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Triflic anhydride-mediated synthesis of oxazoles

Armin Thalhammer, Jasmin Mecinović, Christopher J. Schofield *

The Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK

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ABSTRACT

N-Acyl amino acid esters undergo triflic anhydride-mediated cyclodehydration to form oxazoles and bisoxazoles in a simple one-pot transformation.

The oxazole group[1] is a key element of a number of biologically active natural products, including diazonamides,[2] inthomycins,[3] calyculins and phorboxazoles (for a recent review see Ref. 4), and has been extensively used in medicinal chemistry. In connection with studies on the inhibition of Fe(II) and 2-oxoglutarate-dependent non-haem oxygenases, we required an efficient and mild synthetic method for the preparation of 2-methoxycarbonyl oxazoles and bisoxazoles from readily available *N*-oxalyl amino acid esters.

A widely used approach for oxazole synthesis is the cyclodehydration of peptide precursors, known as the Robinson–Gabriel synthesis.[5] A variety of dehydrating reagents, including H_2SO_4,[5] $POCl_3$,[6] $SOCl_2$,[7] $(CF_3CO_2)_2O$,[8] $COCl_2$,[9] *p*-TsOH[10] and CF_3SO_3H[11], have been applied for oxazole synthesis. In the total synthesis of oxazole-based natural products, oxazoline formation from *N*-acylated serine residues followed by mild oxidation to the desired oxazoles has also been explored.[4] Recently, oxazole formation via N,O-acylation of oximes with acyl chlorides followed by cyclodehydration under microwave heating has been described.[12]

Wipf and co-workers[13] have reported the cyclization of *N*-acyl amino acid esters using $PPh_3/I_2/Et_3N$ to give oxazoles under mild conditions and have applied this protocol to the synthesis of the peptide antibiotic (−)-muscoride A.[14] Recently, Movassaghi et al. reported the use of Tf_2O/2-chloropyridine as a versatile and mild dehydrating reagent for the formation of isoquinolines and β-carbolines;[15] they also observed that *N*-benzoyl phenylalanine methyl ester underwent oxazole formation under these conditions.

While oxazole formation from *N*-acyl aminoketones has been explored extensively, comparatively little work has been done on related *N*-acyl amino acid esters. Here, we describe studies on the scope of Tf_2O [$(CF_3SO_2)_2O$] for the synthesis of trisubstituted oxazoles and bisoxazoles from a set of readily prepared amino acid and peptide derivatives.

Initially, we optimized the conditions for the Tf_2O-mediated preparation of trisubstituted oxazole **2a** from dimethyloxalylphenylalanine **1a** (Table 1). Et_3N was found to be a suitable base affording oxazole **2a** in 69% yield after 3 h; slightly lower yields were obtained when other bases, for example, pyridine, were used. While the addition of a base might be desirable with acid-sensitive substrates, the reaction also occurred in the absence of base to afford **2a** (57%). Treatment of **1a** with 1 equiv of Tf_2O in the presence of 1.1 equiv of Et_3N yielded only 28% of **2a**, whereas the yield of **2a** was improved (to 91%) by employing 3 equiv of Tf_2O. Of a selection of commonly used organic solvents, CH_2Cl_2 gave the highest yields and polymerization as occured with THF was not observed; nor did it form a biphasic reaction mixture as observed with Et_2O.

The optimized protocol[16] was then used for the preparation of di- and trisubstituted[17] oxazoles **2b–i** from the readily accessible *N*-acyl amino acid methyl esters **1b–i** (Table 2). The compatibility of the method with common amino acid derivatives was studied first. When dimethyloxalylglycine **1b**, an in vivo inhibitor of HIF (hypoxia-inducible factor) hydroxylases,[18,19] was treated with 2 equiv of Tf_2O, oxazole **2b** was formed in 56% and 74% yields, after 2 h and 4 h, in the presence of Et_3N and pyridine, respectively. The alanine derivative **2c**, an intermediate in the synthesis of pyridoxine derivatives,[9,20] was obtained in 75% yield. In contrast, lower yields of 18–25% have been reported with other dehydrating reagents.[9] Up to 10% of *N*-methyloxalyl dehydroalanine methyl ester was observed as a by-product in the reaction with **2c**.

The scope of the method was then tested with a set of *N*-acyl substituents, giving oxazoles **2e–g** in 41–80% yield. The *N*-formyl derivative **1h** afforded a complex mixture of oligomers under standard reaction conditions, consistent with the reported formation of oligomerization-prone isonitriles from formamides in the presence of Tf_2O/pyridine.[21] Interestingly, *N*-Boc-protected phenylalanine methyl ester underwent dimerization to form urea **6** under standard reaction conditions. This reaction may proceed via imino triflate **3**, which can undergo loss of its *t*-butyl group to afford isocyanate **4** (Fig. 1). Nucleophilic addition of **1i** and

* Corresponding author. Tel.: +44 1865 275625; fax: +44 1865 275674.
E-mail address: christopher.schofield@chem.ox.ac.uk (C.J. Schofield).

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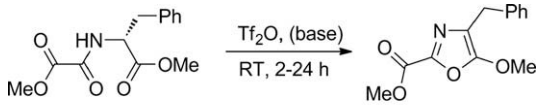
Table 1
Optimization of reaction conditions for Tf_2O-mediated oxazole formation

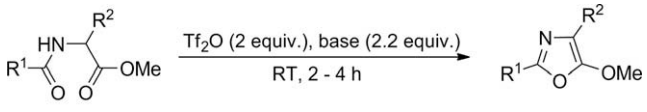


1a 2a

Entry	Tf_2O (equiv)	Base (equiv)	Solvent	Time (h)	Yield[a] (%)
1	2	Pyridine (2.2)	CH_2Cl_2	3	15
2	2	2-Chloropyridine (2.2)	CH_2Cl_2	3	52
3	2	K_2CO_3 (2.2)	CH_2Cl_2	3	50
4	1	Et_3N (1.1)	CH_2Cl_2	3	28
5	2	Et_3N (2.2)	CH_2Cl_2	3	69
6	3	Et_3N (3.3)	CH_2Cl_2	3	91
7	2	Et_3N (2.2)	Et_2O	2	14[b]
8	2	Et_3N (2.2)	THF	2	0[c]
9	2	None	CH_2Cl_2	2	57
10	0	Pyridine or Et_3N (2.2)	CH_2Cl_2	24	0

[a] Isolated yields.
[b] Addition of Tf_2O resulted in an apparently biphasic reaction mixture.
[c] Reaction mixture underwent apparent polymerization.

Table 2
Scope of the Tf_2O-mediated synthesis of oxazoles



1 2

Entry	1/2	R^1	R^2	Base	Time (h)	Yield[a] (%)
1	**1b/2b**	CO_2Me	H	Et_3N	2	56
2	**1b/2b**	CO_2Me	H	Pyridine	4	74
3	**1b/2b**	CO_2Me	H	—	2	51
4	**1c/2c**	CO_2Me	Me	Et_3N	2	75
5	**1c/2c**	CO_2Me	Me	Pyridine	2	33
6	**1c/2c**	CO_2Me	Me	Pyridine	4	50
7	**1d/2d**	CO_2Me	$CH_2CH(CH_3)_2$	Et_3N	2	56
8	**1d/2d**	CO_2Me	$CH_2CH(CH_3)_2$	Pyridine	2	64
9	**1d/2d**	CO_2Me	$CH_2CH(CH_3)_2$	—	2	57
10	**1e/2e**	Me	CH_2Ph	Et_3N	2	49
11	**1e/2e**	Me	CH_2Ph	Pyridine	2	63
12	**1e/2e**	Me	CH_2Ph	—	2	41
13	**1f/2f**	Ph	CH_2Ph	Et_3N	2	67
14	**1f/2f**	Ph	CH_2Ph	Pyridine	2	73
15	**1f/2f**	Ph	CH_2Ph	—	2	47
16	**1g/2g**	CH_2Ph	CH_2Ph	Et_3N	2	52
17	**1g/2g**	CH_2Ph	CH_2Ph	Pyridine	2	80
18	**1g/2g**	CH_2Ph	CH_2Ph	—	2	49
19	**1h/2h**	H	CH_2Ph	Et_3N	2	0
20	**1h/2h**	H	CH_2Ph	Pyridine	2	0
21	**1i/2i**	OtBu	CH_2Ph	Et_3N	4	0[b]
22	**1i/2i**	OtBu	CH_2Ph	Pyridine	4	0[b]

[a] Isolated yields.
[b] Formation of urea **6** (Fig. 1) was observed in 63% yield (with Et_3N) and 77% yield (with pyridine).

subsequent N-deprotection can then afford urea **6** rather than oxazole **2i**.

Wasserman and co-workers have shown by isotope labelling studies that the cyclodehydration of *N*-acyl-2-aminoketones with sulfuric acid proceeds via nucleophilic addition/elimination of the amide oxygen onto the carbonyl group.[22] In contrast, in the reaction of *N*-acyl amino acid esters with Tf_2O, activation of the amide rather than ester moiety is likely. An initially formed *O*-triflyliminium triflate **7** can undergo deprotonation to the imino triflate **8**, which can subsequently eliminate triflate to form the nitrilium ion **9** (Fig. 2). This proposal is in agreement with previous studies on electrophilic activation of simple secondary amides with Tf_2O/

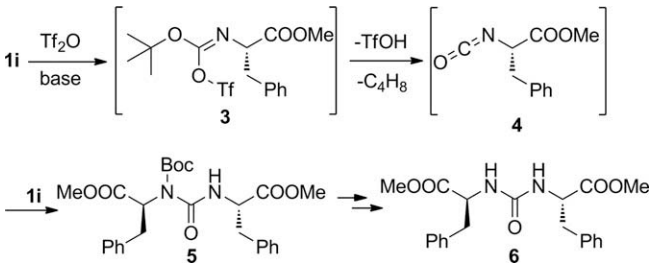


Figure 1. Proposed mechanism for formation of urea **6** from *N*Boc–Phe–OMe with Tf_2O and base, showing a possible isocyanate intermediate.

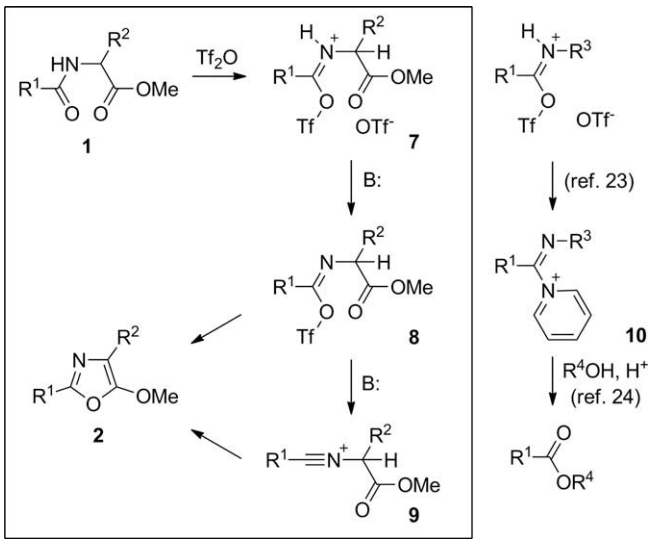


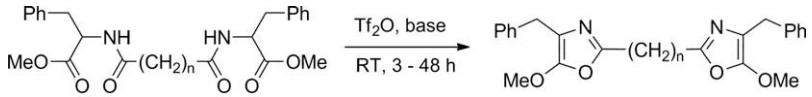
Figure 2. Proposed outline mechanism for oxazole formation.

pyridine,[23,24] where analogues of **8** and/or **9** were suggested in the formation of the pyridinium intermediate **10.** It is therefore possible that oxazoles **2** are formed by intramolecular attack of the ester carbonyl oxygen on the electrophilic carbon of intermediates **8** and/or **9**. The formation of urea **6** as described above is consistent with this mechanism.

We then turned our attention to the application of Tf_2O-mediated oxazole formation to synthetically more challenging bisoxazoles, exemplified by compounds **12a–e** (Table 3). Bisoxazoles of type **12a–b** are attractive scaffolds for designing bidentate metalloenzyme inhibitors, because the corresponding bisamides **11a–e** can be prepared easily from amino acid derivatives. Bisoxazoles have been prepared previously by oxidation of in situ-generated bisoxazolidines[25] or by cyclodehydration of activated amide derivatives.[26] Formation of two adjacent symmetrical oxazole rings as in **12a** was achieved with Tf_2O/Et_3N (31%, unoptimized, 48 h). When the reaction was quenched after 6 h, a mixture of starting material and a monocyclized oxazole was obtained. The preparation of bisoxazoles with longer alkyl linkers proceeded faster, although in mediocre yields. Attempted cyclization of malonyl and succinyl bisamides **11b** and **11c**, respectively, resulted in the formation of highly coloured products, possibly via cyclization followed by Tf_2O-mediated oxidation of the bridging methylene protons to yield conjugated aromatic systems.

Overall, we conclude that Tf_2O is a suitable reagent for the synthesis of highly functionalized oxazoles from *N*-acyl amino acid esters.

Table 3
Formation of bisoxazoles with Tf_2O (4 equiv) and base



11 **12**

Entry	**11/12**	*n*	Base (equiv)	Time (h)	Yield[a] (%)
1	**11a/12a**	0	Pyridine (4.4)	48	31
2	**11b/12b**	1	Pyridine (4.4)	6	0
3	**11c/12c**	2	Et_3N (4.4)	6	0
4	**11d/12d**	3	Et_3N (4.4)	3	33
5	**11e/12e**	10	Et_3N (4.4)	14	42

[a] Isolated yields.

Acknowledgements

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Supplementary data

General experimental section, general procedures and spectral characterization data for all new compounds (^1H, ^{13}C NMR, IR, HRMS data). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.080.

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16. *Representative typical procedure*: To a stirred solution of **1a** (100 mg, 0.38 mmol, 1 equiv) and Et_3N (116 μL, 0.83 mmol, 2.2 equiv) in dry CH_2Cl_2 (1 mL) under a nitrogen atmosphere at 0 °C was added Tf_2O (127 μL, 0.75 mmol, 2 equiv). The resulting solution was stirred vigorously and allowed to warm to room temperature. After 3 h, the mixture was washed with 1 M HCl (3 mL) and satd $NaHCO_3$ (3 mL). The organic layer was purified by column chromatography (silica gel, hexane/ethyl acetate) to afford oxazole **2a** (64 mg, 69%) as a colourless liquid.
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