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Thionation Using Fluorous Lawesson's Reagent

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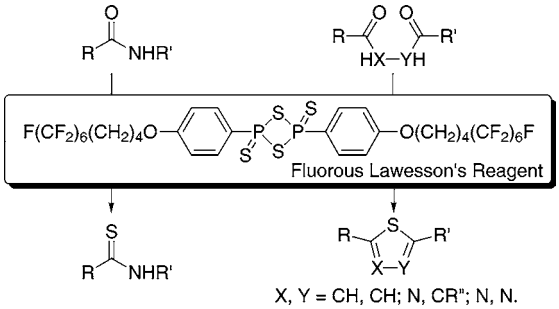
ABSTRACT



Thionation of amides, 1,4-diketones, *N*-(2-oxoalkyl)amides, *N,N'*-acylhydrazines, and acyl-protected uridines with the use of a fluorous analogue of the Lawesson's reagent leads to thioamides, thiophenes, 1,3-thiazoles, 1,3,4-thiadiazoles, and acyl-protected 4-thiouridines. The isolation of the final products in high yields is achieved in most cases by a simple filtration (fluorous solid-phase extraction).

Fluorous chemistry, which targets resource- and time-consuming separation, exploits the different phase affinities of organic and fluorous molecules.[1,2] Fluorous allure is introduced into molecules by means of various fluorous ponytails which are attached onto different reaction components: reactants, catalysts, or reagents. The last two options provide tools that can usually be applied for broad synthetic transformations.

Many applications of the fluorous synthetic approach have been developed over the past few years. Several well-known organic reactions have been adapted for various fluorous protocols. These include, among others, the Swern[3] and Baeyer−Villiger[4] oxidations, Friedel−Crafts acylation,[5] and the Mitsunobu reaction.[6] In this paper, we report the synthesis and reactions of a fluorous analogue of the Lawesson's reagent (LR).[7]

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (LR) is an efficient thionation reagent.[7] Its broad applications range from the conversion of carbonyl compounds into their thiocarbonyl analogues, through to the synthesis of sulfur and non-sulfur containing heterocycles,[8] and the solid-phase synthesis of oligodeoxyribonucleoside

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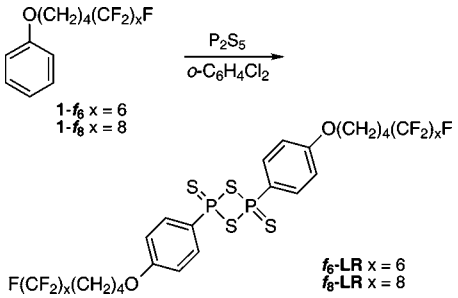
Scheme 1. Synthesis of Fluorous Lawesson's Reagents f_6-**LR** and f_8-**LR**

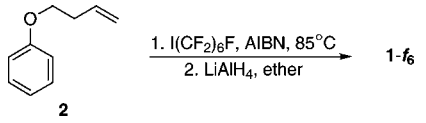


phosphorothioates.[9] A variety of experimental protocols have been developed for the use of LR.[8] Since chromatographic isolation of the desired product from the spent LR limits the utility of the reagent, we turned our attention to fluorous chemistry as a possible solution to the ever-present LR separation problems. The synthesis and application of fluorous Lawesson's reagent (***f*-LR**) for various thionation reactions, followed by a fluorous workup protocol based on solid-phase extraction, are presented below.

The most straightforward approach to append fluorous affinity to the LR would include extension of the methyl group of the phosphorus ligand with a fluorous ponytail $F(CF_2)_m(CH_2)_n$. Such a route involves minimal modification of the original reagent. This strategy also provides an opportunity for fine-tuning the electronic properties of the anisole derivative by manipulating the length of the methylene spacers (n). The $C_6H_4OCH_2$ unit does not completely insulate the reactive center from the electron-withdrawing effect of the fluorines;[10] thus, to avoid low reactivity of an insufficiently electron-rich fluorous anisole toward phosphorus, we embedded four methylene spacers ($n = 4$). Efforts toward the synthesis of fluorous LR with ponytails containing fewer methylene groups, such as $F(CF_2)_8(CH_2)_3$, directly attached to the aromatic ring, were unsuccessful.[11] Considering the above, a fluorous anisole was developed from inexpensive phenol. Etherification of phenol with fluoroalkyl bromide $F(CF_2)_8(CH_2)_4Br$[12] or iodide $F(CF_2)_8(CH_2)_4I$[13] gave heptadecafluorododecyl phenyl ether (**1**-f_8) with yields comparable to those reported for similar reactions.[14] Treatment of the fluorous anisole **1**-f_8 with phosphorus pentasulfide in *o*-dichlorobenzene at 170 °C gave, after 4 h, a fluorous Lawesson's reagent (f_8-**LR**) in 51% yield (Scheme 1).

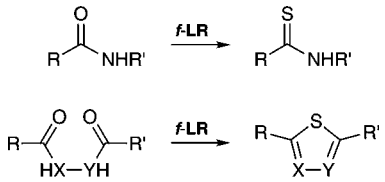
The perfluoroalkyl group $F(CF_2)_8$ (abbreviated R_{f8}) was applied initially. However, it is now known that a lower fluorous content may be sufficient for fluorous solid-phase separation (the light fluorous approach).[2a,15] To explore this

Scheme 2. Synthesis of Fluorous Anisole **1**-f_6



option, the ponytails were trimmed from R_{f8} to $F(CF_2)_6$ (R_{f6}), which lowered the molecular formula of ***f*-LR** by C_4F_8. Concurrently, to target a higher preparation efficiency of the fluorous component, the perfluoroalkyl moiety was introduced during the last stage of the synthesis of the fluorous anisole (**1**-f_6). Radical addition of perfluorohexyl iodide, $F(CF_2)_6I$, to the double bond of but-3-en-1-yl phenyl ether (**2**)[16] gave an iodide that was subsequently reduced without isolation to tridecafluorodecyl phenyl ether (**1**-f_6), in reactions analogous to a known procedure (Scheme 2).[17] Reaction of the fluorous ether **1**-f_6 (6 equiv) with P_2S_5 (1 equiv), following a similar procedure as for f_8-**LR** (170 °C, 3 h, Scheme 1), gave f_6-**LR** in 39% yield. Both ***f*-LR**s precipitated from the reaction mixture at room temperature and were isolated by simple filtration. This offered an opportunity to recover the remaining fluorous anisole **1**-f_6, which could be reused for further synthesis of f_6-**LR** (similarly anisole **1**-f_8 was reused for the synthesis of f_8-**LR**). Both f_6-**LR** and f_8-**LR** reagents are less odiferous than regular LR, but unfortunately are still not odorless. The IR fragments matched the pattern of the original LR. Spectral characterization by ^1H, ^{13}C, and ^{31}P NMR confirmed the structure. Mass spectra for both f_6-**LR** and f_8-**LR** exhibited intense half-molecular ions (100% and 90% for $[M/2]^+$) and their accurate high-resolution peaks. Both ***f*-LR** reagents were used as prepared for further transformations.

Scheme 3. Synthesis of Thioamides (Top) and Sulfur Heterocycles (Bottom)



X, Y = CH, CH; N, CH or CR"; N, N.

A comparison of the reactivity and separation of each fluorous Lawesson's reagent was investigated by thionation of the carbonyl of a simple amide (Scheme 3).[18] Conversion of benzamide (**3a**) to thiobenzamide (**4a**) with the use of f_8-**LR** and f_6-**LR** was accomplished in THF at 55 °C within

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(11) For a concurrent approach to fluorous Lawesson's reagent based upon implementation of the fluorous ponytail *ortho* to the methoxy group by the Wittig reaction of cinnamaldehyde derivative with $R_{f8}CH_2CH_2PPh_3^+I^-$, see: Kaleta, Z.; Tárkányi, G.; Gömöry, Á.; Kálmán, F.; Nagy, T.; Soós, T. *Org. Lett.* **2006**, *8*, 1093−1095.

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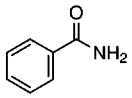
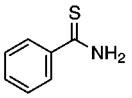
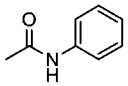
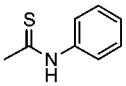
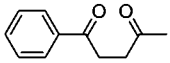
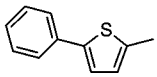
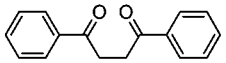
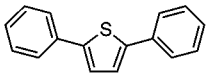
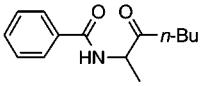
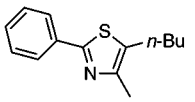
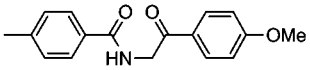
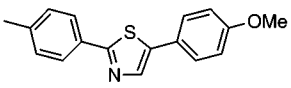
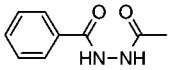
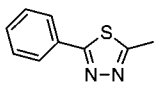
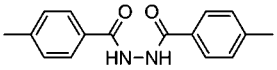
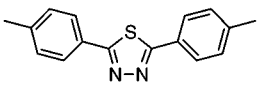
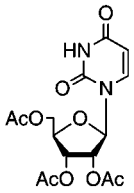
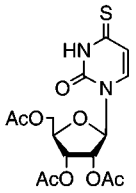
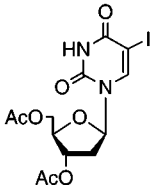
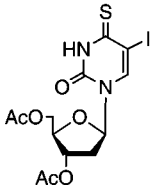
Table 1. Thionation with the Use of Fluorous Lawesson's Reagents[a]

entry	reactant	(number)	product	(number)	reaction time[b]	yield (%)
1		**3a**		**4a**	4 h[c] 4 h	94 92
2		**3b**		**4b**	6 h	97
3		**5a**		**6a**	4 h	88
4		**5b**		**6b**	6 h	92
5		**7a**		**8a**	6 h	48[d]
6		**7b**		**8b**	3 min[e]	82[d]
7		**9a**		**10a**	6 h	94
8		**9b**		**10b**	6 h	93
9		**11a**		**12a**	17 h	94
10		**11b**		**12b**	4 h[f]	56[g]

[a] For a representative procedure, see ref 26. [b] Reactions were carried out on a ca. 0.1−0.5 mmol scale with 1.0−2.0 equiv of f_6-**LR** in THF at 55 °C unless referenced otherwise. [c] Reaction using f_8-**LR**. [d] After recrystallization. [e] Microwave, solvent-free. [f] Dioxane, 100 °C. [g] After silica gel column chromatography.

4 h in 94% and 92% yields, respectively (Table 1, entry 1) and revealed that the f_8-**LR** offered no distinct advantage over f_6-**LR**. Thus, all of the remaining experiments were carried out with the use of f_6-**LR**. Analogously (THF, 55 °C, 6 h), acetanilide (**3b**) was converted into thioacetanilide (**4b**, Table 1, entry 2). The reaction was carried out with an equimolar ratio of **3b** and f_6-**LR**, on a 0.2 mmol scale. After the addition of alumina, the solvent was removed and the resulting solid was placed on a fluorous reversed-phase silica gel. Elution with acetonitrile gave **4b** in 97% yield.

The reactivity of f_6-**LR** was further examined for the synthesis of a variety of five-membered ring heterocycles (Scheme 3). Since thiophenes represent an important class

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(17) Johansson, G.; Percec, V.; Ungar, G.; Zhou, J. P. *Macromolecules* **1996**, *29*, 646−660.
(18) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229−238.
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of compounds, commercially available symmetrical and unsymmetrical 1,4-diketones (**5a**,**b**) were converted into 2,5-substituted thiophenes (**6a**,**b**).[19] These reactions were carried out in a manner analogous to that above (THF, 55 °C, 6 h). Isolation by solid-phase extraction afforded **6a**/**b** in 88/92% yield. Synthesis of two representative 1,3-thiazoles[20] was also attempted. First, *N*-(1-methyl-2-oxohexyl)benzamide (**7a**) was treated with ***f*$_6$-LR** (entry 5). The formation of two organic products was observed. These products were separated from the spent LR by fluorous solid-phase extractive workup. Both thiazole (**8a**) and an analogous oxazole (tentatively confirmed by GC/MS) were detected in an 81:19 ratio, as determined by ^{1}H NMR. Crystallization gave **8a** in 48% yield. Thus, alternative reaction conditions were sought. A microwave protocol has been successfully applied in LR chemistry.[21] Therefore, ***f*$_6$-LR** and *N*-[2-(4-methoxyphenyl)-2-oxoethyl]-4-methylbenzamide (**7b**) were combined and the solvent-free mixture was irradiated in a conventional microwave at atmospheric pressure (entry 6). A too short or too long irradiation time led to incomplete conversion or decomposition; the optimal reaction time was found to be 3 min. Fluorous workup gave a 2,5-diaryl-substituted 1,3-thiazole (**8b**) which contained a small amount of impurity (but not oxazole), as observed by TLC. Recrystallization gave **8b** in 82% yield.

The applications of ***f*$_6$-LR** were further extended; starting from *N*′-acylbenzohydrazides (**9a**,**b**), two 1,3,4-thiadiazoles (**10a**,**b**)[22] were synthesized by the solution-phase protocol in 94% and 93% yield (entries 7 and 8). Finally, entries 9 and 10 illustrate that two acyl-protected representative pyrimidine nucleosides, uridine and 2′-deoxy-5-iodouridine[23] (**11a** and **11b**), can be converted into their 4-thiouridine derivatives (**12a**,**b**).[24] Although acetylated thiouridine **12a** was isolated in 94% yield (THF, 55 °C, 17 h), 5-iodouridine (**11b**) reacted sluggishly under the same conditions. Thus, for the reaction of **11b** with ***f*$_6$-LR**, a higher temperature but shorter reaction time (dioxane, 100 °C, 4 h) was applied. The yield of isolated nucleoside **12b** was lower (56%), and formation of other products prompted an additional purification by silica gel column chromatography. Complex thionation reactions of related 2′-deoxy-5,6-dihydropyrimidines with the use of nonfluorous LR are well-documented.[25]

The purity of all sulfur-containing products was confirmed by ^{1}H and ^{13}C NMR. After solid-phase extraction, no fluorous LR or its byproducts were observed by ^{1}H NMR in any of the isolated material.

In summary, the fluorous approach offers new avenues for solutions to the separation problems encountered with Lawesson's reagent by simplifying the isolation protocol, including elimination of column chromatography, and thus improving yields. We have demonstrated that ***f*-LR** can be applied for the high-yield synthesis of a variety of thio compounds, including heterocycles. We have applied a user-friendly workup based upon solid-phase extraction without the need for fluorous solvents. Our approach can supply thioamides, thiophenes, thiazoles, thiadiazoles, and 4-thiouridines for automated combinatorial chemistry protocols. The selected examples include important synthetic and materials chemistry intermediates and biologically active structural motifs.

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Supporting Information Available: Synthetic procedures, analytical and spectral characterization data, and spectra for compounds **1**, ***f*-LR**, **4**, **6**, **8**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) **2-Methyl-5-phenylthiophene (6a).**[19] A Schlenk tube was charged under N_2 with **5a** (0.0352 g, 0.200 mmol), ***f*$_6$-LR** (0.225 g, 0.200 mmol), and THF (4 mL), and placed into a 55 °C oil bath. After 4 h, when the reaction was completed as determined by TLC, alumina (2 g) was added and the solvent was evaporated. The resulting solid was placed on a short column packed with fluorous reverse phase silica (2 g). The column was eluted with acetonitrile (20 mL) to give **6a** as a white solid (0.0307 g, 0.176 mmol, 88%).