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An efficient, continuous flow technique for the chemoselective synthesis of thioacetals

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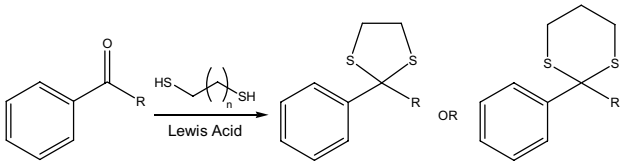
Abstract—By optimizing a reagent's residence time within a packed-bed reactor, it is possible to overcome selectivity issues frequently encountered in stirred reaction vessels. This important feature is demonstrated for the chemoselective protection of 4-acetylbenzaldehyde whereby 1-[4-1,3-dithian-2-yl-phenyl]ethanone is obtained in excellent yield and purity. In addition, the generality of the technique is highlighted via the protection of numerous aldehydes and ketones affording the respective thioacetal/ketal in excellent yield (>99.1%) and purity (>99.9%), with space–time yields in the range of 0.44–1.10 g h^{-1}.

1,3-Dithianes are versatile reagents employed in the formation of C–C bonds, with the conjugate addition of lithiated 1,3-dithianes to α,β-unsaturated ketones, aldehydes, esters, and lactones widely reported in modern organic synthesis.[1] Additionally, *S*,*S*-acetals form an important class of carbonyl protecting groups that, unlike their respective oxygen containing analogues, are hydrolytically stable and tolerant to a wide pH range.[2] Due to their overwhelming stability to an array of reaction conditions, deprotection is not easily achieved. Consequently, many approaches have been reported with reagent selection determined by the sensitivity and stability of the particular substrate.

Owing to the synthetic utility of 1,3-dithianes and 1,3-dithiolanes, many techniques have been described for their preparation based on the condensation of a carbonyl compound with the respective dithiol (Scheme 1). To promote the reaction, an array of Lewis or Bronsted acid catalysts have been reported including zinc or magnesium triflate,[3] titanium tetrachloride,[4] boron trifluoride,[5] and lithium perchlorate,[6] frequently in conjunction with an excess of dithiol (0.1–5.0 equiv). Subsequent purification is therefore required, not only to remove the excess thiolating agent, but also the acid catalyst, prior to performing subsequent reaction steps.



Scheme 1. General reaction scheme illustrating the protection of carbonyl moieties as their respective 1,3-dithiolane ($n = 1$) or 1,3-dithiane ($n = 2$).

The use of heterogeneous catalysts, such as Amberlyst-15 (A-15) **1**,[7] natural kaolinitic clay,[8] silica-supported *p*-toluenesulfonic acid[9,10] addressed the problem of catalyst recovery, whereby employing a simple filtration at the end of the reaction enables isolation, and potential recovery/reuse, of the catalyst. Again, an excess of dithiol is often employed, demanding additional purification steps to be performed. Although solid-supported reagents and catalysts have many advantages over their solution phase analogues, one limitation is mechanical degradation of the support (due to stirring or agitation of reaction mixtures) which leads to reduced reagent lifetimes and difficulties with efficient reagent recycle. Consequently, by performing reactions within continuous flow reactors,[11] such as the one described herein, the support undergoes minimal mechanical stress, affording extended reagent lifetimes, along with ease of catalyst recycling and reproducibility between reactions. Furthermore, automation of the technique offers increased reaction control, reduced operator dependency and facilitates rapid reaction optimization.

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In pursuit of an atom efficient technique for the protection of carbonyl moieties, we investigated the continuous flow synthesis of 1,3-dithianes and 1,3-dithiolanes, proposing that careful optimization of the reaction conditions would allow the synthesis and isolation of analytically pure products, by simply removing the reaction solvent.

To manipulate reactants and products within the flow reactor, the pumping mechanism selected was electroosmotic flow (EOF) as compared to pressure-driven (PD) flow, EOF generates minimal back-pressure; a particularly important feature for packed-bed reactors. EOF therefore enables reaction systems to be scaled without being limited by the reactor's pressure tolerance, a frequently encountered problem in PD systems. The technique also enables precise control over flow rate, as it is not limited by an incremental stepper motor, thus affording pulse-free flow. In addition, the absence of mechanical pump drivers reduces the footprint of the set-up, which simply consists of a power supply. Again, automation of the system enables remote operation of the reactors, reducing greatly the amount of valuable fume cupboard space required to perform such reactions. While EOF has predominantly been employed as a pumping mechanism within miniaturized reaction systems for the manipulation of nl quantities of material,[12] we recently reported its use within a flow reactor of millimeter dimensions, enabling access to flow rates in the range of 0.1–500.0 μl min^{-1}.[13]

As Figure 1 illustrates, the reaction set-up employed herein consists of a borosilicate glass capillary (3.0 mm (i.d.) × 30.0 mm (length)), packed with A-15 **1** (0.055 g, 0.231 mmol) attached to borosilicate glass reagent reservoirs via two rubber septa (No. 9, Suba Seal). To perform a reaction, the packed-bed is filled with anhydrous MeCN (to form a complete electrical circuit) and a solution containing the reactants is then placed in reservoir A along with an aliquot of solvent in reservoir B. Platinum electrodes (0.5 mm (o.d.) × 2.5 cm (length)) are placed in each reservoir and the reaction mixture pumped through the packed-bed by application of a positive voltage (50–200 V cm^{-1}) to reservoir A; the reaction products are subsequently collected in reservoir B (0 V cm^{-1}) (Fig. 2). Unless otherwise stated optimization reactions are performed for 10 min, prior to analysis by GC–MS whereby the percentage conversion of carbonyl compound to product is determined. Once optimized (Fig. 3), the reactor is operated continuously for 1 h, after which the reaction products are removed from reservoir B, concentrated in vacuo and the crude product dissolved in $CDCl_3$ prior to additional purity evaluation by NMR spectroscopy.

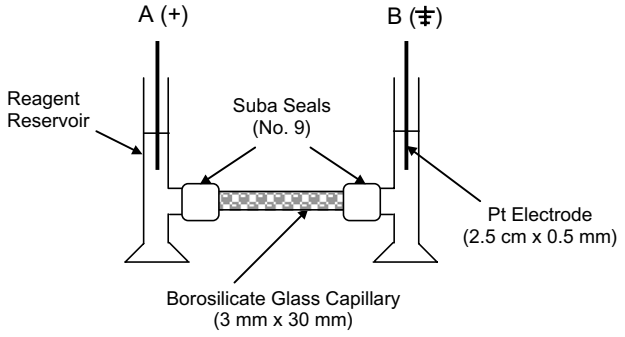


Figure 1. Schematic illustrating the reaction set-up used for the continuous flow synthesis of 1,3-dithianes and 1,3-dithiolanes.

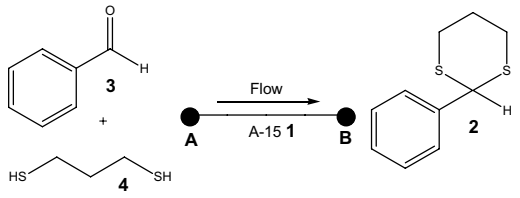


Figure 2. Schematic illustrating the continuous flow synthesis of 2-phenyl-1,3-dithiane **2**.

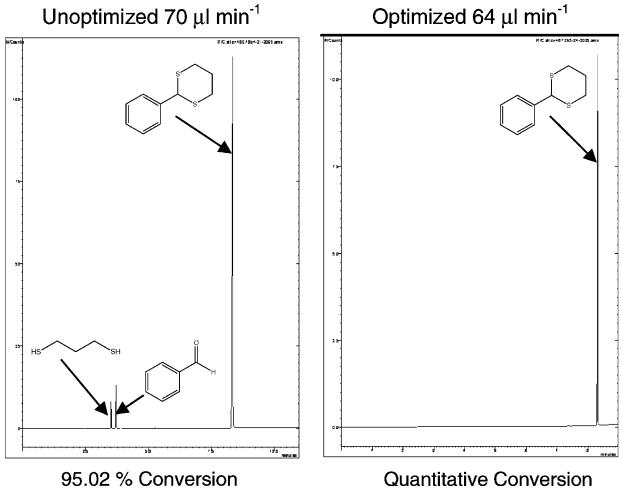
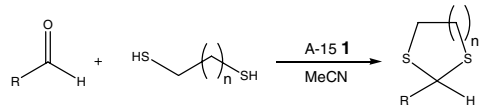


Figure 3. Gas chromatograms illustrating the difference between an optimized and an unoptimized system for the synthesis of 2-phenyl-1,3-dithiane **2**, under continuous flow.

Using the set-up illustrated in Figures 1 and 2, the reactor's performance was assessed using the synthesis of 2-phenyl-1,3-dithiane **2** as a model reaction. Employing an applied field of 200 V cm^{-1}, a pre-mixed solution of benzaldehyde **3** and 1,3-propanedithiol **4** (1.0 M, 1:1 in MeCN) was pumped through the packed-bed at a flow rate of 63.7 μl min^{-1} (residence time = 75.4 s) and the reaction products evaluated every 10 min, off-line by GC–MS (Fig. 3). Typical reaction data from the optimization process afforded quantitative conversion of benzaldehyde **3** to 2-phenyl-1,3-dithiane **2** (99.992%). In addition, the reaction reproducibility (5.0×10^{-3}% RSD) obtained over 2.5 h confirms effective recycle of the acid catalyst, generating 9.42 mmol of product **2** with 0.231 mmol of catalyst; representing a turnover of 41 times, so far.

Having established the ability to perform a model thioacetalization under continuous flow conditions, the next step was to evaluate the generality of the technique, firstly investigating the protection of an array of substituted aldehydes as the respective 1,3-dithiane. As

Table 1. Summary of the results obtained for the thioacetalization of ten substituted aldehydes under continuous flow conditions (200 V cm^{-1})



Aldehyde	n[a]	Flow rate (μl min^{-1})	Yield[b] (g)	Yield (%)
Benzaldehyde	2	63.7	1.96[c]	99.97
	1	63.4	0.69	99.97
4-Bromobenzaldehyde	2	61.4	1.01	99.92
	1	61.2	0.96	99.96
4-Chlorobenzaldehyde	2	61.7	0.85	99.91
	1	61.9	0.80	99.95
4-Cyanobenzaldehyde	2	65.4	0.87	99.94
	1	64.6	0.80	99.96
4-Benzyloxybenzaldehyde	2	61.1	1.10	99.22
	1	60.9	1.05	99.93
4-Methylbenzaldehyde	2	69.7	0.88	99.97
	1	69.0	0.81	99.93
4-Biphenylcarboxaldehyde	2	63.0	1.02	99.06
	1	63.0	0.97	99.97
2-Naphthaldehyde	2	60.4	0.89	99.94
	1	60.2	0.84	99.98
2-Furaldehyde **5**	2	67.9	0.76	99.92
	1	67.5	0.69	99.97
3,5-Dimethoxybenzaldehyde	2	67.9	1.04	99.91
	1	67.7	0.982	99.93

[a] 1,2-Ethanedithiol **6** ($n = 1$) and 1,3-propanedithiol **4** ($n = 2$).
[b] Unless otherwise stated, reactions were performed for 1 h.
[c] Reaction conducted for 2.5 h.

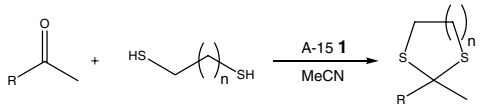
Table 1 illustrates, employing a stoichiometric quantity of dithiol, and an average residence time of 76 s (~62.9 μl min^{-1}), afforded the respective dithiane, in excellent yield and purity. Importantly no sign of substituent effect was observed, with even difficult to protect compounds such as 2-furaldehyde **5** being reacted with ease. Furthermore, substitution of 1,3-propanedithiol **4** with 1,2-ethanedithiol **6** afforded the synthesis of 1,3-dithiolanes in excellent yields and purities, employing analogous reaction conditions to those previously optimized for the 1,3-dithianes. Compared to a typical batch reaction, the use of a flow reactor enabled a dramatic reduction in reaction time, from 24 h to 76 s; an observation, which is attributed to the high surface-to-volume ratio obtained between the catalyst and reactants. Furthermore, the use of a closed reaction system, such as the one described herein, facilitates the efficient reaction of odorous compounds, affording reaction products of excellent purity without the need for additional purification.

As the preparation of thioketals is kinetically less favorable than their respective thioacetals, extended reaction times are frequently employed (24–120 h), along with an excess of the dithiol or extreme reaction temperatures.[7]

Based on the encouraging results summarized in Table 1, our investigation progressed on to the protection of ketones, determining whether the aforementioned reductions in reaction time were also attainable for the synthesis of thioketals. Utilizing a comparable technique to that employed for the thioacetalizations, a pre-mixed solution of ketone and dithiol (1.0 M, 1:1 in MeCN) was mobilized through the packed-bed, using an applied field of 50 V cm^{-1}. As the results in Table 2 demonstrate, in all cases excellent yields were obtained, with throughputs in the range of 0.44–0.70 g h^{-1}. Importantly, no substituent effects were observed, with even highly substituted ketones, which are normally difficult to protect, proving facile in this system.

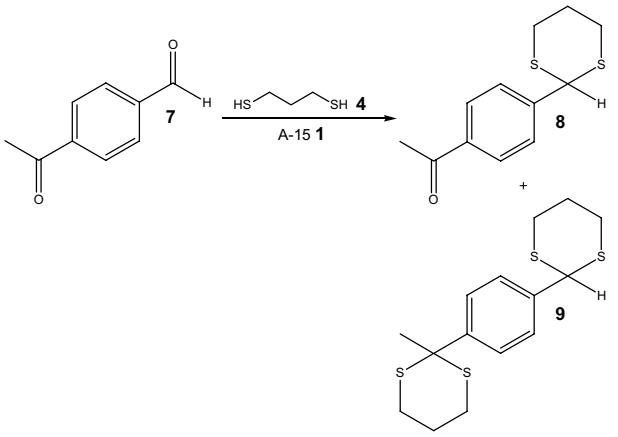
Having demonstrated the different reaction conditions required to quantitatively protect both aldehydic and ketonic moieties within a continuous flow reactor, we investigated the ability to chemoselectively protect an aldehyde in the presence of a ketone (Scheme 2). Under reaction conditions previously optimized for the protection of aldehydes, a pre-mixed solution of 4-acetylbenzaldehyde **7** and 1,3-propanedithiol **4** (1.0 M) in MeCN was mobilized through the packed-bed (200 V cm^{-1}) at a flow rate of 65.2 μl min^{-1}, affording 1-[4-1,3-dithian-2-yl-phenyl]ethanone **8** in quantitative yield. Conducting the reaction under such flow conditions, afforded superior results compared to those obtained in an analogous batch reaction, enabling selectivity toward protection of the formyl group. As Figure 4 illustrates, in an analogous batch reaction (24 h), incomplete conversion of 4-acetylbenzaldehyde **7** to the respective 1,3-dithiane **8** was observed, along with competing di-protection to afford 2-[4-1,3-dithian-2-yl-phenyl]-2-methyl-1,3-dithiane **9**.

Table 2. Summary of the results obtained for the protection of ketones, under continuous flow, as their respective thioketal (50 V cm^{-1})



Ketone	n[a]	Flow rate (μl min^{-1})	Yield[b] (g)	Yield (%)
Acetophenone	2	41.5	0.52	99.57
	1	41.3	0.48	99.96
Propiophenone	2	40.2	0.54	99.97
	1	40.3	0.51	99.96
Butyrophenone	2	41.6	0.59	99.90
	1	41.6	0.56	99.90
Cyclohexanone	2	42.2	0.47	99.62
	1	42.1	0.44	99.98
Benzophenone	2	40.2	0.57	99.81
	1	40.1	0.65	99.91
4-Nitroacetophenone	2	40.9	0.63	99.95
	1	41.0	0.59	99.95
2-Methoxyacetophenone	2	40.9	0.59	99.93
	1	41.9	0.57	99.93
4-Chloroacetophenone	2	40.9	0.60	99.87
	1	40.8	0.60	99.91
4-Hydroxyacetophenone	2	42.2	0.57	99.76
	1	42.1	0.53	99.83
4-Bromoacetophenone	2	40.2	0.70	99.94
	1	40.1	0.66	99.97

[a] 1,2-Ethanedithiol **6** ($n = 1$) and 1,3-propanedithiol **4** ($n = 2$).
[b] Unless otherwise stated reactions were performed for 1 h.



Scheme 2. Possible reaction products obtained from the protection of 4-acetylbenzaldehyde **7** as its respective 1,3-dithiane **8**.

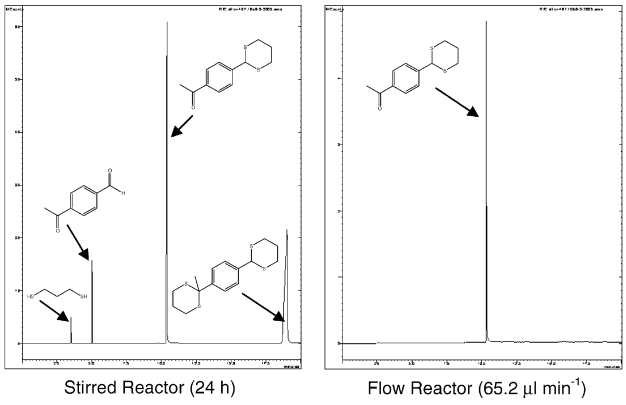


Figure 4. Gas chromatograms illustrating the chemoselectivity obtained in a flow reactor compared to a traditional stirred reactor.

Further to the excellent isolated yields obtained when conducting reactions under continuous flow, an additional advantage of the technique is the ability to recycle the solid-supported catalyst with ease. This is illustrated herein whereby 128.5 mmol of thioacetals and ketals were synthesized using 0.231 mmol of catalyst, representing an impressive turnover number of 556, with no sign of degradation to date. Although A-15 **1** is capable of being turned over this number of times in batch, it is a difficult undertaking when using traditional reaction methodology as the catalyst must be filtered from the reaction mixture in order to be re-used. In addition, the mechanical degradation that the catalyst undergoes when used repeatedly increases the difficulties associated with efficient filtration.

In conclusion, we have developed a simple and efficient technique that enables the chemoselective protection of aldehydes, based solely on reactant residence time within a packed-bed reactor.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.027.

References and notes

1. (a) Seebach, D. J. *Synthesis* **1969**, 17; (b) Corey, E. J.; Seebach, D. J. *J. Org. Chem.* **1966**, *31*, 4097; (c) Bulman Page, P. C.; van Niel, M. B.; Prodger, J. *Tetrahedron* **1989**, *45*, 7643; (d) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147, and references cited therein.
2. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, second ed.; Wiley: New York, 1991.
3. Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.
4. Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, *24*, 1289.
5. Wilson, G. E., Jr.; Huang, M. G.; Schloman, W. W. *J. Org. Chem.* **1968**, *33*, 21343.
6. Tietze, L. F.; Weigand, B.; Wulff, C. *Synthesis* **2000**, 69.
7. Perni, R. B. *Synth. Commun.* **1989**, *19*, 2383.
8. Ponde, D.; Sudalai, B. A.; Ravindranathan, T.; Deshpande, V. H. *Tetrahedron Lett.* **1996**, *37*, 4605.
9. Ali, M. H.; Gomes, M. G. *Synthesis* **2005**, *8*, 1326.
10. Kitamori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, *51*, 1427.
11. (a) Jas, G.; Kirschning, A. *Chem. Eur. J.* **2003**, *9*, 5708; (b) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem. Eur. J.* **2006**, *12*, 5972; (c) Hodge, P. *Curr. Opin. Chem. Biol.* **2003**, *1*, 2419.
12. Haswell, S. J. *Analyst* **1997**, *112*, 1R.
13. Wiles, C.; Watts, P.; Haswell, S. J. *Chem. Commun.* **2007**, 966.