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A new and simple method for the synthesis of highly functionalised pyrrolizidines, indolizidines and pyrroloazepines

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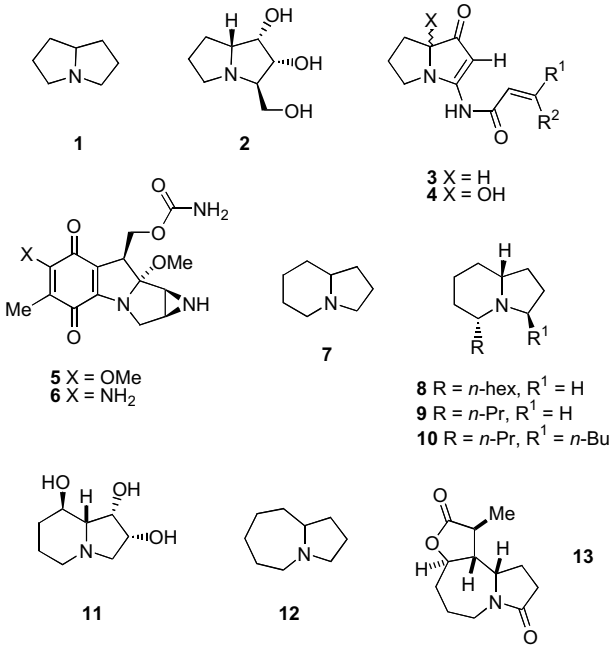
ABSTRACT

The reaction of 5-, 6- and 7-membered cyclic thioimidates with cyclopropenones gives access to highly functionalised pyrrolizidines, indolizidines and pyrroloazepines via a formal [3+2] cycloaddition process.

Current interest in the pyrrolizidine nucleus **1** is typified by the role of polyhydroxylated pyrrolizidines, such as hyacinthacine A_1 **2**, as glycosidase inhibitors important in the possible treatment of various cancers, diabetes and viral infections such as AIDS.[1] Many non-polyhydroxylated pyrrolizidines have also attracted interest, examples being the jenamidines **3** and **4**, which inhibit leukaemia cell lines at clinically useful levels and show a range of other antitumour and antibiotic properties.[2] The pyrrolizidine nucleus is also seen embedded in more complex natural products such as UCS1025A, an antiproliferative telomerase inhibitor,[3] and mitomycins A and C **5** and **6**, potent and clinically prescribed antitumour agents.[4] The indolizidine nucleus **7** is present in several classes of important alkaloid natural products,[5] such as indolizidines 209D **8**,[6] 167B **9**[6] and 223AB **10**[7] which are secreted by the skin of the frog species *dendrobatidae*, and are noted for their ability to block nicotinic receptor channels and to function as potent analgesics or as potential leads in the search for treatments for Alzheimer's disease and other neurological disorders.[5–7] Polyhydroxylated indolizidines,[5,8] such as castanospermine[9] and swainsonine[10] **11**, are of interest as antiviral, antitumour, and immunoregulatory agents and, like their pyrrolizidine counterparts, have attracted interest as glycosidase inhibitors and as potential antidiabetic agents.[5,8–11] The pyrroloazepine nucleus **12** is present in the stemona alkaloids, a group of bioactive molecules of which stenoamide **13** is typical,[12] and which have attracted interest, for example, as possible treatments for a range of respiratory diseases.



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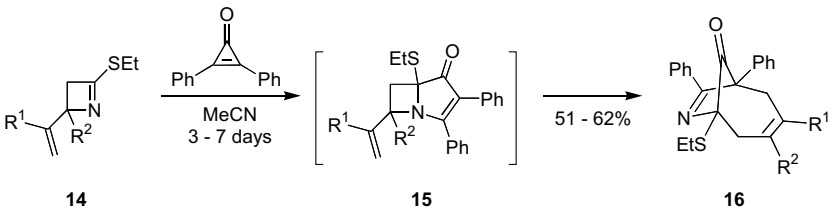
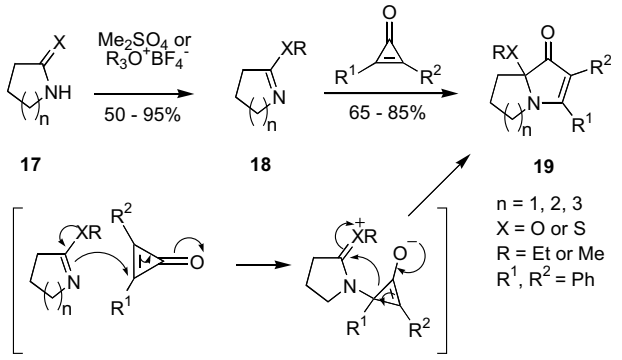


$R^1 = R^2 = H$; $R^1 = R^2 = Me$; $R^1 = H$, $R^2 = Me$

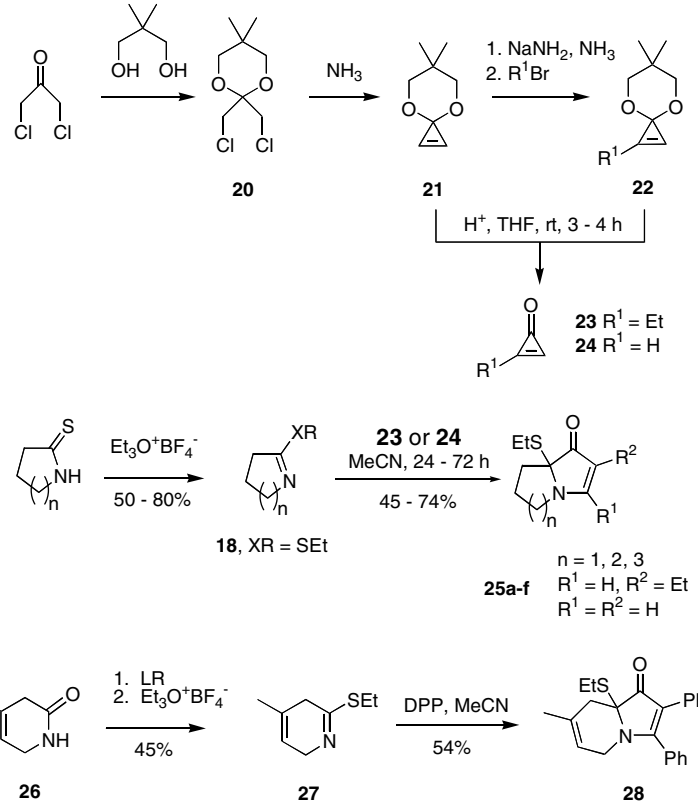
Scheme 1.

Our work began as part of an ongoing series of projects concerned with the reactions of cyclopropenones[13] and other small ring systems.[14,15] Working with small ring cyclic thioimidates, as shown in Scheme 1, we were able to show that 4-vinyl-1-azetines **14**[13] underwent an expected reaction with diphenylcyclopropenone (DPP), whereby the 1-azetine took part in a formal [2+3] cycloaddition[16] with the cyclopropenone to furnish the adduct **15** which underwent an unexpected aza-Cope rearrangement to furnish the 7-azabicyclo[4.2.1]nonenes **16** which are interesting analogues[13b] of the 9-azabicyclo[4.2.1]nonene nucleus that is present in the homotropane alkaloid natural product class, of which the potent neurotoxin anatoxin-a is the most well-known member.

We have now investigated the reactions of a variety of 5-, 6- and 7-membered cyclic thioimidates **18** (X = S) with a range of cyclopropenones (Scheme 2) and report the results herein. The major impetus for this work was its potential to provide a rapid access to the highly sought after pyrrolizidine, indolizidine and pyrroloazepine nuclei **19,** which would be replete with easily manipulated functional groups for future applications, including natural product target synthesis. Cyclic thioimidates **18** (X = S) were readily available by alkylation of the appropriate thiolactam **17** (X = S) with triethyloxonium tetrafluoroborate (Meerwein's reagent) in dichloromethane (~50–80% yield)[17] or with neat dimethyl sulfate (90–95% yield), whereby the thiolactams were accessed by thiation of the corresponding lactam **17** (X = O) with Lawesson's reagent (>90%). We were pleased to observe that



Scheme 2.



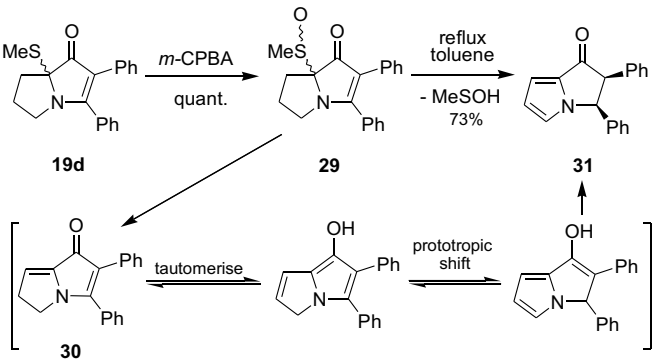
Scheme 3.

reactions of compounds **18** with commercially available diphenylcyclopropenone proceeded well to furnish the requisite highly functionalised pyrrolizidines, indolizidines and pyrroloazepines **19a–f** ($R^1 = R^2 = Ph$; XR = SEt or SMe, $n = 1$, 2 or 3; 6 examples) in good to excellent yields, as shown in Scheme 2, which also shows a suggested mechanism for the reaction based upon earlier precedents.[13,16,18]

Having successfully accessed the diphenyl adducts from the commercially available diphenylcyclopropenone, we next extended the process to more useful cyclopropenone substitution patterns. Cyclopropenone chemistry is of some interest in the literature,[18] including some natural products,[19] and the extraterrestrial occurrence of the parent system.[20] We accessed monoalkyl and unsubstituted cyclopropenones using the chemistry shown in Scheme 3.[19] Thus, acetal **20** was cyclised in liquid ammonia to generate the cyclopropenone acetal **21**. Deprotonation and alkylation gave the alkylated cyclopropenone acetal **22**. A wide selection of cyclopropenones is available via this route.[19] In this study we only investigated the reactions of the mono-ethyl and unsubstituted variants as we felt it would be of most interest to establish the regiochemical outcome of reactions involving the mono-substituted system, and that the unsubstituted system offered a substrate which would be most suited to future manipulations. Deprotection of the cyclopropenone acetals **21** and **22** gave the ethyl and unsubstituted cyclopropenones **23** and **24** which were reacted with the three cyclic thioimidates **18** (XR = SEt; $n = 1$–3) to furnish a series of six pyrrolizidines, indolizidines and pyrroloazepines **25**, in good yields,[21] as shown in Scheme 3. The non-symmetric ethylcyclopropenone **23** ($R^1 = H$, $R^2 = Et$) gave only single regioisomers as shown in Scheme 3 (structures confirmed by HMBC), presumably due to the imidate nitrogen attacking the cyclopropenone at the least hindered carbon in the initial stages of the reaction (see Scheme 2 for mechanism). It is also possible to further vary the nature of the imidate partner in the reaction. As an example, the dihydropyridine **27**, available from treatment of the readily accessible[22] lactam **26** with Lawesson's reagent (LR) and Meerwein's reagent, gave access to the indolizidine **28** on reaction with DPP in a yield of 54%.

The reactions detailed in Schemes 2 and 3 show that one of the strengths of this route to pyrrolizidines, indolizidines and pyrroloazepines is the versatility of the reaction due to the high level of diversity available in the two reaction partners.

A second potential strength lies with the easily manipulated functionality that is available within the adducts **19**, **25** and **28** which will enable future applications to be developed in the synthesis of natural products and interesting non-natural analogues of the pyrrolizidines, indolizidines and pyrroloazepines. The result of one such process, the desulfurisation of compound **19d**, is shown in Scheme 4. Oxidation of the sulfide moiety in compound **19d** gave the sulfoxide **29** as a 3:2 mixture of diastereoisomers, which on treatment in toluene at reflux underwent β-elimination of methyl sulfenic acid to furnish the final isolated product **31**. The structure of product **31**[23] was assigned on the basis of extensive NMR studies (COSY, HSQC, HMBC and NOESY) which showed, for example: the presence of the two sp^3 CHs α and β to the carbonyl; a clear CO–CHPh–CHPh chain; three extra CH groups in the aromatic region (due to the new pyrrole ring); a strong nOe between the two phenyl rings indicative of a cis relationship between these two groups; a lack of any nOe between either of the two sp^3 CHs and the *ortho* protons of the phenyl ring on the neighbouring carbon indicating that each of these Hs is trans rather than cis to the phenyl group on the neighbouring carbon. That these two protons are cis to each other is also consistent with literature precedent and with the observed coupling constant of 4.4 Hz (with 8–11 Hz being typical of a trans relationship).[3b,10c,24] Further evidence for the formation of compound **31** lies with a plausible



Scheme 4.

mechanistic rationale, whereby a tautomerism-prototropic shift-tautomerism sequence starting from the unstable initial product **30** leads to product **31** as shown in Scheme 4. The incoming proton in the final tautomerism enters from the least sterically hindered face, that is, trans to the existing phenyl group, resulting in the two phenyl groups being cis to each other.

We are currently exploring other desulfurisation reactions of compounds **19**, **25** and **28** and analogues, together with other transformations such as conjugate additions, reductions, dihydroxylations, epoxidations, aziridations, Wittig homologations and bridgehead thioether/ether manipulations together with possible asymmetric versions of the cyclopropenone addition reaction. Studies towards the total syntheses of the jenamidines **3** and **4** and other natural products **8**–**11** are also underway.

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21. All new compounds gave satisfactory $^{1}H/^{13}C$ NMR spectra (including DEPT, COSY, HSQC and HMBC spectra), mass spectra, HRMS/microanalysis and IR spectra. Typical procedure: *Synthesis of 3-ethyl-5-ethylthio-1-azabicyclo[3.3.0]oct-2-en-4-one* (**25a**, $n = 1$, $R^1 = H$, $R^2 = Et$). To 5-ethylthio-3,4-dihydro-2*H*-pyrrole (**18**, $n = 1$, XR = SEt; 0.20 g, 1.55 mmol) dissolved in freshly distilled anhydrous acetonitrile (5 mL) was added, in one portion, with stirring, 2-ethylcyclopropenone[19] (**23**, 0.15 g, 1.83 mmol). The solution was stirred under an atmosphere of dry nitrogen at room temperature for 24 h, after which time TLC confirmed that the reaction had gone to completion. The solvent was removed by reduced pressure rotary evaporation, and the crude sample was purified by column chromatography (eluent: petroleum ether: ethyl acetate, 4:1, silica gel [Aldrich] 70–230 mesh, 60 Å, 10 g) to yield the title compound (0.24 g, 74%) as a clear yellow oil. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.47; H, 7.82; N, 6.39. IR: ν_{max} (neat, cm^{-1}): 2966 (m), 2930 (m), 1681 (s), 1591 (s), 1456 (w), 1375 (m). ^{1}H NMR (500 MHz, $CDCl_3$), δ_H: 7.41 (1H, s, C=C*H*), 3.38 (1H, ddd, *J* 11.1, 6.3, 3.9, CH_2CHHN), 3.15 (1H, ddd, *J* 11.1, 7.0, 4.0, CH_2CHHN), 2.38 (2H, q, *J* 7.5, S–CH_2CH_3), 2.09 (2H, q, *J* 7.6, C–CH_2CH_3), 1.99 (2H, m, CH_2CSEt), 1.79 (2H, m, $CH_2CH_2CH_2$), 1.09 (3H, t, *J* 7.6, C–CH_2CH_3), 1.00 (3H, t, *J* 7.5, S–CH_2CH_3); ^{13}C: δ_c (125 MHz, $CDCl_3$): 203.64 (C=O), 164.95 (CH), 121.36 (q), 80.01 (q), 48.83 (CH_2), 33.78 (CH_2), 26.57 (CH_2), 23.12 (CH_2), 15.73 (CH_2), 14.05 (CH_3), 12.99 (CH_3). *m*/*z* (electrospray) HRMS: found, 212.1108, calcd for $C_{11}H_{17}NOS + H^+ = 212.1105$.
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23. *Procedure and data for compound* **31**: To a solution of *5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one* (**19d**, $n = 1$, XR = SMe, $R^1 = R^2 = Ph$) (110 mg, 0.34 mmol) in dichloromethane (7 mL) was added *m*-CPBA (60 mg, 0.34 mmol) in dichloromethane (3 mL) and the whole was stirred at 0 °C for 4.5 h at which point TLC analysis showed no starting material. A solution of saturated aqueous sodium thiosulfate (10 mL) was added and the mixture was allowed to warm to room temperature and added to a solution of saturated aqueous sodium hydrogen carbonate (10 mL). The crude sulfoxide was extracted into dichloromethane (3×10 mL), the extracts were dried ($MgSO_4$), and the solvent was removed. The crude sulfoxide was dissolved in freshly distilled, anhydrous toluene under an atmosphere of dry nitrogen and heated overnight at reflux to give, after removal of the solvent and purification by flash silica column chromatography (eluent: petroleum ether: ethyl acetate, 9:2), *2,3-diphenyl-1-azabicyclo[3.3.0]oct-5,7-dien-4-one* (**31**) as a pale yellow solid (68 mg, 73%), mp 132–134 °C. Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.38; H, 5.49; N, 5.37. IR: ν_{max} (neat, cm^{-1}): 2975 (w), 2925 (w), 1693 (s), 1575 (m), 1556 (m), 1521 (s), 1374 (s), 1274 (m), 1132 (s), 1018 (m), 996 (m), 669 (s); ^{1}H NMR (500 MHz, $CDCl_3$), δ_H: 7.44–7.30 (6H, m, Ar), 7.18 (2H, dd, *J* 7.6, 1.4 Ar), 7.10 (2H, m, Ar), 6.95 (2H, br s, Ar), 6.66 (1H, dd, *J* 3.8, 2.5 pyrroleNC*H*), 5.48 (1H, d, *J* 4.4 *CH*Ph), 4.12 (1H, d, *J* 4.4 *CH*Ph). ^{13}C: δ_c (100 MHz, $CDCl_3$): 188.31 (q), 139.53 (q), 137.24 (q), 132.91 (q), 129.29 (CH), 129.11 (CH), 128.72 (CH), 128.24 (CH), 127.77 (CH), 126.15 (CH), 122.85 (CH), 117.71 (CH), 108.70 (CH), 67.51 (CH), 67.44 (CH); *m*/*z* (electrospray) HRMS: calcd for $C_{19}H_{15}NO + Na^+ = 296.1046$, found: 296.1055.
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