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Convenient method for the synthesis of 5-(4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione (ADT-OMe) and 5-(4-hydroxyphenyl)-3*H*-1,2-dithiol-3-thione (ADT-OH) using microwave irradiation

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ABSTRACT

A convenient method is described for the rapid synthesis of 5-(4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione (ADT-OMe) from anethole and elemental sulfur using microwave irradiation. Various reaction conditions were applied to reduce the reaction time from several hours to 10 min, resulting in an improvement in yield and overcoming the undesired by-product formation associated with conventional methods. 5-(4-Hydroxyphenyl)-3*H*-1,2-dithiol-3-thione (ADT-OH) was obtained by the deprotection of ADT-OMe using pyridine hydrochloride under microwave irradiation.

Introduction

Hydrogen sulfide (H_2S) has attracted increasing research interest as an important signaling molecule, endowed with a variety of cytoprotective activities. Alterations to endogenous H_2S production is related to cardiovascular, gastrointestinal and central nervous systems disorders.[1,2] Thus, the administration of exogenous H_2S donors has been associated with promising preclinical and early clinical data.[3]

Inorganic salts such as NaSH and Na_2S were initially studied as exogenous H_2S donors, however, they cause rapid H_2S release into cells. Since H_2S is a highly toxic gas, the excessive amounts released from inorganic salts can result in cytotoxicity. This limitation prompted the development of organic compounds that act as slow release H_2S donors.[4]

An important class of H_2S donors are the 1,2-dithiole-3-thiones, specifically 5-(4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione (ADT-OMe, **1**) which is used for the treatment of dry mouth. The deprotected derivative 5-(4-hydroxyphenyl)-3*H*-1,2-dithiol-3-thione (ADT-OH, **2**) and its esters with known NSAIDs display significantly reduced gastrotoxicity compared to the parent drugs.[5,6]

Most reported methods for the synthesis of ADT-OMe utilise anethole and elemental sulfur at high temperatures, either in solution or neat, with extended reaction times. The synthesis of ADT-OMe without solvent was first described by Böttcher and co-workers, who extensively examined the effect of reaction conditions and the formation of major by-products according to the temperature and the equivalents of sulfur.[7] In recent reports, dimethylformamide (DMF) or dimethylacetamide (DMA) were used as solvents at elevated temperatures (145–170 °C) to afford ADT-OMe in 34% yield after 6–8 h.[8,9]

Results and discussion

Synthesis of ADT-OMe

The synthesis of ADT-OMe (**1**, Scheme 1) from anethole and sulfur was studied under a series of conventional and microwave promoted conditions (Table 1). Most reactions were performed neat to achieve temperatures higher than the boiling point of commonly used solvents.

Initial experiments were based on recently reported conventional methods and resulted in the formation of complex mixtures with yields lower than 5%. The use of sulfur (7 eq.) and heating at 150 °C (oil bath) in DMF for 6 h did not produce ADT-OMe (Entry 1). This was supported by literature reports that the reactions of olefins with sulfur at temperatures of up to 140 °C yielded a complex mixture of polysulfides. Upon increasing the temperature, the yield of 1,2-dithiole-3-thiones also increased, reaching a maximum at 190–210 °C.[10] Moreover, Böttcher and co-workers reported that a 1:7 anethole to sulfur ratio resulted in considerable amounts of unreacted sulfur.[7] Based on these observations, a neat mixture of anethole and sulfur (4 eq.) was heated gradually to 220 °C in a sand

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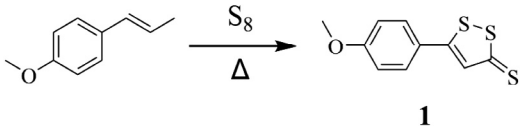


Scheme 1. Synthesis of ADT-OMe (**1**).

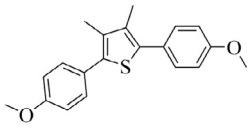


Fig. 2. 2,5-Bis(4-methoxyphenyl)-3,4-dimethylthiophene (**3**).

bath for 4 h. Compound **1** was isolated in very low yield (3%), along with a complex mixture of non-identified by-products (Entry 2). To avoid by-product formation which occurs below 180 °C,[7] the experiment was repeated by rapidly immersing the reaction mixture in an oil bath that had been already heated to 200 °C. The mixture melted almost immediately and ADT-OMe was afforded in 29% yield after 4 h (Entry 3).

Next, microwave irradiation was applied in a closed vessel using DMF as the solvent at 140 °C; this resulted in the formation of a complex mixture and the absence of ADT-OMe (Entry 4). Upon increasing the temperature to 170 °C, a high internal pressure developed and the experiment was stopped after 5 min. In this case, anethole was completely consumed and ADT-OMe was isolated in 12% yield (Entry 5).

For subsequent microwave assisted reactions, we opted to use an open vessel setup equipped with a condenser to prevent the development of internal pressure. As in Entry 3, the goal was to minimize the time required to reach the final temperature. It is worth noting that the reaction is exothermic at >150 °C. Polar intermediates and/or transition states could act as molecular radiators, improving the absorption of microwave irradiation and resulting in a steep rise in temperature.[11,12] Moreover, the observed exothermic effect might be due to an improvement of reaction homogeneity since elemental sulfur melts at >150 °C. The detailed data of the temperature increase was obtained from the microwave reactor's software and each T(t) diagram helped to select the next possible reaction conditions (Fig. 1).

Firstly, irradiation at 220 °C (200 W) for 10 min without solvent, led to the full consumption of anethole, as illustrated by crude ^{1}H NMR spectroscopy. Traces of 2,5-bis(4-methoxyphenyl)-3,4-dimethylthiophene (**3**), an anethole dimer by-product (Fig. 2 and ESI), were observed and ADT-OMe was isolated in 18% yield (Entry 6). The depicted dimer was first reported by Böttcher and coworkers.[7]

Increasing the reaction time to 20 min resulted in a viscous solid mixture without an improved yield (Entry 7). Further increases (240 °C) led to a decreased yield (Entry 8) suggesting that a lower temperature at 200 W with a 10 min reaction time would be suitable.

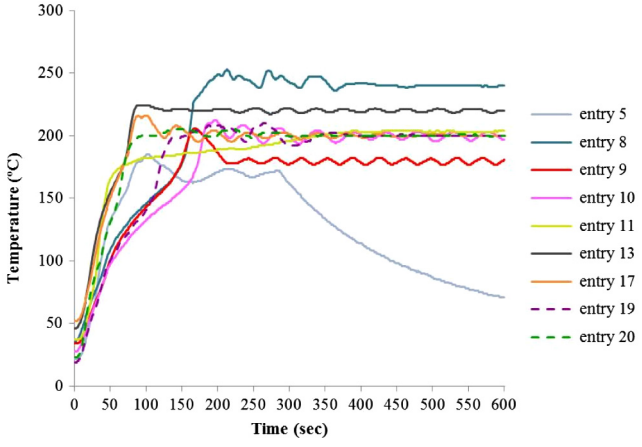


Fig. 1. T(t) diagram of selected reaction conditions.

Conducting the reaction at 180 °C gave a complex reaction mixture containing unreacted anethole, ADT-OMe, 1-methoxy-4-propylbenzene (dihydroanethole), and dimer **3** (Entry 9). Increasing the temperature to 200 °C afforded ADT-OMe in 32% yield (Entry 10) with some dihydroanethole. These conditions were also applied using the high boiling point solvent *N*-methyl-pyrrolidone (NMP, Entry 11). The homogeneous solution and the absorption of microwave irradiation by the highly polar solvent limits the microwave effects on the reactants,[12] resulting in a smoother temperature increase (Fig. 1) which may explain the lower yield in contrast with solvent-free experiments. Reducing the sulfur equivalents to 3 decreased the yield of **1** and enhanced by-product formation (Entry 12). Therefore, the 1:4 anethole to sulfur ratio at 200 °C (200 W) for 10 min were so far the optimum reaction conditions.

Additional experiments were performed by increasing the power to 250 or 300 W (Entries 13–17), using temperatures between 200 and 220 °C. Although the desired temperature was reached in 75 s (instead of 150 s with 200 W) this rapid heating favored the formation of dihydroanethole. Furthermore, the combination of high power and 220 °C resulted in slightly lower yields (30%) with a significant increase of anethole hydrogenation. Shorter reaction times under these conditions resulted in a lower yield (Entry 16). In this case, the crude ^{1}H NMR spectrum showed a lower amount of dihydroanethole compared to the 10 min entries, suggesting that its formation is favored as the reaction proceeds and is faster than the formation of **1**.

In line with these results, a lower temperature (200 °C, 250 W) was applied to afford ADT-OMe in 35% yield after 10 min (Entry 17). Although the yield is comparable to entry 10, the hydrogenated by-product was significantly present in the NMR spectrum.

Moreover, to investigate the effect of allotropic forms of cyclooctasulfur, molten sulfur and hot anethole were mixed at ~160 °C in the microwave tube and the reaction performed at 200 °C (200 W) for 10 min. However, compound **1** was obtained in 33% yield and the crude reaction mixture had the same composition as the other neat experiments (Entry 18).

Finally, we endeavored to control the formation of polymeric side-products. Anethole, like styrene, may generate radicals and initiate self-polymerization at elevated temperatures. According to the literature, thermal polymerization reactions can be controlled using a stable radical mediator such as 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).[13] Thus, catalytic TEMPO (0.02 eq.) was added to the reaction mixture (Entry 19), using the conditions in Entry 10 which afforded the highest yield with the least side-products. In this case, neither the yield nor the T(t) diagram were significantly affected (Fig. 1). However, when a higher loading of TEMPO (0.1 eq.) was used (Entry 20), the T(t) curve (Fig. 1) was similar to the curves of the 300 and 250 W experiments, indicating that the addition of a stable radical probably favors the formation of other reactive intermediates and helps achieve the steep temperature increase using milder microwave conditions. Under these conditions, a slight increase in yield (37%) was observed, while dihydroanethole formation was reduced in comparison to Entry 17; based on the crude ^{1}H NMR spectra (ESI). The formation of multiple undesired by-products was significantly restricted, although polymeric by-products, insoluble in organic solvents, were not completely avoided.

Table 1
Reaction optimization for the synthesis of ADT-OMe **1**.

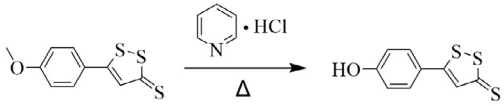
Entry	Sulfur (eq.)	Solvent	Power (W)	Temp. (°C)	Time	Yield **1** (%)
1	7	DMF	-[a]	150	6 h	–
2	4	Neat	-[a]	220	4 h	3%
3	4	Neat	-[a]	200	4 h	29%
4	7	DMF	200[b]	140	1 h	–
5	7	DMF	200[b]	170	5 min	12%
6	4	Neat	200[c]	220	10 min	18%
7	4	Neat	200[c]	220	20 min	18%
8	4	Neat	200[c]	240	10 min	9%
9	4	Neat	200[c]	180	10 min	12%
10	4	Neat	200[c]	200	10 min	32%
11	4	NMP	200[c]	200	10 min	24%
12	3	Neat	200[c]	200	10 min	25%
13	4	Neat	300[c]	220	10 min	30%
14	4	Neat	250[c]	220	10 min	30%
15	5	Neat	250[c]	220	10 min	22%
16	4	Neat	250[c]	220	7 min	19%
17	4	Neat	250[c]	200	10 min	35%
18	4	Neat[d]	200[c]	200	10 min	33%
19	4	Neat[e]	200[c]	200	10 min	35%
20	4	Neat[f]	200[c]	200	10 min	37%

[a] Oil/sand bath.
[b] Closed vessel.
[c] Open vessel.
[d] Molten sulfur.
[e] TEMPO (10 mg, 0.02 eq.).
[f] TEMPO (50 mg, 0.1 eq.); Reagents and conditions: anethole (500 mg, 3.37 mmol), solvent-free or solvent (1 mL).

Deprotection of ADT-OMe

The solvent-free deprotection of ADT-OMe using pyridine hydrochloride (6 eq.) with a reaction time of 30 min has been reported in the literature (Scheme 2).[8,9]

Microwave irradiation was also applied to reduce the reaction time and the equivalents of py·HCl (Table 2). The use of py·HCl (3 eq.) and a reaction duration of 10 or 20 min furnished **2** in 63% and 29% yield (Entries 1 and 2), respectively. Comparatively, ADT-OH was isolated in 81% yield using 6 eq. of py·HCl (Entry 3). However, these results were not reproducible with an open vessel setup since the reaction mixture spurted into the condenser; the yield was constantly 80% using a closed vessel under the same conditions (Entry 4). Furthermore, gas release was reduced after 5 min during the open vessel experiments, which could imply the end of the reaction. This was confirmed by reducing the reaction time to 7 min, which afforded ADT-OH in 79% yield (Entry 5). The effect of a longer reaction time (20 min) was also tested, but resulted in reduced yield (Entry 6).



1 **2**

Scheme 2. Synthesis of ADT-OH **2**.

Table 2
Reaction optimization for the deprotection of ADT-OMe **1**.

Entry	py·HCl (eq.)	Time	Yield **2** (%)
1	3	10 min	63%[a]
2	3	20 min	29%[a]
3	6	10 min	81%[a]
4	6	10 min	80%[b]
5	6	7 min	79%[b]
6	6	20 min	58%[b]

Reagents and conditions: solvent-free, 200 °C, 200 W.
[a] Open vessel.
[b] Closed vessel.

Conclusion

A convenient, solvent-free and rapid method was developed for the preparation of ADT-OMe. Although the overall yield was not significantly improved in comparison with previously reported synthetic procedures, the reaction time was reduced to 10 min instead of several hours. Moreover, the number of sulfur equivalents was reduced. The deprotection of ADT-OMe was also performed using microwave irradiation, resulting in a reduced reaction time.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.05.010.

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