Synthesis and Reactivity of Novel Pyrazolothiatriazines and Thiadiazines

A thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

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Faculty of Science and Engineering

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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

Acknowledgements

I would like to offer my sincerest gratitude to my supervisors: Assoc. Prof. Mike Perkins and Dr. Craig Francis. Mike, your Medicinal Chemistry degree was a fascinating course and I enjoyed my time as an undergraduate thoroughly. I was especially captivated by your unique style of teaching and your own interest in your field really shone through. During my postgraduate studies, your patience and immense knowledge were most valuable to me. I very much appreciate that you gave me room to work on my own ideas while still providing me with the direction I needed. Your genuine interest and engagement in my research was most encouraging, as you were always optimistic when I obtained some of those 'what the..?' results. Craig, you've been able to provide so much input into my postgraduate studies and it is hard for me to think of you as an external supervisor. Being just an e-mail or phone call away was as if you were here at Flinders. You were always keen to hear about my results and I appreciate the patience you showed when some of my progress reports came a little late. Furthermore, your guidance enabled me to stay on track and remain motivated through the more challenging stretches and you have been an excellent mentor. I attribute the level of my PhD research, publications, and experiences gained to the both of you. I have been so lucky to have had two knowledgeable, supportive and welcoming supervisors.

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I lastly want to take this opportunity to thank my friends and family who, despite being at the end of this section, were essential in holding me together and keeping me sane. Mr. Maynard, you got me through my undergraduate exam periods and somehow you've been able to put up with me during my crazy-thesis-writing-period as well. Thankyou for always being there for me.

Mum and Dad, stop asking when I'll get a real job.

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]thiatriazine 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]thiatriazine 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]thiatriazine 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.

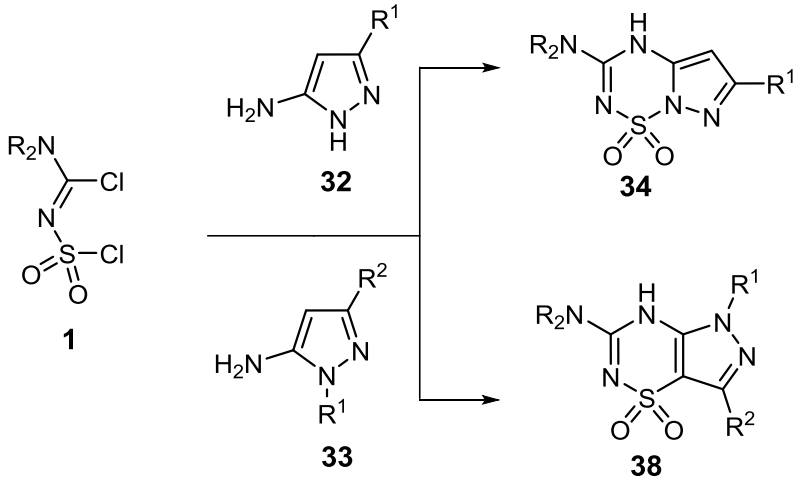
ICOS 19 – The RACI 19th International Conference on Organic Synthesis, Melbourne Convention centre (Melbourne, VIC), 1-6th July **2012**, awarded a student bursary for a poster presentation from the RACI.

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.

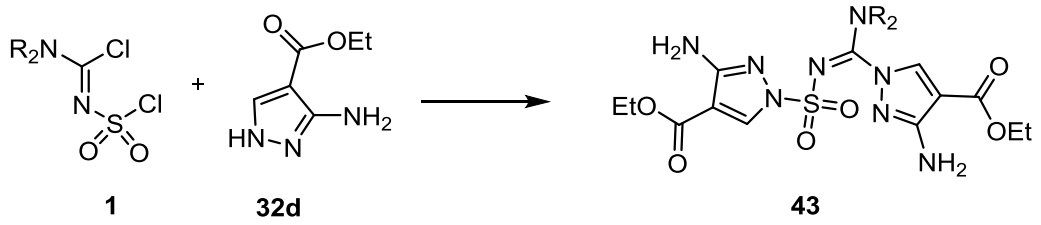
CTx Annual Retreat, Balgownie Estate (Yarra Valley, VIC), 5th December **2012**, 30th November **2011**, Poster presentations.

Abstract

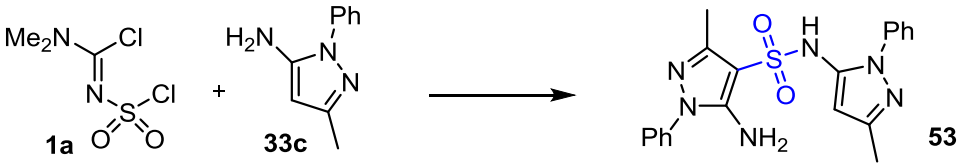
This research extends a body of work on the use of 1,3-dielectrophilic species: *N*,*N*-dialkyl *N*'-chlorosulfonyl chloroformamidines **1** to generate novel, low molecular weight heterocyclic compounds. The versatility of the dichloride compounds **1** was demonstrated by a series of reactions with 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.



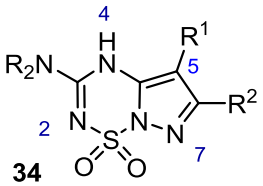
In some circumstances, the 4-ester substituted pyrazole **32d** gave rise to bis-adducts **43** (or intermediate chlorides) by reaction at the ring nitrogen N1 instead.

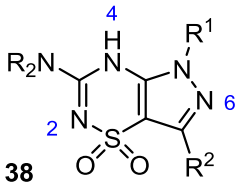


An unexpected sulfonamide product **53** was isolated in one instance from a reaction between pyrazole **33c** and dichloride compound **1a**, which appeared to have formed via rearrangement of an intermediate similar to bis-adducts **43**.

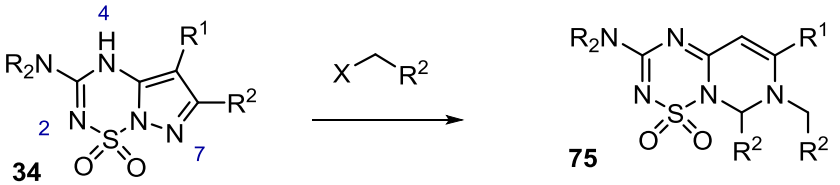


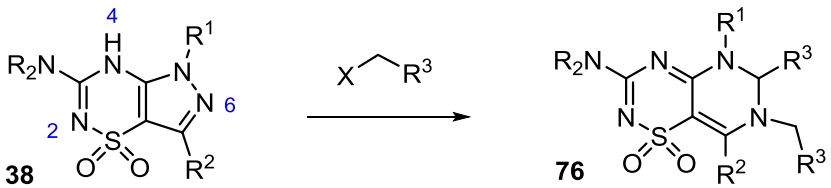
Fused pyrazole compounds **34** and **38** were shown to possess three nucleophilic NH sites which underwent a range of substitution reactions.



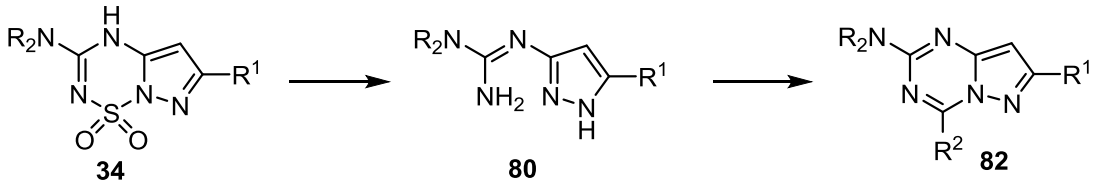


Methylation of representative substrates of compounds **34** occurred at both N4 and N7. Benzylation occurred preferentially at pyrazole nitrogen N7, but also at the pyrazole carbon C5 (when R^1=H). Alkylation with α-halo esters occurred at both N4 and N7, but the latter derivatives, under the reaction 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**.

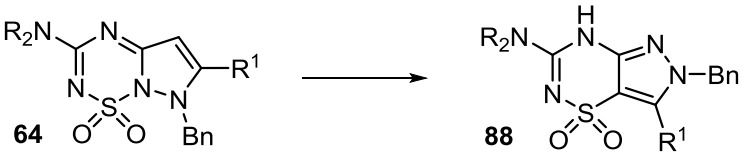




The tendency of some representative pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **34** to undergo ring cleavage at the sulfamide moiety was observed under a variety of conditions. Extrusion of the sulfur dioxide moiety was exploited for supplementary chemical transformations to produce pyrazolo[1,5-*b*][1,2,4]triazines **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]thaitraizine 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_2O	Acetic anhydride
Ac	Acetyl
aq	Aqueous
Bn	Benzyl
Boc	*Tertiary*-butylcarbonyl
Boc_2O	Di-*tertiary*-butyl dicarbonate
Bu^n_4NBr	Tetra-*n*-butyl ammonium bromide
$Bu^n_4NHSO_4$	Tetra-*n*-butyl ammonium hydrogen sulfate
Bz_2O	Benzoic anhydride
CCDC	Cambridge Crystallographic Data Centre
$CDCl_3$	Deuterochloroform
CH_2Cl_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*H*)-one
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated dimethylsulfoxide
DNA	Deoxy-ribonucleic acid
EI	Electron Ionisation
ES	Electrospray
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	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
$^{i}Pr_2NEt$	N,N'-diisopropylethylamine
J	Coupling constant (Hz)
m.p.	Melting point
m/z	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
*n*BuLi	*n*Butyllithium
NH_4OH	Aqueous ammonia
NIS	N-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Correlation Spectroscopy
[O]	Oxidation
ORTEP	Oak-Ridge Thermal Ellipsoid Plot
PEPPSI-^{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
p-TsOH	Para-toluenesulfonic acid
QSAR	Quantitative Structure Activity Relationship
R_F	Retardation factor
RNA	Ribonucleic acid
rt	Room temperature
t-BuOH	Tertiary-butanol
t-BuOK	Potassium tertiary-butoxide
TFA	Trifluroacetic acid
TFAA	Trifluroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TsCl	p-toluene sulfonyl chloride
UV	Ultraviolet
X4	Mixed hexanes

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