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Silver Acetate Catalysed Cycloadditions of Isocyanoacetates

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Abstract: Silver acetate is an efficient catalyst for the cycloaddition of methyl isocyanoacetate with Michael-acceptors under mild conditions to give Δ^1- or Δ^2-pyrrolines in good yields. In the case of acrolein, novel chemoselectivity was observed. In the absence of a suitable olefin isocyanoacetates undergo silver acetate catalysed cyclodimerisation to give imidazoles in excellent yields. The mechanism of the cycloadditions has been probed. The reaction has been combined with azomethine ylide 1,3-dipolar cycloadditions in a one-pot sequential cascade process to afford the 7-azabicyclo[2.2.1]heptane ring system, a characteristic structural feature of the naturally occurring potent analgesic epibatidine.

INTRODUCTION

Isocyanides have been found to be versatile reagents in heterocyclic synthesis,[1] particularly since the α-metallation of isocyanides was first accomplished by Schöllkopf.[2] Most notably, the aldol-like cycloaddition of isocyanides with carbonyl compounds to give 2-oxazolines has been extensively studied and, especially in the case of the reaction with aldehydes, has been brought to a high degree of sophistication with excellent levels of asymmetric induction being achieved by the use of chiral gold(I)[3]- and silver(I)[4,5]-ferrocenylbisphosphine catalysts.

The cycloaddition with carbon-carbon multiple bonds, however, has received less attention. Early work by Schöllkopf resulted in a two-step synthesis of pyrrolines by heating initially formed Michael-adducts under basic conditions to effect cyclisation.[6] Van Leusen and co-workers developed a one-pot synthesis of pyrroles by the reaction of tosylmethylisocyanide (TosMIC) with Michael-acceptors in the presence of sodium hydride, the initially generated pyrroline undergoing *in situ* elimination of toluenesulfonate to form the pyrrole.[7,8] Barton and Zard have reported a similar pyrrole synthesis involving the cycloaddition of isocyanoacetates to nitroolefins and subsequent nitronate elimination.[9,10] In an alternative approach, Saegusa and co-workers identified copper(I) oxide as a suitable catalyst for the cycloaddition of ethyl isocyanoacetate, benzylisocyanide,[11] and allylisocyanide[12] with a range of Michael-acceptors, although the yields were sometimes low. The reaction was postulated to proceed *via* organocopper complexes formed by replacement of an acidic α-proton by copper(I).

In work that appears to have gone largely unnoticed, Fehlhammer *et al.* exploited the increased acidity of α-protons in isocyanides coordinated to metals at the terminal carbon to achieve α-deprotonation with triethylamine[13,14] (this principle similarly provides the basis for the aforementioned gold catalysed aldol reaction). Utilising platinum and palladium complexes in stoichiometric quantities, the cycloadducts were isolated as C-2 metallated species. Fehlhammer remarked upon the analogy between terminally metallated, α-

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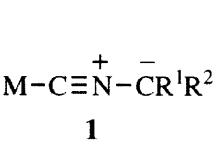
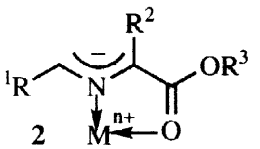
deprotonated, isocyanides **1** and nitrile ylides, but did not investigate whether a stepwise or concerted mechanism was operating. In conjunction with our studies of the concerted 1,3-dipolar cycloadditions of metallo-azomethine ylides **2**,[15] we were intrigued both by this analogy and by the opportunity of developing a mild catalytic procedure for the cycloaddition of isocyanoacetates with activated olefins.



1



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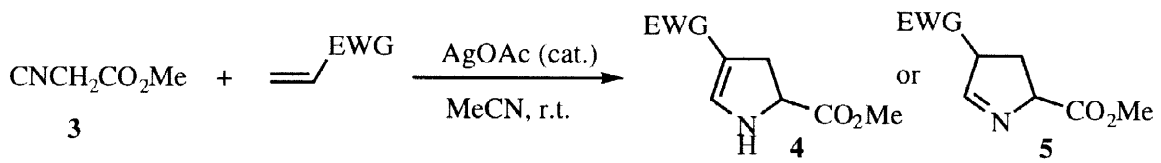
RESULTS AND DISCUSSION

Reaction with Olefins

Silver acetate was found to be an efficient catalyst for the cycloaddition of methyl isocyanoacetate **3** with a range of olefins (1.1 - 3 mole equivalents) bearing conjugated activating groups (Scheme 1). The reactions proceed smoothly at ambient temperature with 0.2 - 2 mol% catalyst to give, depending on the nature of the olefin, either Δ^2-pyrroline **4**, or Δ^1-pyrroline **5** cycloadducts in good yields (Tables 1 and 2). Addition of a tertiary amine base is not required. No reaction is observed either in the absence of catalyst or on attempted catalysis by acetic acid. Silver acetate appears to be the catalyst of choice, with the nature of the counter-ion playing a significant role. Use of silver triflate as the catalyst, either alone or even in combination with triethylamine, leads to a marked increase in reaction time.



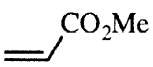
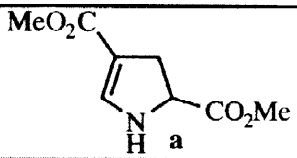
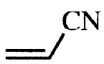
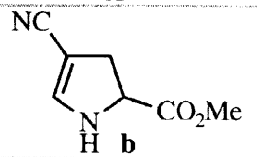
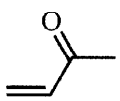
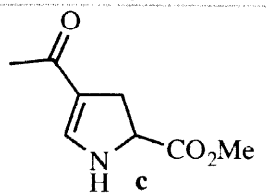
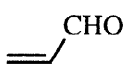
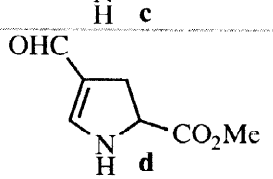
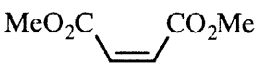
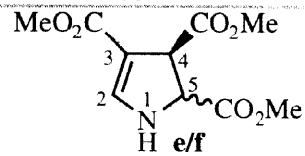
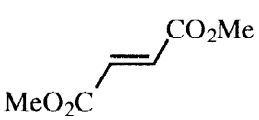
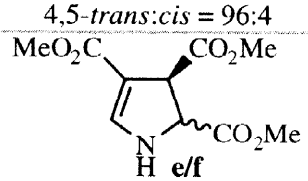
Scheme 1

In the reaction with acyclic olefins bearing a proton geminal to the electron withdrawing group (EWG) rapid tautomerism of the initially formed Δ^1-pyrrolines (which could not be detected) affords the thermodynamically more stable Δ^2-pyrrolines (Table 1). Δ^1-Pyrrolines may be obtained in cases in which such tautomerism is either prevented due to formation of a fused ring system, or is rendered impossible due to lack of the requisite geminal proton (Table 2).

Assignments of relative stereochemistry for cycloadducts **4e/4f** were made based on the H-4/H-5 coupling constants and in accordance with literature precedent.[16] Similar assignments for **5a/5b** were confirmed by NOE experiments which showed a 23% enhancement at H-5 on irradiation of H-4 for *cis*-**5b** compared to a corresponding enhancement of 6% for *trans*-**5a**. Interestingly, H-3/H-5 coupling was observed for both **5a** and **5b** (^5J = 2.5 Hz and 1.4 Hz respectively). The stereochemistry of cycloadducts **5c/5d** was determined by single crystal X-ray analysis (see Experimental).

The good yield of pyrroline cycloadduct obtained in the reaction with acrolein (entry 4, Table 1) is particularly notable in the light of reports that use of stoichiometric sodium hydride[7] or zinc chloride[17] causes

Table 1. Synthesis of Δ^2-Pyrrolines[a]

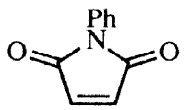
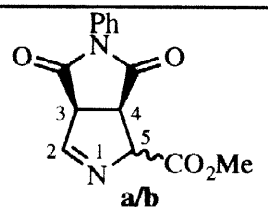
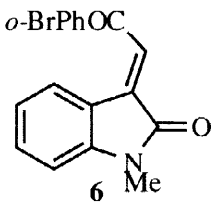
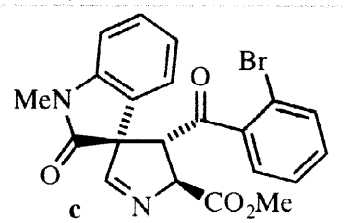
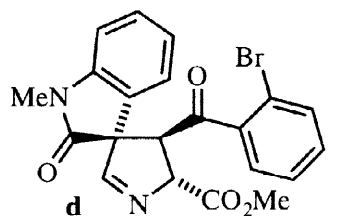
Entry	Isocyanide concentration	Olefin	AgOAc mol% [b]	Time (h)	Yield (%)	Product [c] **4**
1	0.15 M		1	2	67	 **a**
2	0.15 M		1	1	72	 **b**
3	0.15 M		1	1	82	 **c**
4	0.15 M		0.2	4	73	 **d**
5	1.1 M		2	1.5	65	 **e/f** 4,5-*trans*:*cis* = 96:4
6	1.1 M		2	0.5	88	 **e/f** 4,5-*trans*:*cis* = 62:38

(a) Reactions carried out in MeCN at 20-22 °C in the dark and under an atmosphere of argon. (b) Based on isocyanide. (c) Stereoisomer ratios determined from ^{1}H NMR spectrum of the crude reaction mixture.

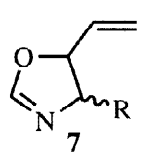
analogous isocyanides to undergo cycloadditions exclusively to the carbonyl group, thus forming oxazolines **7**. Use of catalytic Au(I),[18] $AgClO_4$,[4c] or Cu_2O[19] in the reaction of isocyanoacetates with substituted α,β-unsaturated aldehydes also gives rise to oxazolines as the only reported products. The chemoselectivity for addition to the olefinic double bond observed in the silver acetate catalysed reaction was found to be enhanced by increased dilution of the reaction medium and decreased catalyst loading. The factors dictating this selectivity, however, remain unclear at present.

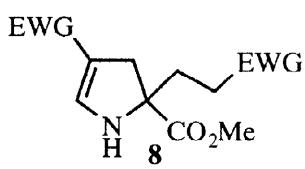
Reactions with other mono-substituted olefins (entries 1-3, Table 1) were also run under moderately dilute conditions, but in these cases to prevent formation of significant quantities of C-5 disubstituted cycloadducts **8**, which result from a conjugate addition to a second molecule of olefin. That the additional side-

Table 2. Synthesis of Δ^1-Pyrrolines.[a]

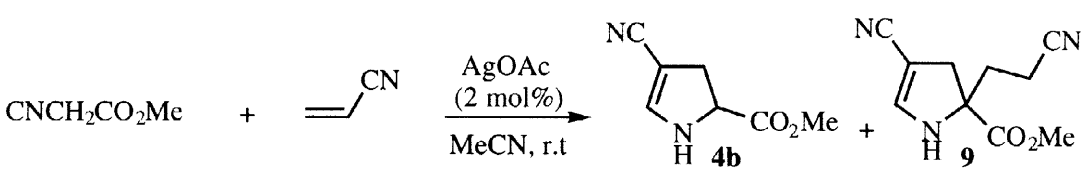
Entry	Olefin	AgOAc mol% [b]	Time (h)	Yield (%)	Product [c] **5**
1		2	3	88	 **a/b** 4,5-*trans*:*cis* = 64:36
2	 **6**	2	0.5	85	 **c**  **d** **c:d** = 83:17

(a) Reactions carried out in MeCN in the dark at 20-22 °C and under an atmosphere of argon. (b) Based on isocyanide. (c) Stereoisomer ratios determined from ^{1}H NMR spectrum of the crude reaction mixture.


7


8

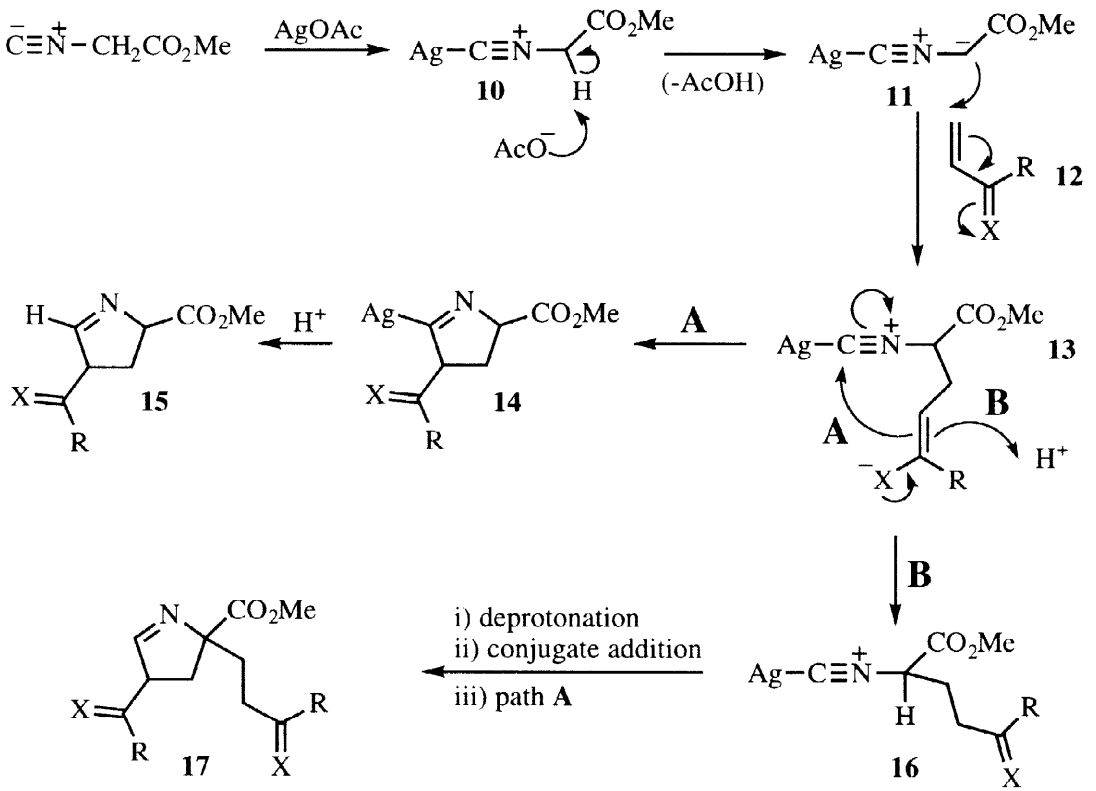
chain was being incorporated by alkylation of the isocyanide prior to cycloaddition, and not by alkylation of the cycloadduct, was demonstrated by the observation that suppression of this alkylation is independent of the olefin concentration (Scheme 2). Importantly, in the case of the reaction run at 0.055 M no further formation of **9** was observed either on extended reaction time (14 h) or on subsequent treatment with an additional 20 mol% AgOAc.



1.1 M	1.65 M	15 min	56%	14%
0.055 M	1.65 M	40 min	71%	trace

Scheme 2

These results are most readily explained by a step-wise, rather than concerted, mechanism (Scheme 3). α-Deprotonation of metallated isocyanide **10** by the acetate anion generates the nucleophile **11** which undergoes conjugate addition to the Michael acceptor **12** to give an enolate-like species **13**. This intermediate may suffer either of two fates. Ring closure (path **A**) followed by protonation of the resultant C-2 metallated pyrroline gives the expected 1:1 addition product **15**. Direct protonation (path **B**), on the other hand, generates an alkylated isocyanide **16**. A second deprotonation and conjugate addition sequence, this time proceeding via path **A**, would afford the alkylated cycloadduct **17**. Dilution of the reaction medium helps to favour path **A**, an intramolecular process, over path **B**, an intermolecular process. It should be noted that although AcO^-/AcOH must perform the initial deprotonation/protonation sequence, the product pyrroline may itself subsequently function as a base in this process. Depiction of the silver-coordinated isocyanide as structure **10** is a simplification since it is likely that the silver will bear further coordinated isocyanide ligands.[4a]



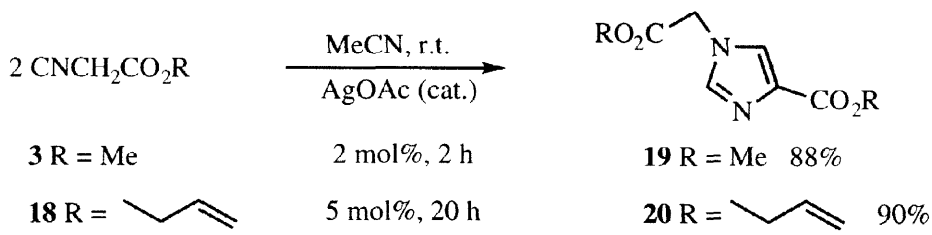
Scheme 3

The stepwise mechanism of the cycloaddition was confirmed by investigation of the reaction (entry 2, Table 2) of methyl isocyanoacetate with trisubstituted olefin **6**, obtained from *N*-methyl isatin by the general procedure of Lindwall and Maclennan.[20] The major stereoisomer **5c** has maintained the *trans* relationship of the amide and ketone carbonyl groups present in the olefin. In the minor isomer **5d**, however, these groups have a *cis* orientation, indicating that rotation has occurred about the original carbon-carbon double bond during the cycloaddition. Both isomers display a *trans* relationship at C-4/C-5. The olefin and both the products were found to maintain their stereochemical integrity under the reaction conditions. Thus, importantly, no *E*/*Z*-isomerisation of **6** takes place over the course of the reaction, and the cycloadducts **5c** and **5d** are not

interconverted. Consequently, the rotation about the original olefinic double bond of **6** that leads to **5d** must occur in an intermediate species generated by a stepwise mechanism (e.g. see intermediate **13**, Scheme 3).

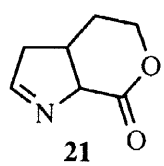
Isocyanoacetate Cyclodimerisation

It was observed that, in the absence of a suitable olefin, isocyanoacetates readily undergo cyclodimerisation on treatment with catalytic silver acetate to give imidazoles in excellent yield (Scheme 4). The base-induced decomposition of TosMIC has been previously observed to afford an analogous imidazole, albeit in low yield, resulting from cyclodimerisation.[8c] Similarly to the reaction with olefins, a marked difference in the efficiency of silver triflate and silver acetate as a catalyst for the cyclodimerisation was observed. In the presence of 10 mol% AgOTf/20 mol% Et_3N, under otherwise identical conditions, cyclodimerisation of **3** was still incomplete after 96 h.



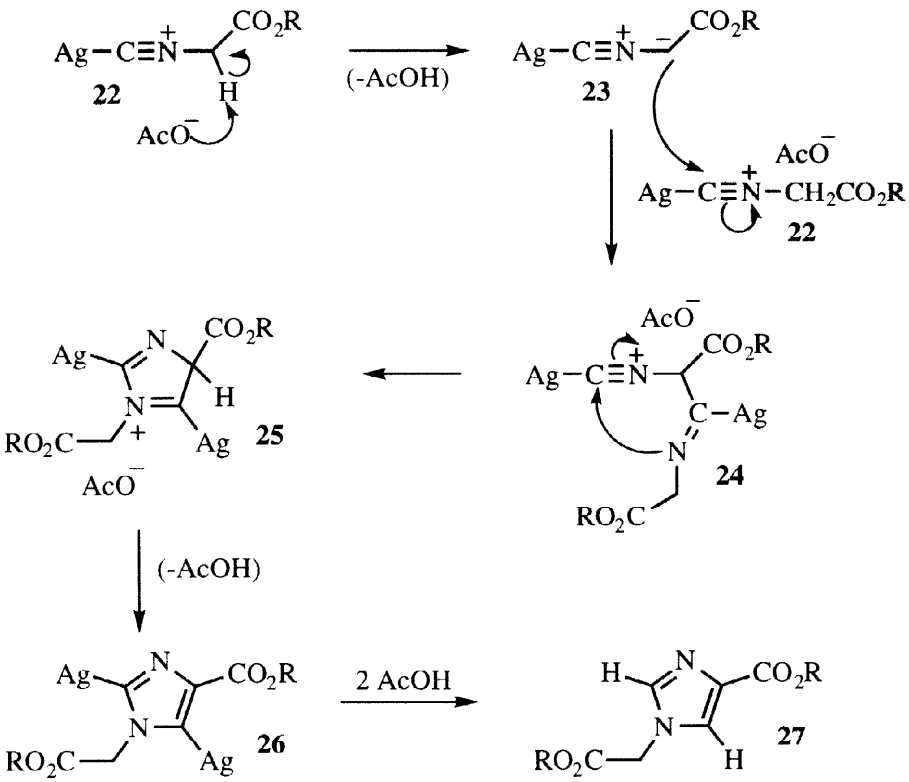
Scheme 4

At 0.05 M isocyanoacetate **18** underwent clean cyclodimerisation without any addition to the olefinic bond being detected, as would be expected if pyrroline formation requires a stepwise conjugate-addition/cyclisation sequence. Even at 0.01 M only starting material and imidazole **20** were present after 24 h. Potential product pyrroline **21**, the result of an intramolecular cyclisation, could not be detected.



21

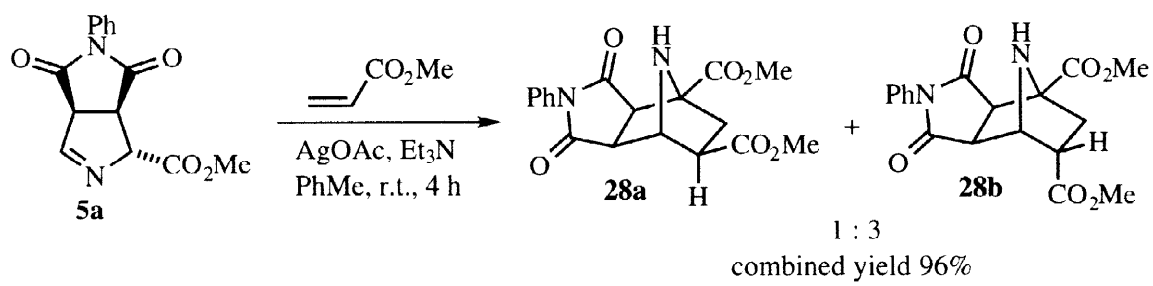
Initial trial experiments utilising stoichiometric quantities of silver acetate in the attempted cycloaddition of methyl isocyanoacetate with methyl acrylate led to predominant cyclodimerisation of the isocyanide, whereas in the presence of a catalytic quantity of silver acetate pyrroline formation takes place smoothly (Table 1). This strongly suggests that each of the isocyanide molecules participating in the dimerisation is coordinated to a silver cation, such coordination serving to activate the isocyano group to nucleophilic attack (Scheme 5). The resulting intermediate **24** undergoes ring closure followed by aromatisation and double protonation to give the product imidazole **27**.



Scheme 5

Synthesis of 7-Azabicyclo[2.2.1]heptanes

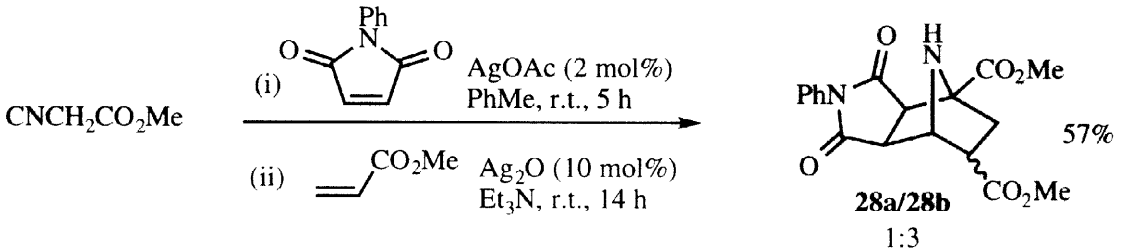
Participation of Δ^1-pyrroline **5a** in a 1,3-dipolar cycloaddition with methyl acrylate, *via* metallo-azomethine ylide formation,[15] leads to an efficient synthesis of the 7-azabicyclo[2.2.1]heptane framework[21] (Scheme 6). This provides an unusual example of a metallo-azomethine ylide undergoing an *exo*-selective 1,3-dipolar cycloaddition (a potential nomenclature trap arises here - the *exo* transition state of the cycloaddition leads to a cycloadduct in which the -CO_2Me group derived from methyl acrylate occupies an *endo*-position on the 7-azabicyclo[2.2.1]heptane).



Scheme 6

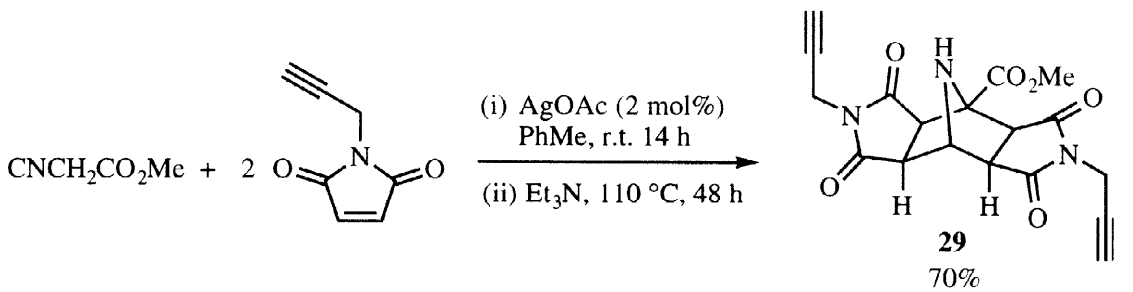
The compatibility of the metallo-azomethine ylide cycloaddition reaction conditions with those of the isocyanoacetate cycloaddition has allowed the development of a one-pot sequential cascade process. Thus, the mixture of *trans/cis* pyrrolines **4a/4b,** obtained from methyl isocyanoacetate and *N*-phenyl maleimide, may be

reacted *in situ* using our recently developed catalytic silver(I) oxide conditions for metallo-azomethine ylide generation[22] to afford the same 1:3 mixture of cycloadducts **28a** and **28b** in moderate yield (Scheme 7).



Scheme 7

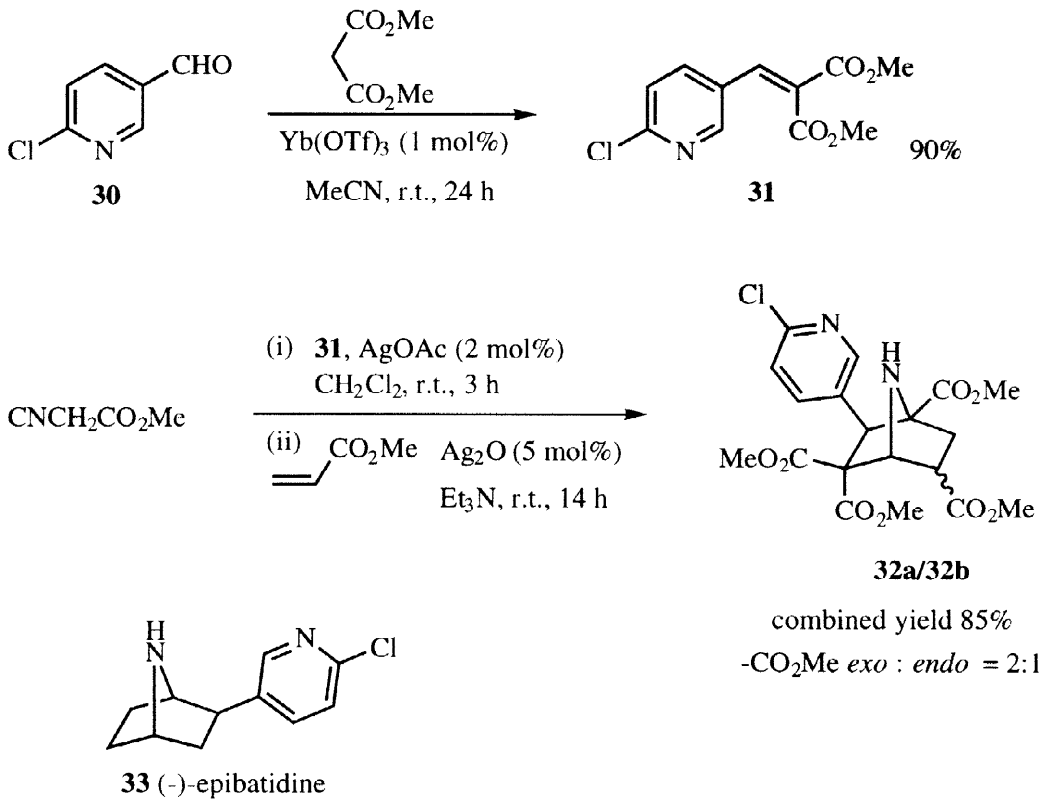
Alternatively, azomethine ylide generation may be also be achieved *via* thermal 1,2-prototropy.[15a] Thus, reaction of methyl isocyanoacetate with 2 equivalents of *N*-propargyl maleimide[23] in the presence of 2 mol% silver acetate, initially at room temperature, leads to formation of a Δ^1-pyrroline, which, without isolation, then undergoes reaction with the second equivalent of *N*-propargyl maleimide on heating to reflux (Scheme 8). The addition of triethylamine serves to catalyse the 1,2-prototropy. This one-pot process furnishes **29** as a single stereoisomer in good yield.



Scheme 8

Application of the one-pot tandem cycloaddition process to olefin **31** (Scheme 9) generates in excellent yield cycloadducts **32a/32b**, which are structurally related to the dendrobatid alkaloid epibatidine **33**, a potent analgesic.[21,24] In contrast to the reaction leading to **28a/28b**, the 1,3-dipolar cycloaddition of the intermediate pyrroline proceeds *via* an *endo*-selective transition state. Notably, stereospecific *exo*-orientation of the chloropyridyl moiety is accomplished, as confirmed by NOE experiments which showed a 17% enhancement at H-2 on irradiation of H-6_{endo} for both **32a** and **32b**. Olefin **31** was efficiently obtained by ytterbium(III) triflate catalysed condensation of aldehyde **30**[25] with dimethyl malonate. To the best of our knowledge this constitutes the first example of the use of rare earth triflate catalysis in a Knoevenagel condensation.[26]

In summary, the silver acetate catalysed cycloaddition of methyl isocyanoacetate with Michael-acceptors provides a mild, efficient, and rapid entry to Δ^1- and Δ^2-pyrrolines. Corresponding azomethine ylides may be generated from the Δ^1-pyrrolines either by heating or on treatment with Ag(I) and triethylamine at room temperature, allowing a one-pot cascade synthesis of functionalised 7-azabicyclo[2.2.1]heptanes.



Scheme 9

EXPERIMENTAL

General: Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were performed using a Carlo Erba MOD 1106 instrument. Mass spectra were recorded on a V.G.-AutoSpec instrument operating at 70 eV and accurate molecular weights were determined using perfluorokerosine as an internal standard. Nuclear magnetic resonance spectra, which are quoted at 300 MHz unless otherwise stated, were recorded at 300 MHz on a General Electric QE300 instrument and at 400 MHz on a Bruker WP400 instrument. Deuteriochloroform was used as the solvent unless otherwise stated and chemical shifts are given in parts per million (δ) referenced to tetramethylsilane or residual protonated solvent. The term ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40-60 °C. Flash column chromatography employed silica gel 60 (Merck 230-400). Methyl isocyanoacetate was obtained from Aldrich Chemical Co. as a dark red oil of 95+% purity. It may be readily purified to a colourless oil by elution (1:1 v/v ether-petroleum ether) through a short pad of silica gel (although material obtained in this way still discolours slowly on storage under argon at 4 °C). However, all reactions reported here were performed using the methyl isocyanoacetate as received and quantities were calculated assuming 100% purity. Acetonitrile was distilled from phosphorous pentoxide and then potassium carbonate. Toluene, dichloromethane, and triethylamine were distilled from calcium hydride. All other commercially available reagents were used as received. All reactions involving silver(I) salts were carried out in the dark.

General Procedure for the Synthesis of Pyrrolines.

Methyl isocyanoacetate was added dropwise over 5 min to a stirred mixture of silver acetate and the appropriate olefin in acetonitrile under argon at room temperature (20 - 22 °C). The resulting solution was stirred until completion of reaction (TLC or NMR monitoring). The reaction mixture was then concentrated *in vacuo* and the residue purified by flash column chromatography.

(±)-Dimethyl 2,3-dihydro-1*H*-pyrrole-2,4-dicarboxylate (4a).

Obtained from methyl isocyanoacetate (0.20 ml, 2.2 mmol), methyl acrylate (0.59 ml, 6.6 mmol), and silver acetate (3.7 mg, 0.022 mmol) in acetonitrile (15 ml). Flash column chromatography (4:1 v/v ether:petroleum ether) afforded the ***product*** (0.272 g, 67%) as a colourless oil. δ (^{1}H): 7.22 (s, br, 1H, C=CH), 4.70 (s, br, 1H, NH), 4.43 (dd, 1H J 6.4 and 11.5 Hz, C<u>H</u>CO$_2$Me), 3.77 (s, 3H, OMe), 3.67 (s, 3H, OMe), and 3.13-2.95 (m, 2H, CH$_2$). m/z (%): 185 (M$^+$, 20), 154 (22), 126 (100), 99 (10), 94 (68), 82 (36), 71 (9), 67 (63), 59 (47), 55 (21), and 39 (51). Found: C, 51.6; H, 6.0; N, 7.6. $C_8H_{11}NO_4$ requires: C, 51.9; H, 6.0; N, 7.55 %.

(±)-Methyl 4-cyano-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4b).

Obtained from methyl isocyanoacetate (0.20 ml, 2.2 mmol), acrylonitrile (0.43 ml, 6.5 mmol), and silver acetate (3.7 mg, 0.022 mmol) in acetonitrile (15 ml). Flash column chromatography (4:1 v/v ether:petroleum ether) afforded the ***product*** (0.240 g, 72%) as a colourless oil. δ (^{1}H): 7.03 (s, br, 1H, C=CH), 5.01 (s, br, 1H, NH), 4.45 (dd, 1H, J 6.63 and 11.9 Hz, C<u>H</u>CO$_2$Me), 3.79 (s, 3H, OMe), and 3.14-2.95 (m, 2H, CH$_2$). m/z (%): 152 (M$^+$, 21), 93 (100), 66 (20), and 39 (6). Found: C, 55.05; H, 5.1; N, 18.6. $C_7H_8N_2O_2$ requires: C, 55.25; H, 5.3; N, 18.4 %.

(±)-Methyl 4-acetyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4c).

Obtained from methyl isocyanoacetate (0.20 ml, 2.2 mmol), methyl vinyl ketone (0.54 ml, 6.6 mmol), and silver acetate (3.7 mg, 0.022 mmol) in acetonitrile (15 ml). Evaporation of solvent was performed at < 25°C. Flash column chromatography (ethyl acetate) afforded the ***product*** (0.305 g, 82%) as a colourless powder which precipitated from ether-petroleum ether as an amorphous solid (accompanied by severe discoloration). δ (^{1}H): 7.31 (s, br, 1H, C=CH), 5.63 (s, br, 1H, NH), 4.50 (dd, 1H, J 6.5 and 12.2 Hz, C<u>H</u>CO$_2$Me), 3.76 (s, 3H, OMe), 4.14-2.96 (m, 2H, CH$_2$), and 2.17 (s, 3H, COMe). m/z (%): 169 (M$^+$, 29), 120 (8), 110 (40), 94 (25), 91 (11), 77 (20), 68 (52), 51 (18), and 43 (100). Found: C, 56.75; H, 6.4; N, 8.4. $C_8H_{11}NO_3$ requires: C, 56.8; H, 6.55; N, 8.3 %.

(±)-Methyl 4-formyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4d).

Obtained from methyl isocyanoacetate (0.60 ml, 6.6 mmol), acrolein (1.31 ml, 19.7 mmol), and silver acetate (2.2 mg, 0.013 mmol) in acetonitrile (45 ml). Evaporation of solvent was performed at < 30°C. Flash column chromatography (ethyl acetate) afforded the ***product*** (0.744 g, 73%) as a colourless oil which rapidly discoloured to dark yellow-orange. δ (^{1}H): 9.21 (s, 1H, CHO), 7.35 (s, 1H, C=CH), 6.94 (s, br, 1H, NH), 4.62 (dd, 1H, J 6.6 and 12.4 Hz, C<u>H</u>CO$_2$Me), 3.77 (s, 3H, OMe), and 3.16-2.94 (m, 2H, CH$_2$). m/z (%): 155 (M$^+$, 27), 96 (32), 68 (100), and 41 (41). Found (HRMS): 155.0578. $C_7H_9NO_3$ requires: 155.0582.

(±)-*trans*-Trimethyl 2,3-dihydro-1*H*-pyrrole-2,3,4-tricarboxylate (4e) and (±)-*cis*-trimethyl 2,3-dihydro-1*H*-pyrrole-2,3,4-tricarboxylate (4f).

Obtained from methyl isocyanoacetate (0.20ml, 2.2 mmol), dimethyl fumarate (0.476 g, 3.3 mmol), and silver acetate (7.4 mg, 0.044 mmol) in acetonitrile (2 ml). Purification by flash column chromatography (3:2 to 4:1 v/v ethyl acetate:petroleum ether gradient elution) gave an inseparable mixture of the stereoisomeric ***products*** (0.470 g, 88%) as a colourless viscous oil.

Pyrrolines **(4e)** and **(4f)** were also obtained from methyl isocyanoacetate (0.20 ml, 2.2 mmol), dimethyl maleate (0.41 ml, 3.3 mmol) and silver acetate (7.4 mg, 0.044 mmol) in acetonitrile (2 ml). Purification by flash column chromatography (3:2 to 4:1 v/v ethyl acetate:petroleum ether gradient elution) afforded an inseparable mixture of the stereoisomeric ***products*** (0.340 g, 65%) as a colourless viscous oil. m/z (%) (as mixed isomers): 243 (M^+, 13), 212 (11), 184 (92), 152 (64), 140 (58), 125 (16), 108 (20), 94 (100), 81 (28), 66 (14), 59 (58), 53 (9), and 39 (27). Found (as mixed isomers): C, 49.1; H, 5.55; N, 5.45. $C_{10}H_{13}NO_6$ requires: C, 49.4; H, 5.4; N, 5.75 %.

***trans*-Pyrroline (4e)** δ (^{1}H): 7.33 (s, br, 1H, C=CH), 4.99 (s, br, 1H, NH), 4.68 (d, 1H, J 5.1 Hz, NC<u>H</u>CO_2Me), 4.16 (d, 1H, J 5.1 Hz, C<u>H</u>CO_2Me), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), and 3.68 (s, 3H, OMe).

***cis*-Pyrroline (4f)** δ (^{1}H): 7.38 (s, br, 1H, C=CH), 5.14 (s, br, 1H, NH), 4.79 (d, 1H, J 12.4 Hz, NC<u>H</u>CO_2Me), 4.28 (d, 1H, J 12.4 Hz, C<u>H</u>CO_2Me), 3.74 (s, 3H, OMe), 3.71 (s, 3H, OMe), and 3.66 (s, 3H, OMe).

(±)-*trans*-Methyl 4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-1-carboxylate (5a) and (±)-*cis*-methyl 4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-1-carboxylate (5b).

Obtained from methyl isocyanoacetate (0.20 ml, 2.2 mmol), *N*-phenyl maleimide (0.588 g, 3.3 mmol), and silver acetate (7.4 mg, 0.044 mmol) in acetonitrile (15 ml). Purification by flash column chromatography (ether to 1:1 v/v ether:ethyl acetate gradient elution) afforded first **(5a)** (0.324 g, 54%) as an off-white solid, followed by **(5b)** (0.204 g, 34%) as an off-white solid. Pyrroline **(5a)** precipitated from ethyl acetate as a colourless amorphous solid, m.p. 173-175 °C. Pyrroline **(5b)** precipitated from dichloromethane-petroleum ether as a colourless amorphous solid, m.p. 79-81 °C.

***trans*-Pyrroline (5a)** δ (^{1}H, 400 MHz): 7.76 (dd, 1H, J 1.2 and 2.5 Hz, N=CH), 7.47-7.37 (m, 3H, ArH), 7.23-7.20 (m, 2H, ArH), 5.31 (q, 1H, J 2.5 Hz, C<u>H</u>CO_2Me), 4.40 (ddd, 1H, J 1.2, 2.5, and 8.3 Hz, N=CHC<u>H</u>), 4.01 (dd, 1H, J 2.5 and 8.4 Hz, C<u>H</u>CHCO_2Me), and 3.83 (s, 3H, OMe). m/z (%): 272 (M^+, 100), 213 (14), 174 (13), 153 (12), 125 (16), 119 (45), 94 (61), and 40 (21). Found: C, 61.65; H, 4.5; N, 10.2. $C_{14}H_{12}N_2O_4$ requires: C, 61.75; H, 4.45; N, 10.3 %.

***cis*-Pyrroline (5b)** δ (^{1}H, 400 MHz): 7.87 (dd, 1H J 1.4 Hz, N=CH), 7.49-7.39 (m, 3H, ArH), 7.26-7.23 (m, 2H, ArH), 5.29 (ddd, 1H, J 1.4, 2.4, and 9.8 Hz, C<u>H</u>CO_2Me), 4.39 (dt, 1H, J 1.4 and 8.9 Hz, N=CHC<u>H</u>), and 3.86 (dd, 1H, J 8.9 and 9.8 Hz, C<u>H</u>CHCO_2Me) and 3.79 (s, 3H, OMe). m/z (%): 272 (M^+, 100), 213 (7), 153 (31), 125 (50), 119 (48), and 94 (77). Found C, 62.0; H, 4.4; N, 10.1. $C_{14}H_{12}N_2O_4$ requires C, 61.75; H, 4.45; N, 10.3 %.

3-[2-(2-Bromophenyl)-2-oxoethylidine]-1-methyl-1,3-dihydroindole-2-one (6).

A mixture of *N*-methylisatin (2.50 g, 15.5 mmol), 2'-bromoacetophenone (2.10 ml, 15.6 mmol) and diethylamine (5 drops) in ethanol (50 ml) was stirred at room temperature for 24 h. The mixture was concentrated *in vacuo* to approximately half volume and the precipitate was collected by filtration to give the tertiary alcohol as a pale yellow solid (4.09 g, 73%), m.p. 142-143 °C, which was used directly without further purification. δ (^{1}H): 7.53 (d, 1H, J 7.3 Hz, ArH), 7.42 (d, 1H, J 7.3 Hz, ArH), 7.27 (m, 4H, ArH), 7.05 (t, 1H, J 7.5 Hz, ArH), 6.83 (d, 1H, J 7.8 Hz, ArH), 4.80 (s, br, 1H, OH), 3.78 (d, 1H, J 16.9 Hz), CH<u>H</u>), 3.58 (d, 1H, J 16.9 Hz, CH<u>H</u>), and 3.18 (s, 3H, NMe). m/z (%): 361 (M^+, 3), 359 (3), 343 (13), 341 (13), 262 (67), 234 (85), 219 (11), 200 (19), 198 (19), 185 (97), 183 (100), 161 (55), 133 (29), 104 (76), 89 (21), 76 (52), 63 (30), and 50 (58).

The alcohol (4.09 g) was added to a mixture of ethanol (10 ml) and concentrated hydrochloric acid (20 ml) and stirred at room temperature for 48 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was purified by flash column chromatography (1:1 v/v ether:petroleum ether) to give the ***product*** as a deep red solid (3.25 g, 61% from *N*-methylisatin) which crystallised from ether-petroleum ether as deep red needles, m.p. 113-114 °C. δ (^{1}H, 400 MHz): 8.60 (d, 1H, J 7.7 Hz, ArH), 7. 65 (m, 3H, ArH and C=CH), 7.40 (m, 3H, ArH), 7.08 (t, 1H, J 7.7 Hz, ArH), 6.82 (d, 1H, J 7.8 Hz, ArH), and 3.26 (s, 3H, NMe). m/z (%): 343 (M^+, 16), 341 (16), 262 (98), 234 (100), 219 (14), 186 (21), 158 (12), 130 (12), 117 (23), and 89 (17). Found: C, 59.75; H, 3.6; N, 4.0; Br, 23.5. $C_{17}H_{12}NO_2Br$ requires: C, 59.65; H, 3.55; N, 4.1; Br, 23.35 %.

(±)-Methyl 4'-(2-bromobenzyl)-1-methyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-pyrrole]-5'-carboxylates (5c) and (5d).

Obtained from methyl isocyanoacetate (0.10 ml, 1.1 mmol), 3-[2-(2-bromophenyl)-2-oxoethylidine]-1-methyl-1,3-dihydroindole-2-one **(6)** (0.414 g, 1.2 mmol), and silver acetate (3.7 mg, 0.022 mmol) in acetonitrile (2 ml). Purification by flash column chromatography (85:12:3 v/v/v ether:petroleum ether:triethylamine to 97:3 v/v ether:triethylamine gradient elution) afforded a poorly separable mixture of the stereoisomeric ***products*** as an off-white solid (0.413g, 85%). Repeated flash column chromatography (98:2 v/v ether:triethylamine) allowed samples of the separated isomers to be obtained. Pyrroline **(5d)** (minor isomer, faster elution) crystallised from ether-petroleum ether as colourless plates, m.p. 164-166 °C. Pyrroline **(5c)** (major isomer, slower elution) crystallised from ether as colourless prisms, m.p. 168-170 °C. Found (as mixed isomers): C, 57.3; H, 3.95; N, 6.5; Br, 17.8. $C_{21}H_{17}N_2O_4Br$ requires: C, 57.15; H, 3.9; N, 6.35; Br, 18.1 %.

Pyrroline (5c) δ (^{1}H): 7.41-6.84 (m, 8H, ArH and N=CH), 6.57 (d, 1H, J 7.9 Hz, ArH), 5.75 (dd, 1H, J 3.0 and 8.7 Hz, C<u>H</u>CO_2Me), 5.15 (d, 1H, J 8.7 Hz, C<u>H</u>COAr), 3.90 (s, 3H, OMe), and 2.88 (s, 3H, NMe). m/z (%): 442 (M^+, 8), 440 (8), 344 (12), 257 (100), 230 (90), 185 (59), 183 (60), 170 (27), 157 (24), 155 (25), 143 (9), 115 (14), and 76 (15).

Pyrroline (5d) δ (^{1}H): 7.38-6.97 (m, 8H, ArH and N=CH), 6.57 (d, 1H, J 7.8 Hz, ArH), 5.71 (dd, 1H, J 3.3 and 8.2 Hz, C<u>H</u>CO_2Me), 4.96 (d, 1H, J 8.2 Hz, C<u>H</u>COAr), 3.87 (s, 3H, OMe), and 2.89 (s, 3H, NMe). m/z (%): 442 (M^+, 13), 440 (13), 344 (13), 342 (12), 257 (70), 230 (100), 185 (84), 183 (84), 170 (50), 157 (46), 155 (50), 143 (18), 115 (28), and 76 (35).

Single crystal X-ray diffraction analysis of **5c** *and* **5d** - Crystallographic data for **5c** were measured on a Stoe STADI4 4-circle diffractometer using ω-θ scans whilst data for **5d** were collected on a Nonius KappaCCD area-detector diffractometer using 1° ϕ-slices. Both structures were solved by direct methods using SHELXS-86[27] and were refined by full-matrix least-squares (based on F^2) using SHELXL-93.[28] The weighting scheme used in both refinements was $w = [\sigma^2(F_O^2) + (xP)^2 + yP]^{-1}$ where $P = (F_O^2 + 2F_C^2)/3$. In both cases all non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. Both refinements included an isotropic extinction parameter, x, so that $F_C^* = kF_C[1+0.001*x*F_C^2*\lambda^3]^{-1/4}$ where k is the overall scale factor. The residuals wR_2 and R_1, given below, are defined as $wR_2=(\Sigma[w(F_O-F_C^2)^2] / \Sigma[wF_O^4])^{1/2}$ and $R_1=\Sigma||F_O|-|F_C|| / \Sigma|F_O|$.

Crystal data for **5c** - $C_{21}H_{17}BrN_2O_4$, 0.63 x 0.55 x 0.42 mm, M = 441.28, triclinic, space group P-1, a = 7.5655(5), b = 10.7960(8), c = 12.2563(10) Å, α = 84.115(7)°, β = 78.075(8)°, γ = 70.921(8)°, U = 924.99(12) Å^3, Z = 2, D_C = 1.58 Mg m^{-3}, μ = 3.30 mm^{-1}, F(000) = 448, T = 150K.

Data collection - Graphite monochromated Cu-$K\alpha$ radiation, λ = 1.54184 Å, scan speeds 1.5 - 8.0° min^{-1}, ω scan widths 1.05° + α-doublet splitting, 4.0 < 2θ < 130.0°, 3488 Data collected 2874 of which were unique, R_{int}=0.0445, R_{sig} = 0.0102. There were 2861 reflections with $F_O > 4.0\ \sigma(F_O)$.

Structure refinement - Number of parameters = 256, isotropic extinction parameter, x = 0.0082(7), goodness of fit, s = 1.105; weighting parameters x, y = 0.0662, 1.7866; $wR2$ = 0.1174, $R1$ = 0.0411.

Crystal data for **5d** - $C_{21}H_{17}BrN_2O_4$, 0.42 x 0.28 x 0.20 mm, M = 441.28, monoclinic, space group $P2_1/n$, a = 7.6979(2), b = 36.0202(10), c = 13.7133(4) Å, β = 91.5070(14)°, U = 3801.1(2) Å^3, Z = 8, D_C = 1.54 Mg m^{-3}, μ = 2.193 mm^{-1}, F(000) = 1792, T = 190 K.

Data collection - Graphite monochromated Mo-$K\alpha$ radiation, λ = 0.71074 Å. The detector was positioned with a 36° offset in 2θ and a full 360° rotation of 1.0° ϕ-slices were measured at χ=0°. 'Cusp' data was measured at χ=90° and comprised 1° omega-slices over 55°. 6.0 < 2θ < 60.0°. 37229 Data measured, 10644 unique, R_{int}=0.0363, R_{sig} = 0.0981, 5692 reflections with $F_O > 4.0\ \sigma(F_O)$.

Structure refinement - Number of parameters = 510, goodness of fit, s = 0.901; weighting parameters x, y = 0.0713, 0.0000; $wR2$ = 0.1451, $R1$ = 0.0544.

Selected bond lengths and angles for **5c** and **5d** are listed in Tables 3 and 4 respectively. Supplementary data-sets for both structures, which include hydrogen co-ordinates, all thermal parameters and complete sets of bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

Table 3. Interatomic distances (Å) and angles between interatomic vectors (°) for **5c** with e.s.d.s in parentheses.

C(1)-C(2)	1.370(5)	C(1)-C(6)	1.395(5)
C(1)-C(9)	1.514(4)	C(2)-C(3)	1.401(5)
C(3)-C(4)	1.380(5)	C(4)-C(5)	1.395(5)
C(5)-C(6)	1.378(5)	C(6)-N(7)	1.411(4)
N(7)-C(8)	1.358(4)	N(7)-C(71)	1.458(4)
C(8)-O(81)	1.223(4)	C(8)-C(9)	1.535(4)
C(9)-C(10)	1.513(5)	C(9)-C(13)	1.567(4)
C(10)-N(11)	1.266(5)	N(11)-C(12)	1.472(4)
C(12)-C(22)	1.512(5)	C(12)-C(13)	1.546(5)
C(13)-C(14)	1.521(5)	O(141)-C(14)	1.203(4)

C(14)-C(15)	1.506(5)	C(15)-C(16)	1.395(5)
C(15)-C(20)	1.399(5)	C(16)-C(17)	1.391(5)
C(17)-C(18)	1.382(5)	C(18)-C(19)	1.374(5)
C(19)-C(20)	1.391(5)	C(20)-Br(21)	1.897(3)
C(22)-O(221)	1.199(4)	C(22)-O(23)	1.331(4)
O(23)-C(24)	1.441(4)		

Table 4. Interatomic distances (Å) and angles between interatomic vectors (°) for **5d** with e.s.d.s in parentheses.

	Molecule 1		
C(1)-C(14)	1.518(4)	C(1)-C(2)	1.547(3)
C(1)-C(5)	1.561(3)	C(2)-N(3)	1.480(3)
C(2)-C(21)	1.506(4)	C(21)-O(21)	1.198(4)
C(21)-O(22)	1.334(4)	O(22)-C(22)	1.448(4)
N(3)-C(4)	1.264(3)	C(4)-C(5)	1.502(3)
C(5)-C(13)	1.522(3)	C(5)-C(6)	1.541(3)
C(6)-O(6)	1.212(3)	C(6)-N(7)	1.360(3)
N(7)-C(8)	1.404(3)	N(7)-C(7)	1.449(3)
C(8)-C(9)	1.383(4)	C(8)-C(13)	1.388(4)
C(9)-C(10)	1.384(4)	C(10)-C(11)	1.372(5)
C(11)-C(12)	1.390(4)	C(12)-C(13)	1.372(4)
O(14)-C(14)	1.216(3)	C(14)-C(15)	1.498(4)
C(15)-C(20)	1.393(4)	C(15)-C(16)	1.409(4)
C(16)-C(17)	1.410(5)	C(16)-Br(16)	1.890(4)
C(17)-C(18)	1.367(5)	C(18)-C(19)	1.371(5)
C(19)-C(20)	1.396(4)		
	Molecule 2		
C(1)-C(2)	1.531(3)	C(1)-C(14)	1.532(4)
C(1)-C(5)	1.558(4)	C(2)-N(3)	1.477(3)
C(2)-C(21)	1.512(4)	C(21)-O(21)	1.192(4)
C(21)-O(22)	1.312(3)	O(22)-C(22)	1.450(3)
N(3)-C(4)	1.270(3)	C(4)-C(5)	1.515(4)
C(5)-C(13)	1.499(4)	C(5)-C(6)	1.541(4)
C(6)-O(6)	1.212(3)	C(6)-N(7)	1.363(4)
N(7)-C(8)	1.402(4)	N(7)-C(7)	1.452(4)
C(8)-C(9)	1.377(4)	C(8)-C(13)	1.391(4)
C(9)-C(10)	1.387(5)	C(10)-C(11)	1.374(5)
C(11)-C(12)	1.386(4)	C(12)-C(13)	1.377(4)
O(14)-C(14)	1.209(3)	C(14)-C(15)	1.485(4)
C(15)-C(20)	1.394(4)	C(15)-C(16)	1.394(4)
C(16)-C(17)	1.382(5)	C(16)-Br(16)	1.897(3)
C(17)-C(18)	1.369(5)	C(18)-C(19)	1.372(5)
C(19)-C(20)	1.380(4)		

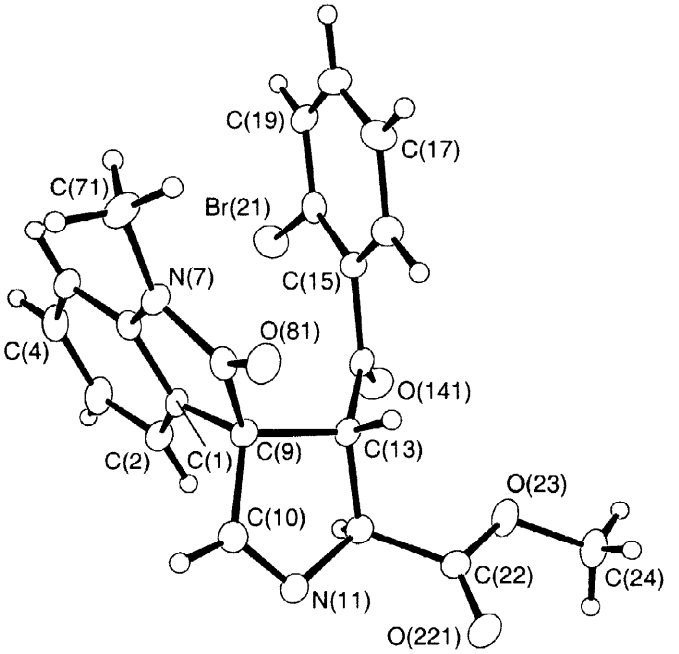


Figure 1. ORTEP[29] representation of the molecular structure of **5c.** Thermal ellipsoids are shown at the 40% probability level

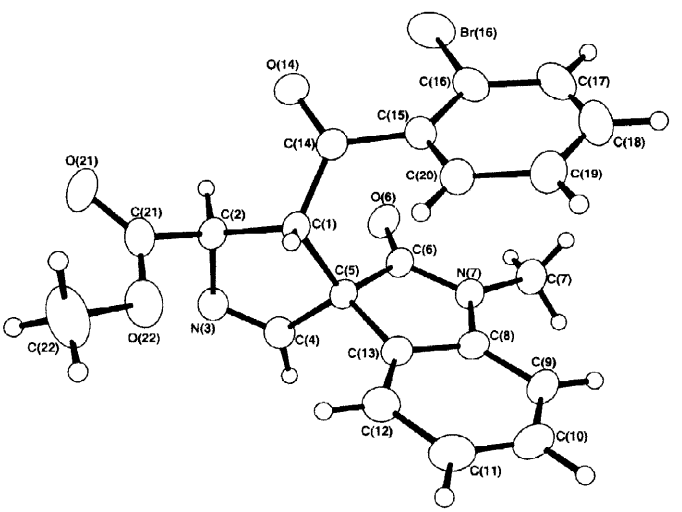


Figure 2. ORTEP[29] representation of the molecular structure of **5d**. Note that the structural asymmetric unit contains two molecules which differ only in the relative orientation of the 2-bromobenzoyl substituent. In the interests of brevity only one molecule is shown.

(±)-Methyl 4-cyano-2-(2-cyanoethyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (9).

Obtained from methyl isocyanoacetate (0.20 ml, 2.2 mmol), acrylonitrile (0.22 ml, 3.3 mmol), and silver acetate (7.4 mg, 0.044 mmol), in acetonitrile (2 ml). Purification by flash column chromatography (4:1 v/v ether:petroleum ether) afforded first (**4b**) (0.187 g, 56%) as a colourless oil, followed by the ***product*** (**9**) (0.064 g, 14%) as a colourless oil. δ (^{1}H): 6.95 (s, br, 1H, C=CH), 5.05 (s, br, 1H, NH), 3.83 (s, 3H, OMe), 3.23 (d, 1H, J 15.5 Hz, CHH), 2.74 (d, 1H, J 15.5 Hz, CHH), 2.42 (m, 2H, CH_2CN), and 2.18 (m, 2H, $NCCH_2$). m/z (%): 205 (M^+, 7), 146 (35), 105 (100), 92 (7), 80 (8), 59 (8), 55 (15), and 39 (10). Found (HRMS): 205.0854. $C_{10}H_{11}N_3O_2$ requires: 205.0851.

Methyl 1-methoxycarbonylmethyl-1*H*-imidazole-4-carboxylate (19).

Methyl isocyanoacetate (0.20 ml, 2.2 mmol) was added to a suspension of silver acetate (7.4 mg, 0.044 mmol) in acetonitrile (2 ml) under argon. The resulting solution was stirred at room temperature for 2 h and then quenched by addition of saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure the residue was purified by flash column chromatography (ethyl acetate) to give the ***product*** as a colourless solid (0.192 g, 88%) which crystallised from ethyl acetate as colourless plates, m.p. 142 -143 °C. δ (^{1}H): 7.67 (d, 1H, J 1.0 Hz, CH), 7.54 (d, 1H, J 1.0 Hz, CH), 4.78 (s, 2H, CH_2CO_2Me), 3.89 (s, 3H, OMe), and 3.80 (s, 3H, OMe). m/z (%): 198 (M^+, 30), 167 (100), 140 (55), 111 (110), 108 (11), 81 (11), 72, (9), 59 (15), 53 (31), and 45 (15). Found: C, 48.6; H, 5.2; N, 14.2. $C_8H_{10}N_2O_4$ requires: C, 48.5; H, 5.1; N, 14.15 %.

But-3-enyl isocyanoacetate (18).

Potassium isocyanoacetate[30] (0.246 g, 2.0 mmol) and 4-bromobut-1-ene (0.30 ml, 3.0 mmol) were heated in DMF (4 ml) at 55 °C under argon for 4 h. After cooling to room temperature the reaction mixture was diluted with dichloromethane and washed with brine (x3). The combined aqueous layers were extracted once with dichloromethane, the combined organic layers dried ($MgSO_4$) and then concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether to 3:2 v/v petroleum ether:ether gradient elution) afforded the ***product*** (0.213 g, 75%) as a colourless oil. δ (^{1}H): 5.84-5.71 (m, 1H, CH_2=CH), 5.18-5.09 (m, 2H, CH=CH_2), 4.30-4.26 (m, 4H, NCH_2 and OCH_2), and 2.44 (q, 2H, J 6.7 Hz, OCH_2CH_2). m/z (%): 138 (M^+ -1, 1), 110 (27), 94 (28), 83 (10), 68 (93), 55 (100), and 40 (49). Found: C, 60.3; H, 6.5; N, 9.95. $C_7H_9NO_2$ requires: C, 60.4; H, 6.5; N, 10.05 %.

But-3-enyl 1-(but-3-enyloxycarbonylmethyl)-1*H*-imidazole-4-carboxylate (20).

Silver acetate (8.3 mg, 0.05 mmol) was added to a solution of but-3-enyl isocyanoacetate (0.139 g, 1.0 mmol) in acetonitrile (20 ml) under argon. The resulting solution was stirred at room temperature for 20 h. and then concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate) to give the ***product*** (0.125g, 90%) as a colourless oil which solidified on standing to a colourless waxy solid, m.p. 35 - 36 °C. δ (^{1}H): 7.57 (d, 1H, J 1.0 Hz, CH), 7.47 (d, 1H, J 1.0 Hz, CH), 5.84-5.60 (m, 2H, 2x CH_2=CH), 5.1-5.0 (m, 4H, 2x CH=CH_2), 4.71 (s, 2H, NCH_2), 4.27 (t, 2H, J 6.9 Hz, OCH_2), 4.17 (t, 2H, J 6.6 Hz, OCH_2), 2.44 (q, 2H, J 6.9 Hz, OCH_2CH_2), and 2.33 (q, 2H, J 6.6 Hz, OCH_2CH_2). m/z (%): 278 (M^+, 8), 248 (7), 233 (11), 207

(100), 166 (13), 153 (51), 122 (9), 108 (8), and 55 (19). Found: C, 60.55; H, 6.4; N, 9.95. $C_{14}H_{18}N_2O_4$ requires: C, 60.4; H, 6.5; N, 10.05 %.

(±)-*exo*-Methoxycarbonyl cycloadduct (28a) and (±)-*endo*-methoxycarbonyl cycloadduct (28b).

A mixture of pyrroline **(5a)** (0.109 g, 0.4 mmol), methyl acrylate (0.072 ml, 0.8 mmol), silver acetate (0.067 g, 0.4 mmol) and triethylamine (0.084 ml, 0.6 mmol) was stirred in toluene (2 ml) at room temperature under argon. After 4 h the reaction mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane (x3). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ether to 1:1 v/v ether:ethyl acetate gradient elution) to give first **(28a)** as a colourless solid (0.032 g, 22%), which crystallised from dichloromethane-petroleum ether as colourless needles, m.p. 136-139 °C, followed by **(28b)** as a colourless solid (0.105 g, 73%), which crystallised from ethyl acetate as small colourless rods, m.p. 207-210 °C.

Cycloadduct (28a) δ (^{1}H): 7.47-7.27 (m, 3H, ArH), 7.24-7.23 (m, 2H, ArH), 4.26 (s, 1H, NCH), 3.85 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.19 (d, 1H, J 7.1 Hz, CHCON), 2.98 (d, 1H, J 7.1 Hz, CHCON), 2.87 (dd, 1H, J 8.5 and 4.7 Hz, $CHCO_2Me$), 2.61 (s, br, 1H, NH), 2.29 (dd, 1H, J 8.5 and 13.2 Hz, CHH), and 2.12 (dd, 1H, J 4.7 and 13.2 Hz, CHH). m/z (%): 358 (M^+, 6), 327 (13), 299 (6), 272 (57), 240 (27), 212 (8), 185 (53), 175 (32), 152 (21), 126 (100), 94 (37), 82 (11), 67 (14), and 59 (19). Found: C, 60.2; H, 5.0; N, 7.7. $C_{18}H_{18}N_2O_6$ requires: C, 60.35; H, 5.05; N, 7.8 %.

Cycloadduct (28b) δ (^{1}H): 7.48-7.37 (m, 3H, ArH), 7.28-7.25 (m, 2H, ArH), 4.18 (d, 1H, J 4.6 Hz, NCH), 3.81 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.13-3.08 (m, 2H, CHCON and CHH), 2.96 (d, 1H, J 7.2 Hz, CHCON), 2.71 (s, br, 1H, NH), 2.18 (dd, 1H, J 8.5 and 12.9 Hz, CHH), and 1.99-1.92 (m, 1H, $CHCO_2Me$). m/z (%): 358 (M^+, 10), 327 (15), 272 (54), 240 (23), 212 (7), 185 (32), 152 (33), 126 (100), 94 (53), 82 (15), 77 (14), 67 (21), and 55 (36). Found: C, 60.35; H, 5.15; N, 7.65. $C_{18}H_{18}N_2O_6$ requires: C, 60.35; H, 5.05; N, 7.8 %.

One-pot synthesis of (28a)/(28b) from methyl isocyanoacetate.

Methyl isocyanoacetate (0.10 ml, 1.1 mmol) was added dropwise to a mixture of *N*-phenyl maleimide (0.173 g, 1.0 mmol) and silver acetate (3.7 mg, 0.022 mmol) in toluene (5 ml) under argon, and the resulting solution was stirred at room temperature for 5 h. Methyl acrylate (0.18 ml, 2.0 mmol) was then added, followed by triethylamine (0.21 ml, 1.5 mmol) and silver(I) oxide (23.2 mg, 0.1 mmol) and stirring was continued at room temperature for 16 h. The reaction was quenched by addition of saturated aqueous ammonium chloride, and extracted with dichloromethane (x3). The combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash column chromatography (ether to 1:1 v/v ether:ethyl acetate gradient elution) to give first **(28a)** (0.050 g, 14%) as a colourless solid, followed by **(28b)** (0.155 g, 43%) as a colourless solid.

(±)-Cycloadduct (29).

Methyl isocyanoacetate (0.10 ml, 1.1 mmol) was added dropwise to a mixture of *N*-propargyl maleimide[23] (0.297 g, 2.2 mmol) and silver acetate (3.7 mg, 0.022 mmol) in toluene (8 ml), under argon. The resulting solution was stirred at room temperature for 14 h. Triethylamine (0.15 ml, 1.1 mmol) was added and the reaction mixture was heated at reflux for 30 h. The mixture was allowed to cool and concentrated *in vacuo*. The residue was taken up in dichloromethane and filtered through Celite. The solvent was evaporated under

reduced pressure and the residue was purified by flash column chromatography (1:1 to 7:3 v/v ethyl acetate:petroleum ether gradient elution) to give the ***product*** as a colourless solid (0.285 g, 70%) which crystallised from dichloromethane-petroleum ether as colourless prisms, m.p. 181-182 °C. δ (^{1}H) (D-6 acetone): 4.10 (d, 4H, J 1.6 Hz, 2x NCH_2), 3.80 (s, 3H, OMe), 3.53 (d, 2H, J 7.0 Hz, 2x CHCO), 3.35 (d, 2H, J 7.0 Hz, 2x CHCO), 3.20 (s, br, 1H, NH), 2.82 (s, 1H, NCH), 2.64 (t, 2H, J 1.6 Hz, 2x C≡CH). m/z (%): 369 (M^+, 2), 338 (3), 310 (2), 234 (100), 202 (48), 152 (16), 125 (40), and 94 (42). Found: C, 58.35; H, 4.1; N, 11.1. $C_{18}H_{15}N_3O_6$ requires: C, 58.55; H, 4.1; N, 11.4 %.

Dimethyl-2-(6-chloropyridin-3-ylmethylene)-malonate (31).

A solution of dimethyl malonate (0.425 g, 3.15 mmol), 6-chloropyridine-3-carboxaldehyde[25] (0.425 g, 3.0 mmol) and ytterbium triflate (18.6 mg, 0.03 mmol) in acetonitrile (3 ml) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (x3) and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography (15:9:1 v/v/v petroleum ether:dichloromethane:ethyl acetate) to give the ***product*** (0.693 g, 90%) as a colourless solid, which crystallised from dichloromethane-petroleum ether as colourless plates, m.p. 89-90 °C. δ (^{1}H, 400 MHz): 8.42 (d, 1H, J 2.5 Hz, ArH), 7.69 (m, 2H, ArH and C=CH), 7.34 (d, 1H, J 8.5 Hz, ArH), 3.85 (s, 3H, OMe), and 3.84 (s, 3H, OMe). m/z(%): 257 (M^+, 7), 255 (22), 242 (20), 240 (56), 226 (26), 224 (70), 210 (10), 208 (28), 197 (27), 195 (79), 166 (25), 164 (47), 158 (36), 156 (100), 139 (26), 137 (70), 102 (76), 75 (45), and 59 (89). Found: C, 51.75; H, 4.0; N, 5.25; Cl, 13.8. $C_{11}H_{10}NO_4Cl$ requires: C, 51.7; H, 3.95; N, 5.5; Cl, 13.85 %.

(±)-Tetramethyl *exo*-2-(6-chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane-1,3,3-*exo*-5-tetracarboxylate (32a) and (±)-tetramethyl *exo*-2-(6-chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane-1,3,3-*endo*-5-tetracarboxylate (32b).

Methyl isocyanoacetate (0.21 ml, 2.3 mmol) was added dropwise to a mixture of olefin **(31)** (0.511 g, 2.0 mmol) and silver acetate (6.7 mg, 0.04 mmol) in dichloromethane (12 ml) under argon, and the resulting solution was stirred at room temperature for 3 h. Methyl acrylate (0.36 ml, 4.0 mmol) was then added, followed by triethylamine (0.56 ml, 4.0 mmol) and silver(I) oxide (23 mg, 0.1 mmol), and the resulting mixture was stirred at room temperature for 14 h. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (3:2 to 9:1 v/v ether:petroleum ether gradient elution) to give first **(32a)** (0.482 g, 55%) as a colourless solid, followed by **(32b)** (0.267 g, 30%). Cycloadduct **(32a)** crystallised from ethyl acetate-petroleum ether as colourless needles, m.p. 158-160 °C, and cycloadduct **(32b)** crystallised from ethyl acetate-petroleum ether as colourless rods, m.p. 153-154 °C.

Cycloadduct (32a) δ (^{1}H, 400 MHz): 8.30 (d, 1H, J 2.3 Hz, ArH), 7.85 (dd, 1H, J 2.3 and 8.4 Hz, ArH), 7.16 (d, 1H, J 8.4 Hz, ArH), 4.46 (s, 1H, C<u>H</u>NH), 4.13 (s, 1H, ArC<u>H</u>C(CO_2Me)$_2$), 3.81 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.10 (s, 3H, OMe), 3.03 (s, br, 1H, NH), 2.59 (dd, 1H, J 4.3 and 8.6 Hz, C<u>H</u>CO_2Me), 2.31 (dd, 1H, J 8.6 and 13.1 Hz, CH<u>H</u>), and 2.15 (dd, 1H, J 4.3 and 13.1 Hz, CH<u>H</u>). m/z (%): 441 (M^+, < 1%), 409 (4), 377(4), 349 (4), 317 (4), 289 (4), 258 (34), 256 (92), 185 (40), 153 (10), 126 (100), 94 (14), and 59 (26). Found: C, 51.75; H, 4.7; N, 6.45; Cl, 8.15. $C_{19}H_{21}N_2O_8Cl$ requires: C, 51.75; H, 4.8; N, 6.35; Cl, 8.05 %.

Cycloadduct (32b) δ (^{1}H, 400 MHz): 8.28 (s, br, 1H, ArH), 7.87 (d, br, 1H, ArH), 7.16 (d, 1H, J 8.4 Hz, ArH), 4.33 (d, 1H, J 4.7 Hz, C<u>H</u>NH), 4.10 (s, 1H, ArC<u>H</u>C(CO_2Me)$_2$), 3.77 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.17 (dd, 1H, J 6.1 and 8.5 Hz, C<u>H</u>H), 3.09 (s, 3H, OMe), 2.92 (s, br, 1H, NH), 1.99 (ddd, 1H, J 4.9, 6.0, and 13.6 Hz, C<u>H</u>CO_2Me), and 1.87 (dd, 1H, J 8.5 and 13.6 Hz, C<u>H</u>H). m/z (%): 441 (M^+, <1%), 409 (6%), 377 (5), 349 (10), 258 (31), 256 (88), 185 (29), 153 (26), 126 (100), 94 (17), 59 (24). **Found:** C, 51.5; H, 4.65; N, 6.3; Cl, 8.0. $C_{19}H_{21}N_2O_8Cl$ requires: C, 51.75; H, 4.8; N, 6.35; Cl, 8.05 %.

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