Tetrahedron Letters 53 (2012) 2273–2276

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel sugar based intramolecular Ugi 3CC for the *N*-alkyl-3-oxo-4-aryl-octahydrofuro[2,3-*f*][1,4]oxazepine-5-carboxamides

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ARTICLE INFO

Article history:
Received 3 November 2011
Revised 10 February 2012
Accepted 11 February 2012
Available online 26 February 2012

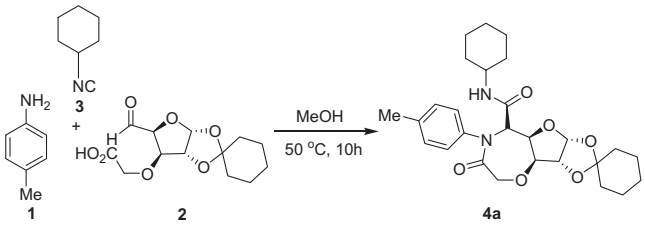
Keywords:
Ugi three component coupling
Carboxy tethered sugar aldehyde
Oxazepine derivatives

ABSTRACT

An intramolecular Ugi reaction of 3-carboxy tethered sugar aldehyde with aryl amines and isocyanides has been accomplished to produce a novel class of carbohydrate derivatives, 3-oxo-4-aryl-octahydrofuro[2,3-*f*][1,4]oxazepine-5-carboxamides in good yields. The stereochemistry of the products was assigned by NMR studies. This is the first report on intramolecular Ugi reaction of 3-carboxy tethered sugar aldehyde, aryl amine, and isonitrile.

In recent years; the pharmaceutical industry has focused more and more on diversity-oriented combinatorial libraries.[1] Multicomponent reactions (MCRs) are powerful tools for generating combinatorial libraries to drug discovery.[2] MCRs are atom efficient and are extremely convergent, producing a high molecular complexity in a single step process.[3] Of these, isocyanide based MCRs such as Ugi[4] and Passerini reactions are the most popular especially in medicinal chemistry.[5] The ability of isonitriles to undergo facile addition either with nucleophile or with electrophile under mild conditions makes them useful reactants for the development of novel MCRs.[6,7] Recently, a new version of isocyanide-based MCRs with keto acids have been developed as bifunctional reagents.[8] The coupling of keto acids with amines and isocyanides provides the carbamoyl derivatives of four-, five-, six-, seven-, and eight-membered lactams.[9–11] However, to the best of our knowledge, there are no reports on the isocyanide-based Ugi reaction of bifunctional sugar aldehydo carboxylic acid, aryl amine, and isonitrile.

Following our interest on the synthesis of sugar annulated heterocycles[12] we herein report a novel strategy for the synthesis of *N*-alkyl-3-oxo-4-aryl-octahydrofuro[2,3-*f*][1,4]oxazepine-5-carboxamide derivatives via intramolecular Ugi reaction. Initially, we attempted the coupling of *p*-toluidine (**1**) with 3-carboxy sugar aldehyde (**2**) and cyclohexyl isocyanide (**3**). Interestingly, the



Scheme 1. Preparation of oxazepine **4a** via three-component reaction.

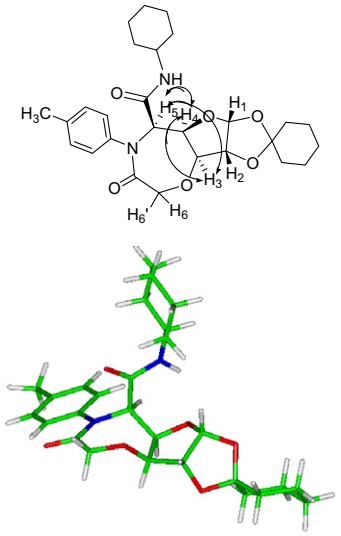


Figure 1. Characteristic nOe's and energy-minimized structure of **4a**.

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doi:10.1016/j.tetlet.2012.02.048

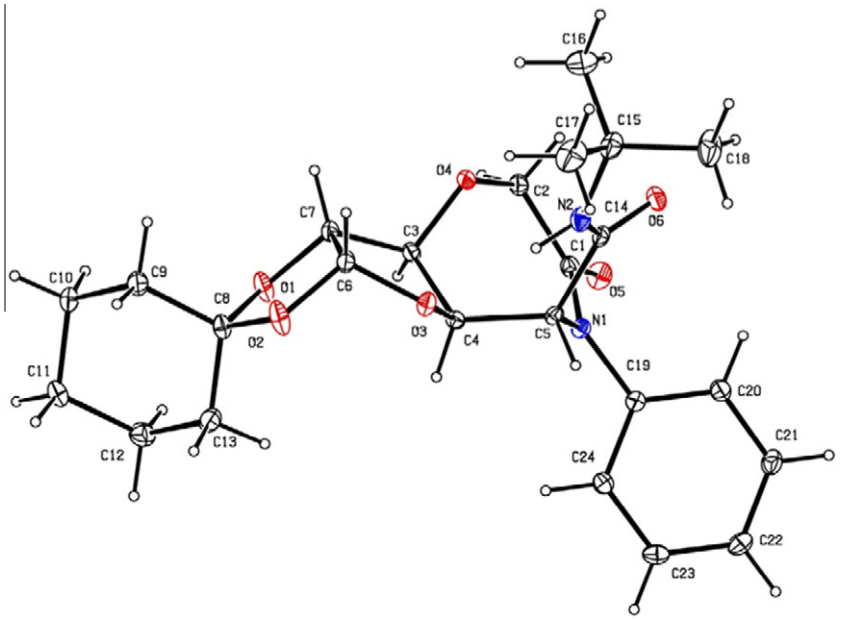


Figure 2. X-ray crystal structure of **4f**.

Table 1
Sugar based intramolecular Ugi reaction

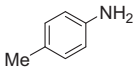
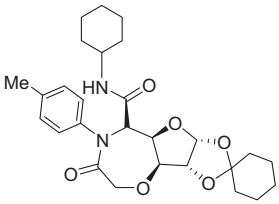
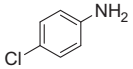
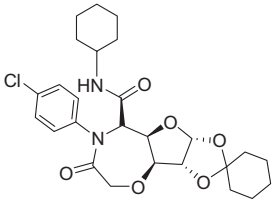
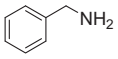
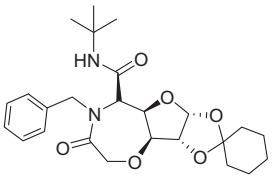
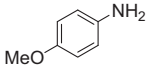
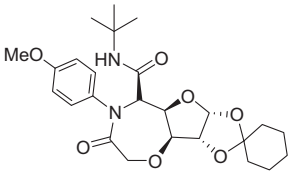
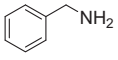
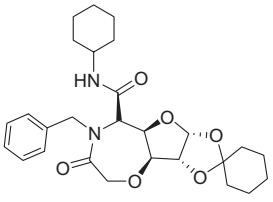
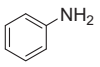
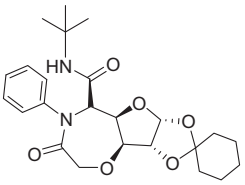
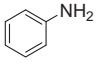
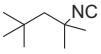
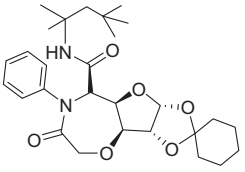
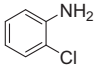
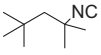
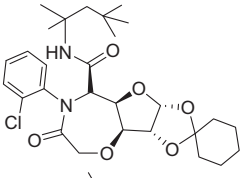
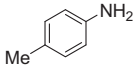
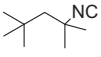
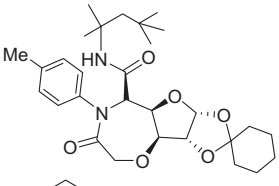
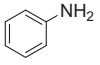
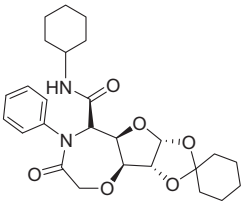
Entry	Aryl amine (**1**)	Isonitrile (**3**)	Product[a] (**4**)	Time (h)	Yield[b] (%)
a				10	82
b				10	77
c				12	72
d				13	78
e				11	84

Table 1 (*continued*)

Entry	Aryl amine (**1**)	Isonitrile (**3**)	Product[a] (**4**)	Time (h)	Yield[b] (%)
f				10	83
g				13	75
h				13	70
i				13	72
j				10	83

[a] All the reactions were characterized by NMR, IR, and mass spectroscopy.
[b] Isolated yields after chromatography.

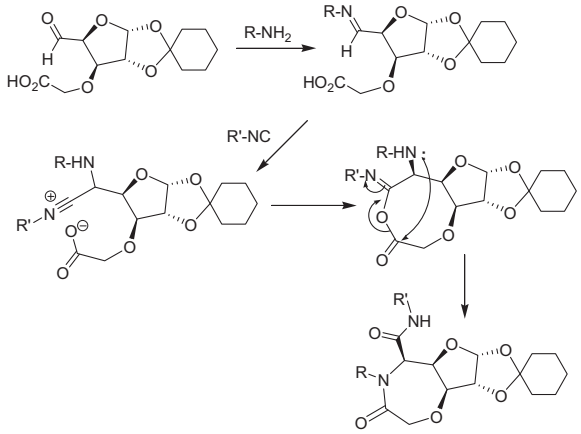
reaction proceeded smoothly in methanol at 50 °C and the desired sugar annulated oxazepine derivative **4a** was obtained in 82% yields (Scheme 1).

The stereochemistry of **4a** was confirmed by nOe studies. The presence of strong nOe between H4 and H5 indicates that both are *cis*. The nOe cross peaks between H3 and H5 also suggest that H3 and H5 are also *cis* to each other. The energy-minimized structure further supports the assigned structure for **4a** (Fig. 1).

The structure of product **4f** was further confirmed by X-ray crystallography (Fig. 2).[13]

This result provided the incentive for further study of reactions with various aryl amines such as aniline, *p*-chloroaniline, *p*-methoxyaniline, and *o*-chloroaniline (Table 1). The 3CC reaction was also successful with benzyl amine (Table 1, entries c and e). In all the cases, the reactions are clean and provide the desired oxazepine derivatives in good yields. Other isocyanides such as *t*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide also participated effectively in this reaction (Table 1, entries c, d and f–i). As solvent, methanol appeared to give the best results. A variety of functional groups such as cyclic acetal, *N*-alkyl amide, and cyclic lactam are well-tolerated.

Mechanistically, we assume that imine may be formed in situ from sugar aldehyde and aryl amine. Followed by the attack of isocyanide on imine would give iminolactone. This adduct undergoes simultaneously an intramolecular cyclization with a secondary amine to give the seven-membered lactam as depicted in Scheme 2.



Scheme 2. A plausible reaction pathway.

The products were fully characterized and confirmed by NMR, IR, and mass spectrometry. The scope and generality of this process is illustrated with respect to various aryl amines and isonitriles and the results are presented in Table 1.[14]

In summary, we have demonstrated for the first time the sugar based intramolecular Ugi reaction for the synthesis of highly functionalized furo[2,3-*f*][1,4]oxazepine derivatives from readily avail-

able precursors under neutral conditions. It is entirely a new strategy to produce sugar annulated oxazepine derivatives in a single-step process.

Acknowledgment

N.M. thanks CSIR, New Delhi for the award of a fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.048.

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13. CCDC 862973 contains Supplementary Crystallographic Data for the structure **4f**.
14. *Typical procedure*: A mixture of sugar aldehydo carboxylic acid (246 mg, 1 mm**o**l) and *p*-toluidine (107 mg, 1 mmol) in MeOH (5 mL) was stirred for 30 min at room temperature and then cyclohexylisocyanide (130.8 mg, 1.2 mmol) was added at room temperature and the resulting mixture was stirred at 50 °C for 10 h. After complete conversion, as monitored by TLC, the mixture was concentrated in vacuo and purified by column chromatography using ethyl acetate–hexane (1:9) as eluent to afford the product as a pale yellow solid. The spectral data can be found in Supplementary data. Compound **4a**: Solid, mp 90–95 °C. IR: ν 3038, 1728, 1611, 1508, 1219, 772, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7 7.08 (m, 4H), 6.40 (d, J = 8.2 Hz, 1H) 5.94 (d, J = 3.6 Hz, 1H), 5.12 (dd = 4.5, 6.4 Hz, 1H), 4.60 (d, J = 3.6 Hz, 1H), 4.54 (d, J = 16.2 Hz, 1H), 4.30 (d, J = 4.5 Hz, 1H), 4.25 (d, J = 16.2 Hz, 1H), 4.21 (d, J = 6.4 Hz, 1H), 3.83 (m, 1H), 2.34 (s, 3H), 2.00–1.00 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 166.5, 142.2, 137.0, 129.9, 126.6, 113.8, 105.6, 84.1, 83.9, 83.1, 74.1, 62.5, 48.3, 37.1, 36.2, 33.4, 33.1, 25.6, 24.9, 24.8, 23.9, 23.6, 21.2; LC–MS: m/z: 485 (M+H). HRMS calcd for $C_{27}H_{36}N_2O_6Na$: 507.2471, found: 507.2454. Compound **4b**: Solid, mp 108–112 °C. IR: ν 3387, 2933, 2855, 1678, 1524, 1491, 1414, 1219, 1124, 1039, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.3 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 8.9 Hz, 2H), 6.42 (d, J = 7.9 Hz, 1H), 5.94 (d, J = 3.9 Hz, 1H), 5.10 (dd, J = 4.9,5.9 Hz, 1H), 4.60 (d, J = 3.9 Hz, 1H), 4.53 (d, J = 16.8 Hz, 1H), 4.29 (d, J = 4.9 Hz, 1H), 4.24 (d, J = 16.8 Hz, 1H), 4.19 (d, J = 5.9 Hz, 1H), 3.80 (m, 1H), 2.00–1.12 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7, 171.4, 133.6, 129.4, 128.4, 113.8, 105.6, 84.0, 83.8, 74.1, 62.4, 48.3, 37.1, 36.1, 33.4, 33.1, 29.7, 28.4, 25.6, 24.8, 24.7, 23.9, 23.5, 23.1; LC–MS: m/z: 505 (M+H); HRMS calcd for $C_{26}H_{33}N_2O_6Na$: 527.1924, found: 527.1913.