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Intramolecular 1,3-dipolar cycloaddition as a route to triazolobenzodiazepines and pyrrolobenzodiazepines

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ABSTRACT

Intramolecular 1,3-dipolar cycloaddition between an alkyne and an azide leads to a series of 1,2,3-triazolo-fused 1,4-benzodiazepines, 1,2,5-benzothiadiazepines, pyrrolobenzodiazepines and pyrrolobenzothiadiazepines (eight examples). The products are privileged structures in medicinal chemistry. The precursor azido alkynes are obtained, usually as transient intermediates, by treatment of the corresponding aldehydes (derived from α-amino acids) with the Bestmann–Ohira reagent.

There is interest in the 1,4-benzodiazepine nucleus as a privileged structure in medicinal chemistry, and hence new properties and new routes continue to appear.[1] Tricyclic benzodiazepines (see Fig. 1) fused at the *a*-face such as flumazenil (**1**)[2] and estazolam (**2**)[3] have achieved clinical success in the treatment of CNS disorders, where the former, when ^{18}F labelled, is also a useful ligand for positron emission tomography.[2e] Benzodiazepines with *a*-fused 1,2,3-triazolo and tetrazolo rings have also attracted attention in the medicinal chemistry literature.[4] The pyrrolobenzodiazepines (PBDs) such as DC-81 (**3**) and neothramycin (**4**) are sequence-specific DNA interactive antitumour antibiotics.[5] The related bretazanil (**5**) has attracted interest in the treatment of CNS disorders and for its potential usefulness against neurodegenerative diseases.[6] 1,2,5-Benzothiadiazepines have attracted less interest than their carbonyl analogues, but are nonetheless attractive targets with a range of properties including potential as antiarrhythmic agents,[7] tumour necrosis factor-α-converting enzyme (TACE) inhibitors[8] and as hypolipidaemic agents,[9] as discussed in a recent review.[10] The related pyrrolobenzothiadiazepines such as compound (**6**) have attracted interest as PBD analogues,[10] as candidates for the treatment of chronic myelogenous leukaemia[11] and as non-nucleosidic reverse transcriptase inhibitors.[12]

As part of a programme of work focusing on new routes to benzodiazepines, benzothiadiazepines and pyrrolobenzothiadiazepines,[13–16] we have recently shown that intramolecular 1,3-dipolar cycloaddition between the azide and alkene moieties that are present in compounds (**7**) and (**8**) allow access to aziridinopyrrolobenzodiazepines (**9**) and aziridinopyrrolobenzothiadiazepines (**10**).[17] In continuation of this work, we report the results of our efforts with intramolecular azide to alkyne cycloadditions and describe herein the synthesis of a series of eight triazolo-fused 1,4-benzodiazepines, pyrrolobenzodiazepines, 1,2,5-benzothiadiazepines and pyrrolobenzothiadiazepines.

Our previous work with the alkene systems (**7**) and (**8**) began by coupling the proline-derived unstable alkene (**11**) (Scheme 1) with

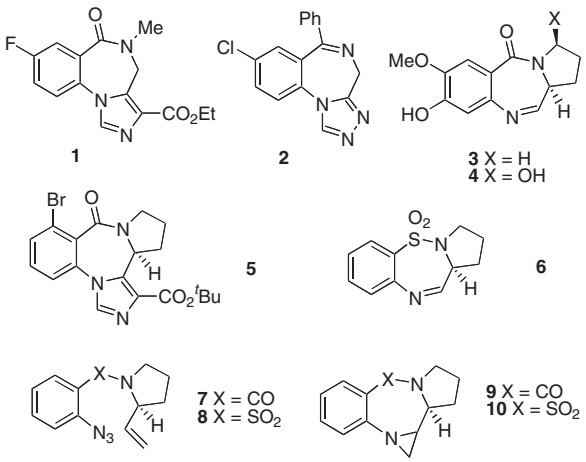

Figure 1. Important tricyclic and tetracyclic benzodiazepines.

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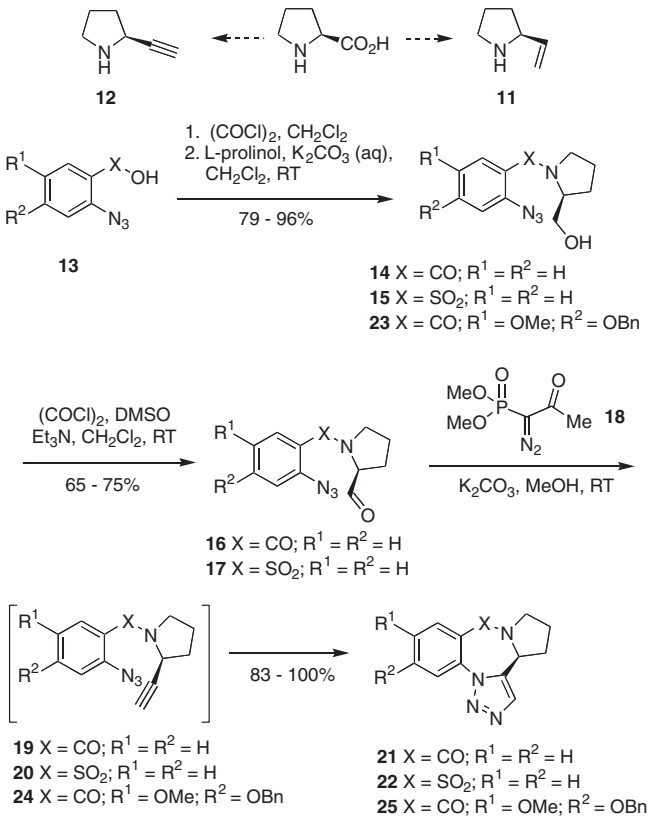


Scheme 1. Synthesis of tetracyclic PBD analogues.

2-azidobenzenesulfonic acid or 2-azidobenzoic acid. We found the corresponding approach with the alkyne derivative (**12**) tedious and low yielding when we attempted to access the alkyne (**12**) from proline (although this approach to a series of triazolopyrrolobenzodiazepines has been reported recently[18]) and sought instead to access the desired alkyne precursors (**19**) and (**20**), directly from the readily available aldehydes (**16**) and (**17**). Thus, L-prolinol was coupled to 2-azidobenzoic acid or 2-azidobenzenesulfonic acid to give the alcohols (**14**) (mixture of rotamers) and (**15**) in yields of 79% and 96%, respectively. Oxidation was best performed via the Swern protocol which gave yields consistently in the 70–75% range (Dess–Martin oxidation gave higher yields, but only when freshly prepared reagent was used). The conversion of the aldehydes into the alkynes (**19**) and (**20**) was achieved via the use of the Bestmann–Ohira reagent (**18**).[19] In fact, compounds (**19**) and (**20**) could not be detected and the only products were the triazoles (**21**) and (**22**) which were isolated in 83% and quantitative yield, respectively. The structures of the final products were determined by the usual spectroscopic techniques,[20] but were confirmed by X-ray crystallographic studies (see Fig. 2).[21]

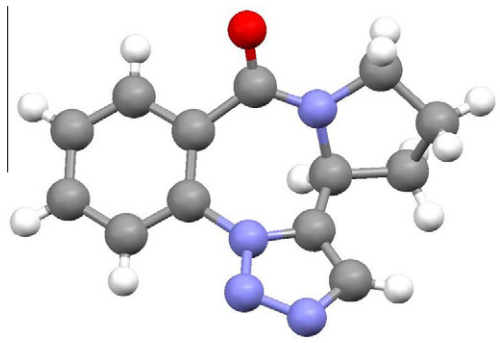


Figure 2. Crystal structure for compound (**21**).

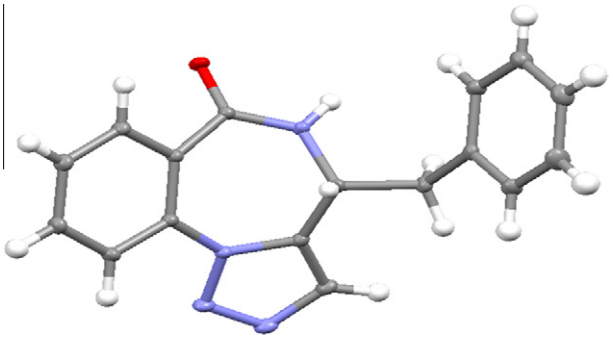
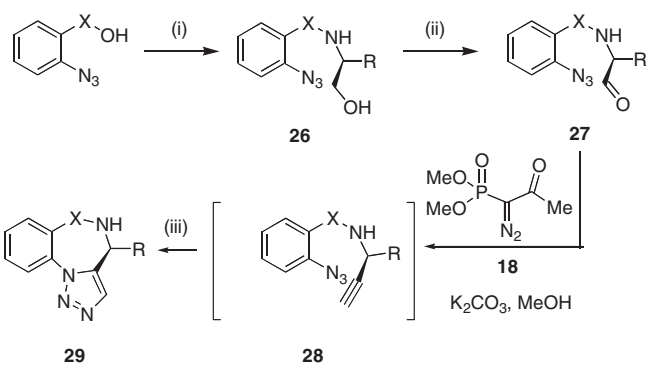


Figure 3. Crystal structure for compound (**29d**).



Scheme 2. Synthesis of triazolobenzodiazepine derivatives. Reagents and conditions: (i) $(COCl)_2$, CH_2Cl_2, rt, then L-amino alcohol, K_2CO_3, CH_2Cl_2, rt; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt; (iii) see Table 1.

Table 1
Triazolobenzodiazepines and triazolobenzothiadiazepines (**29**) produced via Scheme 2[23]

Entry	R/X	% Yield (**26**)	% Yield (**27**)	% Yield (**29**) [from (**27**)]
a	*i*-Pr/SO_2	55	72	83
b	*i*-Pr/CO	88	70	77[a]
c	$PhCH_2/SO_2$	81	65	73[a]
d	$PhCH_2$/CO	93	72	80[a,b]
e	Indol-3yl-CH_2/CO	90	40	54

[a] Intermediate (**28**) could be isolated in these cases. Cycloaddition was brought about by heating the pure alkyne at reflux in chloroform.[23]
[b] Structure confirmed by X-ray crystallographic studies (see Fig. 3).[21]

We next extended our process to include a pyrrolobenzodiazepine with the substitution pattern present in the natural products DC-81 (**3**) and neothramycin (**4**). Thus, the readily available[5] azidobenzoic acid (**13**) (R^1 = OMe, R^2 = OBn, X = CO) was coupled to L-prolinol to give the alcohol (**23**) in 87% yield with subsequent oxidation giving the expected aldehyde in 65% yield. Reaction with the Bestmann–Ohira reagent again proceeded with concomitant cyclisation of the presumed intermediate alkyne (**24**) to form the desired triazolopyrrolobenzodiazepine (**25**) in 84% yield.

With a successful protocol in place, we next extended it to amino acids other than proline in order to show that we could provide access to a short series of triazolobenzodiazepines and triazolobenzothiadiazepines (**29**), as shown in Scheme 2 and Table 1. The only similar reported approaches to triazolobenzodiazepines are limited to the alkyne (**12**),[18] as discussed above, or the use of propargylamines in the coupling step (including an elegant Ugi sequence) rather than amino alcohols.[4a,22] It is also noteworthy that

Alajarín[3b] has reported a non-alkyne-based approach to triazolobenzodiazepines. We are aware of no other published approaches to the triazolobenzothiadiazepines such as (**22**) and (**29a/c**) (X = SO_2).

We are currently exploring other intramolecular 1,3-dipolar cycloadditions for the synthesis of tricyclic benzodiazepines and benzothiadiazepines and tetracyclic pyrrolobenzodiazepines and pyrrolobenzothiadiazepines.

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20. All new compounds gave satisfactory $^1H/^{13}C$ NMR spectra (including DEPT, COSY, HSQC and HMBC spectra), mass spectra, HRMS/microanalysis and IR spectra. *Typical procedure*: *synthesis of 1,2,3-triazolo[1,5-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 9,9-dioxide* (**22**): To the aldehyde (**17**) (300 mg, 1.07 mmol) in anhydrous MeOH (5 mL) were added K_2CO_3 (296 mg, 2.14 mmol) and the Bestmann–Ohira reagent[19] (247 mg, 1.29 mmol). The mixture was stirred at room temperature under an atmosphere of dry N_2 for 22 h, whereupon saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated by reduced pressure rotary evaporation. Purification on a column of silica gel (20 g) using EtOAc and hexane (3:1) as the eluent gave the title compound (295 mg, 100%) as a yellow solid, mp 175–177 °C. Anal. Calcd for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.38; H, 4.49; N, 20.37. IR: ν_{max} (neat, cm^{-1}): 2924 (w), 1604 (s), 1558 (m), 1541 (m), 1485 (w), 1457 (w), 1356 (m), 1265 (m), 1170 (s), 1119 (m); ^1H NMR (400 MHz, $CDCl_3$), δ_H: 1.63–1.73 (1H, m, C*H*H), 1.88–2.09 (2H, m, CH_2), 2.27 (1H, dddd, *J* 2.8, 6.2, 6.6, 12.4, CHC*H*HCH$_2$), 3.12 (1H, ddd, *J* 6.6, 9.9, 9.9, NCH*H*), 3.68 (1H, ddd, *J* 2.4, 7.5, 9.9, NC*H*HCH$_2$), 5.19 (1H, dd, *J* 6.2, 10.2, NC*H*CH$_2$), 7.62, (1H, dt, *J* 1.0, 7.7, ArH), 7.79 (1H, s, triazole-CH), 7.83 (1H, dt, *J* 1.5, 8.0), 8.10 (1H, dd, *J* 1.5, 7.7), 8.15 (1H, dd, *J* 1.0, 8.0, ArH). ^{13}C: δ_C (100 MHz, $CDCl_3$): 24.4 (CH_2), 35.4 (CH_2), 50.0 (CH_2), 55.1 (CH), 125.4 (CH), 128.7 (CH), 129.3 (CH), 130.9 (q), 133.5 (q), 134.1 (CH), 134.4 (CH), 136.8 (q); *m*/*z* (electrospray) HRMS: calcd for $C_{12}H_{12}N_4O_2S + H^+$ = 277.0754, found: 277.0752.
21. The structures of compounds (**21**), (**22**) and (**29d**) were confirmed by single crystal X-ray crystallographic studies. Full details can be found in: Chambers, C., Ph.D. Thesis, University of Huddersfield, 2009. Crystallographic data for these compounds have been deposited at the Cambridge Crystallographic Data Centre as CIF depositions with file numbers CCDC 782152-782154. Copies of these data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk or fax +44(0)1223 336033.
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23. All new compounds reported in Table 1 gave satisfactory $^1H/^{13}C$ NMR spectra (including DEPT, COSY, HSQC and HMBC spectra), mass spectra, HRMS/microanalysis and IR spectra. As a typical example, in which the alkyne could be isolated, 3-*iso*-propyl-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepin-5-one (**29b**) was obtained as follows: To the aldehyde (**27b**) (118 mg, 0.48 mmol) in anhydrous MeOH (5 mL) were added K_2CO_3 (132 mg, 0.96 mmol) and the Bestmann–Ohira reagent[19] (111 mg, 0.58 mmol). The mixture was stirred at room temperature under an atmosphere of dry N_2 for 4 h, whereupon saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated by reduced pressure rotary evaporation. Purification on a column of silica gel (20 g) using EtOAc and hexane (1:3) as the eluent gave the alkyne (90 mg, 78%). The alkyne (73 mg, 0.30 mmol) was dissolved in anhydrous $CHCl_3$ (10 ml) and heated at reflux for 72 h. The solvent was removed and the residue was purified on a column of silica gel (10 g) using EtOAc and hexane (1:1) as the eluent to yield the product as a pale yellow solid (72 mg, 99%), mp 124–126 °C. IR: ν_{max} (neat, cm^{-1}): 3174 (m), 3047 (m), 2958, 2860 (w), 1651 (s), 1605 (m), 1580 (m), 1469 (s), 1395 (s), 1350 (m), 1245 (m), 990 (m), 842 (m), 754 (s); ^1H NMR (400 MHz, $CDCl_3$), δ_H: 1.00 (3H, d, *J* 6.0, Me), 1.18 (3H, d, *J* 6.6, Me), 2.20–2.26 (1H, br m, C*H*Me$_2$), 4.13 (1H, dd, *J* 6.4, 9.8, NHC*H*), 7.59 (1H, dt, *J* 7.7, 1.1, NC*H*HCH$_2$), 7.68, (1H, s, triazole-CH), 7.74 (1H, dt, *J* 8.0, 1.5, ArH), 8.05 (1H, dd, *J* 8.0, 0.8, ArH), 8.11 (2H, dd + br s, *J* 7.7, 1.5, ArH + NH); ^{13}C: δ_C (100 MHz, $CDCl_3$): 19.2 (Me), 20.3 (Me), 29.3 (CH), 52.2 (CH), 123.0 (CH), 126.2 (q), 129.1 (CH), 130.6 (CH), 131.7 (CH), 133.3 (CH), 133.5 (q), 138.4 (q), 168.1 (q); *m*/*z* (electrospray) HRMS: calcd for $C_{13}H_{14}N_4O + Na^+$ = 265.1060, found: 265.1064.