

Synthesis and Reactivity of Novel Pyrazolothiazines and Thiadiazines

A thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

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Declaration

I hereby declare that this thesis was carried out at the School of Chemical and Physical Sciences at the Flinders University of South Australia. I certify that the thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university. To the best of my knowledge the document does not contain any material previously published or written by another person except where acknowledgement by citation of the original publication is made in the text.

Rebecca Norman
19th January 2015

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Publications and Presentations

The following list represents publications that have resulted from research outlined in this thesis and presentations that were given at various conferences, symposia and meetings.

Publications

1. Rebecca E. Norman; Michael V. Perkins; Andris J. Liepa; Craig L. Francis, *Australian Journal of Chemistry* **2013**, 66, 1323. ‘The First Pyrazolo[1,5-*b*][1,2,4,6]thiazine Derivatives and their Unusual Reactions with Acylating Agents’
2. Rebecca E. Norman; Michael V. Perkins; Andris J. Liepa; Craig L. Francis, *Australian Journal of Chemistry* **2015**, 68, *in press*. ‘Substitution Reactions of Pyrazolo[1,5-*b*][1,2,4,6]thiazine 1,1-Dioxides.’
3. Rebecca E. Norman; Michael V. Perkins; Andris J. Liepa; Craig L. Francis, *Australian Journal of Chemistry* **2015**, *in press*. ‘Synthesis and Reactivity of Novel Pyrazolo[3,4-*e*][1,2,4]Thiadiazine Derivatives.’
4. Rebecca E. Norman; Michael V. Perkins; Andris J. Liepa; Craig L. Francis, *Australian Journal of Chemistry* **2015**, *in CSIRO internal review*. ‘Cleavage and Rearrangement of Pyrazolo[1,5-*b*][1,2,4,6]thiazine 1,1-Dioxides.’

Manuscripts in preparation:

1. Chee Ling Tong, Rebecca E. Norman, Michael V. Perkins, Kevin Jarrett, Craig E. Buckley, Xiaofei Duan, Robert N. Lamb, Colin L. Raston, to be titled: ‘One-pot synthesis of PdO/SBA-15 under neutral conditions: synthesis, characterization, and catalytic properties.’

External Presentations

ICOS 20 – The RACI 20th International Conference on Organic Synthesis, ELTE convention centre (Budapest, Hungary), 29th June -4th July **2014**, 15 minute oral presentation.

The Southern Highlands Conference on Heterocyclic Chemistry, Gibraltar Hotel (Bowral, NSW), 25th-27th August **2013**, Received a Postgraduate Student Award for a 45 minute oral presentation.

The RACI Adelaide Synthetic Chemistry Symposium, Adelaide University (Adelaide, SA), 10th December **2012**, 25 minute oral presentation.

The 37th Annual Synthesis Symposium, BIO21 Institute, Melbourne University (Parkville, VIC), 7th December **2012**, Poster Presentation.

CSIRO - Materials Science and Engineering (Clayton, VIC), 30 minute oral presentations annually.

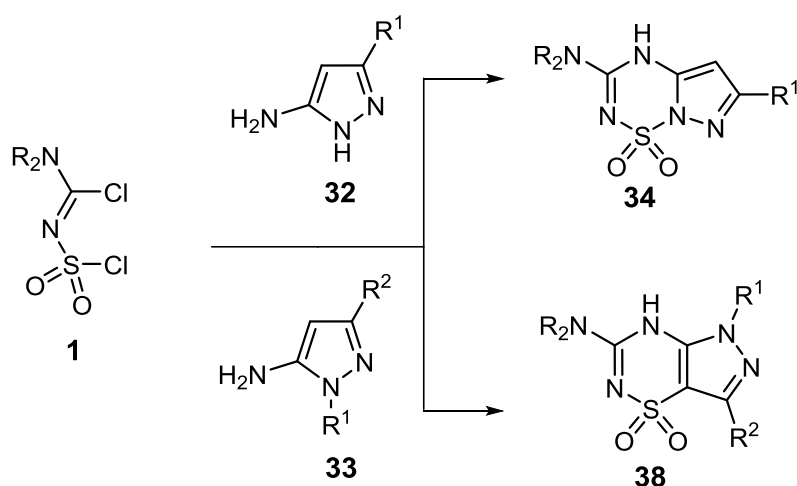
ICOS 19 – The RACI 19th International Conference on Organic Synthesis, Melbourne Convention centre (Melbourne, VIC), 1-6th July **2012**, awarded a student bursary for a poster presentation from the RACI.

CTx Annual Postgraduate Research Symposium, Monash Institute of Pharmaceutical Sciences (Parkville, VIC), 11th October **2013**, 19th October **2012**, 7th November **2011**, Poster presentations and short (5min) oral communications.

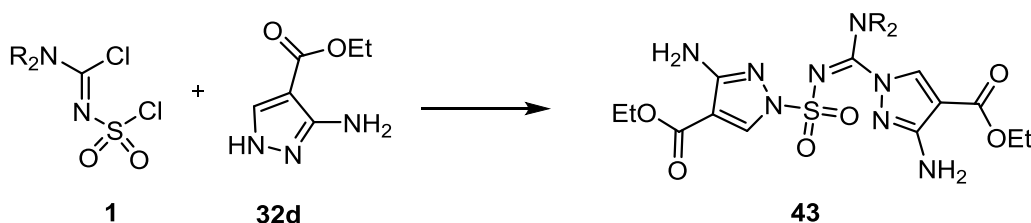
CTx Annual Retreat, Balgownie Estate (Yarra Valley, VIC), 5th December **2012**, 30th November **2011**, Poster presentations.

Abstract

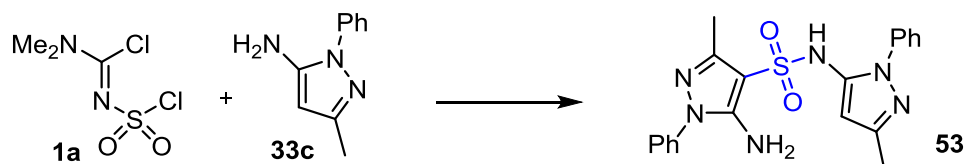
This research extends a body of work on the use of 1,3-dielectrophilic species: *N,N*-dialkyl *N'*-chlorosulfonyl chloroformamidines **1** to generate novel, low molecular weight heterocyclic compounds. The versatility of the dichloride compounds **1** was demonstrated by a series of reactions with readily available 3-aminopyrazoles **32**. These selectively furnished representatives of the previously unreported pyrazolo[1,5-*b*][1,2,4,6]thiatriazine ring system, compounds **34**. The dielectrophiles **1** were also condensed with 1-substituted 5-aminopyrazoles **33** to provide novel pyrazolo[3,4-*e*][1,2,4]thiadiazine dioxides **38** as the sole isolated products.



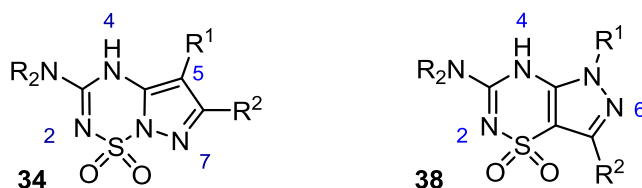
In some circumstances, the 4-ester substituted pyrazole **32d** gave rise to bis-adducts **43** (or intermediate chlorides) by reaction at the ring nitrogen N1 instead.



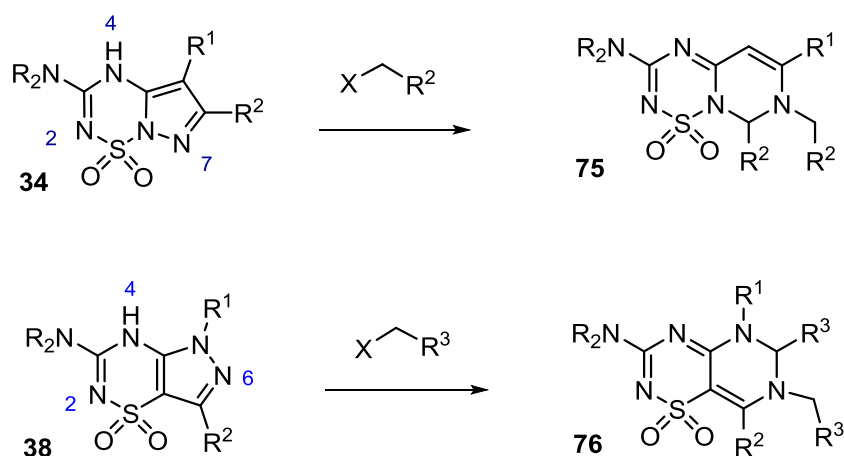
An unexpected sulfonamide product **53** was isolated in one instance from a reaction between pyrazole **33c** and dichloride compound **1a**, which appeared to have formed via rearrangement of an intermediate similar to bis-adducts **43**.



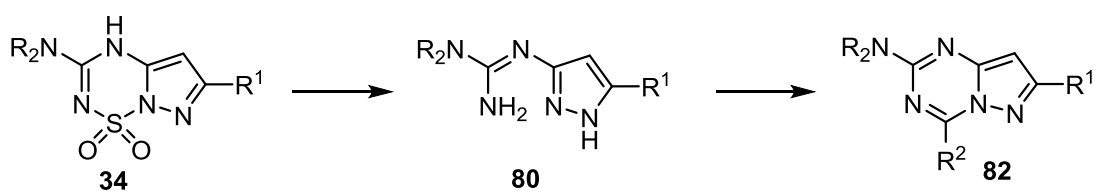
Fused pyrazole compounds **34** and **38** were shown to possess three nucleophilic NH sites which underwent a range of substitution reactions.



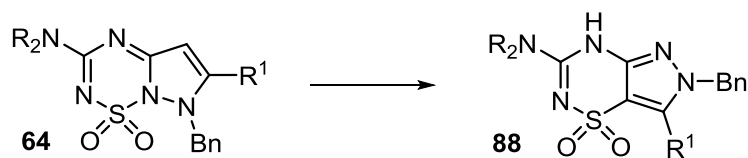
Methylation of representative substrates of compounds **34** occurred at both N4 and N7. Benzylation occurred preferentially at pyrazole nitrogen N7, but also at the pyrazole carbon C5 (when R¹=H). Alkylation with α -halo esters occurred at both N4 and N7, but the latter derivatives, under the reaction conditions, underwent a ring expansion to afford the first reported pyrimido[1,6-*b*][1,2,4,6]thiatriazine derivatives **75**. The tautomeric NH moieties of compounds **38** were reactive towards a selection of alkylating agents including benzylic halides, dimethyl sulfate and ethyl bromoacetate and alkylation occurred mostly at either thiadiazine ring nitrogens N2 or N4. A similar ‘ring expansion’ of the fused pyrazole ring gave the rare pyrimido[4,5-*e*][1,2,4]thiadiazine ring system **76**.



The tendency of some representative pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **34** to undergo ring cleavage at the sulfamide moiety was observed under a variety of conditions. Extrusion of the sulfur dioxide moiety was exploited for supplementary chemical transformations to produce pyrazolo[1,5-*b*][1,2,4]triazines **82** by the formation of guanidines **80** as intermediates. A range of cheap and commercially available electrophiles such as acid anhydrides and orthoesters were utilised to afford compounds **82**.



The pyrazolo[1,5-*b*][1,2,4,6]thiatriazine ring system **34** underwent a nucleophilic addition of C5 to *N*-acylpyridinium or *N*-acylpyridazinium species; revealed by the attempted acylation with pyridine as acyl-transfer agent. Sulfonylation, thiolation and bromination was also achieved with selective reaction at C5. Bromination or tosylation of pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **34** afforded unstable 5-bromo or 5-tosyl derivatives, respectively, which were not synthetically useful due to insufficient stability. The susceptibility of the sulfamide moiety towards nucleophilic attack by a series of alcohols and amines was also established. An unusual rearrangement occurred upon heating fused pyrazolothiatriazine derivatives **64** affording isomeric thiadiazine dioxides **88**.



These results provided insight into the relative thermal and chemical stabilities of both systems **34** and **38**, and derivatives thereof, as well as general patterns of reactivity and selectivity of various substitution reactions.

Abbreviations

A number of common, non-standard abbreviations have been used throughout this thesis. Given here are the abbreviations followed by the standard name.

Ac ₂ O	Acetic anhydride
Ac	Acetyl
aq	Aqueous
Bn	Benzyl
Boc	<i>Tertiary</i> -butylcarbonyl
Boc ₂ O	Di- <i>tertiary</i> -butyl dicarbonate
Bu ⁿ ₄ NBr	Tetra- <i>n</i> -butyl ammonium bromide
Bu ⁿ ₄ NHSO ₄	Tetra- <i>n</i> -butyl ammonium hydrogen sulfate
Bz ₂ O	Benzoic anhydride
CCDC	Cambridge Crystallographic Data Centre
CDCl ₃	Deuteriochloroform
CH ₂ Cl ₂	Dichloromethane
CHCl ₃	Chloroform
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CTx	Cancer Therapeutics Cooperative Research Centre
DCC	N,N-dicyclohexyl carbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
dec.	Decomposition point
DMAc	N,N-dimethyl acetamide
DMAP	N,N-dimethylamino pyridine
DME	Dimethoxy ethane
DMF	N,N-dimethyl formamide
DMPU	1,3-dimethyltetrahydropyrimidin-2(1 <i>H</i>)-one
DMSO	Dimethylsulfoxide
DMSO- <i>d</i> ₆	Deuterated dimethylsulfoxide
DNA	Deoxy-ribonucleic acid
EI	Electron Ionisation
ES	Electrospray
Et	Ethyl
Et ₂ O	Diethyl ether
Et ₃ N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron Withdrawing Group
HCl	Hydrochloric acid
HETCOR	Heteronuclear Correlation Spectroscopy

HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HMQC	Heteronuclear Single-Quantum Correlation Spectroscopy
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
¹ Pr ₂ NEt	N,N'-diisopropylethylamine
<i>J</i>	Coupling constant (Hz)
m.p.	Melting point
<i>m/z</i>	Mass to charge ratio
MeCN	Acetonitrile
MeOH	Methanol
MeOTs	Methyl p-toluenesulfonate
MS	Mass spectrometry
MsOH	Methane sulfonic acid
MWI	Microwave irradiation
NBS	N-bromosuccinimide
<i>n</i> BuLi	<i>n</i> Butyllithium
NH ₄ OH	Aqueous ammonia
NIS	N-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
<i>n</i> Oe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Correlation Spectroscopy
[O]	Oxidation
ORTEP	Oak-Ridge Thermal Ellipsoid Plot
PEPPSI- <i>i</i> pr	1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	Phenyl
PMB	Para-methoxybenzyl
PPh ₃	Triphenylphosphine
ppm	Parts per million
<i>p</i> -TsOH	Para-toluenesulfonic acid
QSAR	Quantitative Structure Activity Relationship
R _F	Retardation factor
RNA	Ribonucleic acid
rt	Room temperature
<i>t</i> -BuOH	Tertiary-butanol
<i>t</i> -BuOK	Potassium tertiary-butoxide
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TsCl	p-toluene sulfonyl chloride
UV	Ultraviolet
X4	Mixed hexanes

Table of Contents

Chapter 1: General Introduction	1
1.1 The Importance of Heterocycles in Drug Discovery and Industry	1
1.2 Synthesis of <i>N,N</i> -Dialkyl <i>N'</i> -Chlorosulfonyl Chloroformamidines.....	4
1.3 <i>N,N</i> -dialkyl <i>N'</i> -chlorosulfonyl chloroformamidines as ambident dielectrophilic reagents	7
1.4 The history of research on <i>N,N</i> – dialkyl <i>N'</i> -chlorosulfonyl chloroformamidines as synthons for novel ring systems	9
1.5 Project aims	16
1.6 Previous studies of 3-aminopyrazoles with <i>N,N</i> -dialkyl <i>N'</i> -chlorosulfonyl chloroformamidines	18
1.7 Thiatriazine and Thiadiazine Rings in Organic Synthesis	20
1.8 Nomenclature of Uncommon Sulfur and Nitrogen Containing Heterocycles	22
1.9 X-Ray Crystallography	25
1.9.1 X-Ray diffraction	25
1.9.2 The crystal lattice.....	26
1.9.3 An Overview of Single Crystal X-ray Diffraction.....	27
1.9.4 The X-ray Diffractometer	28
1.9.5 X-Ray refinement	31
1.10 Doctoral research contributions to this study	33
Chapter 2: Synthesis of pyrazolo[1,5-<i>b</i>] [1,2,4,6]thiatriazine 1,1 dioxides.....	35
2.1 Introductory remarks.....	35
2.1.1 Novel, low molecular weight ring systems containing synthetic handles	35
2.1.2 Reactions of aminopyrazoles as 1,2/1,3 dinucleophilic systems	36
2.1.3 The selectivity of condensation between <i>N,N</i> -dialkyl <i>N'</i> -chlorosulfonyl chloroformamidines and 3-aminopyrazoles.....	38
2.2 Synthesis of the <i>N,N</i> -dialkyl <i>N'</i> -chlorosulfonyl chloroformamidines.....	40
2.3 Synthesis of the novel fused pyrazolo[1,5- <i>b</i>] [1,2,4,6]thiatriazine 1,1 dioxides ...	41
2.3.1 General methods and materials for synthesis	42
2.3.2 Reactions of dichlorides with 3-amino pyrazole bidentate nucleophiles	43
2.3.4 Mechanism of formation	47
2.3.5 Bulky substituents on the C4 position of the pyrazole ring	49
2.3.6 The influence of reaction conditions	50

2.4	Characteristic NMR behaviour of pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazine dioxides....	51
2.5	General physical properties of the pyrazolothiatriazine ring system	54
2.5.1	Stability	54
2.5.2	Solubility and polarity	55
2.5.3	Miscellaneous properties.....	56
2.6	Bis-adducts and uncyclised dichlorides	57
2.6.1	Two bis-adducts – characterisation by X-ray crystallography.....	57
2.6.2	Dilution effects (and formation of mono adducts)	59
2.7	Conclusions.....	60
Chapter 3: Reactions of <i>N,N</i>-Dialkyl <i>N'</i>-Chlorosulfonyl Chloroformamidines with 1-substituted 5-amino pyrazoles.....		62
3.1	Introductory remarks	62
3.1.1	Modified aminopyrazoles in the pursuit of an isomeric core structure to the pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazine dioxides.....	62
3.1.2	The <i>N</i> -substituted 5-amino pyrazole system as a reactive 1,3-CCN dinucleophile	63
3.2	Synthesis of the novel fused pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazine 1,1 dioxides.....	65
3.2.1	General methods and substrate synthesis.....	65
3.2.2	Summary of results	66
3.2.3	Mechanism of formation	70
3.2.4	The influence of reaction conditions	71
3.2.5	Chemical and physical properties of the new ring system	72
3.2.6	Characteristic NMR behaviour	73
3.3	Sulfamic acid side products	75
3.3.1	Trapping the sulfamic acid intermediate	76
3.3.2	An unusual sulfur dioxide bridged dimer	77
3.4	Reactivity of fused pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazines with acylating agents.....	80
3.5	Conclusions.....	81
Chapter 4: Pyrazolo[1,5-<i>b</i>][1,2,4,6]thiatriazine ring system modifications on a nucleophilic carbon.....		82
4.1	Introductory remarks	82
4.2	The susceptibility of pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazine dioxides towards acylation	83
4.3	Reactions of pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazine dioxides with <i>N</i> -acylpyridinium species	85
4.3.1	Proposed Mechanism of the Reaction with Pyridine.....	86
4.3.2	Literature precedent for nucleophilic aromatic substitution of pyridine	87

4.3.3	Summary of results	90
4.3.4	Extension to other pyridine derivatives	91
4.3.5	NMR analysis of pyrid(az)ine adducts 55	93
4.4	Mannich Reaction at C5	96
4.4.1	Mechanism of Formation of Methylene-bridged Dimers	98
4.4.2	Alternative Approaches to Synthesis of Dialkylaminomethyl Derivatives	99
4.5	Sulfonylation of pyrazolothiadiazines	100
4.6	Dimethylthiolation of C5 by dimethylsulfoxide and trifluoroacetic anhydride ...	103
4.6.1	Mechanism of dimethylthiolation	105
4.7	Halogenation of the pyrazole ring	106
4.8	Attempted Nitration of C5	108
4.9	Conclusions	108
Chapter 5: Alkylation of pyrazolo[3,4-<i>e</i>][1,2,4]thiadiazines and pyrazolo[1,5-<i>b</i>][1,2,4,6]thiatriazines.		110
5.1	Introductory remarks	110
5.2	Alkylation Reactions of fused pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazine 1,1 dioxides .	112
5.2.1	Benylation	113
5.2.2	Methylation	119
5.3	Alkylations of pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazine 1,1 dioxides.....	121
5.4	Ring expansions of fused pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazines	124
5.4.1	Mechanism of formation	126
5.4.2	Substrate scope	127
5.4.3	General characteristics of pyrimido[1,6- <i>b</i>][1,2,4,6]thiatriazine dioxides	130
5.5	Ring expansions of fused pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazines	131
5.5.1	Mechanism of formation	132
5.5.2	Substrate scope	132
5.5.3	Susceptibility of pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazines to bromination	135
5.6	The application of ester functionality as a precursor to additional derivatives. .	137
5.7	General notes on the reactivity of pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazines and pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazines as nucleophiles	140
5.8	Conclusion.....	141
Chapter 6: Reactions to form pyrazolo[1,5-<i>a</i>][1,3,5]triazine compounds from pyrazolo-[1,5-<i>b</i>][1,2,4,6]thiatriazines		142
6.1	Introductory remarks	142
6.2	he extrusion of SO ₂ N ₇ -tedyrazolo-thiatriazine.....	142

6.3	The action of phosphoryl chloride and DMF to form fused pyrazolo[1,5- <i>a</i>][1,3,5]triazines.....	145
6.3.1	Substrate scope of the Vilsmeier-Haack reagent mediated triazine formation	147
6.4	Pyrazolo[1,5- <i>a</i>][1,3,5]triazines as biologically relevant compounds.....	149
6.5	The action of trifluoroacetic anhydride on the pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazine system.	150
6.5.1	Mechanism of the formation of pyrazolo-guanidines substituted with sulfonic acid ..	152
6.6	The formation of pyrazolo guanidines as precursors to triazine rings.....	158
6.6.1	The formation of pyrazolo-guanidines by other means	160
6.7	Formation of fused pyrazolo-triazines from dielectrophilic reagents.....	161
6.7.1	Triazine rings from amides and phosphoryl chloride.....	161
6.7.2	Formation of fused pyrazolo-triazines by condensation with orthoesters.....	163
6.7.3	Condensation of amines by DMF-DMA.....	164
6.7.4	Condensation of amines by aldehydes	164
6.7.5	Condensation of amines by acid chlorides	165
6.7.6	Condensation of amines by anhydrides.....	166
6.8	The reaction of pyrazolo[1,5- <i>a</i>][1,3,5]triazines with electrophilic bromine	168
6.9	General conclusions.....	168
Chapter 7: Rearrangements and other transformations of <i>N</i>-alkylated pyrazolo[1,5-<i>b</i>][1,2,4,6]thiatriazine dioxides.....		170
7.1	Introductory remarks	170
7.2	Forming activated intermediates towards aryl coupling	171
7.3	The rearrangement of <i>N</i> 7 benzyl pyrazolothiatriazines to the isomeric <i>N</i> 6 benzyl pyrazolo-thiadiazines.....	174
7.3.1	Mechanism of formation	178
7.4	Cleavage of the thiatriazine ring by nucleophilic attack of the sulfamide moiety	180
7.4.1	Alcoholysis of benzylated pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazines.....	180
7.4.2	Aminolysis of benzylated pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazines	183
7.5	Attempts to remove <i>N</i> -benzyl and <i>N</i> -(<i>p</i> -chloro)benzyl substituents by other means	184
7.6	Attempted removal of PMB amine protecting group	185
7.7	The ring expansion of pyrazolothiatriazines by “dissolving metal reduction”	186
7.8	General conclusions.....	187
Chapter 8: X-Ray crystallography		189
8.1	Introductory remarks	189

8.2	Crystallisation methods	189
8.3	Loading of single crystals into the diffractometer	191
8.4	Characterisation of pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazines by X-ray crystallography..	192
8.4.1	Structural elucidation and ellipsoid plots	192
8.4.2	General crystal properties	195
8.5	Characterisation of pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazines by X-ray crystallography	196
8.5.1	Structural elucidation and ellipsoid plots	196
8.5.2	General crystal properties	198
8.6	Characterisation of alkyl substituted pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazines by X-ray crystallography.....	199
8.7	Characterisation of alkyl substituted pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazines by X-ray crystallography.....	201
8.8	Characterisation of bis-adduct 43a	207
8.9	Characterisation of miscellaneous transformation products of the pyrazolo[1,5- <i>b</i>] [1,2,4,6]thiatriazine 1,1-dioxides and pyrazolo[3,4- <i>e</i>][1,2,4]thiadiazine 1,1-dioxides. ...	209
8.10	A summary of X-ray crystal diffraction experiments	212
Chapter 9: Experimental		215
9.1	Methods and Materials.....	215
9.2	General synthesis procedure for 3-dialkylamino-4 <i>H</i> -pyrazolo[1,5- <i>b</i>] [1,2,4,6]thiatriazine 1,1-dioxides 34a-l	216
9.3	General synthesis procedure for 3-dialkylamino-4 <i>H</i> -pyrazolo[3,4- <i>e</i>] [1,2,4]thiadiazine 1,1-dioxides 38a-i	221
9.4	Synthesis of 5-(pyridin-4-yl)- and 5-(pyridazin-4-yl)-pyrazolo[1,5- <i>b</i>] [1,2,4,6]thiatriazine adducts	231
9.5	Synthesis of “methylene dimers” and methylation from attempted Mannich reactions	234
9.6	Synthesis of products from <i>p</i> -toluenesulfonylation experiments	237
9.7	Synthesis of 5-dimethylthio derivatives	239
9.8	Synthesis of 5-bromo-pyrazolo[1,5- <i>b</i>][1,2,4,6]thiatriazine derivatives.....	241
9.9	General synthesis procedures for benzylated 3-dialkylamino-pyrazolo[1,5- <i>b</i>] [1,2,4,6]thiatriazine 1,1-dioxides 64a-67g	243
9.10	Synthesis of N4-alkylated pyrazolo[1,5- <i>b</i>][1,2,4,6] thiatriazines 73 , N7-alkylated pyrazolo[1,5- <i>b</i>][1,2,4,6] thiatriazines 74 , and 7,8-dihydropyrimido[1,6- <i>b</i>][1,2,4,6] thiatriazines 75	266

9.11	Synthesis of N4-alkylated pyrazolo[3,4- <i>e</i>][1,2,4] thiadiazines 78 , N6-alkylated pyrazolo[3,4- <i>e</i>][1,2,4] thiadiazines 77 , 6,7-dihydropyrimido[4,5- <i>e</i>][1,2,4] thiadiazines 76 and N2-alkylated pyrazolo[3,4- <i>e</i>][1,2,4] thiadiazines 79	274
9.12	Synthesis of guanidine derivatives via the extrusion of SO ₂	279
9.13	Synthesis of pyrazolo[1,5- <i>a</i>][1,3,5]triazine derivatives	281
9.14	Synthesis of pyrazolo-thiadiazines from rearrangement of pyrazolothiatriazines	294
9.15	Synthesis of compounds arising from nucleophilic attack on the sulfamide moiety.	298
9.16	Synthesis of a dihydropyrimido[1,6- <i>b</i>][1,2,4,6]thiatriazine	307
9.17	X-ray Crystallography.....	308
REFERENCE LIST		309
Appendices		320
	Appendix A: Spectral data for chapter 4	321
	Appendix B: Spectral data for chapter 5	323
	Appendix C: Spectral data for chapter 7	325
	Appendix D: X-ray crystallography data	326