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COMMUNICATION

Gold-catalysed synthesis of amino acid-derived 2,5-disubstituted oxazoles†

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Amino acid-derived propargylic amides are cyclised in a one-pot, Au(III)-catalysed operation to yield 5-bromomethyl oxazoles. These compounds are further elaborated to *bis*-heterocycles, dipeptide mimics and more.

The oxazole heterocycle is a prevalent subunit in many natural and synthetic bioactive small molecules.[1] Natural products such as diazonamide A (**1**)[2] and bengazole (**2**)[3] (Fig. 1) are just two of the multitude of scaffolds which incorporate the motif. Their inclusion in compounds with antiviral, antibacterial, antineoplastic and antineuropathic activity highlights the significance of the oxazole nucleus in medicinal chemistry.[4]

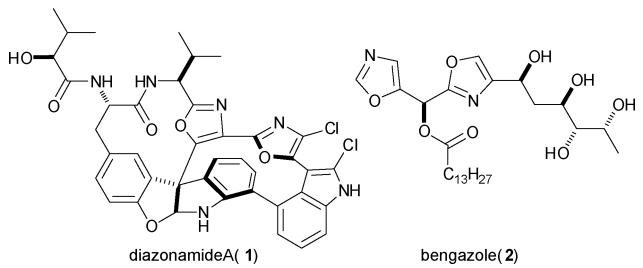
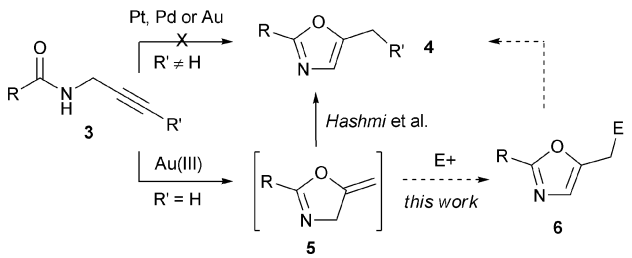


Fig. 1 Diazonamide A (**1**) and bengazole (**2**).

Many naturally occurring oxazoles are derived from the enzymatic post-translational modification of peptide-based precursors *via* dehydrative cyclisation of serine or threonine residues onto a preceding carbonyl, followed by a two electron oxidation.[5,6] This transformation endows favourable pharmacological properties including resistance to proteases and increased cell permeability.[7] As such, these heterocycles have been valued as subunits in peptidomimetic design and other medicinal chemistry programmes.[8] Laboratory preparations of oxazoles include conventional cyclodehydration of acyclic precursors,[9] oxidation of oxazolines,[10] functionalisation (*via* metallation) of readily available oxazole starting materials,[11] copper-catalysed amidation of vinyl halides followed by cyclisation[12] and others.[1,9,13]

Based on our studies related to the cycloisomerisation of ω-hydroxy alkynes,[14] we postulated that cycloisomerisation of propargylic amides would provide access to a wide range of 2,5-disubstituted oxazoles. Unfortunately, we were unsuccessful in identifying conditions to perform this transformation on internal alkynes (Scheme 1, **3** → **4**, R′ ≠ H),[15] thereby severely limiting the scope of this reaction to the synthesis of 5-Me-substituted oxazoles (**4**, R′ = H). During these explorative studies, Hashmi *et al.* reported that the Au(III)-catalysed cyclisation of terminal propargylic amides **3** (R′ = H) yields 5-methyl-substituted oxazoles **4** (R′ = H) *via* an isolable methyleneoxazoline intermediate of type **5** (Scheme 1).[16,17] From these studies, we postulated that one could intercept this intermediate *in situ* with an electrophile to generate oxazoles bearing a reactive handle at the 5-methylene position (**6**), thus providing an entry to expand the range of available oxazoles *via* subsequent manipulation at this position (**6** → **4**, R′ ≠ H). Herein, we report the reduction of this concept to practice.



Scheme 1 Experimental design.

A preliminary screen identified bromine as the most competent electrophile to trap the methyleneoxazoline intermediate **5** (generated *in situ* from the Au(III)-catalysed cycloisomerisation of terminal propargylic amides **3**), delivering bromomethyl oxazole (**6**, E = Br) in good yield.[18–22] Many naturally occurring oxazoles bear amino acid-derived side chains, thus the scope was extended to include these moieties. Initial experiments revealed that Fmoc-protected amino acid-derived propargylic amides were not ideal substrates, however Boc-protected amide **3a** was converted to 5-bromomethyl derivative **7a** in 50% yield (Table 1). The modest yield was attributed to opportunistic HBr catalysing the cleavage of the Boc group. A screen of bases revealed that 2,6-lutidine best ameliorated this effect to give **7a** in 88% yield with no epimerization of the stereogenic centre.[22]

Having optimised the reaction conditions, the substrate scope was expanded as shown in Scheme 2. The reactions proceeded with similar efficiency and could be performed on a gram-scale

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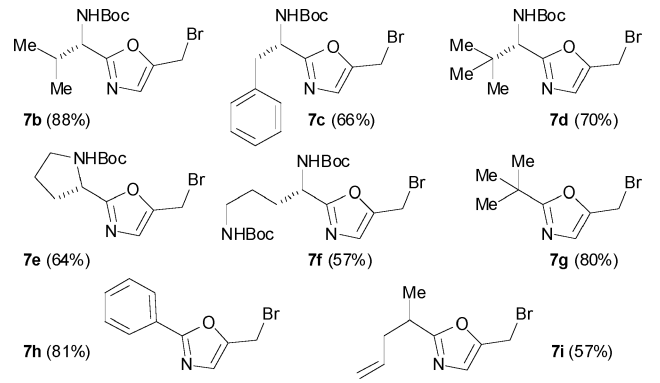
† Electronic supplementary information (ESI) available: Experimental details, spectroscopic data and copies of NMR spectra for new compounds. See DOI: 10.1039/c1ob05390f

Table 1 Optimisation of amino acid-derived oxazole formation

Base	Yield[a]	Base	Yield[a]
none	50	pyridine	55
i-Pr_2NEt	51	2,4,6-collidine	82
K_2CO_3	52	2,6-lutidine	88

[a] Isolated yield (%).



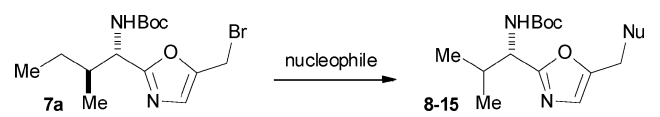
Scheme 2 5-Bromomethyl oxazoles derived from sequential cycloisomerisation–bromination of propargylic amides. Reaction conditions: amide **3** (0.2 M in $CHCl_3$), 5 mol% $AuCl_3$, RT; 2,6-lutidine (1.1 eq), Br_2 (1.0 eq, 2.0 M in $CHCl_3$), 0 °C to RT. Isolated yields in brackets.

without complication, highlighting their utility in the preparation of large quantities of these interesting 5-bromomethyl oxazoles.[23]

Next, we explored the displacement of the bromide with a variety of nucleophiles. The substrates proved extremely versatile, reacting with a wide range of nucleophiles in good to excellent yields (Table 2). The success of the azide (**12**, 98%) and L-valinol (**15**, 71%) substitutions prompted us to focus on these transformations for further elaboration.

First, we sought to take advantage of the Huisgen 1,3-dipolar cycloaddition to access 1,4-disubstituted 1,2,3-triazoles.[24,25] This heterocycle is known to be biologically inert and is therefore commonly used as a robust linking group in medicinal chemistry and in the preparation of optically active chemical probes.[25a] We were able to successfully employ modified Sharpless conditions

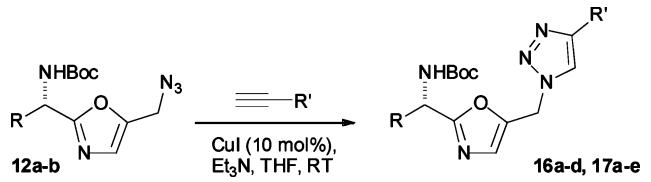
Table 2 Nucleophilic substitution of bromide **7a**[a]



Nucleophile	Product	Yield[b]	Nucleophile	Product	Yield[b]
KCN	**8**	71	NaN_3	**12a**	98
t-$BuNH_2$	**9**	81	NaOAc[c]	**13**	86
PhOH	**10**	89	$H_2N(CH_2)_5OH$	**14**	65
PhSH	**11**	61	L-valinol	**15**	71

[a] See the ESI† for experimental details. [b] Isolated yield (%). [c] Substrate for this reaction was **7b**.

Table 3 *bis*-Heterocycles by dipolar cycloaddition[a]



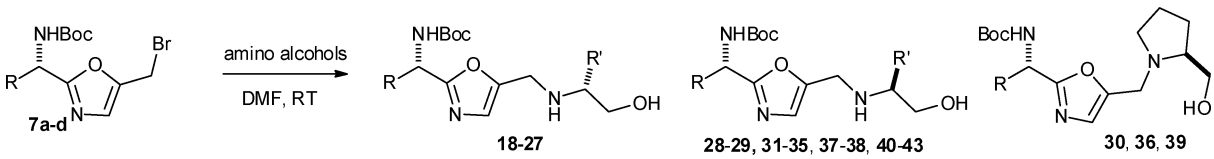
Azide	R	R′	Product	Yield
12a	(*S*)-CHMeEt		**16a**	70
12b	$CHMe_2$		**17a**	72
12a	(*S*)-CHMeEt		**16b**	81
12b	$CHMe_2$		**17b**	84
12a	(S)-CHMeEt	OMe	**16c**	84
12b	$CHMe_2$		**17c**	85
12a	(*S*)-CHMeEt		**16d**	80
12b	$CHMe_2$		**17d**	88
12b	$CHMe_2$	$-(CH_2)_5Me$	**17e**	64

[a] Reaction conditions: azide (0.1 M in THF), alkyne (1.0 eq), Et_3N (1.2 eq) and 10 mol% CuI, RT, 16 h. [b] Isolated yield (%).

(10 mol% CuI, Et_3N)[26] in the coupling between azido oxazoles **12a–b** with a range of commercially available alkynes to produce the *bis*-heterocycles **16a–d** and **17a–e** in good yields (Table 3). The cycloaddition proceeded well regardless of the nature of the alkyne substituent—aromatic and alkyl (cyclic and acyclic) groups were tolerated.

The success of the bromide displacement by amino alcohols inspired the preparation of peptidomimetics expressing two amino acid side chains. Compounds of this type have potential use in biological research; it is well documented that they are metabolically more stable and benefit from improved bioavailability profiles than peptides themselves.[27] As shown in Table 4, direct displacement of bromomethyl oxazoles with amino alcohols provided efficient access to oxazoyl-based peptidomimetics bearing two stereocentres. To the best of our knowledge, these are the only examples of dipeptide isosteres with this 2,5-oxazole substitution pattern. Additionally, these adducts, like other amino alcohols that have enjoyed success as organocatalysts[28] and as ligands in metal-based catalysis,[29] may be useful in asymmetric catalysis. Owing to the ready availability of amino alcohols, a range of peptidomimetics (**18–43**) were prepared. The modular nature of these adducts allows for rapid assembly, covering a wide chemical space. Indeed, the direct displacement of bromide provided a useful entry to products of this type, with good yields for L-prolinol, D- and L-phenylalaninol and L-tyrosinol; only L-tryptophanol suffered poor conversion (**33**, 22%). Additionally, no precautions were taken to prevent over *N*-alkylation or alcohol substitution;[30] the reported dialkylamines were the only products observed.

Table 4 Peptidomimetic library development[a]



7	AA	Amino alcohol[a]	Product	Yield[b]	7	AA	Amino alcohol[a]	Product	Yield[b]
a	Ile	D-valinol	**18**	66	**c**	Phe	L-valinol	**37**	63
a	Ile	L-phenylalaninol	**28**	57	**c**	Phe	D-valinol	**22**	68
a	Ile	D-phenylalaninol	**19**	60	**c**	Phe	L-phenylalaninol	**38**	62
a	Ile	L-isoleucinol	**29**	59	**c**	Phe	D-phenylalaninol	**23**	63
a	Ile	L-prolinol	**30**	63	**c**	Phe	L-prolinol	**39**	50
a	Ile	L-leucinol	**31**	46	**e**	Pro	L-valinol	**40**	55
a	Ile	L-tyrosinol	**32**	48	**e**	Pro	D-valinol	**24**	54
a	Ile	L-tryptophanol	**33**	22	**e**	Pro	L-phenylalaninol	**41**	60
b	Val	L-valinol	**34**	78	**e**	Pro	D-phenylalaninol	**25**	58
b	Val	D-valinol	**20**	64	**d**	*t*-BuGly	L-valinol	**42**	72
b	Val	L-phenylalaninol	**35**	57	**d**	*t*-BuGly	D-valinol	**26**	75
b	Val	D-phenylalaninol	**21**	60	**d**	*t*-BuGly	L-phenylalaninol	**43**	67
b	Val	L-prolinol	**36**	87	**d**	*t*-BuGly	D-phenylalaninol	**27**	79

[a] Reaction conditions: azide (0.2 M in DMF), amino alcohol (2.2 eq), RT, 16 h. [b] Isolated yield (%).

In this report, we demonstrated that 5-bromomethyl oxazoles can be prepared from propargylic amides in a one-pot Au(III)-catalysed procedure in good yields (57–88%). Additionally, amino acid-derived propargylic amides provided access to a multitude of chiral, potentially biologically relevant novel oxazole building blocks. The ease of further elaboration was clearly established in reactions with a range of nucleophiles, including amino alcohols, to give a unique class of *bis*-amino acid-derived oxazoles. Alternatively, azido oxazole derivatives **12** were further elaborated to the corresponding triazolyl-oxazoyl *bis*-heterocycles **16** and **17** *via* a Cu(I)-catalysed 1,3-dipolar cycloaddition with a range of alkynes. Further studies on the bioactivity and solution conformations of these molecules are ongoing and will be reported in due course.

Acknowledgements

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17 We screened several catalysts including $Ph_3PAuCl/AgOTf$, $Ph_3PAuMe/TfOH$, AuCl, $PdCl_2$, and $[CH_2CH_2PtCl_2]_2$. None of these were able to induce cycloisomerisation of *N*-(prop-2-yn-1-yl)pivalamide ($CDCl_3$, RT, 1 h) and >90% starting material was recovered in all cases. The use of $NaAuCl_4{\cdot}2H_2O$ resulted in hydration of the terminal alkyne to a methylketone. As reported by Hashmi *et al.*; (ref. 16), only $AuCl_3$ was effective in the cycloisomerisation of terminal propargylamides to 5-Me-substituted oxazoles.

18 Hashmi *et al.* reported the trapping of the intermediate vinyl gold species with *N*-halosuccinimides, albeit in low to modest yield. See:

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22 See the ESI† for details.

23 Yields are for purified material. The actual yields are in most cases higher because of partial hydrolysis of the bromide during chromatography. The reaction is sufficiently clean that the bromides can be processed in subsequent chemistry without purification, with, in general, improved overall yields for the combined process.

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