Synthesis and Use of 2,4,6-Tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trisulfide (TMPT) as a Novel Amide Thionating Agent

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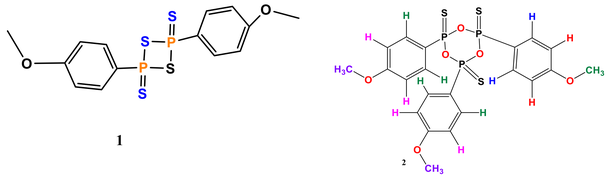
Introduction

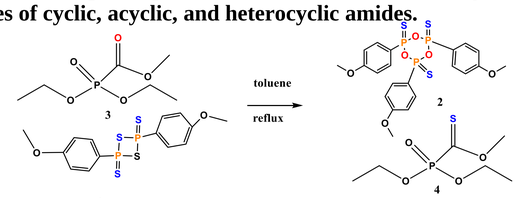
Thionation reactions are important transformations in organic chemistry, where an oxygen moiety is converted to sulfur in a wide variety of substrates such as carbonyl containing compounds amides, ethers and alcohols. Typically, these reactions occur under inert atmosphere using a thionation reagent such as 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiaphosphetane (Lawesson's reagent, 1). A by product from Lawesson's reagent was isolated and characterized earlier in our lab by ^{1}H NMR spectroscopy and by single crystal X ray crystallography. The structure of 2,4,6-tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trisulfide, 2, which is abbreviated as TMPT is found in figure 1.



1 2

Figure 1. Structure of Lawesson's reagent and TMPT

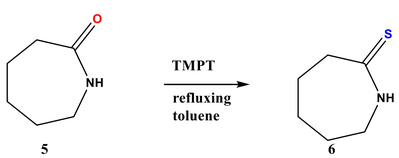
Efforts were concentrated on improved synthesis of TMPT, free from contamination of Lawesson's reagent in order to explore the potential of TMPT as a novel thionating reagent. One such route published route explored in figure 2 provided sufficient TMPT to study the thionation of a series of cyclic, acyclic, and heterocyclic amides.



3 1 2 4

Figure 2. Synthesis of TMPT

Next, we focused on exploring the thionation with TMPT. Towards this goal, we chose several cylic, acylic and heterocylic thioamides.
The cyclic amide ϵ-Caprolactam (azepane-2-one) was subjected to thionation with TMPT in refluxing toluene (figure 3) . Increasing the reaction times resulted in a decrease in percent yield (Table 1). The same trends were observed for thionation of 2- pyrrolidone in Figure 4 and Table 2.

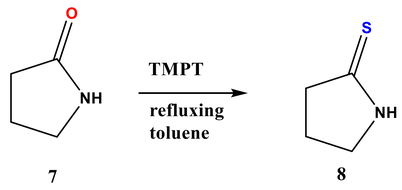


5 6

Figure 3 Synthesis of Azepane-2-thione, 6

Table 1 Reaction of ϵ-Caprolactam (azepane-2-one) and TMPT

Reaction Conditions	TMPT Equivalence	% yield
Refluxing toluene, 13.5 h	0.50	29
Refluxing toluene, 8 h	0.50	51



7 8

Figure 4. Synthesis of Pyrrolidine-2-thione, 8

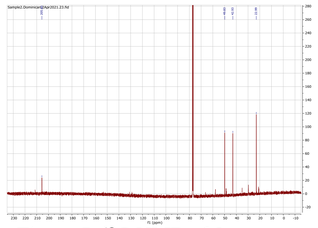
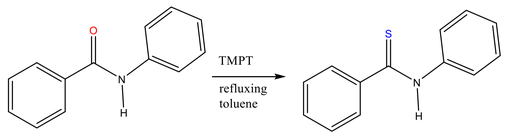


Figure 5. ^{13}C NMR of 8

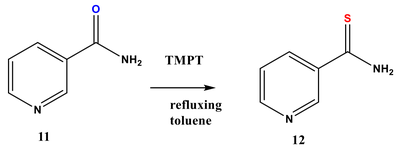
Table 2 Reaction of 2-Pyrrolidone and TMPT

Reaction Conditions	Equivalence of TMPT	% yield
Refluxing toluene 12 h	0.50	47
Refluxing toluene 7 h	0.50	61



9 10

Figure 6. Synthesis of N-phenylbenzenecarbothioamide, 10



11 12

Figure 7. Synthesis of Thionicotinamide, 12

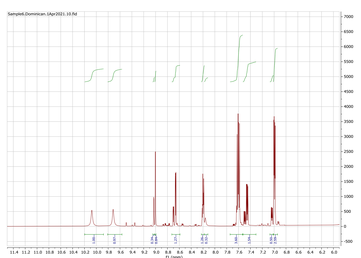


Figure 8. ^{1}H NMR spectra of 12

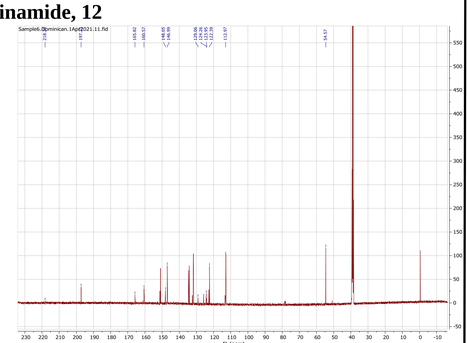


Figure 9. ^{13}C NMR spectra of 12

Table 3 Reaction of Acylic and Heterocylic Amides and TMPT

Substrate	Conditions	TMPT Equivalence	Product	% yield
9	Refluxing toluene, 22 h	0.50	10	79
11	Refluxing toluene, 6.5 h	0.50	12 + other compounds	-

Conclusion

- **A method of synthesizing high purity of TMPT was utilized in this project.**
- **Broadened scope of the project to include acylic and heterocylic amides.**
- **Repeated the studied reactions to determine reproducibility and average yields.**
- **Further purification of thionicotinamide, 12, to determine percent yield and identity of other compounds in the reaction mixture**

Future Work

- **Expand the investigations with more amides for structural diversity**
- **Explore mechanistic studies**

Acknowledgements

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- **We would also like to acknowledge Dr. Dean Olson, NMR Lab, University of Illinois at Urbana-Champaign for his assistance with NMR spectra.**

Experimental Procedures

Synthesis of 2,4,6-tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trisulfide (TMPT), 2
To a 250 mL round bottom flask, 5 mL of Triethyl phosphonoformate (0.5 eq. 5.60 g, 26.2 mmol) and 90 mL of acetonitrile was added. Using a funnel, 5.3 g (13.1 mmol) of Lawesson's Reagent was added to the flask and rinsed with remaining acetonitrile (4.5 mL). The reaction was done under nitrogen for 2 hrs and then refluxed at 82°C for 6 hrs. The mixture appeared to be off-white and cloudy which turned yellow after 35 minutes. The precipitate was pale yellow. Afte heating for 6 hrs, the solution turned yellow. A TLC (4:1 Hexanes to EtoAc) was done which then led to a filtration, in which a white solid was separated and dried to yield 1.5578 g (NP-III-13-1). (Rf values: 0.62 and 0.21-yellow solution, 0.00-white solid) The white solid was recrystallized. 51.2 mL of EtoAc was added to a 250 mL Erlenmeyer flask and the entire contents of NP-III-13-1 (1.5578 g) was added along with a stirrer. The flask was heated at 82°C on a hot plate, causing the solid to go into solution after 3 min. The flask was then removed from the hot plate and parafilmed with holes.

Synthesis of Azepane-2-thione, 6
To a 50 mL rb flask, E-Caprolactam (17 mg, 0.150 mmol), Lawesson's Reagent (29 mg, 0.0514 mmol), a stir bar and 10.0 mL of anhydrous toluene were added. The mixture was stirred and heated under reflux at for 13.5 hrs. A TLC was then done at a 3:1 ratio of Hexanes: EtoAc. The Hanessian's Stain was used to visualize spot for E-Caprolactam and treating it at 550°C. The resulting filtrate was concentrated in vacuo and purified by column chromatography (eluent 4/1 hexanes/EtOAc) to yield 57 mg of nicotimade, 29.4% yield.
To a 50 mL rb flask, 1.0421 g of E-Caprolactam, 1.7982 g of Lawesson's Reagent, a stir bar and 25.0 mL of acetonitrile were added. The mixture was stirred at room temp and left to stir overnight for 21 hrs. A TLC was then done at a 3:1 ratio of Hexanes: EtoAc. The reactant (DE-I-01) was heated under reflux for 4 hrs and a sample was taken to take another TLC at the same ratio. Rf values: (DE-61-1= 0.321, Trimer= 0.528, 0.00, E-Caprolactam= 0.0943, DE-I-01= 0.547, 0.358, 0.226, 0.00). The Hanessian's Stain was used to visualize spot for E-Caprolactam and treating it at 550°C. The mixture was then heated under reflux for 4 hrs

Synthesis of Pyrrolidine-2-thione, 8
To a 250 mL rb flask, 52 mg (0.612 mmol) of 2-Pyrillidinone, 174 mg (0.305 mmol) of Trimer (0.877 mmol), and 10 mL Toluene and a stirrer were added. Mixture was heated under reflux for 12 hrs. A column was done and a TLC was done at a 2:1 ratio EtoAc to Hexanes. (Rf values: 0.17, 0.183 and 0.31) The TLC was visualized using Hanessian's Stain and treated at 550°C. 3 different compounds were collected from the column (DE-62-1)
To a 250 mL rb flask, 149.3 mg (1.754 mmol) of 2-Pyrillidinone , 500 mg of Trimer (0.877 mmol), and 20 mL Toluene and a stirrer were added. Mixture was heated under reflux for 7 hrs. A TLC was done at a 3:1 ratio Hexanes to EtoAc. The product (DE-I-13) had a MW of 101.11 g/mol. The resulting mixture was filtrated in which there was a dark, gunky product (I-14-2) and a white, solid precipitate (I-14-1). A TLC was done on this in a 2:1 ratio Hexanes to EtoAc.
To a 250 mL rb flask, 100 mg (1.17 mmol) of 2-Pyrillidinone, 446 mg of Trimer (0.783 mmol), and 15 mL Toluene and a stirrer were added. Mixture was heated under reflux for 5.5 hrs. A TLC was done at a 3:1 ratio Hexanes to EtoAc. The product (DE-I-13) had a MW of 101.11 g/mol. The resulting mixture was filtrated in which there was a dark, gunky product (I-14-2) and a white, solid precipitate (I-14-1). A TLC was done on this in a 2:1 ratio Hexanes to EtoAc.

Synthesis of N-phenylbenzenecarbothioamide , 10
To a 50 mL round bottom flask equipped with condenser was added benzanilide (16 mg, 0.587mmol), TMPT (167mg, 0.293 mmol), and anhydrous toluene (10 mL). The reaction mixture was refluxed for 22 hours until all the starting benzanilide was consumed as indicated by TLC(7/1 Hexans/EtoAc, Rf=0.25). Upon cooling to room temperature, a clear yellow precipitant appeared which was removed by filtration. The reaction was concentrated in vacuo to yield a yellow solid which was purified by means of column chromatography (eluent 7/1 hexanes/EtOAc) to a yellow solid (6.1mg,) and yellow semi-liquid compound (33.1mg) (79.4% yield)

Synthesis of Thionicotinamide, 12
To a 50 mL round bottom flask equipped with condenser was added Nicotinamide (71.614 mg, 0.586 mmol), TMPT (0.5 equ., 167mg, 0.293 mmol), and anhydrous toluene (10 mL). The reaction mixture was refluxed for 6.5 hours until all the starting Nicotimade was consumed as indicated by TLC. Upon cooling to room temperature, a white precipitant appeared which was removed by filtration. The resulting filtrate was concentrated in vacuo and purified by column chromatography (eluent 4/1 hexanes/EtOAc) to yield The reaction was concentrated in vacuo to yield a yellow solid which was purified by column chromatography (eluent 3/1 hexanes/EtOAc) to yield 49 mg.