Bioorganic & Medicinal Chemistry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Seven-membered ring scaffolds for drug discovery: Access to functionalised azepanes and oxepanes through diazocarbonyl chemistry

Andrew Nortcliffe, Christopher J. Moody *

School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK

ARTICLE INFO

Article history:
Received 30 October 2014
Revised 22 December 2014
Accepted 6 January 2015
Available online xxxx

Keywords:
Seven-membered rings
Azepane
Oxepane
Diazocarbonyl
Medicinal chemistry

ABSTRACT

Functionalised azepane and oxepane scaffolds were prepared using diazocarbonyl chemistry and elaborated to show their potential use in library synthesis. Key dicarbonyl containing seven-membered rings were functionalised via diastereoselective Luche reduction of the ketone followed by manipulation of the ester and amine groups. Further scaffolds could be accessed by C-alkylation of the dicarbonyl compounds. In addition, an oxepane containing amino acid could be prepared via a diastereoselective enamine reduction.

1. Introduction

Seven-membered ring heterocycles are widely found in both natural products and medicinally active molecules. These include the azepanes claviciptic acid, imipramine and balanol, and the oxepanes (+)-isolaurepan, doxepin and hemibrevetoxin B (Fig. 1).[1]

Azepanes feature in the top 100 frequently used ring systems in small molecules,[2] with the dibenzazepine scaffold featuring in a wide number of analgesic and antipsychotic agents.[3,4] Synthetic methods towards the synthesis of azepane containing scaffolds have garnered significant attention,[5,6] with a wide range of reported methodologies for their preparation, including ring-closing metathesis,[7] ring-expansion,[7,8] halo-cyclisation[9] and intramolecular reductive amination.[10] Oxepane scaffolds are widely found in polyether containing natural products such as the brevetoxin[11,12] and ciguatoxin families.[13,14] Relative to five- and six-membered oxygen containing heterocycles, oxepanes are synthetically more challenging to prepare due to enthalpic and entropic constraints.[15–17] Methods towards oxepanes are diverse,[5,6,18] with recent notable examples including organocatalytic intramolecular oxa-conjugate addition,[19] iron(III) catalysed Prins cyclisation,[20] and ring-closing ene–yne metathesis.[21]

Seven-membered rings are often flanked by aromatic ring systems and these bi- and tricyclic systems have interesting activity on the central nervous system.[1] However, this type of scaffold adds significant sp^2 character to the overall compound. In an effort to synthesise scaffolds rich in sp^3 character we report the preparation of azepane and oxepane cores through diazocarbonyl chemistry.

2. Results and discussion

Diazo compounds have attracted great interest in organic synthesis due to their versatility as synthetic intermediates.[22] The diazo group can easily be introduced into activated methylene groups via Regitz diazo-transfer using sulfonyl azides as the transfer reagent.[23] Diazocarbonyl compounds generated by this method are bench stable with predictable reactivity that can be attuned to the synthetic task at hand. The main synthetic feature is the generation of a carbene or metal carbenoid to generate a reactive intermediate that undergoes a wide range of C–H and X–H insertions (X = O, N, S, Si, P). These insertion reactions provide a valuable disconnection in organic synthesis. Diazoalkanes are also used in the Lewis acid-catalysed ring expansion of cyclic ketones[24,25] that proceed via a Tiffeneau–Demjanov-type intermediate, wherein the loss of molecular nitrogen drives the one-carbon ring expanded cyclic ketone.

Herein, we report the synthesis of an azepane and oxepane scaffold using these two aspects of diazocarbonyl chemistry as the key

* Corresponding author. Tel.: +44 115 846 8500; fax: +44 115 951 3564.
E-mail address: c.j.moody@nottingham.ac.uk (C.J. Moody).

http://dx.doi.org/10.1016/j.bmc.2015.01.010
0968-0896/

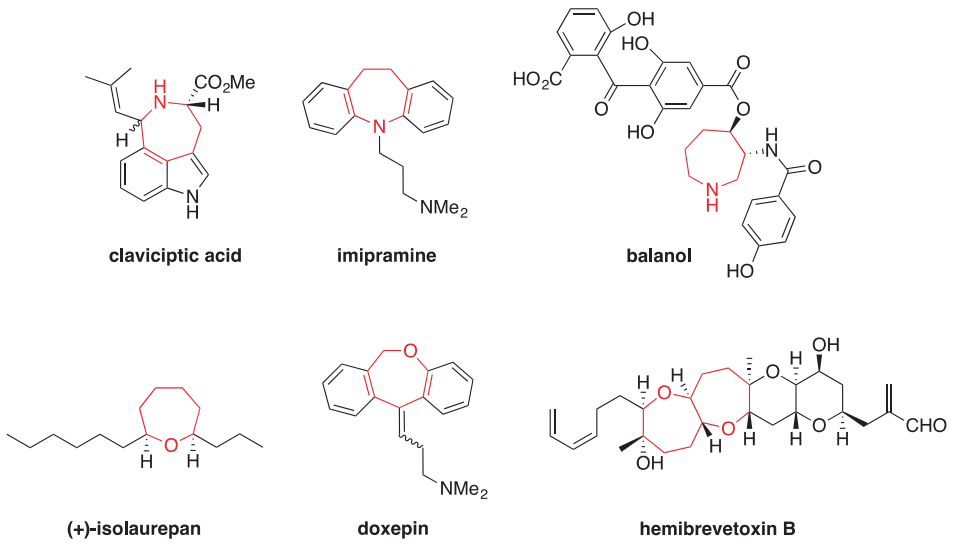
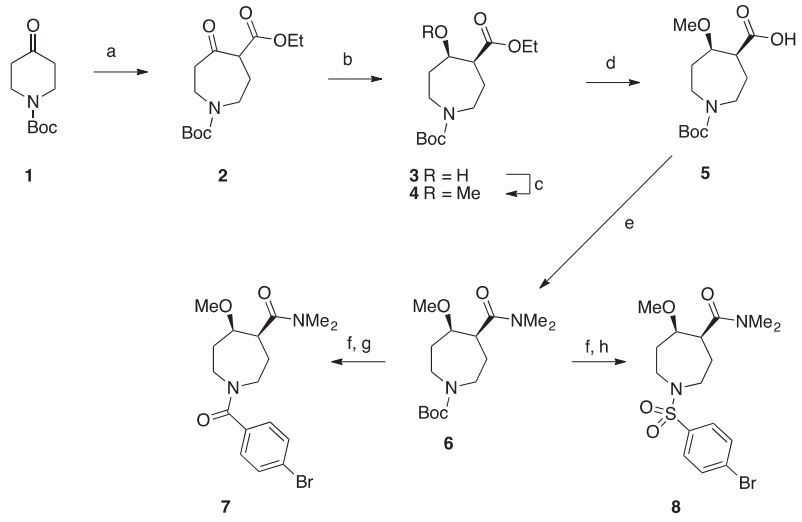


Figure 1. Azepane and oxepane containing natural products and pharmaceuticals.



Scheme 1. Synthesis of compounds **2–8**. Reagents and conditions: (a) ethyl diazoacetate, $BF_3{\cdot}OEt_2$, Et_2O, −20 to 0 °C, rt, 3 h, 85%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 1 h, 62%; (c) trimethyloxonium tetrafluoroborate, proton sponge, CH_2Cl_2, 0 °C–rt, 16 h, 81%; (d) LiOH, THF/MeOH/H_2O, 0 °C–rt, 16 h, 82%; (e) dimethylamine hydrochloride, HATU, *i*PrNEt$_2$, DMF/CH_2Cl_2 (1:1), 0 °C–rt, 16 h, 90%; (f) 4 M HCl/dioxane solution, CH_2Cl_2, rt, 16 h, quant.; (g) 4-bromobenzoic acid, HATU, *i*PrNEt$_2$, DMF/CH_2C_{l2} (1:1), 0 °C–rt, 16 h, 50%; (h) 4-bromobenzenesulfonyl chloride, pyridine, NEt_3, CH_2Cl_2, 0 °C–rt, 16 h, 96%.

steps for the generation of the seven-membered ring. In addition, we describe the synthetic manipulation of these structures to allow for further structural elaboration suitable for the preparation of compound libraries.

2.1. Azepane scaffold

The Tiffeneau–Demjanov-type ring expansion of *N*-Boc-piperidone **1** to the corresponding dicarbonyl azepane **2** is widely documented in the literature.[8] However, the use of **2** has generally been restricted to its reactions as a 1,3-dicarbonyl building block for the preparation of spirocyclic hydantion,[26] fused pyrimidine[27] or pyrazolone scaffolds.[28] We sought to use azepane **2** as core scaffold with no further ring fusion.

In our hands, the ring expansion of **1** provided the desired azepane **2** in 85% without the need for chromatographic purification (Scheme 1). Diastereoselective reduction of the ketone under Luche conditions at −78 °C furnished the *syn*-β-ketoalcohol **3** in 62% in a 19:1 ratio of separable diastereomers (Scheme 1).[29] Alcohol **3** exists in two ring conformers which readily invert on the NMR timescale. This ring inversion results in complication of the NMR spectra for this compound and later compounds in this series. Attempts to *O*-alkylate the alcohol **3** using NaH or Ag_2O as a base with MeI or BnBr were unsuccessful, as was benzylation using benzyl trichloroacetimidate/TfOH. Methylation was accomplished using trimethyloxonium tetrafluoroborate and proton sponge to afford the methyl ether **4** in 81% yield (Scheme 1). Ester hydrolysis and subsequent amide formation with dimethylamine as a model amine furnished the amide **6** in 90% yield (Scheme 1). Deprotection of the *tert*-butoxycarbonyl group with hydrochloric acid with subsequent amide formation or sulfonylation provided the elaborated scaffolds **7** and **8** (Scheme 1).

Azepane **2** also underwent C-alkylation using caesium carbonate and iodomethane to provide the quaternary carbon centre in ester **9** (Scheme 2). Following similar steps as previously described, Luche reduction provided *syn*-alcohol **10** in a 9:1 ratio of separable diastereomers (Scheme 2).[29] Ester hydrolysis of alcohol **10** provided carboxylic acid **11**, which was effectively transformed into the dimethylamide **12** in 50% yield (Scheme 1). Deprotection of the Boc-group of dimethylamide **12** with HCl provided the desired