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

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Key-words:

Seven-membered rings
Azepane
Oxepane
Diazocarbonyl
Medicinal Chemistry

Graphical Abstract

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 clavicipic acid, imipramine and balanol, and the oxepanes (+)-isolaurepan, doxepin and hemibrevetoxin B (Figure 1).

![Figure 1: Azepane and oxepane containing natural products and pharmaceuticals.](image_url)

Azepanes feature in the top 100 frequently used ring systems in small molecules, with the dibenzazepine scaffold featuring in a wide number of analgesic and antipsychotic agents. Synthetic methods towards the synthesis of azepane containing scaffolds have garnered significant attention, with a wide range of reported methodologies for their preparation, including ring-closing metathesis, ring-expansion, halo-cyclisation and intramolecular reductive amination. Oxepane scaffolds are widely found in polyether containing natural products such as the brevetoxin and ciguatoxin families. Relative to five- and six-membered oxygen containing heterocycles, oxepanes are synthetically more challenging due to enthalpic and entropic constraints. Methods towards oxepanes are diverse.
with recent notable examples including organocatalytic intramolecular oxa-conjugate addition,\textsuperscript{19} iron(III) catalysed Prins cyclisation,\textsuperscript{20} and ring-closing ene-yne metathesis.\textsuperscript{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.\textsuperscript{1} However, this type of scaffold adds significant sp\textsuperscript{2} character to the overall compound. In an effort to synthesise scaffolds rich in sp\textsuperscript{3} character we report the preparation of azepane and oxepane cores through diazocarbonyl chemistry.

\section*{2. Results and discussion}

Diazo compounds have attracted great interest in organic synthesis due to their versatility as synthetic intermediates.\textsuperscript{22} The diazo group can easily be introduced into activated methylene groups via Regitz diazo-transfer using sulfonyl azides as the transfer reagent.\textsuperscript{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 (\(\text{X} = \text{O, N, S, Si, P}\)). These insertion reactions provide a valuable disconnection in organic synthesis. Diazoalkanes are also used in the Lewis acid-catalysed ring expansion of cyclic ketones\textsuperscript{24,25} that proceed via a Tiffenau-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 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. 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 pyrimidine27 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 Ag₂O 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).
Scheme 1: Synthesis of compounds 2-8. Reagents and conditions: (a) ethyl diazoacetate, BF₃.OEt₂, Et₂O, -20 °C to 0 °C, rt, 3 h, 85%; (b) NaBH₄, CeCl₃.7H₂O, MeOH, -78 °C, 1 h, 62%; (c) trimethyloxonium tetrafluoroborate, proton sponge, CH₂Cl₂, 0 °C to rt, 16 h, 81%; (d) LiOH, THF:MeOH:H₂O, 0 °C to rt, 3 h, 85%; (e) NaBH₄, CeCl₃.7H₂O, MeOH, -78 °C, 1 h, 62%; (f) LiOH, THF:MeOH:H₂O, 0 °C to rt, 16 h, 81%; (g) NaBH₄, CeCl₃.7H₂O, MeOH, -78 °C, 1 h, 62%; (h) LiOH, THF:MeOH:H₂O, 0 °C to rt, 16 h, 81%; (i) dimethylamine hydrochloride, HATU, iPrNEt₂, DMF/CH₂Cl₂ (1:1), 0 °C to rt, 3 h, 85%; (j) 4M HCl/dioxane solution, CH₂Cl₂, rt, 1 h, quant.; (k) 4-bromobenzoic acid, HATU, iPrNEt₂, DMF/CH₂Cl₂ (1:1), 0 °C to rt, 16 h, 50%; (l) 4-bromobenzenesulfonyl chloride, pyridine, NEt₃, CH₂Cl₂, 0 °C to r.t, 16 h, 96%.

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). 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 amine which underwent sulfonylation to give brosylate 13 in 55% yield (Scheme 2).

Similarly, methylation of alcohol 10 with trimethyloxonium tetrafluoroborate/proton sponge furnished the desired methyl ether 14 in 77% yield (Scheme 3). Methyl ether 14 underwent the same transformation to provide acid 15 and dimethylamide 16.
Treatment of 16 with HCl resulted in deprotection of the dimethylamide along with the tert-butoxycarbonyl group, this was confirmed by brosylation to give the acid 17 (Scheme 3). Selective Boc deprotection was accomplished by reaction with trifluoroacetic acid (Scheme 3) followed by amide formation, reductive amination or sulfonylation to provide compounds 18, 19 and 20 respectively (Scheme 3).

Scheme 3: Synthesis of compounds 14-20. Reagents and conditions: (a) trimethyloxonium tetrafluoroborate, proton sponge, CH$_2$Cl$_2$, 0 °C to rt, 16 h, 81%; (b) LiOH, dioxane:H$_2$O, reflux, 16 h, quant.; (c) dimethylamine hydrochloride, HATU, iPrNEt$_2$, DMF/CH$_2$Cl$_2$ (1:1), 0 °C to r.t, 16 h, 72%; (d) 4M HCl/dioxane solution, CH$_2$Cl$_2$, rt, 16 h, quant.; (e) 4-bromobenzenesulfonyl chloride, pyridine, NEt$_3$, CH$_2$Cl$_2$, 0 °C to r.t, 16 h, 45%; (f) TFA, CH$_2$Cl$_2$, rt, 3 h, quant.; (g) 4-bromobenzoic acid, HATU, iPrNEt$_2$, DMF/CH$_2$Cl$_2$ (1:1), 0 °C to r.t, 16 h, 50%; (h) 4-bromobenzaldehyde, Na(OAc)$_3$BH, 1,2-dichloroethane, 0 °C to r.t, 16 h, 62%; (i) 4-bromobenzenesulfonyl chloride, pyridine, NEt$_3$, CH$_2$Cl$_2$, 0 °C to r.t, 16 h, 40%.

2.2 Oxepane scaffold

The key oxepane scaffold 23 was prepared via an intramolecular carbene O-H insertion. The precursor diazocarbonyl compound 22 has previously been reported through the addition of lithiated ethyl diazoacetate to δ-valerolactone 21. In our hands this proved difficult to replicate on decagram scale, and therefore we chose to follow the “one-pot” addition-diazotransfer reported by Chen et al. This proceeded in 78% over 2 steps on a 10 g scale (Scheme 4). Intramolecular O-H insertion was
effected using rhodium(II) acetate in dichloromethane to provide oxepane dicarbonyl ether 23 in 75% on a multigram scale (Scheme 4). Ether 23 was of sufficient purity to be carried onto next step without the need for further purification. Luche reduction (CeCl₃/NaBH₄) provided the alcohol as a 2:1 mixture of diastereomers (Scheme 4), with the syn-alcohol 24 being isolated in 53% yield after chromatography. Interestingly, alcohol 24 exists as a single conformer on the NMR timescale. Methylation with trimethyloxonium tetrafluoroborate/proton sponge gave methyl ether 25 in 87% yield (Scheme 4).

**Scheme 4**: Synthesis of compounds 22-25. Reagents and conditions: (a) i. LDA, THF, -78 °C, 0.5 h, ii. EtOAc, -78 °C, 0.5 h, iii. lactone 21, -78 °C, 2 h; (b) ρ-acetamidobenzenesulfonyl azide, Et₃N, CH₃CN, -0 °C, 16 h, 78%; (c) Rh₂(OAc)₄, CH₂Cl₂, rt, 1.5 h, 75%; (d) NaBH₄, CeCl₃.7H₂O, MeOH, -78 °C, 1 h, 53%; (e) trimethyloxonium tetrafluoroborate, proton sponge, CH₂Cl₂, 0 °C to rt, 16 h, 87%.

Subsequent hydrolysis of esters 24 and 25 provided the corresponding carboxylic acids 26 and 27 respectively (Scheme 5). Functionalisation of these scaffolds via an amide provides a point of further molecular diversity. This was exemplified by formation of the 4-bromobenzylamides 28 and 29 in 88 and 77% yield (Scheme 5).
Scheme 5: Synthesis of compounds 26-29. Reagents and conditions: (a) LiOH, THF:MeOH:H₂O, 0 °C to rt, 16 h, 26 = quant, 27 = quant; (b) 4-bromobenzylamine hydrochloride, HATU, iPrNEt₂, DMF, 0 °C to r.t, 16 h, 28 = 77%, 29 = 88%.

As with the azepane scaffold, a quaternary centre could be accessed by the C-alkylation of oxepane 23 with caesium carbonate and iodomethane providing oxepane 30 in 62% yield on a multigram scale (Scheme 6). Subsequent Luche reduction furnished the alcohol 31 as an inseperable mixture of diastereomers (15:1 ratio) in quantitative yield (Scheme 6). Methylation with Meerweins salt gave the methyl ether 32 in 88% (15:1 dr) (Scheme 6). Subsequent hydrolysis of esters 31 and 32 was undertaken with lithium hydroxide providing carboxylic acids 33 and 34 (15:1 dr) (Scheme 6). Elaboration as the amides was carried out using 4-bromobenzylamine and HATU. The desired amides 35 and 36 were isolated in excellent yield as single diastereomers (Scheme 6).

Scheme 6: Synthesis of compounds 30-36. Reagents and conditions: (a) MeI, Cs₂CO₃, DMF, 0 °C to r.t, 16 h, 62%; (b) NaBH₄, CeCl₃·7H₂O, MeOH, -78 °C, 1 h, quant., 15:1 dr; (c) trimethyloxonium tetrafluoroborate, proton sponge, CH₂Cl₂, 0 °C to r.t, 16 h, 88%, 15:1 dr; (d) LiOH, dioxane:H₂O, reflux, 16 h, 33 = quant, 15:1 dr; 34 = quant, 15:1 dr; (e) 4-bromobenzylamine hydrochloride, HATU, iPrNEt₂, DMF, 0 °C to r.t, 16 h, 35 = 92% (OH), 36 = 80% (OMe).
The β-ketoester oxepane 23 could additionally be converted to Boc-protected amino acid 37 (Scheme 7). Treatment of dicarbonyl compound 23 with ammonium acetate generated the enamine that was immediately reduced with sodium cyanoborohydride to generate the amine (Scheme 7). Boc-protection of the amine with di-tert-butyl dicarbonate provided the syn-Boc-protected amino acid 37 in a 64% yield over 3 steps in 6.5:1 diastereomeric ratio with the trans-isomer (Scheme 7). Ester hydrolysis with lithium hydroxide gave the carboxylic acid 38 in quantitative yield (6.5:1 dr) (Scheme 7). HATU mediated amide coupling of acid 38 with benzylamine gave the amide 39 in 70% yield as a single diastereoisomer (Scheme 7). tert-Butoxycarbonyl deprotection could be accomplished using HCl or trifluoroacetic acid followed by amide formation, reductive amination and sulfonylation to provide compounds 40, 41 and 42 in excellent yield (Scheme 7).

Scheme 7: Synthesis of compounds 37-42. Reagents and conditions: (a) ammonium acetate, MeOH, r.t, 16 h; (b) NaBH₄CN, AcOH, THF, 0 °C, 1 h; (c) Boc₂O, Et₃N, CH₂Cl₂, r.t, 16 h, 64% over 3 steps; (d) LiOH, THF:MeOH:H₂O, r.t, 16 h, quant, 6.5:1 dr; (e) benzylamine, HATU, iPrNEt₂, DMF, 0 °C to r.t, 16 h, 70%; (f) 4 M HCl/dioxane solution, CH₂Cl₂, r.t, 3 h, quant; (g) TFA, CH₂Cl₂, r.t, 3 h, quant; (h) (g) 4-bromobenzoic acid, HATU, iPrNEt₂, DMF (1:1), 0 °C to r.t, 16 h, 94%; (h) 4-bromobenzaldehyde, Na(OAc)₃BH, 1,2-dichloroethane, 0 °C to r.t, 16 h, 82%; (i) 4-bromobenzenesulfonyl chloride, pyridine, NEt₃, CH₂Cl₂, 0 °C to r.t, 16 h, 98%.
3. Conclusion

We have developed a series of azepane and oxepane scaffolds through the use of diazocarbonyl chemistry to construct the seven-membered ring. The scaffolds can be further elaborated and functionalised to allow for the preparation of compound libraries containing seven-membered rings.

4. Acknowledgements

We thank Dr Daniel Hamza (Sygnature Discovery) for helpful discussions. The research leading to these results was done within the European Lead Factory and has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115489, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

5. Supplementary information

Full experimental details and NMR spectra for all compounds are provided in the Supplementary Information.

6. General Experimental Procedures

**C-alkylation**

To a solution of β-ketoester (1 equiv.) in dry DMF at 0 °C, was added caesium carbonate (1.05 equiv.) and stirred for 15 min. Methyl iodide (2.5 equiv) was added slowly. The solution was allowed to warm to room temperature and stirred for 15 h. The solution was concentrated
in vacuo and diluted with ether and water. The organic layer was separated and the aqueous layer extracted with ether. The organic layers were combined and washed with aqueous ammonium chloride (saturated) and brine. The organics were dried over MgSO₄, filtered and the solvent removed under reduced pressure to yield the desired quaternary alkylated product.

**Luche reduction**

To a solution of β-ketoester (1 equiv.) in dry methanol was added CeCl₃.7H₂O (1.05 equiv.) and cooled to -78 °C. Sodium borohydride (0.7 equiv.) was added in small portions. Upon complete addition the solution was stirred for a further hour at -78 °C. The reaction was quenched with aqueous hydrochloric acid (2M) and warmed to room temperature. The reaction mixture was extracted with ether. The organic layers were combined and washed with brine, dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The crude residue was diluted with dichloromethane and evaporated onto silica gel. Purification by silica gel chromatography, eluting with ethyl acetate and light petroleum (5:95 to 15:85), provided the desired alcohol.

**Methylation with Meerwein Salt**

To a solution of alcohol (1 equiv.) in dry dichloromethane at 0 °C was added proton sponge (3-8 equiv.), followed by trimethylxonium tetrafluoroborate (2.5-4 equiv.). The suspension was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with aqueous ammonium chloride (saturated) and diluted with dichloromethane. The reaction mixture was partitioned and the aqueous phase extracted with dichloromethane. The organic layers were combined and washed with aqueous hydrochloric acid (2M) and brine. The organic layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was uptaken in dichloromethane and evaporated onto silica gel. Purification by silica gel chromatography, eluting with ethyl acetate and light petroleum (10:90) provided the desired methyl ether.
Ester hydrolysis for non-quaternary carbon compounds

To a solution of ester (1 equiv.) in THF:methanol:water (4:1:1) was added lithium hydroxide monohydrate (10 equiv.) the suspension was stirred at room temperature for 16 h. The reaction mixture was washed with ether. The aqueous layer was acidified to pH = 1 with aqueous hydrochloric acid (2M) and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure to give the desired carboxylic acid.

Ester hydrolysis for quaternary carbon compounds

To a solution of ester 31 (1 equiv.) in dioxane:H₂O (4:1) was added lithium hydroxide monohydrate (10 equiv.) the reaction mixture was heated under reflux for 16 h. The reaction mixture was cooled to room temperature and washed with ether. The aqueous layer was acidified to pH = 1 with aqueous hydrochloric acid (2M) and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure to give the desired carboxylic acid.

Amide formation

To a solution of carboxylic acid (1 equiv.) in dry DMF at 0 °C was added 4-bromobenzylamine hydrochloride (1.5 equiv.) and diisopropylethylamine (3 equiv.). The reaction mixture was stirred for 15 min and HATU (1.5 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 16 h. Following this time, the solvent was removed under reduced pressure and the residue diluted with ethyl acetate and water. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The organic layers were combined and washed with aqueous hydrochloric acid (2M), aqueous sodium carbonate solution (saturated) and brine. The organic layers were dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was uptaken in dichloromethane and evaporated onto silica gel. Purification by silica gel chromatography provided the desired amide.

7. References


