Preparation and Purification of Zinc Sulphinate Reagents

for Organic Synthesis

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SUPPLEMENTARY INFORMATION

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All the synthesized zinc sulphinate reagents can be represented as (RSO₂)₂Zn but these are most likely dihydrates in their solid state. The X-ray structures and the elemental analyses shown hereafter support this hypothesis.

X-ray structures of TFMS•THF complex and DFMS (2)

X-ray quality crystals of TFMS were obtained by recrystallization from THF. While each zinc atom is hexacoordinate, THF occupies some coordination sites and therefore there are only two trifluoromethanesulphinate units per zinc atom. There are two molecules of THF per molecule of $(CF_3-SO_2)_2Zn$ and the THF most likely displaced two molecules of water during the recrystallization process. (This crystal structure has been deposited at the Cambridge Crystallographic Data Centre with CCDC # 916882.)



 $\label{eq:constraint} \begin{array}{l} Polymeric \ (CF_3-SO_2)_2Zn \cdot [C_4H_8O]_2 \\ \mbox{X-ray analysis obtained by crystallization of TFMS (1) in THF} \end{array}$

The X-ray structure of DFMS (2) shows a polymeric formula of $[(CF_2H-SO_2)_3Zn]_2 \cdot Zn(H_2O)_6$, representing an average of two molecules of water per molecule of $(CF_2H-SO_2)_2Zn$. (This crystal structure has been reported previously with CCDC # 877399, see ref. 3 of this article.)



Note: No evidence of chloride was observed in the crystal structures of TFMS or DFMS.

Mass analysis

The molar masses of the zinc sulphinate reagents prepared in this article are as follows:

TFMS (assume anhydrous):	$(CF_3SO_2)_2Zn = C_2O_4F_6S_2Zn$	→ 331.53 g/mol
TFMS (assume a dihydrate):	$(CF_3SO_2)_2Zn \bullet 2 H_2O = C_2H_4O_6F_6S_2Zn$	→ 367.56 g/mol
DFMS (assume anhydrous):	$(CF_2HSO_2)_2Zn = C_2H_2O_4F_4S_2Zn$	→ 295.55 g/mol
DFMS (assume a dihydrate):	$(CF_2HSO_2)_2Zn \bullet 2 H_2O = C_2H_6O_6F_4S_2Zn$	→ 331.58 g/mol
TFES (assume anhydrous):	$(CF_3CH_2SO_2)_2Zn = C_4H_4O_4F_6S_2Zn$	→ 359.59 g/mol
TFES (assume a dihydrate):	$(CF_3CH_2SO_2)_2Zn \bullet 2 H_2O = C_4H_8O_6F_6S_2Zn$	→ 395.62 g/mol
IPS (assume anhydrous):	$((CH_3)_2CH)_2Zn = C_6H_{14}O_4S_2Zn$	→ 279.70 g/mol
IPS (assume a dihydrate):	$((CH_3)_2CH)_2Zn \bullet 2 H_2O = C_6H_{18}O_6S_2Zn$	→ 315.73 g/mol

Assuming anhydrous salts, the % (by mass) distribution of each atom is as follows:

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Zn salt	%C	% H	%0	%F	%S	%Cl	%Zn
TFMS	7.2	0	19	34	19	0	20
DFMS	8.1	0.68	22	26	22	0	22
TFES	13	1.1	18	32	18	0	18
IPS	26	5.0	23	0	23	0	23

Assuming dihydrate salts, the % (by mass) distribution of each atom is as follows:

Table S2. Calculated values of % by mass for the zinc sulphinate reagents (assuming dihydrates).

Zn salt	%С	%Н	% 0	%F	%S	%Cl	%Zn
TFMS	6.5	1.1	26	31	17	0	18
DFMS	7.2	1.8	29	23	19	0	20
TFES	12	2.0	24	29	16	0	17
IPS	23	5.7	30	0	20	0	21

Elemental analysis before washing with 1:1 EtOAc:CH₂Cl₂ (also see attached data sheets):

Table S3. Experimental values of % by mass for the zinc sulphinate reagents before purification.

Zn salt	%С	%Н	%S	%Cl
TFMS	4.38	2.35	11.55	12.47
DFMS	5.15	2.17	11.79	12.83
TFES	8.72	2.43	11.50	9.86
IPS	16.54	3.95	14.75	16.06

These results suggest that the zinc sulphinate reagents most likely contain $ZnCl_2$ and H_2O . When normalized to 1 equiv. of zinc sulphinate reagent (calculated from %S), almost 1 equiv. of $ZnCl_2$ (calculated from %Cl) and a few equivalents of H_2O (calculated from %H, taking into account the number of hydrogens from the zinc sulphinate salts) were present for each salt that was analyzed:

Table S4. Experimental values for the number of equivalents of each component in the product before purification.

Zn salt	$(RSO_2)_2Zn \cdot 2 H_2O$	ZnCl ₂	H ₂ O
TFMS	1.00 equiv.	0.98 equiv.	6.5 equiv.
DFMS	1.00 equiv.	0.98 equiv.	4.7 equiv.
TFES	1.00 equiv.	0.78 equiv.	4.7 equiv.
IPS	1.00 equiv.	0.98 equiv.	1.5 equiv.

The results in Table S3 also suggest that, for every gram of previously described zinc sulphinate reagent, there is ~0.6 grams of active reagent:

Table S5. Experimental values comparing the number of grams of active reagent within a gram of unpurified reagent.

Zn salt	Mass of unpurified (RSO ₂) ₂ Zn • 2 H ₂ O	Mass of active (RSO ₂) ₂ Zn • 2 H ₂ O
TFMS	1.00 g	0.66 g
DFMS	1.00 g	0.61 g
TFES	1.00 g	0.71 g
IPS	1.00 g	0.72 g

Elemental analysis after washing with 1:1 EtOAc:CH₂Cl₂ (also see attached data sheets):

Table S6. Experimental values of % by mass for the zinc sulphinates after purification.

Zn salt	%C	% H	%S	%Cl
TFMS	6.49	1.04	17.71	0.0
DFMS	7.25	1.74	19.64	0.0
TFES	12.04	2.02	16.45	0.0
IPS	20.36	4.18	19.10	10.36

Table S7. Experimental values for the number of equivalents of each component in the product after purification.

Zn salt	$(RSO_2)_2Zn \cdot 2 H_2O$	ZnCl ₂	H ₂ O
TFMS	1.00 equiv.	0.00 equiv.	0.00 equiv.
DFMS	1.00 equiv.	0.00 equiv.	0.00 equiv.
TFES	1.00 equiv.	0.00 equiv.	0.00 equiv.
IPS	1.00 equiv.*	0.50 equiv.*	0.33 equiv.*

*The structure of IPS might not be a simple mixture of ((CH₃)₂CH–SO₂)₂Zn • 2 H₂O and ZnCl₂.

Elemental analysis of each salt (with the exception of IPS (4)) suggests that these zinc sulphinate reagents are more likely to be dihydrates rather than anhydrous salts (the values of Table S6 resemble those of Table S2 rather than those of Table S1). In the case of IPS (4), there is a certain amount of chloride that cannot be eliminated even after many washes; see Table S8 for the amount of active reagent present in these purified salts.

Table S8. Experimental values comparing the number of grams of active reagent within a gram of purified reagent.

Zn salt	Mass of purified (RSO ₂) ₂ Zn • 2 H ₂ O	Mass of active (RSO ₂) ₂ Zn • 2 H ₂ O
TFMS	1.00 g	1.00 g
DFMS	1.00 g	1.00 g
TFES	1.00 g	1.00 g
IPS	1.00 g	0.81 g

While the amount of chloride in IPS (4) can be reduced after washing, comparing unpurified and purified IPS (4) in a reaction with caffeine (amount of starting material corrected for the % by mass of active reagent) showed that there is no significance difference in reactivity. As such, we recommend that IPS (4) be used in its unpurified form for operational simplicity.

Determination of chloride incorporation

To test for inorganic chloride content, two methods were used, one qualitative and one quantitative.

Qualitative method:

Using QUANTOFIX[®] chloride test strips purchased from MACHEREY-NAGEL GmbH & Co. KG. They are similar to universal indicator papers and the procedure to use them is as follows.

- 1. Dissolve 10 mg of the zinc sulphinate salt in 2 mL water.
- 2. Place the test strip in the solution for 1 s, shake off the excess water, wait 60 s, then read against the provided chart.

Quantitative method:

Submitting samples for elemental analysis (Atlantic Microlab, Inc.). Copies of elemental analysis are provided hereafter.

	ATLA		ICKOF	
Sample No. TFM	IS-B			SUBMITER
			Address ¹	0770 Science Center Drive
6180 Atlantic	Blvd, Suite M 30071		Dept.	an Diego, CA 92121
			1	
PROFESSOR/SI	upervisor:		NAME -	Aichael Collins DATE 12/11/12
PO# / CC#:			PHONE	3858-622-3294
Flement	Theory	Fou	pu	Single
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				on the day the sentine is received y return Include Email Address or Fax # Below
		NO CHARGE FOI	S DUPLICATES	michael.collins@pfizer.com
	DEC 132	012	Date Cor	DEC 1 4 2012
Date neceiver Remarks:				

Elemental analysis of TFMS (1) before washing with 1:1 EtOAc:CH₂Cl₂.

Elemental analysis of TFMS (1) after washing with 1:1 EtOAc:CH₂Cl₂.

	ATL.	ANTIC P	MICROL	AB, INC.
Sample No. DF1	MS-B			SUBMITTER
			Company	/ School Pfizer
6180 Atlantic	Blvd. Suite M		Address	10770 Science Center Drive
Norcross, GA	30071		Dept.	San Diego, CA 92121
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PROFESSOR/SL	JPERVISOR:		NAME	Michael Collins DATE 12/11/12
PO# / CC#:			PHONE	8858-622-3294
Element	Theory	For	pur	Single Duplicate
U	8.1300	515	5.04	Elements Present: C, H, F, O, S, Zn
J	0.0000	1283		Analyze for: C, Cl, H, S
Т	0.6800	217	53	Hygroscopic 🚺 Explosive 🗍 M.PB.P.
S	21.7000	11.79		To be dried: Yes No Q Temp. Vac. Jime
		NO CHARGE PI	R DUPUICATES	on the day the sample is received by them.
				Include Email Address or Fax # Below
				michael.collins@pfizer.com
Date Received _ Remarks:	DEC 13	2012	Date Com	oleted DEC 1 4 2013

Elemental analysis of DFMS (2) before washing with 1:1 EtOAc:CH₂Cl₂.

ROTAD TWO	SUBMITTER	Company / School Pfizer Address 10770 Science Center Drive	Uept. San Diego, CA 92121	NAME Michael Collins DATE 12/17/12	PHUNE 858-622-3294	Single Duplicate	Elements Present: C, H, F, O, S, Zn	Analyze for: C, Cl, H, S	M.P. B.P. B.P.	Temp. Vac. No U Temp. Vac. Time RUSH SERVICE [7] Rush service quarameter analyzese with have	CHI ES Completed and results available by fom EST on the day the sample is received by 11am.	michael.collins@pfizer.com	late Completed DEC 1 9 2012
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Sample No. <u>TFE</u>	S-A2			SUBMITTER
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			Dept.	tan Diego, CA 92121
www.atlanti	cmicrolab.con	11		
PROFESSOR/SL	JPERVISOR: Mich	ael Collins	NAME E	ionn O'Hara DATE 12/17/12
PO# / CC#: 8500	164668		PHONE	858-622-3294
Element	Theory	Fot	Ind	Single Duplicate
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		NO CHARGE FOR	DUPLICATES	on the day the sample is received by tham
				Include Email Address or Fax # Below
				michael.collins@pfizer.com
Date Received	JAN 24	2013	Date Com	Jeted JAN 2 4 2013
Remarks:			:	

Elemental analysis of TFES (3) before washing with 1:1 EtOAc:CH₂Cl₂.

available by 5pm ES on the day the sample is received by flam DATE 12/17/12 Include Email Address or Fax # Below RUSH SERVICE I Rush service guarantees analyses completed and results available by michael.collins@pfizer.com Duplicate _____Time Hygroscopic (Z) Explosive SUBMITTER DEC 1 9 2012 Elements C, H, O, F, S, Zn To be dried: Yes D No J Temp. Vac. J Address 10770 Science Center Drive ATLANTIC MICROLAB, INC. c, cl, H, S San Diego, CA 92121 Company / School Pfizer Michael Collins Single PHONE 858-622-3294 Analyze lor: Date Completed NAME Dept. NO CHARGE FOR DUFLICATES 12.041.99Found 16.**4**5 12.04 8 8 **DEC 1 9 2012** w w w.atlanticmicrolab.com 6180 Atlantic Blvd. Suite M Theory 13.3600 PROFESSOR/SUPERVISOR: 1.1200 0.0000 17.8400 Norcross, GA 30071 Sample No. TFES-A3 Date Received Element PO# / CC#: Remarks: O \overline{O} Ι S

Elemental analysis of TFES (3) after washing with 1:1 EtOAc:CH₂Cl₂.

	ATL	ANTIC I	MICROL	AB, INC.
Sample No. Ipr-	В			SUBMITTER
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Norcross, GA	30071		Dept.	San Diego, CA 92121
www.atlanti	cmicrolab.com	« #	•	
PROFESSOR/SL	JPERVISOR:		NAME -	Michael Collins DATE 12/11/12
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Element	Theory	Fol	pur	Single Duplicate
U	25.7700	16.54	16.3	Elements Present: C, H, O, S, Zn Analyze
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Т	5.0500	3.5	406	To be dried: Yes No J
S	22.9300	14.75		Temp. Vac. Time RUSH SERVICE Review Service analyses will be commissed and restlifts activities by Kann Est
				on the day the sample is received by 11am. Include Email Address or Fax # Below
		NUCHARGEFO	R DUFLICHT 53	michael.collins@pfizer.com
Date Received	DEC 13.	2012	Date Com	pleted DEC 1 4 2012
Remarks:				

Elemental analysis of IPS (4) before washing with 1:1 EtOAc:CH₂Cl₂.

AB, INC.	SUBMITTER	y / School Pfizer	10770 Science Center Drive	San Diego, CA 92121		Michael Collins DATE 12/17/12	858-622-3294	Single Duplicate	Elements Present: C, H, O, S, Zn	for: C, Cl, H, S	Hygroscopic A Explosive	Io be dried: Yes No V Temp. Vac. Time RUSH SERVICE Rush service guarantees analyses will be	on the day the sample is received by 11am on the day the sample is received by 11am Include Ermail Address or Fax # Below	michael.collins@pfizer.com	npleted DEC 1 9 2012
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	Sample No. IPS		6180 Atlantic	Norcross, GA	www.atlanti	PROFESSOR/SI	PO# / CC#:	Element	o	J	I	S			Date Received Remarks:

Elemental analysis of IPS (4) after washing with 1:1 EtOAc:CH₂Cl₂.