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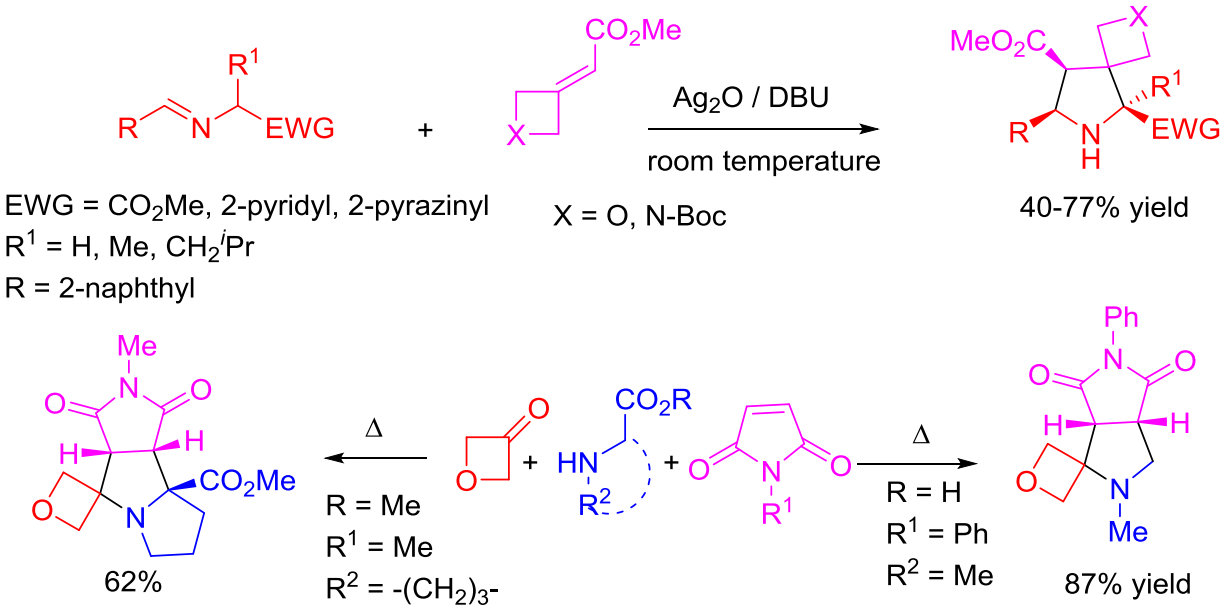
Benjamin Jones, Mitchell Proud and Visuvanathar Sridharan*



Tetrahedron Letters

Synthesis of oxetane/azetidine containing spirocycles via the 1,3-dipolar cycloaddition reaction

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ABSTRACT

Silver catalyzed 1,3-dipolar cycloaddition reactions between methyl 2-(oxetane/azetidine-3 ylidene) acetate as dipolarophiles and imines derived from α–amino acid methyl esters, 2-aminomethyl pyridine and 2-aminomethyl pyrazine afforded oxetane/azetidine containing spirocycles in 40-77% yield. The use of 3-oxetanone used as the carbonyl compound thermal 1,3-dipolar cycloaddition reactions with secondary α-amino acids or methyl esters resulted in oxetane spirocycles in 62-90% yield.

2-Oxa-5-azaspiro[3,4]octane and 2-oxa-6-azaspiro[3,4]octane are important structural motifs possessing a wide range of medicinal properties including anti-viral,[1] anti-proliferative[2] and anti-bacterial activities[3] (Figure 1).

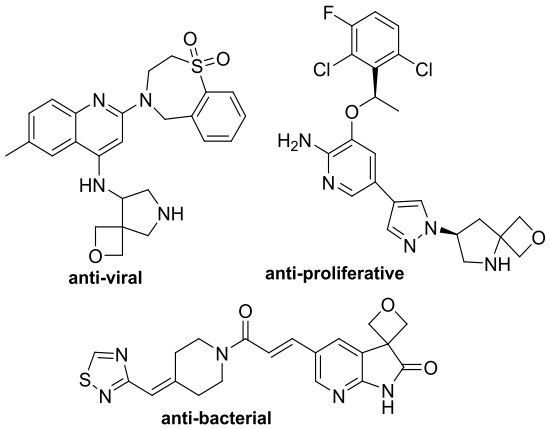

Figure 1. Spiro-oxetane containing bioactive compounds

Carreira and co-workers have introduced oxetanes as promising modules in drug discovery.[4] The four membered oxetane ring has emerged as an excellent replacement for the carbonyl group in medicinal chemistry[5] and also behaves as a less lipophilic molecular module to the gem-dimethyl unit which has resulted in improved solubility and physicochemical properties of bioactive molecules.[6]

In recent years the synthesis of diversely functionalised 3,3-disubstituted oxetanes and 2,2-disubstituted oxetanes have been reported.[7,8] However, strategies for the stereoselective assembly of complex spirocyclic, four membered ring-containing scaffolds are scarce.[9]

The synthesis of novel three dimensional scaffolds is crucial to drug discovery.[10] Obtaining large numbers of diverse, highly three-dimensional, small molecules is thus a major challenge in maintaining high-quality screening collections.

Our group and others have been involved in generating stabilized and non-stabilized azomethine ylides and subsequent 1,3-dipolar cycloaddition reactions either via a metal catalyzed route or a thermal decarboxylation pathway.[11] Asymmetric versions of the above processes are also well documented.[12]

In this communication we report the use of methyl 2-(oxetan-3-ylidene)acetate **1** and tert-butyl-3-(2-methoxy-2-oxo ethylidene)azetidine-1-carboxylate **2** (Figure 2) as dipolarophiles in the silver catalyzed 1,3-dipolar cycloaddition reaction (Scheme 1, a) as well as the thermal 1,3-dipolar cycloaddition reaction either using 3-oxetanone **3** with α-amino acids (Scheme 1, b) or with secondary α-amino acid esters (Scheme 1, c) to generate novel spirocyclic scaffolds containing the oxetane/azetidine moiety.

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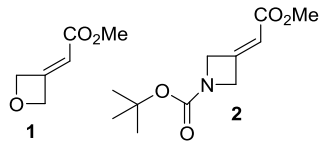
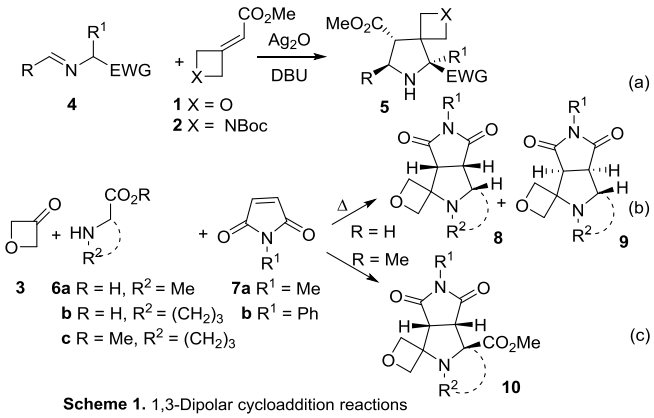
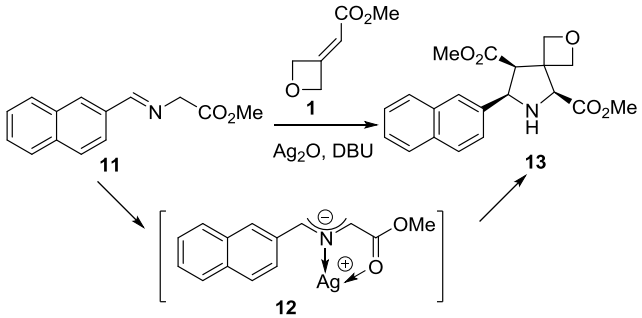


Figure 2. Examined dipolarophiles



Scheme 1. 1,3-Dipolar cycloaddition reactions

Initially we carried out the reaction of glycine, N-methyl 2-(naphthalen-2-yl methyleneamino)acetate **11** (0.5 mmol) with methyl 2-(oxetan-3-ylidene)acetate **1** (0.5 mmol), Ag_2O (10 mol%) and DBU (0.5 mmol) in toluene (10 mL) at room temperature for 16 h which cleanly afforded cycloadduct **13** as a single diastereoisomer in 77% yield (Table 1, entry 1). The relative stereochemistry of cycloadduct **13** was assigned using n.O.e studies (ESI). The cycloaddition was regio- and stereoselective and occurred via the endo transition state of the syn dipole **12** (Scheme 2).

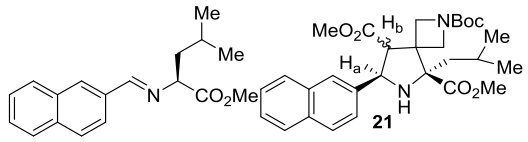


Scheme 2. Formation of the metallo dipole

Next, we explored the cycloaddition reaction by varying the amino acid esters used for imine formation whilst keeping the 2-naphthaldehyde substituent constant throughout the series as this gave the imines as crystalline solids. Thus, the reaction of imines derived from alanine methyl ester/leucine methyl ester and dipolarophile **1** afforded cycloadducts **14** and **15** in moderate yields (Table 1, entries 2-3).

Table 1. Silver catalyzed 1, 3-dipolar cycloaddition reaction[a]

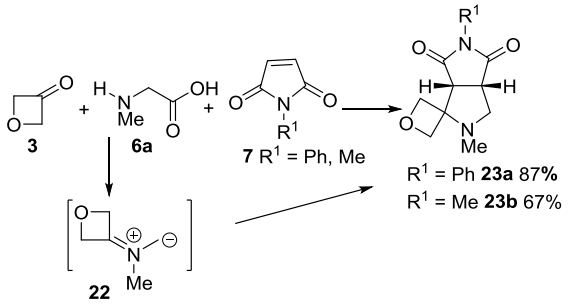
Entry	Imine	Cycloadduct	Yield (%)[b]
1			77
2			40
3			52
4			55
5			58
6			50
7			50
8			52

9		21	40[c]

[a]. Imine (0.5 mmol), dipolarophile (0.5 mmol), DBU (0.5 mmol) and Ag_2O (10 mol %), toluene, room temperature, 16 h. [b]. Isolated yield. [c]. Mixture of endo and exo (1:1 ratio) cycloadducts was obtained.

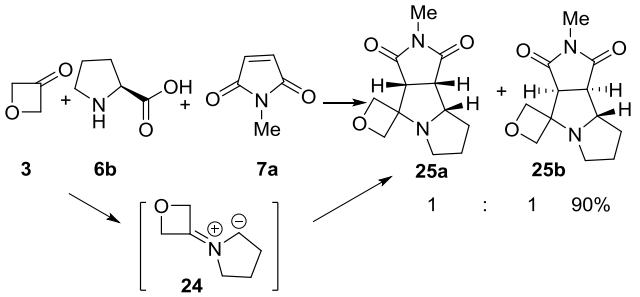
We also varied the imine activating group. Thus, 2-pyridyl and 2-pyrazinyl activating groups on the imine resulted in good yields of cycloadducts **16** and **17** (Table 1, entries 4-5). In the reaction of imine derived from 2-aminomethyl pyridine and dipolarophile **1** a small amount of the minor cycloadduct (16%) was also observed along with the major cycloadduct **16** (Table 1, entry 4). The stereochemistry of the minor cycloadduct was tentatively assigned as the epimer at the pyridyl center since the coupling constants for both major and the minor isomer pyrolidine ring protons (H_a, H_b) doublets were J = 6.8 Hz. Single diastereoisomers were obtained using tert-butyl-3-(2-methoxy-2-oxoethylidene)azetidine-1-carboxylate **2** as a dipolarophile (Table 1, entries 6-8). The imine derived from leucine methyl ester and dipolarophile **2** resulted in an in separable mixture of endo and exo cycloadducts (1:1 ratio) (Table 1, entry 9). Again the stereochemistry of the isomeric cycloadduct was tentatively assigned on the basis of the coupling constants of the pyrolidine protons (H_a, H_b) doublets are endo isomer J = 9.5 Hz and exo isomer J = 8.5 Hz and by assuming both cycloadducts arose via the syn dipole.

We briefly explored the reaction illustrated in Scheme 1, path b. Thus, 3-oxetanone **3** (1 mmol), sarcosine **6a** (1 mmol) and N-phenylmaleimide **7b** (1 mmol) in toluene (10 mL) at 110 °C for 24 h afforded cycloadduct **23a** in 87% yield (Scheme 3). Changing the dipolarophile to N-methylmaleimide resulted the formation of cycloadduct **23b** in 67% yield (Scheme 3).



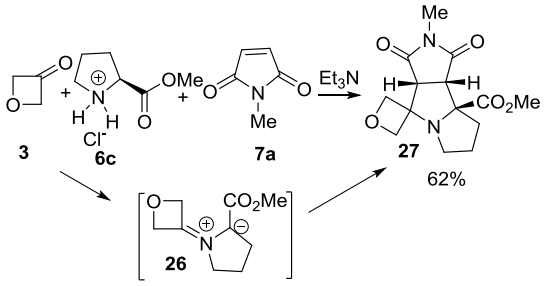
Scheme 3. Three component cycloaddition reaction

Next, we varied the amino acid from sarcosine to proline **6b** in the three component cycloaddition reaction. Thus, proline **6b** (1 mmol), 3-oxetanone **3** (1 mmol) and N-methylmaleimide **7a** (1 mmol) in toluene (10 mL) at 110 °C for 24 h afforded the endo and exo cycloadducts **25a** and **25b** (1:1 ratio) in 90% yield via dipole **24** (Scheme 4). The relative stereochemistry of the cycloadducts were assigned using n.O.e studies.



Scheme 4. Three component cycloaddition cascade

Finally, we explored the reaction illustrated in (Scheme 1, path c). Thus 3-oxetatone 3 (1 mmol), proline methylester hydrochloride (1 mmol), N-methylmaleimide (1 mmol) and triethylamine (1 mmol) in toluene (10 mL) at 110 °C for 24 h afforded endo cycloadduct **27** in 62% yield (Scheme 5).



Scheme 5. Iminium ion route to azomethine ylide

In summary we have successfully carried out two or three component cycloaddition reactions to give oxetane/azetidine containing spirocycles in good yields.

Supporting Information

Supporting Information. Experimental details, characterization data and copies of NMR spectra of novel compounds.

ACKNOWLEDGMENT

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REFERENCES

1. Chen, L.; Feng, L.; Feng, S.; Gao, L.; Guo, T.; Huang, M.; Liang, C.; Liu, Y.; Wang, L.; Wong, J. C. PCT Int. Appl. WO/2013/020993
2. LI, M.; Zhou, X.; Wu, Y. PCT Int. Appl. WO/2014/072930 A3.
3. Mohamed, T.; Hosahalli, S.; Panigrahi, S. K. PCT Int. Appl. WO /2013/148537 A1.
4. (a) Wuitschik, G.; Rogers-Evans, M.; Muller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. Angew. Chem. Int. Ed. **2006,** 45, 7736-7739.
5. Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. J. Med. Chem. **2010,** 53, 3227-3246.
6. Davis, O. A.; Bull, J. A., Synlett **2015,** 26, 1283-1288.

7. (a) Vigo, D.; Stasi, L.; Gagliardi, S. Tetrahedron Lett **2011,** 52, 565-567; (b) Monleon, A.; Glaus, F.; Vergura, S.; Jorgensen, K. A. Angew. Chem. Int. Ed. **2015**, 55, 1-6.
8. Davis, O. A.; Croft, R. A.; Bull, J. A. Chem. Commun. **2015,** 51, 15446-15449.
9. Carreira, E. M.; Fessard, T. C. Chem. Rev. **2014,** 114, 8257-8322.
10. Nadin, A.; Hattotuwagama, C.; Churcher, I. Angew. Chem. Int. Ed. **2012**, 51,1114-1122.
11. (a) Grigg, R.; Sridharan, V. Advances in Cycloaddition.**1993**, 3, 161-204; (b) Coldham, I.; Hufton, R. Chem. Rev.**2005,** 105, 2765-810.
12. (a) Najera, C.; Sansano, J. M. Angew. Chem. Int. Ed. **2005,** 44, 6272-6276; (b) Pandey, G.; Banerjee, P.; Gadre, S. R. Chem. Rev. **2006**, 106, 4484-4517; (c) Aldrio, J.; Carretero, J. C. Chem. Commun. **2014**, 50, 12434-12446.