Preparation and Purification of Zinc Sulphinate Reagents for Organic Synthesis

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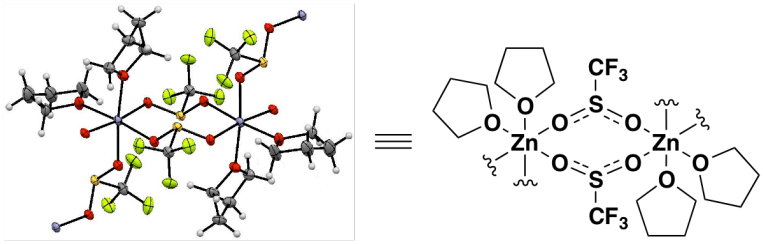
SUPPLEMENTARY INFORMATION

Table of Contents

All the synthesized zinc sulphinate reagents can be represented as $(RSO_2)_2Zn$ 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)

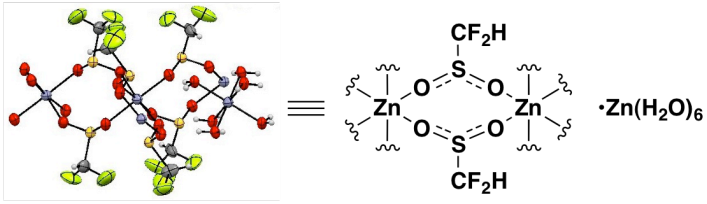
X-ray quality crystals of TFMS were obtained by recrystallization from THF. While each zinc atom is hexacoordinate, THF occupies some coordination sites and therefore there are only two trifluoromethanesulphinate units per zinc atom. There are two molecules of THF per molecule of $(CF_3–SO_2)_2Zn$ and 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.)



Polymeric $(CF_3–SO_2)_2Zn·[C_4H_8O]_2$

X-ray analysis obtained by crystallization of TFMS (**1**) in THF

The X-ray structure of DFMS (**2**) shows a polymeric formula of $[(CF_2H–SO_2)_3Zn]_2•Zn(H_2O)_6$, 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.)



$[(CF_2H–SO_2)_3Zn]_2·Zn(H_2O)_6$
= Polymeric $(CF_2H–SO_2)_2Zn \cdot 2\ H_2O$

DFMS (**2**)

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:

Table S1. Calculated values of % by mass for the zinc sulphinate reagents (assuming anhydrous).

Zn salt	%C	%H	%O	%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	%C	%H	%O	%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:CH_2Cl_2 (also see attached data sheets):

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

Zn salt	%C	%H	%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	$(RSO_2)_2Zn \bullet 2\ H_2O$	$ZnCl_2$	H_2O
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 $(RSO_2)_2Zn \bullet 2\ H_2O$	Mass of active $(RSO_2)_2Zn \bullet 2\ H_2O$
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:CH_2Cl_2 (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	$(RSO_2)_2Zn \bullet 2\ H_2O$	$ZnCl_2$	H_2O
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 $((CH_3)_2CH–SO_2)_2Zn \bullet 2\ H_2O$ and $ZnCl_2$.

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 $(RSO_2)_2Zn \bullet 2\ H_2O$	Mass of active $(RSO_2)_2Zn \bullet 2\ H_2O$
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.

Elemental analysis of TFMS (**1**) before washing with 1:1 EtOAc:CH_2Cl_2.

ATLANTIC MICROLAB, INC.

Sample No. TFMS-B

6180 Atlantic Blvd. Suite M
Norcross, GA 30071

www.atlanticmicrolab.com

PROFESSOR/SUPERVISOR:

PO# / CC#:

SUBMITTER

Company / School Pfizer

Address 10770 Science Center Drive

Dept. San Diego, CA 92121

NAME Michael Collins DATE 12/11/12

PHONE 8858-622-3294

Element	Theory	Found	
C	7.2500	4.38	4.27
Cl	0.0000	12.47	
H	0.0000	2.35	2.35
S	19.3400	11.55	
		NO CHARGE FOR DUPLICATES	

Single ☐ Duplicate ☐

Elements Present: C, F, O, S, Zn

Analyze for: C, Cl, H, S

Hygroscopic ☑ Explosive ☐

M.P. B.P.

To be dried: Yes ☐ No ☑

Temp. Vac. Time

RUSH SERVICE ☐ Rush service guarantees analyses will be completed and results available by 5pm EST on the day the sample is received by 11am.

Include Email Address or Fax # Below

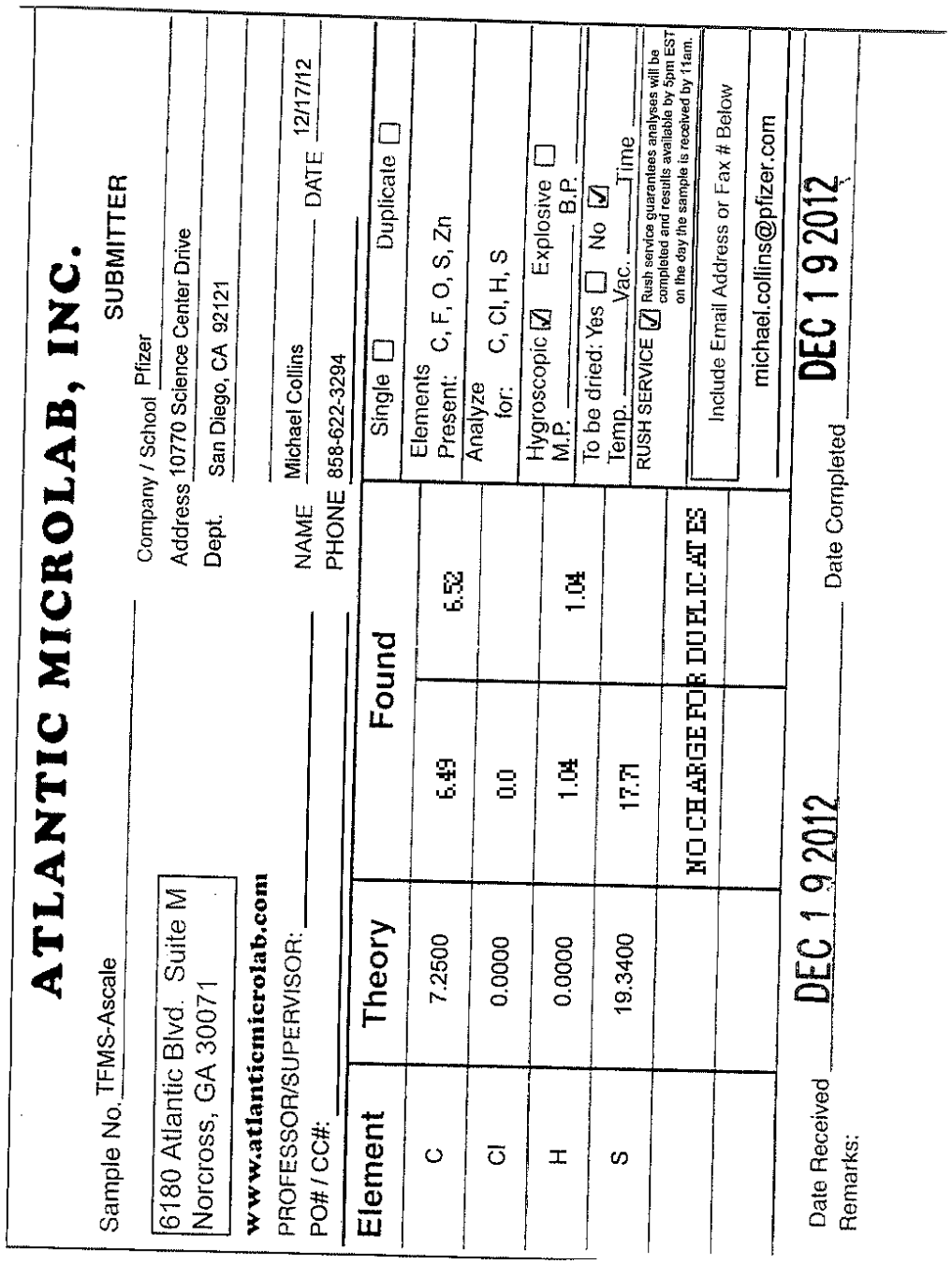
michael.collins@pfizer.com

Date Received DEC 1 3 2012

Date Completed DEC 1 4 2012

Remarks:

Elemental analysis of TFMS (**1**) after washing with 1:1 EtOAc:CH_2Cl_2.



ATLANTIC MICROLAB, INC.

Sample No. TFMS-Ascale

SUBMITTER

Company / School Pfizer

Address 10770 Science Center Drive

Dept. San Diego, CA 92121

6180 Atlantic Blvd. Suite M
Norcross, GA 30071

www.atlanticmicrolab.com

NAME Michael Collins DATE 12/17/12

PHONE 858-622-3294

PROFESSOR/SUPERVISOR:

PO# / CC#:

Element	Theory	Found		
C	7.2500	6.49	6.52	
Cl	0.0000	0.0		
H	0.0000	1.04	1.04	
S	19.3400	17.71		

Single ☐ Duplicate ☐

Elements Present: C, F, O, S, Zn

Analyze for: C, Cl, H, S

Hygroscopic ☑ Explosive ☐
M.P. _____ B.P. _____

To be dried: Yes ☐ No ☑
Temp. _____ Vac. _____ Time _____

RUSH SERVICE ☑ Rush service guarantees analyses will be completed and results available by 5pm EST on the day the sample is received by 11am.

Include Email Address or Fax # Below

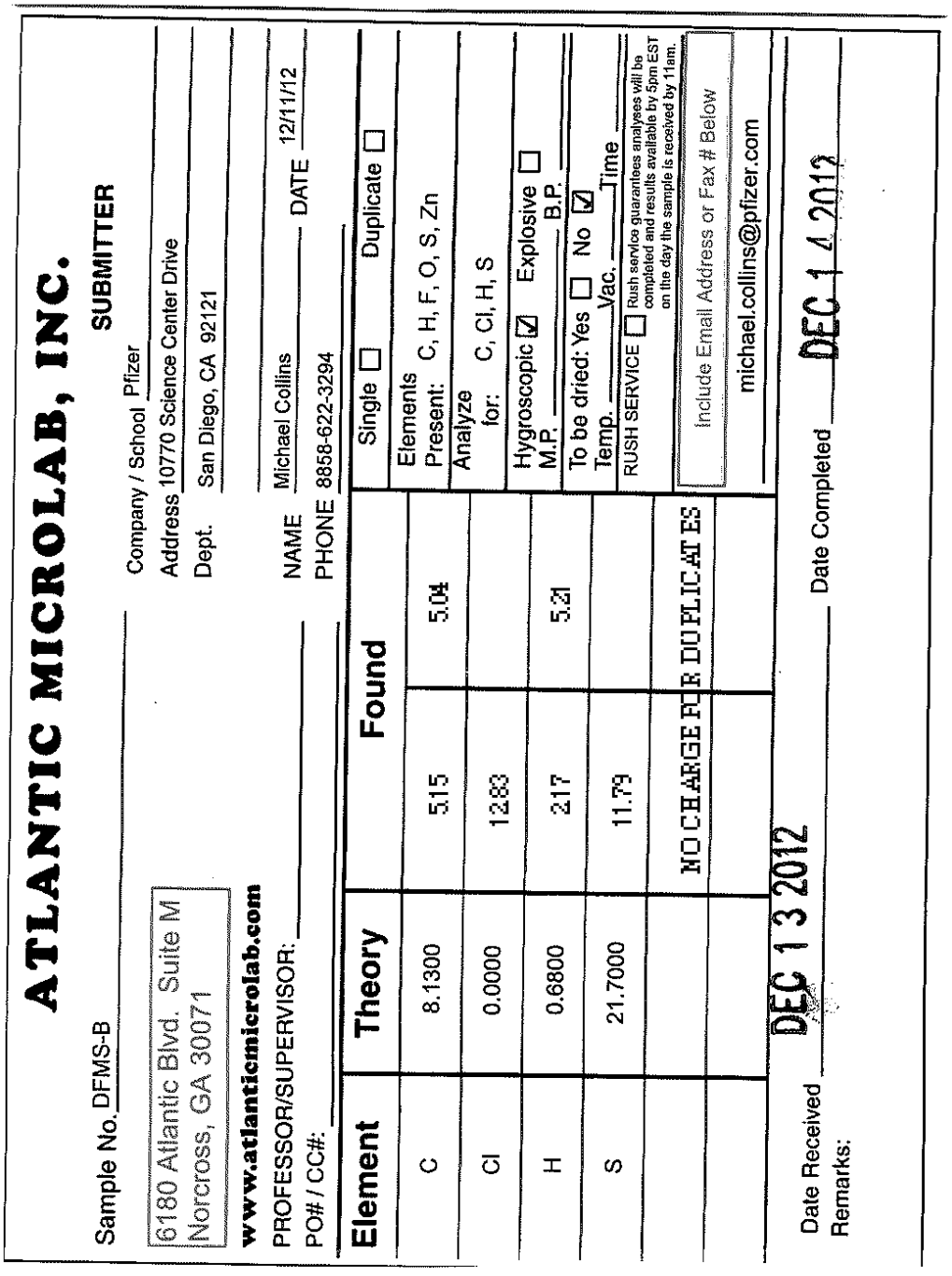
michael.collins@pfizer.com

NO CHARGE FOR DUPLICATES

Date Received DEC 19 2012 Date Completed DEC 19 2012

Remarks:

Elemental analysis of DFMS (**2**) before washing with 1:1 EtOAc:CH_2Cl_2.



ATLANTIC MICROLAB, INC.

Sample No. DFMS-B

6180 Atlantic Blvd. Suite M
Norcross, GA 30071

www.atlanticmicrolab.com

PROFESSOR/SUPERVISOR:

PO# / CC#:

SUBMITTER

Company / School Pfizer

Address 10770 Science Center Drive

Dept. San Diego, CA 92121

NAME Michael Collins DATE 12/11/12

PHONE 8858-622-3294

Element	Theory	Found	
C	8.1300	5.15	5.04
Cl	0.0000	12.83	
H	0.6800	2.17	5.21
S	21.7000	11.79	

Single ☐ Duplicate ☐

Elements Present: C, H, F, O, S, Zn

Analyze for: C, Cl, H, S

Hygroscopic ☑ Explosive ☐

M.P. _____ B.P. _____

To be dried: Yes ☐ No ☑

Temp. _____ Vac. _____ Time _____

RUSH SERVICE ☐ Rush service guarantees analyses will be completed and results available by 5pm EST on the day the sample is received by 11am.

Include Email Address or Fax # Below

michael.collins@pfizer.com

NO CHARGE FOR DUPLICATES

Date Received DEC 13 2012 Date Completed DEC 14 2012

Remarks:

Elemental analysis of DFMS (**2**) after washing with 1:1 EtOAc:CH_2Cl_2.

ATLANTIC MICROLAB, INC.

Sample No. DFMS-Ascale

6180 Atlantic Blvd. Suite M
Norcross, GA 30071

www.atlanticmicrolab.com

PROFESSOR/SUPERVISOR: ______
PO# / CC#: ______

SUBMITTER

Company / School Pfizer
Address 10770 Science Center Drive
Dept. San Diego, CA 92121

NAME Michael Collins DATE 12/17/12
PHONE 858-622-3294

Element	Theory	Found	
C	8.1300	7.25	7.28
Cl	0.0000	0.0	
H	0.6800	1.74	1.79
S	21.7000	19.64	
		NO CHARGE FOR DUPLICATES	

Single ☐ Duplicate ☐

Elements Present: C, H, F, O, S, Zn

Analyze for: C, Cl, H, S

Hygroscopic ☑ Explosive ☐
M.P. ______ B.P. ______

To be dried: Yes ☐ No ☑
Temp. ______ Vac. ______ Time ______

RUSH SERVICE ☑ Rush service guarantees analyses will be completed and results available by 5pm EST on the day the sample is received by 11am.

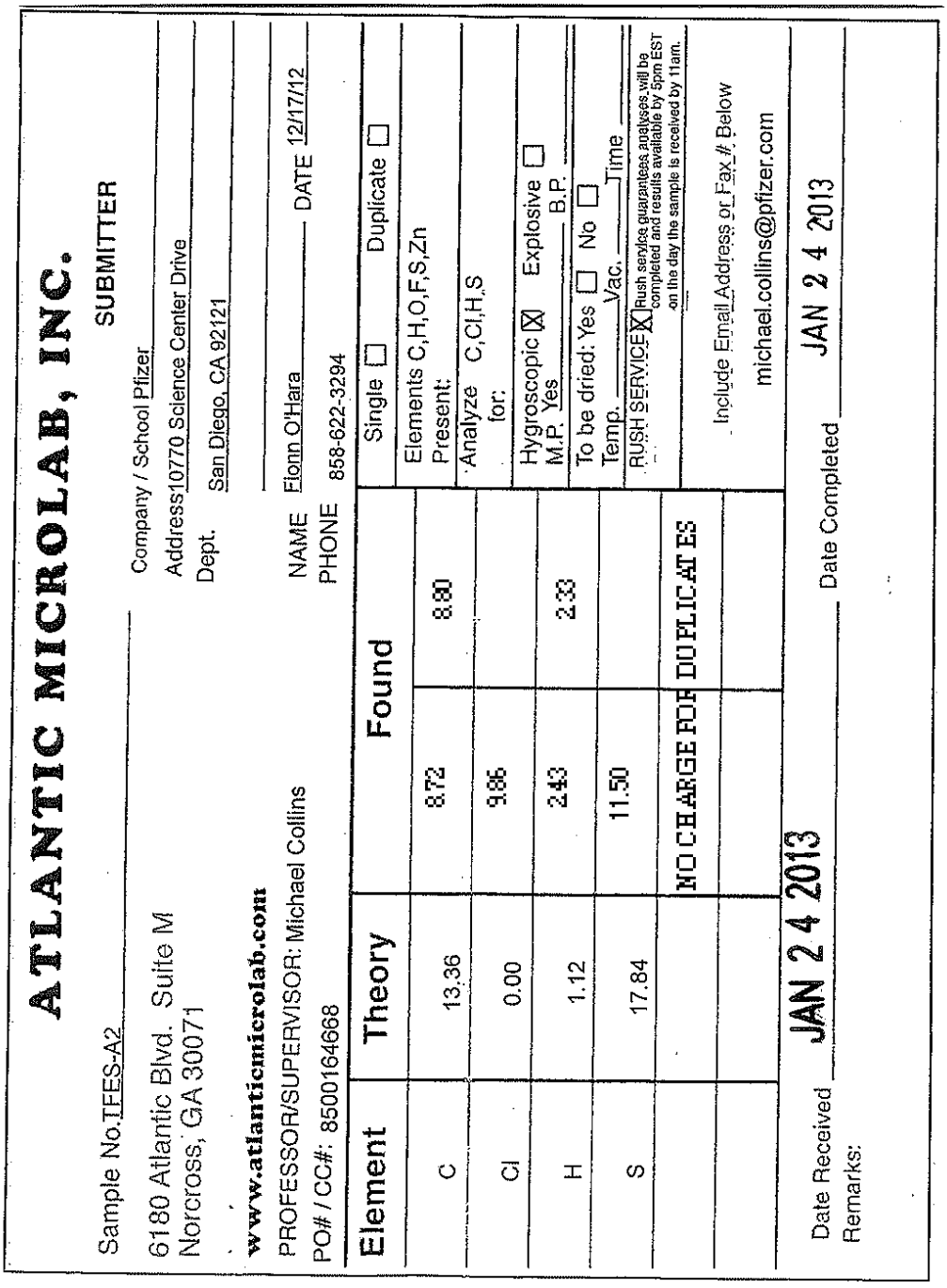
Include Email Address or Fax # Below

michael.collins@pfizer.com

Date Received DEC 19 2012 Date Completed DEC 19 2012

Remarks:

Elemental analysis of TFES (**3**) before washing with 1:1 EtOAc:CH_2Cl_2.



ATLANTIC MICROLAB, INC.

SUBMITTER

Sample No. TFES-A2

Company / School Pfizer

6180 Atlantic Blvd. Suite M
Norcross, GA 30071

Address 10770 Science Center Drive

Dept. San Diego, CA 92121

www.atlanticmicrolab.com

PROFESSOR/SUPERVISOR: Michael Collins

NAME Fionn O'Hara DATE 12/17/12

PO# / CC#: 8500164668

PHONE 858-622-3294

Element	Theory	Found		
C	13.36	8.72	8.80	
Cl	0.00	9.86		
H	1.12	2.43	2.33	
S	17.84	11.50		
		NO CHARGE FOR DUPLICATES		

Single ☐ Duplicate ☐

Elements C,H,O,F,S,Zn Present:

Analyze C,Cl,H,S for:

Hygroscopic ☒ Explosive ☐
M.P. Yes B.P.

To be dried: Yes ☐ No ☐
Temp. Vac. Time

RUSH SERVICE ☒ Rush service guarantees analyses will be completed and results available by 5pm EST on the day the sample is received by 11am.

Include Email Address or Fax # Below

michael.collins@pfizer.com

Date Received JAN 24 2013 Date Completed JAN 24 2013

Remarks:

Elemental analysis of TFES (**3**) after washing with 1:1 EtOAc:CH_2Cl_2.

ATLANTIC MICROLAB, INC.

Sample No. TFES-A3

6180 Atlantic Blvd. Suite M
Norcross, GA 30071

www.atlanticmicrolab.com

PROFESSOR/SUPERVISOR:
PO# / CC#:

SUBMITTER

Company / School Pfizer
Address 10770 Science Center Drive
Dept. San Diego, CA 92121

NAME Michael Collins DATE 12/17/12
PHONE 858-622-3294

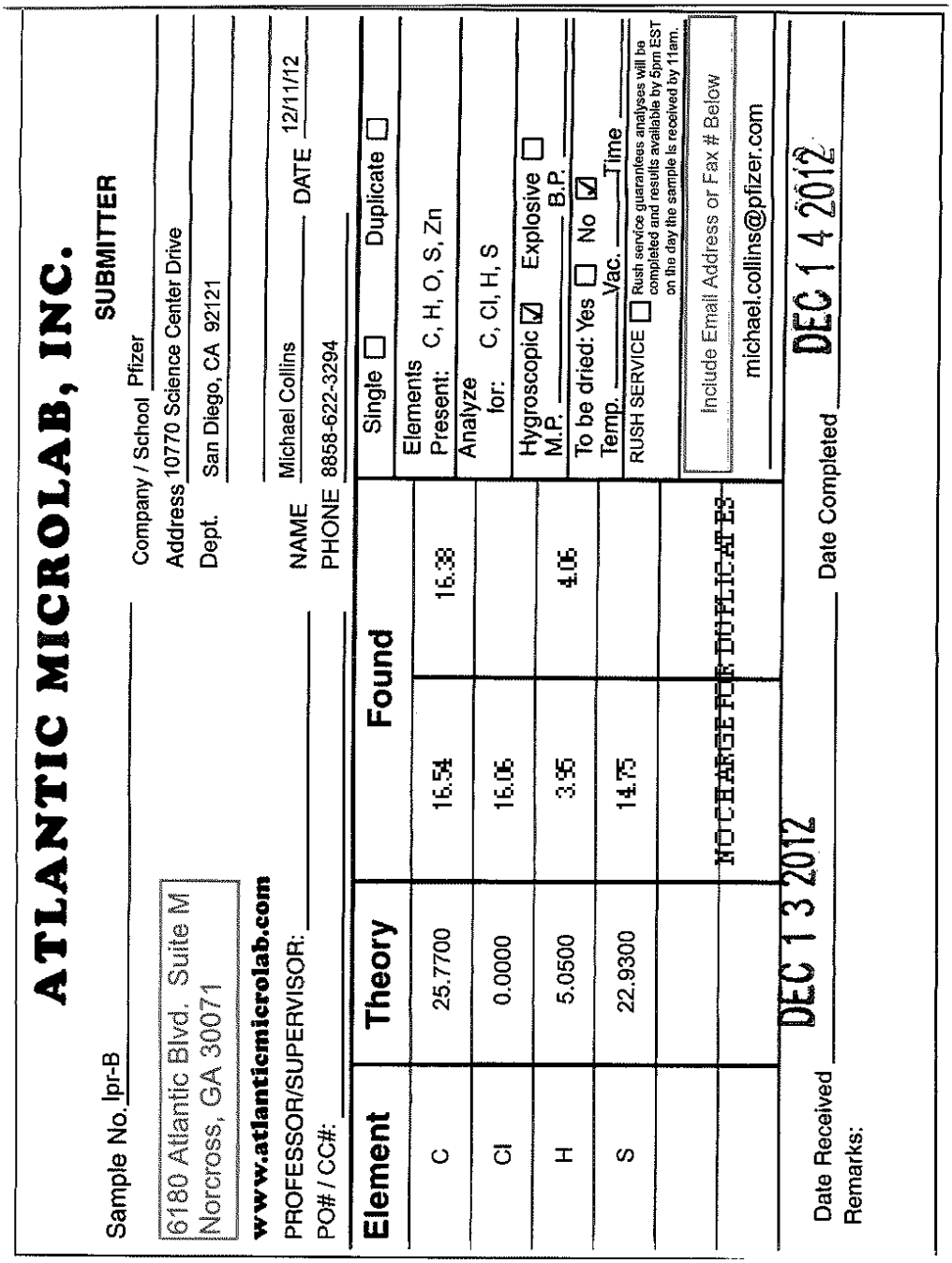
Element	Theory	Found	
C	13.3600	12.04	12.04
Cl	0.0000	0.0	
H	1.1200	2.02	1.97
S	17.8400	16.45	
		NO CHARGE FOR DUPLICATES	

Single ☐ Duplicate ☐
Elements Present: C, H, O, F, S, Zn
Analyze for: C, Cl, H, S
Hygroscopic ☑ Explosive ☐
M.P. ______ B.P. ______
To be dried: Yes ☐ No ☑
Temp. ______ Vac. ______ Time ______
RUSH SERVICE ☑ Rush service guarantees analyses will be completed and results available by 5pm EST on the day the sample is received by 11am.

Include Email Address or Fax # Below
michael.collins@pfizer.com

Date Received DEC 19 2012 Date Completed DEC 19 2012
Remarks:

Elemental analysis of IPS (**4**) before washing with 1:1 EtOAc:CH_2Cl_2.



ATLANTIC MICROLAB, INC.

Sample No. lpr-B

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PO# / CC#: _____

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Company / School Pfizer
Address 10770 Science Center Drive
Dept. San Diego, CA 92121

NAME Michael Collins DATE 12/11/12
PHONE 8858-622-3294

Element	Theory	Found	
C	25.7700	16.54	16.38
Cl	0.0000	16.06	
H	5.0500	3.95	4.06
S	22.9300	14.75	
		NO CHARGE FOR PUBLICATION	

Single ☐ Duplicate ☐

Elements Present: C, H, O, S, Zn

Analyze for: C, Cl, H, S

Hygroscopic ☑ Explosive ☐
M.P. _____ B.P. _____

To be dried: Yes ☐ No ☑
Temp. _____ Vac. _____ Time _____

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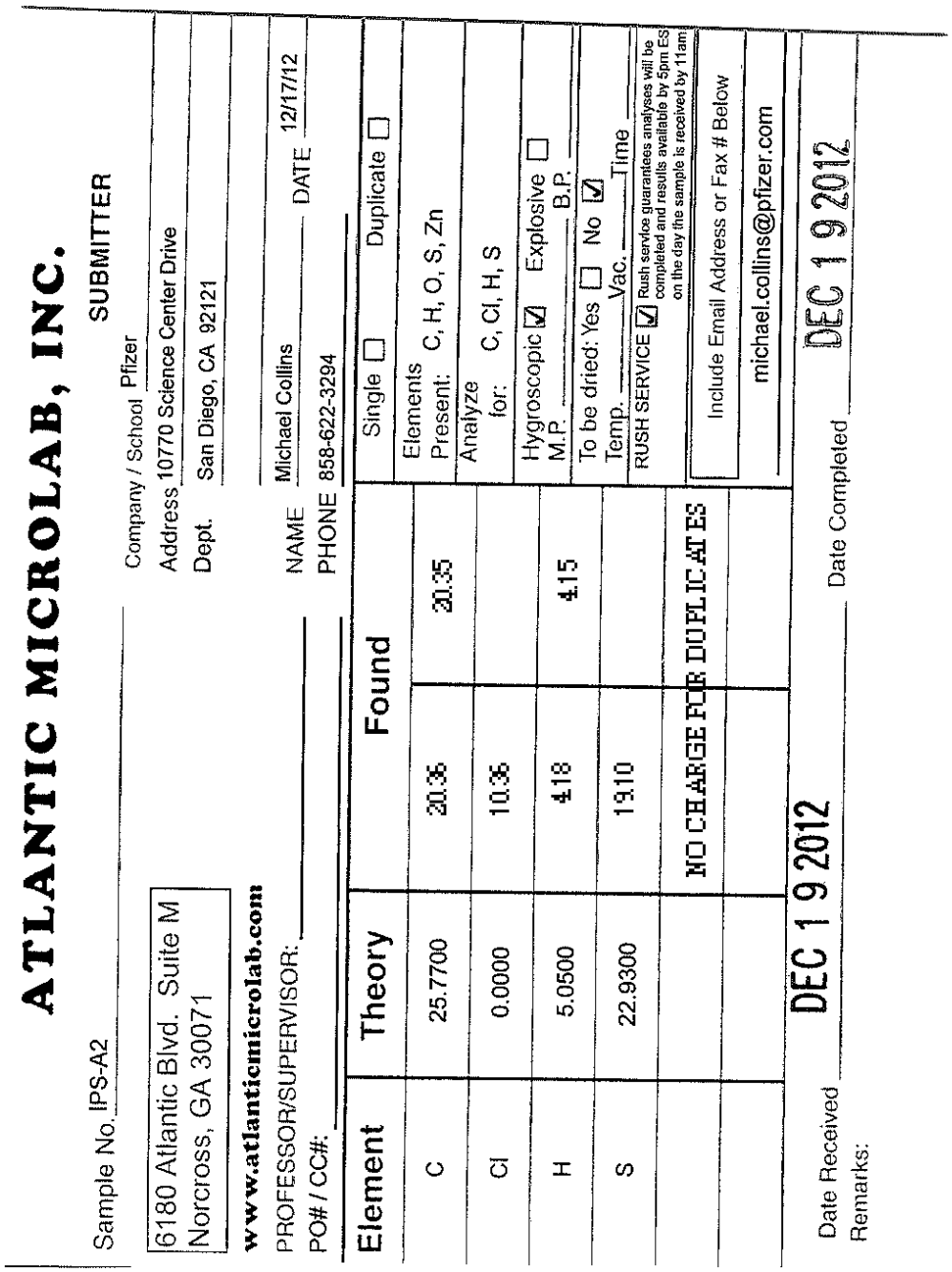
michael.collins@pfizer.com

DEC 13 2012

Date Received _____ Date Completed DEC 14 2012

Remarks: _____

Elemental analysis of IPS (**4**) after washing with 1:1 EtOAc:CH_2Cl_2.



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Sample No. IPS-A2

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PO# / CC#: _____

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Address 10770 Science Center Drive
Dept. San Diego, CA 92121

NAME Michael Collins DATE 12/17/12
PHONE 858-622-3294

Element	Theory	Found	
C	25.7700	20.36	20.35
Cl	0.0000	10.36	
H	5.0500	4.18	4.15
S	22.9300	19.10	
		NO CHARGE FOR DUPLICATES	

Single ☐ Duplicate ☐

Elements Present: C, H, O, S, Zn

Analyze for: C, Cl, H, S

Hygroscopic ☑ Explosive ☐
M.P. _____ B.P. _____

To be dried: Yes ☐ No ☑
Temp. _____ Vac. _____ Time _____

RUSH SERVICE ☑ Rush service guarantees analyses will be completed and results available by 5pm ES on the day the sample is received by 11am

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michael.collins@pfizer.com

DEC 19 2012

Date Received DEC 19 2012 Date Completed DEC 19 2012
Remarks: