Tandem multi-step synthesis of *C*-carboxyazlactones promoted by N-heterocyclic carbenes†

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Received (in Cambridge, UK) 22nd April 2008, Accepted 20th June 2008
First published as an Advance Article on the web 7th July 2008
DOI: 10.1039/b806816j

Cascade reaction sequences incorporating N-heterocyclic carbene-based organocatalysis have been developed that allow the direct preparation of a range of (±)-4-phenoxycarbonylazlactones in good isolated yields (66–84%) from the corresponding *N*-*p*-anisoyl amino acids.

The development of tandem reaction processes that permit the efficient introduction of molecular complexity from simple starting materials in a single reaction sequence is highly desirable. Many such sequential transformations have been used in synthesis, with several reviews dedicated to this topic.[1] The area of organocatalysis has enjoyed immense popularity in the last decade,[2] and a number of organocatalytic processes that incorporate tandem reaction sequences have been developed.[3] N-heterocyclic carbenes (NHCs) are commonly used as ligands in organometallic processes,[4] and in recent years have been employed as organocatalysts in a remarkably diverse series of reactions.[5] As part of a programme of research concerned with developing alternative organocatalytic uses of NHCs,[6] we have previously shown that triazolinylidenes, generated by deprotonation of a triazolium salt with a metallated base such as KHMDS, can efficiently promote the Steglich rearrangement[7,8] of oxazolyl carbonates.[9] As relatively limited studies concerning multi-component reactions incorporating NHC-mediated catalysis have been disclosed,[10] the inclusion of this rearrangement procedure in a tandem reaction sequence was investigated. Oxazolyl carbonates **2** are readily prepared from the corresponding azlactone **1** by treatment with a chloroformate under basic conditions, and given the ability to generate NHCs by deprotonation of an azolium salt, the amalgamation of these two steps into a tandem process was envisaged (Fig. 1).[11,12]

Herein we demonstrate that sub-stoichiometric quantities of NHCs (5 mol%) promote the formation of *C*-carboxyazlactones (±)-**3** from azlactones **1** in a two-step tandem reaction process, and extend this protocol to multi-step reaction sequences.

Primary model studies focused upon optimising the use of NEt_3 to promote carbonate formation and the desired rearrangement to give (±)-**7** from azlactone **4** in the presence of 5 mol% of triazolium salt **5** (pK_a in aqueous solution 17.7).[13–15] Addition of phenyl chloroformate (1.1 equiv.) to a THF solution of triazolium salt **5** (5 mol%), NEt_3 (1.3 equiv.) and azlactone **4** (1 equiv.) gave a 33 : 67 ratio of **6** : (±)-**7** (Table 1, entry 1), with optimal conversion to (±)-**7** observed upon increasing the molar equivalents of NEt_3 and phenyl chloroformate (entry 2). Approximately 20% of carbamate **8** was observed as a by-product of this optimised process,[16] with purification affording (±)-**7** in 81% yield. Increased quantities of NEt_3 and phenyl chloroformate were detrimental to the formation of (±)-**7** (entry 3), giving increased amounts (~70%) of carbamate **8**. A simple control experiment showed that excluding triazolium salt **5** from the reaction manifold gave oxazolyl carbonate **6** and carbamate **8** as the sole reaction products, consistent with the need for *in situ* NHC generation to promote rearrangement of carbonate **6** to (±)-**7**.

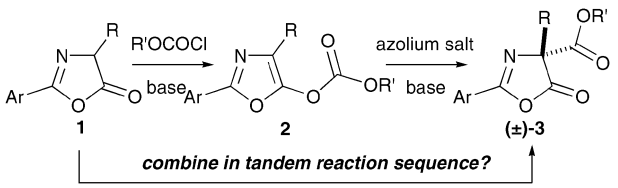
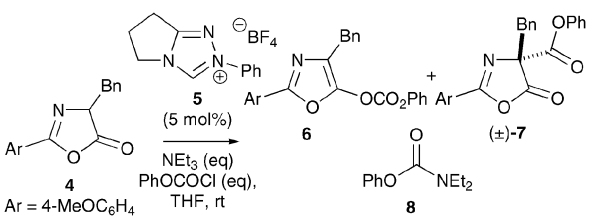


Fig. 1 Proposed two-step carbonate formation–rearrangement protocol.

Table 1 Optimisation of a two-step tandem reaction protocol



Entry	NEt_3 (equiv.)	PhOCOCl (equiv.)	Conversion[a]	Ratio **6** : (±)-**7**[a]
1	1.3	1.1	75%	33 : 67
2	1.5	1.3	>95%	10 : 90 (81%)[b]
3	2.3	1.3	>95%	65 : 35

[a] Reaction conversions and product ratios were judged by ^{1}H NMR spectroscopic analysis of the crude reaction product and were measured with respect to azlactone **4**. [b] Isolated yield of homogeneous (±)-**7** after chromatographic purification.

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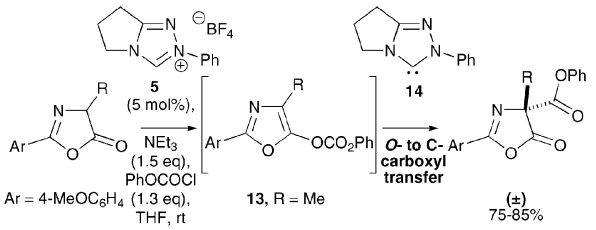
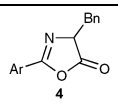
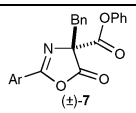
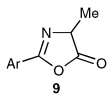
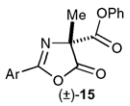
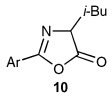
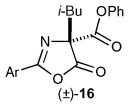
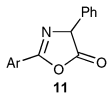
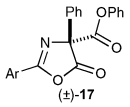
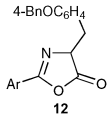
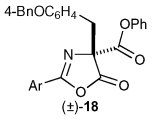
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new products. See DOI: 10.1039/b806816j

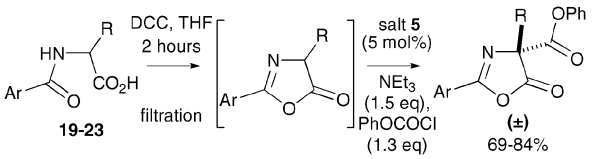
Table 2 Probing the generality of the two-step tandem reaction protocol

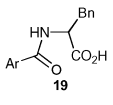
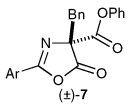
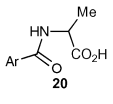
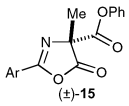
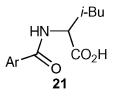
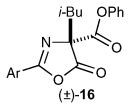
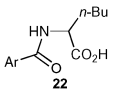
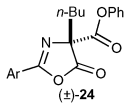
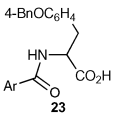
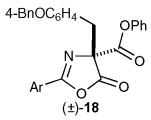


Entry	Azlactone	Product	Yield (%)[a]
1	 **4**	 (±)-**7**	81
2	 **9**	 (±)-**15**	81
3	 **10**	 (±)-**16**	85
4	 **11**	 (±)-**17**	75
5	 **12**	 (±)-**18**	81

[a] Isolated yield of homogeneous product after chromatographic purification.

Table 3 Tandem reaction protocol incorporating DCC coupling, carbonate formation and NHC-promoted *O*- to *C*-carboxyl transfer



Entry	Acid	Product	Yield (%)[a]
1	 **19**	 (±)-**7**	71
2	 **20**	 (±)-**15**	69
3	 **21**	 (±)-**16**	70
4	 **22**	 (±)-**24**	73
5	 **23**	 (±)-**18**	84

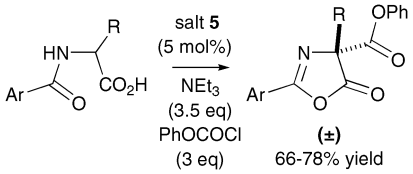
[a] Isolated yield of homogeneous product after chromatographic purification.

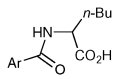
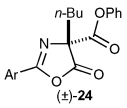
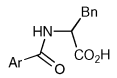
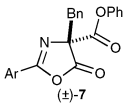
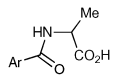
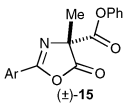
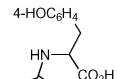
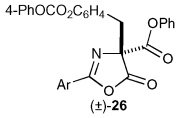
The generality of this two-step tandem reaction process was next established, with azlactones **9–12** readily converted to their corresponding *C*-phenoxycarbonylazlactones under these optimised conditions (Table 2), with chromatographic purification giving (±)-**15**–(±)-**18** in 75–85% isolated yields (entries 2–5).[17] Monitoring the consumption of azlactone **9** in this tandem reaction sequence by ^{1}H NMR spectroscopic analysis confirmed full conversion to oxazolyl carbonate **13** as the sole reaction product after short reaction times (1 to 15 min), with subsequent rearrangement of carbonate **13** to (±)-**15**. This reaction profile is consistent with oxazolyl carbonate **13** being an intermediate in this reaction pathway rather than direct *C*-carboxylation of azlactone **9** promoted by NHC **14** under the reaction conditions.

As azlactones such as **4** and **9–12** are typically prepared from the corresponding *N*-*p*-anisoyl amino acids by carboxylate activation and cyclisation, the incorporation of this transformation into a cascade reaction sequence was investigated (Table 3). Treatment of *N*-*p*-anisoyl phenylalanine **19** with DCC in THF,[8a,c,18] followed by filtration of the urea by-product after 2 h, and sequential addition of triazolium salt **5**, NEt_3 and phenyl chloroformate directly to the filtrate gave good conversion to (±)-**7**, allowing its isolation in 71% yield after chromatography (entry 1). This process also allowed *N*-*p*-anisoyl amino acids **20–23** to be readily converted to the corresponding *C*-phenoxycarbonylazlactones in 69–84% isolated yields (entries 2–5).

As an alternative one-pot procedure for the direct preparation of *C*-phenoxycarbonylazlactones from *N*-*p*-anisoyl amino acids, the use of phenyl chloroformate to promote cyclisation and participate in oxazolyl carbonate formation was attempted.[19] It was anticipated that an excess of phenyl chloroformate would be necessary in this protocol to sequester the phenoxide generated upon azlactone formation in this reaction cycle, generating inert diphenyl carbonate.[20] Addition of phenyl chloroformate (3 equiv.) to a solution of *N*-*p*-anisoyl norleucine **22**, NEt_3 (3.5 equiv.) and triazolium salt **5** (5 mol%) proceeded with complete conversion to (±)-**24** within 10 min, giving diphenyl carbonate in 95% yield and (±)-**24** in 75% yield after chromatography (Table 4, entry 1). To further exemplify this one-pot multi-step protocol, *N*-*p*-anisoyl amino acids **19**, **20** and **25** were directly converted to their corresponding *C*-phenoxycarbonylazlactones (±)-**7**, (±)-**15** and (±)-**26** in 66-78% isolated yield. Notably, *N*-*p*-anisoyl tyrosine **25** could be utilised in this protocol to give directly *O*-phenoxycarbonyl protected azlactone (±)-**26** in 66% isolated yield, involving a reaction sequence that presumably involves initial acid activation and cyclisation, phenolic

Table 4 Tandem multi-step reaction protocol incorporating NHC-promoted *O*- to *C*-carboxyl transfer



Entry	Acid	Product	Yield (%)[a]
1	 **22**	 (±)-**24**	75
2	 **19**	 (±)-**7**	71
3	 **20**	 (±)-**15**	78
4[b]	 **25**	 (±)-**26**	66

[a] Isolated yield of homogeneous product after chromatographic purification. [b] Reaction conditions employed: NEt_3 (5.5 equiv.), PhOCOCl (5 equiv.), salt **5** (10 mol%), THF, rt.

O-protection, oxazolyl carbonate formation and subsequent chemoselective NHC mediated rearrangement to give the desired product.[21] Both of these multi-step reaction protocols are chemically robust as they proceed without employing an inert atmosphere or rigorously dried THF or reagents.

In conclusion, we have shown that NHC **14**, generated from triazolium salt **5** with NEt_3, can promote the rearrangement of oxazolyl carbonates to their corresponding *C*-carboxyazlactones, allowing this NHC mediated rearrangement protocol to be incorporated into tandem multi-step reaction sequences. Current studies are focused upon developing efficient enantioselective versions of these reaction processes alongside developing alternative applications of NHCs in asymmetric catalysis.

The authors would like to thank the Royal Society for a University Research Fellowship (ADS), The Carnegie Trust for the Universities of Scotland for a scholarship (CDC), The Leverhulme Trust (ND), EaStCHEM and the University of St Andrews (JET) for funding.

Notes and references

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15. See supporting information for full details of the methods used for this pK_a determination.
16. An authentic sample of carbamate **8** was prepared by treatment of phenyl chloroformate with NEt_3 in THF at rt, giving carbamate **8** in 68% isolated yield. See supporting information for full details.
17. In each case, the crude reaction product also contained 10–20% of carbamate **8**.
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20. Attempts to use diphenyl carbonate as an alternative to phenyl chloroformate to generate oxazolyl carbonates from azlactones in the presence of NEt_3 returned only starting material.
21. Fries type rearrangement was not observed in this reaction sequence. Furthermore, treatment of diphenyl carbonate with NHC **14** (9 mol%) derived from salt **5** (10 mol%) and KHMDS (9 mol%) returned only starting material after prolonged reaction times or upon heating.

