Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 8294

Received 11th September 2013,
Accepted 1st November 2013

DOI: 10.1039/c3ob41858h

www.rsc.org/obc

Organocatalyzed stereospecific C–C bond formation of β-lactams†

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Herein, we report the development of mild, organocatalyzed routes to novel carbapenam derivatives through aldol, Mannich and Michael C–C bond forming reactions.

Compounds containing β-lactams (Fig. 1) are amongst the most important molecules in clinical use today.[1–3] Most notable is their wide utility as antibacterial agents and as related β-lactamase inhibitors; however, β-lactams are also being explored in other therapeutic areas.[4,5] Given the global challenge of antibiotic resistance,[6] there is an urgent need for increased focus on the discovery and development of antibacterial agents. Bacterial resistance may occur through a number of pathways, *e.g.* production of β-lactamases,[7] efflux pumps, and mutations that alters expression and function of transpeptidase enzymes – the targets of most β-lactam antibiotics.[8,9] As β-lactams function as both transpeptidase- and β-lactamase inhibitors, much work is being devoted to accessing novel analogs of these critical molecular frameworks.[10] However, the commercially viable synthesis of many β-lactams remains challenging due to a high degree of functionalization and chirality combined with the reactive nature of the core bicyclic ring-structures. Furthermore, most β-lactam antibiotics, except carbapenems and aztreonam, are being produced by biosynthetic routes rather than through chemical synthesis. Considering the challenges associated with synthetic modifications of the β-lactam framework, we envisioned that the mild conditions offered by organocatalysis might help overcome some of the limitations of current methodologies and open en route to hitherto unexplored β-lactams.

During the past decade, asymmetric organocatalysis[11–13] has grown extensively as a powerful tool in the construction of

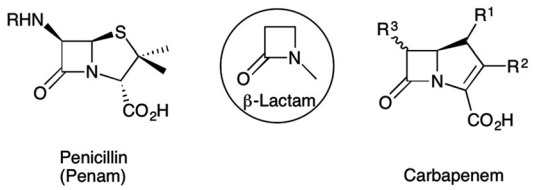
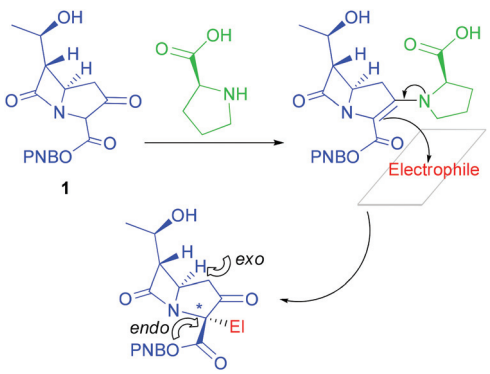


Fig. 1 Examples of β-lactam antibiotics: generic structure of penicillins with a saturated penam core and of synthetic carbapenems (*e.g.* imipenem, thienamycin, and panipenem).



Scheme 1 Novel HOMO rising strategies offering a mild and facile route to carbapenam derivatives.

complex molecular skeletons in synthetic chemistry.[14–19] Aldol,[15,20–24] Mannich[15,25,26] and Michael[15,27,28] reactions are some of the most powerful strategies in synthetic organic chemistry, since it allows the formation of new C–C bonds.[29]

We envisaged that (*2S*,*5R*,*6S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (**1**), the common intermediate for the preparation of clinically used antibiotics imipenem,[30] thienamycin[31,32] and panipenem,[33] could be further substituted *via* HOMO-rising amine catalysis,[34] thereby promoting reactions with electrophilic substrates (Scheme 1).

In order to test our hypothesis, we subjected the "carbapenam ketone" intermediate **1** to a reaction with the benchmark

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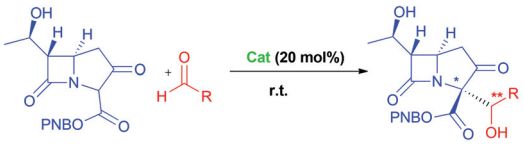
†Electronic supplementary information (ESI) available: Experimental details and copies of NMR spectra. See DOI: 10.1039/c3ob41858h

Table 1 Aldol reaction of carbapenam ketone intermediate **1** with aldehyde *via* enamine activation



1

2, R = H, *d.r.$^{(c)}$ > 99:1,
3, R = Ph, *d.r.$^{(c)}$ > 99:1, **d.r.$^{(c)}$ = 90:10
4, R = 4-NO_2 Ph, 5, R = 4-Me Ph,
6, R = 2, 4-OMe Ph, 7, R = 4-F Ph,
8, R = Et

Entry	R	Catalyst/additive	Time (h)	Solvent	Yield[b] (%)
1	R = H	L-Proline	24	DMSO	73
2	R = H	L-Proline/AcOH	24	DMSO	74
3	R = H	L-Proline/AcOH	8	Neat	76
4	R = H	D-Proline	24	DMSO	70
5	R = H	Pyrrolidine	24	DMSO	NR
6	R = H	Pyrrolidine/AcOH	2	DMSO	60
7	R = H	NEt_3	24	DMSO	NR
8	R = H	NEt_3/AcOH	24	DMSO	NR
9	R = Ph	L-Proline	24	DMSO	NR
10	R = Ph	L-Proline/AcOH	24	DMSO	NR
11	R = Ph	L-Proline/AcOH	6	Neat[a]	60
12	R = Ph	L-Proline/AcOH	24	DMF	25[d]
13	R = Ph	Pyrrolidine/AcOH	24	DMF	55[d]
14	R = 4-NO_2 Ph	Pyrrolidine/AcOH	24	DMF	54[d]
15	R = 4-Me Ph	Pyrrolidine/AcOH	24	DMF	29[d]
16	R = 4-OMe Ph	Pyrrolidine/AcOH	24	DMF	51[d]
17	R = 2,4-OMe Ph	Pyrrolidine/AcOH	24	DMF	26[d]
18	R = 4-F Ph	Pyrrolidine/AcOH	24	DMF	46[d]
19	R = Et	Pyrrolidine/AcOH	48	DMF	70[d]

[a] Reactions were performed at excess amount of aldehyde to serve as a solvent (see ESI). [b] Isolated yields. [c] Diastereomeric ratio determined by ^{1}H NMR. [d] Observed yields from NMR of the crude reaction mixture.

substrate formaldehyde as the electrophile and proline as the catalyst, Table 1. Various solvents such as DMF, DCM and THF were evaluated but no conversion was observed *via* LC-MS except when DMSO was employed (Table 1, entry 1). When the reactions were conducted with reagent grade DMSO as the solvent, we observed the presence of the product and a hydrolyzed form of the starting materials (+18 *m*/*z* on LC-MS). The use of dry DMSO resulted in no detection of the hydrolyzed starting material but also resulted in a slower and low yielding reaction. Acid additives are common additives in the organocatalyzed aldol reactions,[35] so we next investigated the effect of formic and acetic acids. It was observed that there was no difference in the reactivity or yields when acetic acid was used (Table 1, entry 2) whereas formic acid enhanced the hydrolysis side reaction.

Under solvent free conditions, the rate of the reaction was improved significantly (Table 1, entry 3). D-Proline gave similar results as L-proline with respect to reaction times and yields (Table 1, entries 1 and 4), but also with respect to the diastereomeric ratio of the product formed. This result shows that the stereochemical outcome of the reaction is dictated by the chiral ketone **1** rather than the catalyst, as might be expected when considering the unique bent conformation of the cyclobutanone ring at the bicyclic core. This prompted us to evaluate simple pyrrolidine as a catalyst; pyrrolidine on its own did not result in any conversion but when one equivalent of acetic acid was added we obtained the product at a high conversion rate (Table 1, entries 5, 6).

In order to prove that the reaction was indeed operating through the postulated enamine intermediate, and did not simply involve the enol tautomer of ketone **1**, we performed the reaction with triethylamine as a catalyst, with and without acetic acid; however, no reaction was observed in any of these cases (Table 1, entries 7, 8), thus supporting the need for HOMO rising catalysis of the reaction. Aromatic aldehydes, *i.e.* benzaldehyde as the electrophile, did not result in any conversion in DMSO (Table 1, entries 9, 10). However, benzaldehyde and other liquid aldehydes (*e.g.* 4-methyl and 4-fluoro benzaldehyde) gave the corresponding aldol product under neat reaction conditions (Table 1, entry 11) as detected by LC-MS. Unfortunately, purification *via* chromatography for all analogs except the benzaldehyde product **3** proved difficult since the β-lactam ring is prone to hydrolysis during prolonged exposure to silica gel. However, aromatic aldehydes, *i.e.* 4-nitro, 4-methyl, 4-methoxy, 4-fluoro benzaldehyde and propionaldehyde, gave the product upon changing the solvent from DMSO to DMF, utilizing pyrrolidine/AcOH as a catalyst. Again purification proved difficult; crude NMR yield for the reaction of

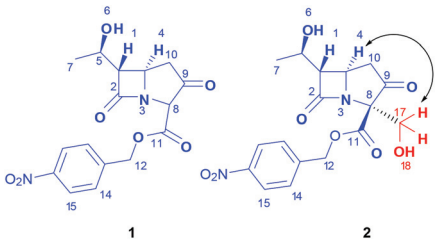


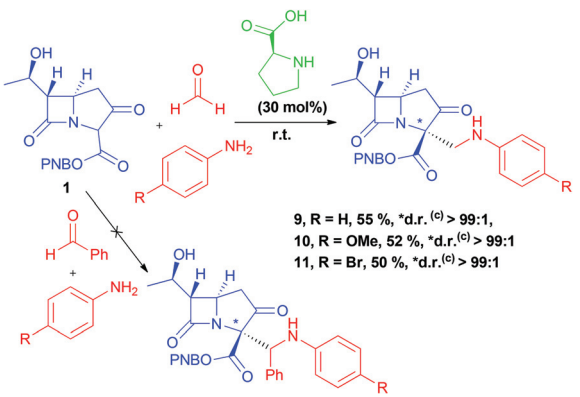
Fig. 2 Aldol product **2**, resulting from L-proline catalyzed transformation of "carbapenam ketone" **1** and Formaldehyde.

these electrophiles with carbapenem ketone **1** was in the range 26–70% as determined by crude NMR (Table 1, entries 12–19).

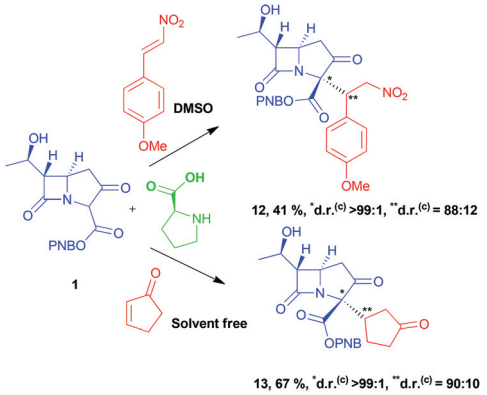
The formation of the new C–C bond in product **2** was confirmed by observing the shift of C_8 from 64.0 ppm (**1**) to 131.6 ppm (**2**) in ^{13}C NMR and disappearance of H_8 as a singlet at 4.76 ppm (**1**) in H-NMR, Fig. 2. In addition, protons at C_{17} showed an HMBC correlation with C_8. The 2D NMR investigation proved the excellent stereoselectivity (d.r. >99 : 1) seen in the crude LC-MS trace and 1D spectra, and through a correlation between H_{17} and H_4 in the NOESY spectra, we could establish the expected *exo* configuration of the newly attached group in **2**. Compound **3** showed similar HMBC correlations and excellent diastereoselectivity as observed with **2** for the formation of the C–C bond at C_8. The newly formed chiral centre C_{17} in compound **3** was determined to be created with a diastereomeric ratio of 90 : 10.

Given the high potential for using organocatalysis for accessing hitherto unexplored derivatives of carbapenam and carbapenem β-lactams, we decided to explore other organocatalyzed processes, *i.e.* Mannich and Michael reactions.

First, we decided to perform the direct asymmetric three-component Mannich reaction of carbapenam intermediate **1** with different amines and aldehydes in DMSO (Scheme 2). In the presence of 30% L-proline, aldehydes and amines were reacted with **1** to give products **9**, **10** and **11** in moderate yields (50% to 55%) respectively. These yields are typical of the one pot Mannich reaction and are attributed to the formation of the competitive aldol reaction side products as noticed by LC-MS. Various aromatic aldehydes were tested as electrophiles, but, similarly to the aldol reaction described above,



Scheme 2 Mannich reactions on carbapenam intermediate **1**.



Scheme 3 Michael reaction on carbapenam intermediate **1**.

only formaldehydes resulted in the formation of the Mannich adducts. A complete NMR assignment of Mannich product **9** proved that the *exo*-product was formed with complete diastereoselectivity, in analogy to the aldol product **2** above. In compound **9**, the absolute configuration at C_8 was confirmed by NOE correlation (see ESI†).

Next, we explored the organocatalyzed Michael reaction to carbapenam intermediate **1** (Scheme 3). The most commonly studied Michael acceptors with enamine catalyzed reactions are nitrostyrenes[28,36] and enones;[37] hence it was decided to test these substrates in this first report. From the optimized conditions reported above, we initiated the study by examining the addition of the carbapenam intermediate **1** to *trans*-4-methoxy-β-nitrostyrene in DMSO catalyzed by L-proline. The reaction offered the product **12** in modest 41% yield in 24 hours. The modest yield was due to low catalytic turnover, as confirmed through LC-MS analysis of the crude mixture, where we noticed a peak that corresponded to the Michael product still bound to the catalyst. To release the product, the adduct had to be stirred with water and monitored by LC-MS until only a minor amount of the trapped product could be detected. Similarly, Michael reaction of carbapenam intermediate **1** with neat cyclopentenone using L-proline as a catalyst produced compound **7** in 67% yield. The observed HMBC correlation between H_{17} and C8 in both compounds (**12** and **13**) proved the formation of the new C–C bond at this position. From the ^1H NMR shifts of H_{17} in compounds **12** and **13**, the diastereomeric ratio was established to be 88 : 12 and 90 : 10 respectively. The configuration at C_8 for **12** was also established by NOE correlation as for the aldol and Mannich reactions above.

In summary, the mild reaction conditions that characterize enamine-based organocatalysis have been shown to offer a new route to chiral β-lactam derivatives. The reaction scope has so far been shown to include aldol, Mannich and Michael reactions. High distereoselectivity was observed in all of the reactions, as would be expected considering the inherent chirality of the starting carbapenam intermediate. This methodology has the potential to offer a widely sought after, new synthetic route to novel and potentially medically useful β-lactam antibiotics.

The full substrate scope for the Mannich and Michael reactions reported here are ongoing in our laboratories.

Acknowledgements

We thank NRF, UKZN and Asphen Pharmacare for financial support.

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