ORGANIC LETTERS

1999
Vol. 1, No. 5
697−700

Microwave-Accelerated Solvent-Free Synthesis of Thioketones, Thiolactones, Thioamides, Thionoesters, and Thioflavonoids

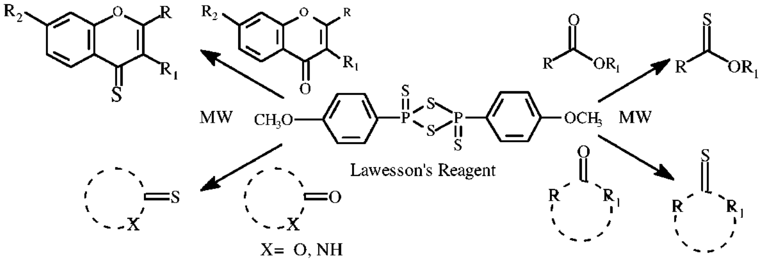
Rajender S. Varma* and Dalip Kumar

Department of Chemistry and Texas Research Institute for Environmental Studies (TRIES), Sam Houston State University, Huntsville, Texas 77341-2117

chm_rsv@shsu.edu

Received April 30, 1999

ABSTRACT



An expeditious, solvent-free, and high yield conversion of ketones, flavones, isoflavones, lactones, amides, and esters to the corresponding thio analogues is described utilizing Lawesson's reagent in a process that circumvents the use of dry solvents and excess of the reagent.

The synthesis of thio analogues of ketones, flavones, isoflavones, lactones, amides, and esters has received considerable attention due to the biological importance of these molecules,[1] their rich photochemistry,[2] and their usefulness as precursors for the synthesis of a variety of organic compounds.[3−6] This basic transformation has been accomplished by several reagents, namely, phosphorus pentasulfide,[7a,b] hydrogen sulfide in the presence of acid,[7c] bis(tricyclohexyltin) sulfide with boron trifluoride,[7d] bis(trimethylsilyl) sulfide with $CoCl_2 \cdot 6H_2O$,[7e] and thiation of *gem*-dichlorides with sodium hydrogen sulfide,[7f] thioacetic acid[7g] or potassium xanthate.[7h] Most of these lengthy procedures, however, require an excess of reagents and involve the use of aromatic hydrocarbon solvents such as toluene, xylene,

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* To whom correspondence should be addressed at the National Risk Management Research Laboratory, U.S. Environmental Protection Agency, 26 W. Martin Luther King Dr., MS 443, Cincinnati, OH 45268.

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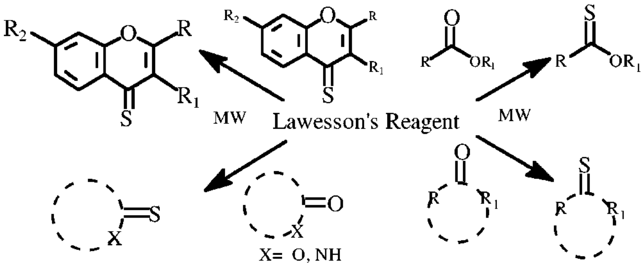
10.1021/ol990629a CCC: $18.00

benzene, or triethylamine and pyridine under dry conditions, affording only moderate yields of products. The 2,4-bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane 2,4-disulfide, known as Lawesson's reagent, has been commonly used for the efficient conversion of oxygen functionalities into their thio analogues.[7i–l] However, these conventional methods usually require excess of the Lawesson's reagent (0.5–3.0 molar equiv) in lengthy reactions (2–25 h) that are conducted in dry hydrocarbon solvents at elevated temperatures and result in generation of side products.

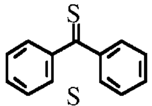
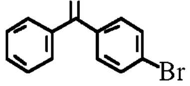
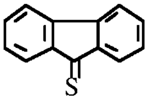
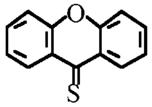
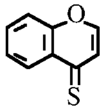
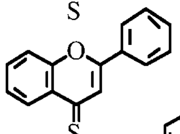
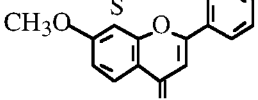
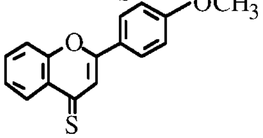
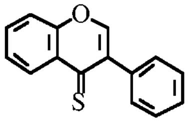
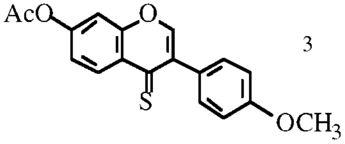
Initially introduced in 1986,[8] the chemical application of microwaves has now become an area of interest for the synthesis of a wide variety of compounds and efficient functional group transformations under solvent-free conditions.[9,10] The advantages of microwave-expedited chemical transformations are cleaner reactions, shorter reaction times, and the ease of manipulation. The reactions under solvent-free conditions are especially appealing as they provide the opportunity to work in an open vessel, thus circumventing the risk of high-pressure development in reaction vessels. In view of the limitation of the existing methods and as a part of our ongoing program to develop solvent-free reactions,[10] we now report a rapid and solventless synthesis of thioketones, thioflavones, thioisoflavones, thiolactones, thioamides, and thionoesters (Scheme 1). The simple process in its entirety involves mixing the substrates with the Lawesson's reagent followed by exposure to microwave irradiation under solventless conditions.

Scheme 1



The most common methods employed for the synthesis of thioketones involves the reaction of ketones with hydrogen sulfide in the presence of acid,[7c] phosphorus pentasulfide in the presence of base,[7a,b] Lawesson's reagent,[7k] or thiation of *gem*-dichlorides with reagents such as sodium hydrogen sulfide,[7f] thioacetic acid,[7g] and potassium xanthate[7h] in dry media. In our process the carbonyl compounds are simply mixed with Lawesson's reagent (0.5 equiv) and then irradiated under solvent-free conditions that do not require any acidic or basic media. We have found that this solvent-free environmentally benign approach is quite general and is applicable for the preparation of a variety of thioketones using an unmodified household microwave oven.

Table 1. Solvent-Free Synthesis of Thioketones, Thioflavones, and Thioisoflavones

Entry	Product[a]	Time (Min)	Yield (%)[b]	Ref.
1		3	97	7k
2		3	96	7k
3		3	86	7m
4		4	96	7m
5		3	95	12e
6		3	92	12d
7		3	95	12a
8		3	94	12a
9		3	94	12a
10		3	92	12b

[a] Products are characterized by comparison of their mp, IR, and NMR (^{1}H and ^{13}C) spectra with those of authentic samples. [b] Yields refer to pure isolated products.

Flavones and isoflavones are well-known naturally occurring plant phenolics with an array of biological activities.[11] The corresponding thio analogues of flavones and isoflavones have received less attention due to limited methods available for their preparation; only moderate yields are obtained (38–

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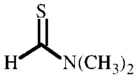
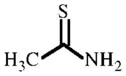
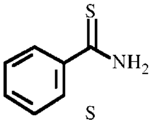
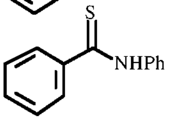
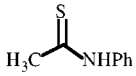
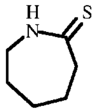
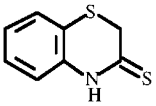
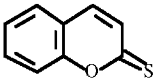
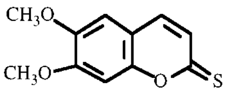
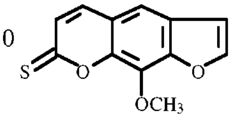
(8) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.

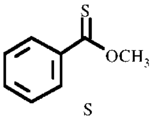
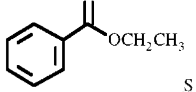
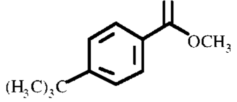
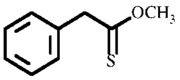
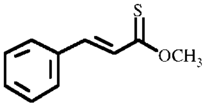
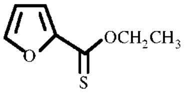
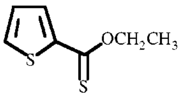
(9) For an overview of solvent-free reactions accelerated by exposure to microwave irradiation see: (a) Varma, R. S. *Green Chem.* **1999**, 43–55. (b) Varma, R. S. *Clean Prod. Processes* **1999**, *1*, 132. (c) Varma, R. S. Microwave-Assisted Reactions under Solvent-Free "Dry" Conditions. In *Microwaves: Theory and Application in Material Processing IV*; Clark, D., Sutton, W., Lewis, D., Eds.; Ceramic Transactions 80; American Ceramic Society: Westerville, OH, 1997; pp 357–365. (d) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (e) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* **1997**, *27*, 18. (f) Majetich, G.; Hicks, R. *J. Microwave Power Electromagn. Energy* **1995**, *30*, 27. (g) Abramovich, R. A. *Org. Prep. Proced. Int.* **1991**, *23*, 683.

Table 2. Synthesis of Thioamides and Thiolactones under Solvent-Free Conditions

Entry	Product[a]	Time (Min)	Yield (%)[b]	Ref.
1		2	97	7l
2		2	87	7l
3		2	93	7l
4		2	97	7l
5		2	96	7l
6		2	88	7l
7		3	98	7n
8		3	98	7o
9		3	94	–
10		3	92	7p

[a] Products are characterized by comparison of their mp, IR, and NMR (^{1}H and ^{13}C) spectra with those of authentic samples. [b] Yields refer to pure isolated products.

Table 3. Solvent-Free Synthesis of Thionoesters

Entry	Product[a]	Time (Min)	Yield (%)[b]	Ref.
1		3	85	16a
2		3	96	16b
3		3	88	16c
4		4	86	16d
5		3	76	16e
6		3	84	16f
7		3	89	16f

[a] All the products are viscous liquids. [b] Products are characterized by comparison of their IR and NMR (^{1}H and ^{13}C) spectra with those of the authentic samples. [b] Yields refer to pure isolated products.

84%) using phosphorus pentasulfide under refluxing conditions in dry benzene or xylene.[12] Our solid-state microwave irradiation protocol affords thioflavones and thioisoflavones in almost quantitative yields by admixing flavones or isoflavones with the Lawesson's reagent (Table 1). A variety of substituents on the aryl ring are well-tolerated, and the reaction leads to completion in all the cases.

This general approach can be extended to the high-yield synthesis of thiolactones and thioamides which are useful precursors for a wide variety of organic molecules.[10n] Various thiocoumarins, related thiolactones, and thioamides (aliphatic, aromatic, and cyclic) exemplify the versatility of this simple protocol (Table 2).[17] In the case of lactones and amides, only 0.5 equiv of Lawesson's reagent is needed for completion of the reaction. The conventional reactions are not only time-consuming and afford poor yield of the desired product but require excess of the reagent due to significant side reactions.

Thionoesters are useful building blocks for the assembly of a variety of organic compounds.[13,14] They can be readily

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(10) For cleavage-deprotection reactions, see: (a) Varma, R. S.; Chatterjee, A. K.; Varma, M. *Tetrahedron Lett.* **1993**, *34*, 3207. (b) Varma, R. S.; Chatterjee, A. K.; Varma, M. *Tetrahedron Lett.* **1993**, *34*, 4603. (c) Varma, R. S.; Varma, M.; Chatterjee, A. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 999. (d) Varma, R. S.; Lamture, J. B.; Varma, M. *Tetrahedron Lett.* **1993**, *34*, 3029. (e) Varma, R. S.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 2623. (f) Varma, R. S.; Meshram, H. M. *Tetrahedron Lett.* **1997**, *38*, 5427. (g) Varma, R. S.; Meshram, H. M. *Tetrahedron Lett.* **1997**, *38*, 7973. (h) Varma, R. S.; Dahiya, R.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 8819. For condensation-cyclization reactions, see: (i) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039. (j) Varma, R. S.; Dahiya, R. *Synlett* **1997**, 1245. (k) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 5131. (l) Varma, R. S.; Saini, R. K. *Synlett* **1997**, 857. (m) Varma, R. S.; Dahiya, R. *J. Org. Chem.* **1998**, *63*, 8038. (n) Varma, R. S.; Kumar, D.; Liesen, P. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4093. For oxidation reactions, see: (o) Varma, R. S.; Dahiya, R. *Tetrahedron Lett.* **1997**, *38*, 2043. (p) Varma, R. S.; Saini, R. K.; Meshram, H. M. *Tetrahedron Lett.* **1997**, *38*, 6525. (q) Varma, R. S.; Dahiya, R.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 7029. (r) Varma, R. S.; Saini, R. K.; Dahiya, R. *Tetrahedron Lett.* **1997**, *38*, 7823. (s) Varma, R. S.; Dahiya, R. *Tetrahedron Lett.* **1998**, *39*, 1307. (t) Varma, R. S.; Saini, R. K. *Tetrahedron Lett.* **1998**, *39*, 1481. For reduction reactions, see: (u) Varma, R. S.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 4337. (v) Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293. (w) Varma, R. S.; Naicker, K. P.; Liesen, P. J. *Tetrahedron Lett.* **1998**, *39*, 8437.

desulfurized with Raney nickel to produce the corresponding ethers.[13] The synthesis of 1,3,4-oxadiazoles,[14] which possess significant activity as herbicides, fungicides, and plant cell growth factors, require thionoesters as precursors.[5,15] Consequently, we have broadened the scope of this solvent-free protocol by preparing valuable thionoesters (Table 3).[16] In this case, our process requires 0.8 equiv of the Lawesson's reagent for complete conversion to the corresponding thioesters, which is a dramatic improvement over existing methods. Normally, 2.0−3.0 equiv of the reagent is needed in lengthy reactions (20−25 h) which is presumably responsible for the decomposition of the Lawesson's reagent.

In conclusion, we have developed a general, rapid, and solvent-free protocol[17] for the synthesis of thio analogues of ketones, flavones, isoflavones, lactones, amides and esters which are widely used in organic synthesis. Our eco-friendly solventless method avoids the use of excess amount of Lawesson's reagent and precludes the use of dry hydrocarbon solvents such as benzene, xylene, triethylamine, or pyridine.

Acknowledgment. We are grateful for financial support to the Texas Research Institute for Environmental Studies (TRIES).

OL990629A

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(14) Reynaud, P.; El Hamad, Y.; Davrinche, C.; Nguyen-Tri-Xuong, E.; Tran, G.; Rinjard, P. *J. Heterocycl. Chem*. **1992**, *29*, 991.

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(17) **Experimental Section: General Procedure.** The preparation of 6,7-dimethoxythiocoumarin is representative of the method employed. A mixture of 6,7-dimethoxycoumarin (1 mmol) and Lawesson's reagent (0.5 mmol, in the case of esters, 0.8 mmol), was taken in a glass tube and mixed thoroughly with a spatula. The glass tube was then placed in an alumina bath inside the microwave oven (900 W) and irradiated for 3 min (see Tables 1−3 for the time required for individual compounds). On completion of the reaction, followed by TLC examination, the colored material was dissolved in dichloromethane and adsorbed on silica gel and purified by silica gel column chromatography using hexane as initial eluent followed by ethyl acetate/hexane (1:9 v/v) which afforded the pure 6,7-dimethoxythiocoumarin: yield 94%; mp 195−96 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 6H, OCH_3), 6.86 (s, 1H, C8−H), 7.01 (s, 1H, C5−H), 7.15 (d, 1H, $J = 9.3$, C3−H), 7.38 (d, 1H, $J = 9.3$, C4−H); ^{13}C NMR ($CDCl_3$) δ 57.21, 57.36,f 100.57, 107.10, 108.09, 114.61, 128.02, 135.93, 148.18, 154.18, 197.80; Mass: [M^+] 222. In the case of flavone (entry 6, Table 1) and coumarin (entry 8, Table 2), the reactions were conducted on relatively larger scale (5 mmol) with reproducible results in terms of yields.