

Synthesis and Application of a Fluorous Lawesson's Reagent: Convenient Chromatography-Free Product Purification

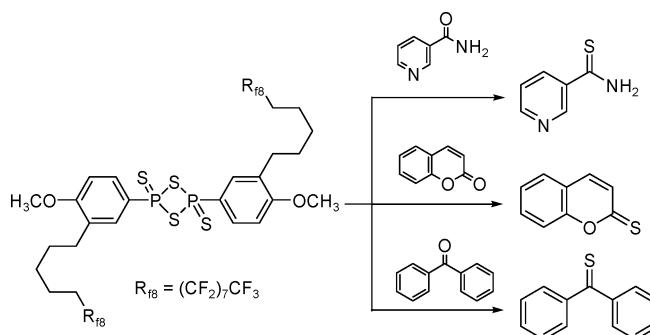
Zoltán Kaleta,[†] Gábor Tárkányi,[‡] Ágnes Gömöry,[‡] Ferenc Kálmán,[§]
Tamás Nagy,[§] and Tibor Soós^{*,†}

Institute of Biomolecular Chemistry, Chemical Research Center of the Hungarian Academy of Science, P.O. Box 17, 1525 Budapest, Hungary, Institute of Structural Chemistry, Chemical Research Center of Hungarian Academy of Science, P.O. Box 17, 1525 Budapest, Hungary, and ComGenex, Inc., 7 Záhony, 1031 Budapest, Hungary

tibor.soos@chemres.hu

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ABSTRACT

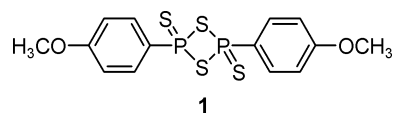


Easy and quick separation with fluorous solid phase extraction.

A fluorous analogue of Lawesson's reagent for thionation of carbonyl compounds has been developed and its use demonstrated on a series of amides, esters, and ketones. The separation of the Lawesson's reagent-derived byproducts can be achieved by a simple fluorous solid-phase extraction.

Organosulfur compounds occupy a uniquely important place in synthetic organic chemistry due to their rich and versatile chemistry.¹ In parallel, this class of compounds has long been of widespread interest by virtue of their ubiquitous biological activity. Thionation, the conversion of the carbonyl group to thiocarbonyl, is a widely applied procedure for the synthesis of organosulfur compounds. Among the reagents

affecting this transformation, Lawesson's reagent (**1**, LR) excels in efficiency and broad utility.²



Several LR protocols have been reported in the literature that demonstrate the utility of this powerful reagent³ but also concomitantly reveal the shortcomings that accompany its

[†] Institute of Biomolecular Chemistry, Chemical Research Center of the Hungarian Academy of Science.

[‡] Institute of Structural Chemistry, Chemical Research Center of Hungarian Academy of Science.

[§] ComGenex, Inc.

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usage. The lack of an extractive procedure to remove the LR-derived byproducts is a commonly cited disadvantage of this reagent. In some cases, the requisite chromatographic separation of the desired product from the LR byproducts can be really cumbersome or impossible, which limits the reagent utility. Herein, we report a possible solution of this long-standing separation problem by the synthesis and application of a fluorous LR.

Recently, much attention has been focused on fluorous chemistry as an alternative solution-phase tagging approach in catalysis and high-throughput synthesis.⁴ The highly hydrophobic perfluoroalkyl tags, in effect, serve as a handle to allow fluorous molecules to be separated efficiently from the reaction mixture via fluorous liquid–liquid or solid–liquid extraction.

To avoid the chromatographic purification step after LR application, we were intrigued with the idea of synthesizing and utilizing a fluorous version of LR. It was hoped that the attached perfluorinated tag would simplify the product isolation via a fluorous reversed-phase solid extraction technique.⁵ Moreover, if the thionation reactions proceed virtually to completion, so that filtration through and washing of reversed-phase fluorous silica cartridges are all that is required to separate product, automation of the process would be relatively easy, which would be an obvious attraction in combinatorial chemistry.

The LR is generally obtained by the reaction of phosphorus pentasulfide (2) with anisole at elevated temperature.⁶ Consistent with this procedure, we envisioned a fluorous Lawesson's reagent to arise from a fluorous anisole having a reactivity toward phosphorus pentasulfide (2) similar to anisole. In our first probe, we have synthesized a series of fluorous anisole derivatives **3a–c** (Figure 1) from the

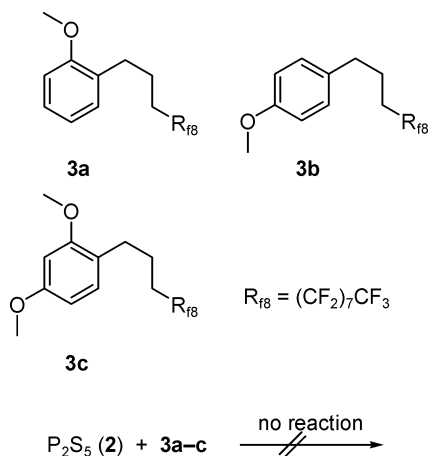


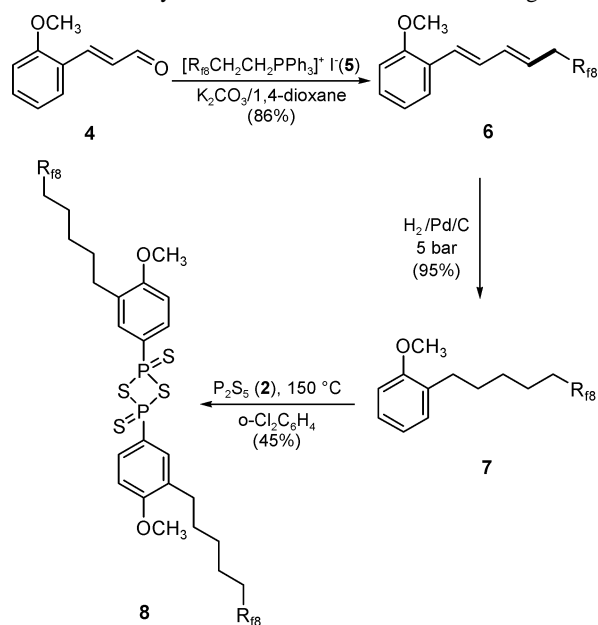
Figure 1. Fluorous anisoles **3a–c** with three methylene spacers.

corresponding aromatic aldehyde using the Wittig reaction as a key step.⁸ The built-in three methylene spacer was hoped to serve as an efficient insulator of the electron-withdrawing effect of the perfluoroalkyl groups.⁹ However, it was finally established that their thermal agitation with phosphorus

pentasulfide (2) failed to give any fluorous Lawesson's reagent, demonstrating the necessity of a longer insulating element.

To increase the number of the insulating methylene segment, we have developed a simple method for the construction of a fluorous anisole derivative **7** with a 5 methylene spacer (Scheme 1). Thus, the reaction of commercially avail-

Scheme 1. Synthesis of Fluorous Lawesson's Reagent **8**



able cinnamaldehyde derivative **4** with Wittig reagent derived from $[R_{18}CH_2CH_2PPh_3]^+I^-$ (**5**) gave the fluorous diene **6**, which was easily hydrogenated to the corresponding fluorous anisole derivative **7**. In fact, this sequence is a vinylogous extension of the Wittig methodology developed by Gladysz and co-workers.⁸ Due to the simplicity of this process, we could synthesize the fluorous anisole **7** on a 10 g scale. Finally, the pivotal thermal reaction between **7** and phosphorus pentasulfide (**2**) was attempted in a molar ratio of 10:1. The reaction was maintained at 150 °C for 4 h, during which time all of the solid starting material dissolved. On cooling, the fluorous Lawesson's reagent **8** precipitated and was washed with hexanes and dried in vacuo. Besides IR

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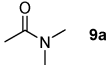
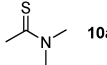
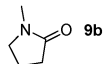
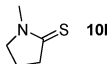
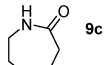
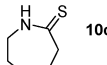
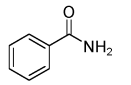
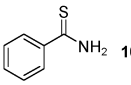
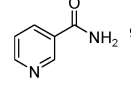
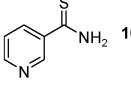
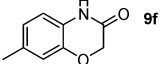
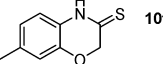
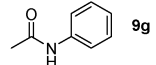
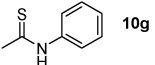
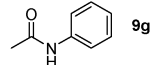
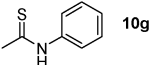
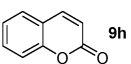
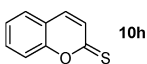
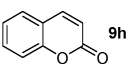
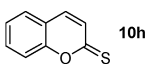
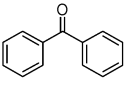
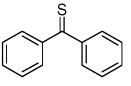
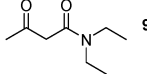
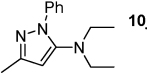
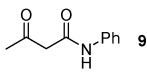
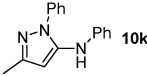
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and MS experiments, further support for the structure and purity of the **8** fluorous LR was gained by DOSY experiments.¹⁰ Finally, the excess fluorous anisole **7** could be easily separated and recycled.

With **8** in hand, we proceeded to investigate its efficiency in thionation reactions (Table 1). In choosing substrates for

Table 1. Application of Fluorous Lawesson's Reagent **8**

entry	substrate	product	time	% yield ^a
1	 9a	 10a	1.5 h	73 ^b
2	 9b	 10b	2 h	88 ^b
3	 9c	 10c	2 h	96 ^b
4	 9d	 10d	1.5 h	97 ^b
5	 9e	 10e	2 h	97 ^b
6	 9f	 10f	1 h	95 ^b
7	 9g	 10g	4 h	95 ^b
8	 9g	 10g	3 min	96 ^c
9	 9h	 10h	24 h	0 ^b
10	 9h	 10h	3 min	85 ^c
11	 9i	 10i	3 min	66 ^c
12	 9j	 10j	17 h	97 ^d
13	 9k	 10k	17 h	98 ^d

^a Isolated yields after fluorous SPE workup. ^b Thermal thionation reaction in THF. ^c Solventless microwave-accelerated thionation. ^d Phenylhydrazine hydrochloride was used as a third component.

comparison, an effort was made to select examples in which cases the original Lawesson's reagent (**1**) had already proved successful. Furthermore, all experiments were run in a 0.2 mmol scale to evaluate the potential of this method in combinatorial chemistry. For all amide substrates examined, thermal thionation by **8** gave the appropriate thioamides **10a–g** in high yields and purity (entries 1–7) after a fluorous solid-phase extraction using MeOH/H₂O 4:1 eluent. It is worth noting that even the thionation of the sparingly soluble nicotinamide (**9e**) proceeded smoothly, and no formation of

nitrile was detected.¹¹ Where the thermal thionation reaction was a little sluggish, a microwave-accelerated solvent-free method was used to facilitate the reaction (entry 7 vs entry 8).¹² The advantage of microwave-expedited thionation was especially appealing as the conversion of coumarin (**9h**) to thioester **10h** only proceeded via solvent-free microwave heating (entry 9 vs entry 10). To illustrate further the utility of the fluorous Lawesson methodology, the conversion of benzophenone (**9i**) to the corresponding thioketone **10i** was chosen (entry 11). The thioketone **10i** was formed again in a microwave-accelerated reaction, followed by fluorous solid-phase extraction with absolute CH₃CN. This fluorous workup made possible the rapid isolation of the relatively unstable **10i** without exposing the reaction product to water. Finally, a three-component, one-pot reaction was attempted using fluorous Lawesson's reagent **8** (entries 12 and 13). Using phenylhydrazine as a third component, the intermediate thioamides cyclized to pyrazol derivatives **10j,k** with excellent chemical yields.

The purifications of the above reactions were straightforward; the solution-phase reaction mixtures (entries 1–7, 12, and 13) were evaporated onto neutral alumina, loaded onto a FluoroFlash SPE cartridges and eluted with 4:1 MeOH/H₂O to provide the pure products with excellent chemical yields. In the case of solvent-free microwave-accelerated reactions, the reaction mixtures were mechanically mixed with neutral alumina, applied to a FluoroFlash cartridge, and eluted with MeOH/H₂O or CH₃CN, respectively (entries 8, 10, and 11). This "mixed sorbent" protocol¹³ made it possible to retain all of the fluorous Lawesson's reagent-derived byproducts while allowing the organic molecules to elute cleanly.

In summary, we have developed, for the first time, a fluorous Lawesson protocol without cumbersome chromatographic workup. This fluorous technique combined with microwave application allowed the rapid synthesis and isolation of organosulfur compounds in submillimolar scale. Since most thionation reactions went to completion, this fluorous method holds promise in parallel synthesis and also in delivering thioamides and thioesters of adequate quality for high-throughput biological screening.

Acknowledgment. T.S. thanks the Bolyai Foundation for an award. Grants OTKA (F37698), 1/A/005/2004 NKFP MediChemBats2, and QLK2-CT-2002-90436 are gratefully acknowledged.

Supporting Information Available: Complete experimental procedures and characterization of novel compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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