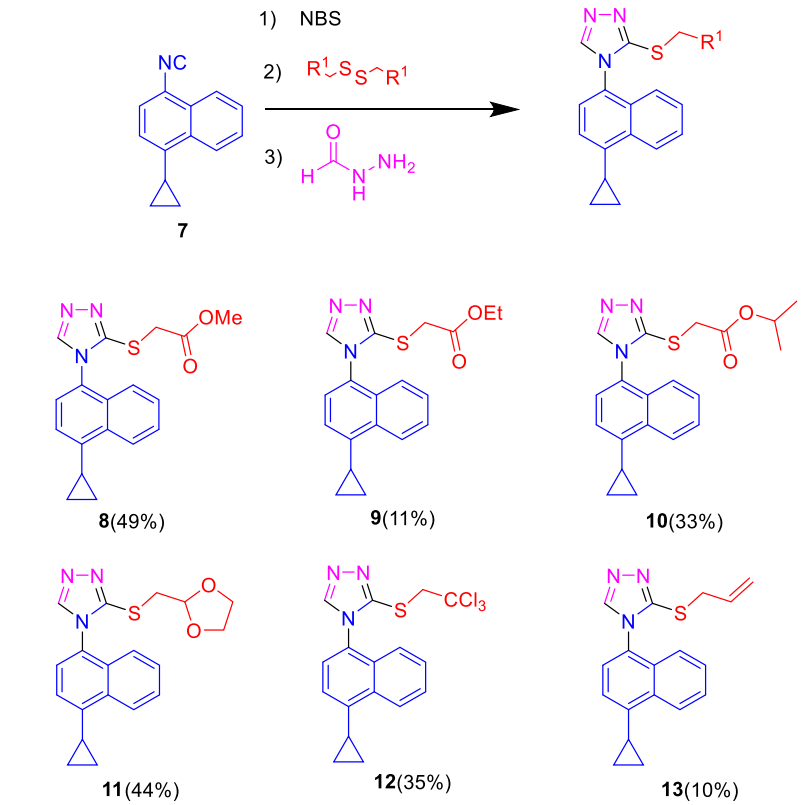


Table 1. Reaction to explore reaction conditions

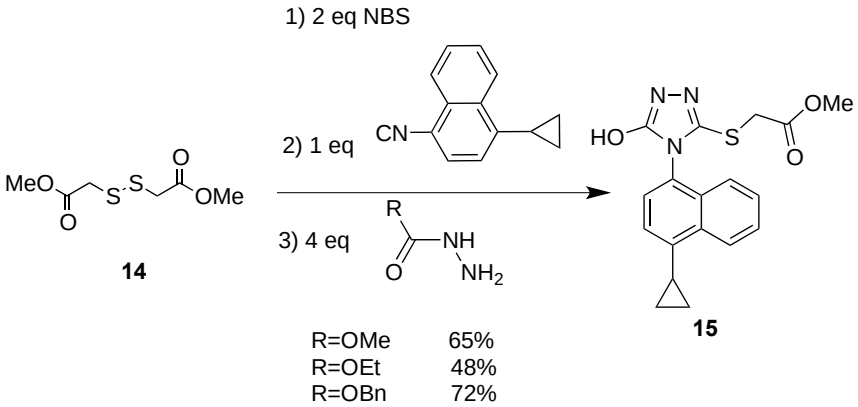
entry	initiator	oxidant	Temperature (°C)	solvent	Ratio (**a:b:c:d:e**)	Yield (%)
1	TEMPO	NBS	70	DCE	1:0.1:1:0.5:2	25
2	TEMPO	NBS	70	DCE	1:0.2:2:1:2	34
3	TEMPO	NBS	70	DCE	1:0.2:2:1:3	40
4	TEMPO	NBS	70	DCE	1:0.2:2:1:4	49
5	TEMPO	NBS	70	DCE	1:0.2:2:1:5	49
6	TEMPO	NCS	70	DCE	1:0.2:2:1:4	24
7	none	NBS	70	DCE	1:0:2:1:4	48
8	TEMPO	NBS	60	DCE	1:0.2:2:1:4	36
9	TEMPO	NBS	50	DCE	1:0.2:2:1:4	31
10	TEMPO	NBS	40	DCE	1:0.2:2:1:4	27
11	TEMPO	NBS	25	DCE	1:0.2:2:1:4	25
12	TEMPO	NBS	70	toluene	1:0.2:2:1:4	19
13	TEMPO	NBS	70	THF	1:0.2:2:1:4	28
14	TEMPO	NBS	70	DMF	1:0.2:2:1:4	33
15	TEMPO	NBS	40	DCM	1:0.2:2:1:4	30

The examples in Scheme 3 showed different disulfides as a reagent in multicomponent reactions. Compounds **8**-**13** can be used to generate our target compounds through subsequent reactions. Therefore, **14** seemed to be the optimal disulfides. With this condition identified, we then investigated optimal examples of hydrazine.



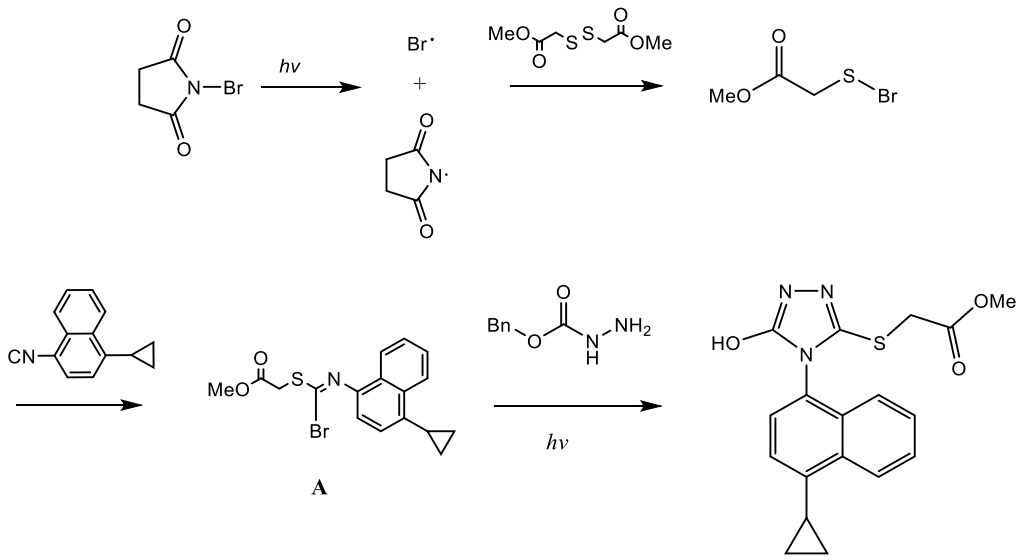
Scheme 3. Substrate scope for reactions of disulfides

Due to formic hydrazide is very active and absorbs moisture easily, we want to replace it with another compound. After experiments, we found benzyl carbazate as raw material that has the best yield (Scheme 4).



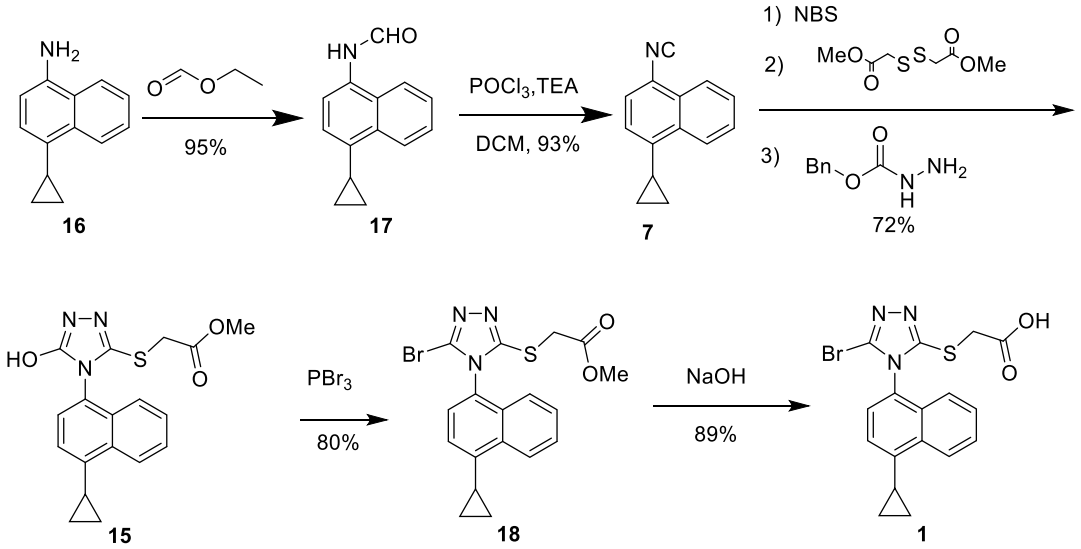
Scheme 4. Substrate scope for reactions of hydrazine

According to these results, the hypothetical mechanism of this multicomponent reaction was proposed as follows (Scheme 5). The radical generated by heating NBS reacts with disulfide to form sulfenyl halide. Sulfenyl halide can react with **7** to produce intermediate **A**. Then using benzyl carbazate as a nucleophile, **15** was obtained after an intramolecular condensation.



Scheme 5. The hypothetical mechanism of the multicomponent reaction

4-Cyclopropylnaphthalen-1-amine hydrochloride (**16**) was used as the starting materials, and *N*-(4-cyclopropylnaphthalen-1-yl)formamide (**17**) was obtained in 95% isolated yield. Compound **17** reacted with $POCl_3$ in DCM to give the key intermediate 1-cyclopropyl-4-isocyanonaphthalene (**7**) in around 93% isolated yield. Methyl 2-((4-(4-cyclopropylnaphthalen-1-yl)-5-hydroxy-4*H*-1,2,4- triazol-3-yl)thio)acetate (**15**) was obtained directly *via* a multicomponent reaction with benzyl carbazate, **7** and **14** in 72% yield. **15** reacts with phosphoric tribromide to produce methyl 2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (**18**) with a yield of 80%. **18** reacts with NaOH to provide **1** in 89% yield. Starting from **16**, the total yield of the route for the synthesis of **1** is 45% (Scheme 6). According to previous studies, overall yields are 4%~21%.



Scheme 6. Our synthetic routes to Lesinurad

In summary, we developed a method characterized by easier workup, more cost-effective syntheses, utilization of less toxic reagents and higher overall yield to synthesize Lesinurad. The synthesis of Lesinurad was achieved in 5 steps starting from **16** with a total yield of 45%. It avoids the use of thiophosgene and the formation of thiols. Construction of the 1,2,4-triazole ring is key step for this synthesis. The yield of this key step reached 72% and did not use TEMPO in reaction.

EXPERIMENTAL

All commercially available reagents were used without purification unless otherwise noted. Column chromatography was performed using silica gel (100–200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ operating at 400 MHz and 100 MHz, respectively. Proton chemical shifts are reported relative to the residual proton signals of the deuterated solvent $CDCl_3$ (7.28 ppm) or TMS. Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (77.10 ppm). Chemical shifts are reported in δ (parts per million) values. Coupling constants *J* are reported in Hz. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), and multiple (m). High-resolution mass spectra were recorded on a Liquid Chromatograph Mass Spectrometer (LCMS-IT-TOF).

Dimethyl 2,2'-disulfanediyldiacetate (14). In a 250 mL vial along with a stirring bar, 2,2'-disulfanediyldiacetic acid (10 g, 66.6 mmol) was added in MeOH (100 mL). The mixture was added H_2SO_4 (1 mL) and stirred under reflux for 3 h. After vacuum concentration, water (50 mL) was added and the mixture was extracted with DCM (75 mL), dried (Na_2SO_4), and concentrated, to give desired product **14**. (13.72 g, 98% yield, colorless liquid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.60 (s, 2H). The ^{1}H NMR spectral data is in agreement with reported.[9]

Diethyl 2,2'-disulfanediyldiacetate. In a 250 mL vial along with a stirring bar, 2,2'-disulfanediyldiacetic acid (10 g, 66.6 mmol) was added in EtOH (100 mL). The mixture was added H_2SO_4 (1 mL) and stirred under reflux for 3 h. After vacuum concentration, water (50 mL) was added and the mixture was extracted with DCM (75 mL), dried (Na_2SO_4), and concentrated, to give desired product diethyl 2,2'-disulfanediyldiacetate (14.756 g, 93% yield, colorless liquid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, J = 7.1 Hz, 2H), 3.59 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H). The ^{1}H NMR spectral data is in agreement with reported.[10]

Diisopropyl 2,2'-disulfanediyldiacetate. In a 250 mL vial along with a stirring bar, 2,2'-disulfanediyldiacetic acid (10 g, 66.6 mmol) was added in isopropyl alcohol (100 mL). The mixture

was added H_2SO_4 (1 mL) and stirred under reflux for 3 h. After vacuum concentration, water (50 mL) was added and the mixture was extracted with DCM (75 mL), dried (Na_2SO_4), and concentrated, to give desired product diisopropyl 2,2'-disulfanediyldiacetate (16.847 g, 95% yield, colorless liquid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 – 4.84 (m, 1H), 3.56 (s, 2H), 1.29 (d, J = 6.3 Hz, 6H). The ^{1}H NMR spectral data is in agreement with reported.[11]

1,2-Bis((1,3-dioxolan-2-yl)methyl)disulfane. A mixture of sulfur powder (0.32 g, 10 mmol), sodium sulfide (1.56 g, 20 mmol) and water (5 mL) was stirred vigorously for 30 min at 50 ºC. After dissolution, the reaction mixture was cooled to room temperature and tetrabutylammonium bromide (4 mol%) was added. A mixture of 2-bromomethyl-1,3-dioxolane (3.34 g, 20 mmol) and $CHCl_3$ (5 mL) was added and the mixture was stirred for an appropriate period at 25 ºC. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with Et_2O (20 mL); the combined organic layers were washed well with water and dried over sodium sulfate. The organic layer was concentrated under reduced pressure to afford 1,2-bis((1,3-dioxolan-2-yl)methyl)disulfane (1.618 g, 68% yield, yellow liquid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (t, J = 4.4 Hz, 1H), 3.88 (ddd, J = 6.9, 3.8, 1.8 Hz, 4H), 2.93 (d, J = 4.5 Hz, 2H). The ^{1}H NMR spectral data is in agreement with reported.[12]

1,2-Bis(2,2,2-trichloroethyl)disulfane. In a 250 mL vial along with a stirring bar, vinylidene chloride (8 g, 80 mmol) and iron(III) chloride anhydrous (0.24 g) were added. The mixture was dropwise added sulfur monochloride (2.7 g, 20 mmol) and stirred at 26 ºC, then slowly rose the reaction temperature to 38 ºC, and then maintained a gentle reflux throughout the remainder of addition period. After standing overnight, the progress of the reaction was monitored by TLC. After completion of the reaction, water (100 mL) was added and the mixture was extracted with EtOAc (3 × 150 mL), dried (Na_2SO_4), and concentrated. The residue was loaded on a silica gel using petroleum ether / EtOAc (16/1) to afford the desired product 1,2-bis(2,2,2-trichloroethyl)disulfane.(5.461 g, 93% yield, colorless liquid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 1H). The ^{1}H NMR spectral data is in agreement with reported.[13]

***N*-(4-Cyclopropylnaphthalen-1-yl)formamide (17).** In a 500 mL vial along with a stirring bar, 4-cyclopropylnaphthalen-1-amine hydrochloride (10.2 g, 46.4 mmol) was added in DCM (150 mL) and water (100 mL). The mixture was added KOH (3.1 g, 55.6 mmol) slowly and stirred for 2 h. After vacuum concentration organic phase, added ethyl formate (150 mL), stirred under reflux overnight, dried (Na_2SO_4), and concentrated, desired product **17**. (9.357 g, 95.57% yield, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.45 (m, 2H), 8.00 (d, J = 3.2 Hz, 1H), 7.99 – 7.71 (m, 1H), 7.71 – 7.39 (m, 2H), 7.39 –

7.21 (m, 2H), 2.36 (dt, *J* = 19.5, 6.9 Hz, 1H), 1.20 – 0.96 (m, 2H), 0.79 (td, *J* = 5.8, 3.1 Hz, 2H). The ^{1}H NMR spectral data is in agreement with reported.[8]

1-Cyclopropyl-4-isocyanonaphthalene (7). *N*-(4-Cyclopropylnaphthalen-1-yl)formamide (9.065 g) and triethylamine (41 mL) were dissolved in DCM (50 mL) and cooled to 0 °C. $POCl_3$ (13 mL) was slowly added and stirring was continued at 0 °C for another 90 min. The progress of the reaction was monitored by TLC. After completion of the reaction, added the solution to aqueous sodium carbonate solution until pH > 7. Water (100 mL) was added and the mixture was extracted with DCM (3 × 150 mL), dried (Na_2SO_4), and concentrated. The residue was loaded on a silica gel using petroleum ether / EtOAc (20/1) to afford the desired product **7**. (7.737 g, 93.31% yield, brown liquid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 7.2, 2.1 Hz, 1H), 8.23 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.86 – 7.63 (m, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 2.49 – 2.31 (m, 1H), 1.24 – 1.10 (m, 2H), 0.90 – 0.77 (m, 2H). The ^{1}H NMR spectral data is in agreement with reported.[8]

General procedure for the preparation of 8-13, 15:

In a 50 mL vial along with a stirring bar, disulfide compounds (1 mmol) was added to NBS (2 mmol) in DCE (10 mL) under nitrogen. The mixture was stirred under reflux for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, added solution slowly to the mixture of hydrazine compounds (5 mmol) and 1-cyclopropyl-4-isocyanonaphthalene (193 mg, 1 mmol) in DCE (10 mL) at 70 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, water (50 mL) was added and the mixture was extracted with DCM (3 × 75 mL), dried (Na_2SO_4), and concentrated. The residue was loaded on a silica gel using petroleum ether / EtOAc (2/1~1/2) to afford the desired product.

Methyl 2-((4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (8). 167 mg, 49% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 7.75 – 7.55 (m, 2H), 7.46 – 7.30 (m, 3H), 4.13 (d, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 2.55 – 2.33 (m, 1H), 1.20 (dd, *J* = 8.5, 1.4 Hz, 2H), 0.88 (dd, *J* = 7.8, 5.5 Hz, 2H). The ^{1}H NMR spectral data is in agreement with reported.[6]

Ethyl 2-((4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (9). 39 mg, 11% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 7.74 – 7.55 (m, 2H), 7.39 (dt, *J* = 8.3, 6.4 Hz, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.11 (d, *J* = 7.5 Hz, 2H), 2.51 – 2.38 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.19 (dd, *J* = 8.5, 1.4 Hz, 2H), 0.88 (dd, *J* = 7.6, 5.6 Hz, 2H). The ^{1}H NMR spectral data is in agreement with reported.[14]

Isopropyl 2-((4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (10). 121 mg, 33% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.68 (s, 1H), 7.62 – 7.44 (m, 3H), 7.31 – 7.22 (m, 1H), 5.06 (dt, *J* = 12.5, 6.3 Hz, 1H), 3.75 (s, 2H), 2.34 (ddd, *J* = 14.2, 8.6, 5.9 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 6H), 1.23 – 0.96 (m, 2H), 0.79 (d, *J* = 4.3 Hz, 2H). The ^{1}H NMR spectral data is in agreement with reported.[6]

3-(((1,3-Dioxolan-2-yl)methyl)thio)-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazole (11). 154 mg, 44% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.4 Hz, 1H), 8.31 (s, 1H), 7.73 – 7.56 (m, 1H), 7.56 – 7.21 (m, 1H), 7.22 (s, 3H), 5.25 (t, *J* = 4.3 Hz, 1H), 3.97 – 3.53 (m, 4H), 3.53 – 3.29 (m, 2H), 2.43 (tt, *J* = 8.5, 5.6 Hz, 1H), 1.18 (dd, *J* = 8.5, 1.3 Hz, 2H), 1.13 – 0.56 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.29, 145.66, 142.73, 134.25, 129.32, 127.70, 127.08, 125.10, 123.04, 122.32, 101.91, 65.36, 35.62, 13.45, 6.87, 1.01. HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_3S$ $[M + H]^+$ 355.1304, found 355.1307.

4-(4-Cyclopropylnaphthalen-1-yl)-3-((2,2,2-trichloroethyl)thio)-4*H*-1,2,4-triazole (12). 140 mg, 35% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.36 (s, 1H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.40 (s, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.69 (q, *J* = 14.3 Hz, 2H), 2.46 (tt, *J* = 8.3, 5.5 Hz, 1H), 1.21 (dd, *J* = 8.5, 1.5 Hz, 2H), 1.07 – 0.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.13, 143.12, 134.30, 129.25, 127.91, 127.25, 125.29, 125.01, 123.07, 122.06, 97.02, 54.74, 13.48, 7.03, 6.82. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}Cl_3N_3S$ $[M + H]^+$ 400.0017, found 400.0018.

3-(Allylthio)-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazole (13). 30 mg, 10% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.4 Hz, 1H), 8.32 (s, 1H), 7.74 – 7.63 (m, 1H), 7.63 – 7.52 (m, 1H), 7.39 – 7.29 (m, 3H), 5.93 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.27 (dd, *J* = 16.9, 1.2 Hz, 1H), 5.13 (d, *J* = 10.2 Hz, 1H), 3.88 (d, *J* = 7.0 Hz, 2H), 2.45 (tt, *J* = 8.4, 5.5 Hz, 1H), 1.19 (dd, *J* = 8.5, 1.5 Hz, 2H), 1.13 – 0.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.57, 142.72, 134.24, 132.47, 129.37, 127.84, 127.68, 127.08, 125.16, 124.98, 123.00, 122.32, 118.94, 35.56, 29.67, 13.43, 6.95, 6.77. HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_3S$ $[M + H]^+$ 309.1249, found 309.1251.

Methyl 2-((4-(4-cyclopropylnaphthalen-1-yl)-5-hydroxy-4*H*-1,2,4-triazol-3-yl)thio)acetate (15). The three examples in Scheme 4 explored the use of hydrazine compounds as nucleophiles. When R^1=OMe, **15** (231 mg, 65%) was obtained. When R^2=OEt, **15** (170 mg, 48%) was obtained. When R^3=OBn, **15** (255 mg, 72%) was obtained. Yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.39 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.57 (dt, *J* = 43.5, 7.4 Hz, 1H), 7.44 (d, *J* = 19.8 Hz, 1H), 7.23 (d, *J* =

7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.16 (s, 2H), 3.77 (s, 3H), 2.36 (ddd, *J* = 13.7, 8.3, 5.7 Hz, 1H), 1.17 – 0.91 (m, 2H), 0.71 (d, *J* = 3.8 Hz, 2H). The ^{1}H NMR spectral data is in agreement with reported.[15]

Methyl 2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (18). 15 (710 mg, 2 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. PBr_3 (813 mg, 3 mmol) was slowly added and stirring was continued. The progress of the reaction was monitored by TLC. After completion of the reaction, added the solution to water (10 mL). Organic phase was added aqueous sodium bicarbonate solution and saturated sodium chloride solution, dried (Na_2SO_4), and concentrated. The residue was loaded on a silica gel using petroleum ether / EtOAc (2/1) to afford the desired product **18** (669 mg, 80% yield, white oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.4 Hz, 1H), 7.65 (dtd, *J* = 16.3, 6.9, 1.1 Hz, 2H), 7.39 (s, 2H), 7.31 – 7.23 (m, 1H), 4.08 (d, *J* = 6.7 Hz, 2H), 3.75 (s, 3H), 2.46 (tt, *J* = 8.5, 5.5 Hz, 1H), 1.22 (dd, *J* = 5.2, 3.7 Hz, 2H), 0.96 – 0.83 (m, 2H). The ^{1}H NMR spectral data is in agreement with reported.[6]

2-((5-Bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid (1). In a 50 mL vial along with a stirring bar, **18** (986 mg, 2.36 mmol) was added THF (10 mL). The mixture was added 1N sodium hydroxide solution (2.5 mL, 2.5 mmol). The progress of the reaction was monitored by TLC. After completion of the reaction, EtOAc (30 mL) was added and the mixture was extracted with water (20 mL). The pH was adjusted to around 5 by progressively adding 1N hydrochloric acid solution. The mixture was extracted with EtOAc (3 × 30 mL) dried (Na_2SO_4), and concentrated, to give desired product **1** (848 mg, 89% yield, white oil.) ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H) , 8.59 (d, *J* = 8.4 Hz, 1H), 7.83 – 7.60 (m, 3H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 4.01 (d, *J* = 1.2 Hz, 2H), 2.77 – 2.42 (m, 1H), 1.16 (dd, *J* = 6.2, 2.1 Hz, 2H), 0.88 (d, *J* = 3.8 Hz, 2H). The ^{1}H NMR spectral data is in agreement with reported.[6]

ACKNOWLEDGEMENTS

We gratefully thank the financial support from the Science and Technology Commission of Shanghai Municipality (17ZR1412000).

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