Synthesis and applications of highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes†

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Bicyclo[1.1.1]pentanes (BCPs) are important bioisosteres of 1,4-disubstituted arenes, tert-buty1 and acetylenic groups that can impart physicochemical benefits on drug candidates. Here we describe the synthesis of BCPs bearing carbon and halogen substituents under exceptionally mild reaction conditions, via triethylborane-initiated atom-transfer radical addition ring-opening of tricyclo[1.1.1.01,3]pentane (TCP) with alkyl halides. This chemistry displays broad substrate scope and functional group tolerance, enabling application to BCP analogues of biologically-relevant targets such as peptides, nucleosides, and pharmaceuticals. The BCP halide products can be converted to the parent phenyl/tert-buty1 surrogates through triethylborane-promoted dehalogenation, or to other derivatives including carbonyls, alcohols, and heterocycles.

Introduction

Bioisosteres are important motifs in drug design,1 enabling the expansion of chemical and intellectual property space2 while also improving biological profiles relative to the parent functionality. Bicyclo[1.1.1]pentanes (BCPs) have shown particularly impressive results in this field as surrogates for 1,4-disubstituted arenes, tert-buty1, and alkyne groups, imparting desirable properties such as membrane permeability, solubility and metabolic stability.3,4 Examples include BCP analogues of the γ-secretase inhibitor BMS-708, 163 (1, Fig. 1a)3 and resveratrol (2),4 in which the BCP serves as a bioisostere for a p-substituted arene due to its comparable positioning of substituents; and of the pulmonary arterial hypertension agent bosentan (3, Fig. 1b), where a mono-substituted BCP replaces a tert-buty1 group.3,4 Despite these favourable attributes, access to carbon-substituted BCPs remains a challenge. Their synthesis typically relies on multistep sequences from a small number of available precursors,9 or requires relatively harsh conditions,10 necessitating early-stage introduction of the BCP and limiting functional group tolerance.

The BCP system is most commonly accessed through ‘strain release’11 reactions of tricyclo[1.1.1.01,3]pentane 4 (TCP),12 where in addition to classical approaches,3,13 recent work has seen the development of elegant methods for the synthesis of heteroatom-substituted BCPs.11,14 The insertion of TCP into C–X bonds would offer an appealing entry to carbon-substituted BCPs, as well as the opportunity for further functionalization of the halide product (5, Fig. 1c).15 To date however, this process has only been achieved using highly activated reagents (e.g. CF3I),15 or by mercury lamp irradiation of an alkyl or aryl halide,16 or methyllithium-promoted alkyl halide addition.16a Despite the importance of these contributions, all display limitations in substrate scope, functional group compatibility, or scalability, due to the constraints of the reaction conditions.

Atom transfer radical addition (ATRA) reactions using chemical initiators are an attractive alternative for TCP ring

Fig. 1 (a) Bicyclo[1.1.1]pentanes (BCPs) as 1,4-disubstituted arene bioisosteres. (b) BCP as a tert-buty1 bioisostere. (c) Approaches to 1-halo-3-substituted BCPs in previous and current work.
opening, but previously required a large excess of the radical precursor, or suffered from the formation of oligomeric ‘staff-fane’ byproducts due to multiple insertions into TCP.\textsuperscript{10,13} Building on our studies of radical-mediated nucleoside alkylation,\textsuperscript{16} we questioned whether triethylborane could serve as an effective initiator\textsuperscript{17} for the synthesis of 1-halo-3-substituted bicyclopentanes (Fig. 1c). Here we report the development of this method as an efficient and highly functional group tolerant route to halogenated BCPs, the utility of which are illustrated through various derivatizations. Importantly, the mild conditions of this chemistry allow the synthesis of bicyclopentanes that could not be accessed using other methods, and open up opportunities for the late-stage functionalization of more complex molecules.

**Results and discussion**

We began our studies using ethyl iodoacetate 7a, and were delighted to observe complete reaction in just 15 min at room temperature using 1.3 equivalents of TCP and 10 mol% triethylborane (1 M in hexane), with the product iodide 5a isolated in 83\% yield (Table 1, entry 1). A mild exotherm was observed on addition of triethylborane to the reaction, which could be avoided by reducing the temperature (entry 2). The amount of initiator could be decreased to 1 mol\% without detriment (entries 2–5), and the quantity of TCP could also be lowered (to 1.1 equiv.), affording 5a in 92\% yield (entry 6). Successful reaction was similarly observed using TCP as a solution in dibutyl ether (0.19 M), which is significant for industrial applications (entry 7). The presence of triethylborane proved crucial, as reactions run in its absence failed to reach completion in the dark or light (entries 8 and 9).\textsuperscript{18} Importantly, no staffane byproducts were observed under the optimized conditions (entry 6).

Use of the equivalent bromoacetate 8a led to incomplete conversion, or significant staffane formation (entry 10).\textsuperscript{19} However, we were pleased to find that 2-bromo-2-nitropropane 8b underwent rapid reaction with 1.3 equivalents of TCP to afford 6b in 67\% yield (entry 11).\textsuperscript{20} As with 7a, full conversion was maintained on cooling the reaction to 0 °C (73\%, entry 12); however, lowering the quantity of triethylborane resulted in incomplete reaction (entry 13). The success of substrate 8b presumably reflects a more efficient bromine atom abstraction by the bicyclopentyl radical in the propagation step compared to ester 8a, due to the greater stability of the tertiary nitro-substituted radical.

The scope of the triethylborane-initiated ATRA was next explored using organohalides featuring a variety of functional groups (Fig. 2).\textsuperscript{21} While the optimized conditions (Table 1, entry

### Table 1 Optimization of triethylborane-promoted tricyclopentane ring-opening

| Entry | Substrate | x (equiv.) | y (mol\%) | T | t | Yield\(^a\) (%) |
|-------|-----------|------------|-----------|---|---|----------------|
| 1     | 7a        | 1.3        | 10        | rt | 15 min | 83             |
| 2     | 7a        | 1.3        | 10        | 0 °C | 15 min | 87             |
| 3     | 7a        | 1.3        | 5         | 0 °C | 15 min | 89             |
| 4     | 7a        | 1.3        | 1         | 0 °C | 15 min | 95             |
| 5     | 7a        | 1.3        | 0.5       | 0 °C | 15 min | (67 : 33)      |
| 6     | 7a        | 1.1        | 1         | 0 °C | 15 min | 92             |
| 7     | 7a        | 2.0        | 10        | rt | 16 h | 98\(^b\)       |
| 8     | 7a        | 2.0        | 0         | rt | 20 h | (60 : 40)\(^c\) |
| 9     | 7a        | 2.0        | 0         | rt | 20 h | (33 : 67)      |
| 10    | 8a        | 1.3        | 10        | rt | 20 h | 47\(^n\)       |
| 11    | 8b        | 1.3        | 10        | rt | 15 min | 67             |
| 12    | 8b        | 1.3        | 10        | 0 °C | 15 min | 73             |
| 13    | 8b        | 1.3        | 1         | 0 °C | 15 min | (60 : 40)      |

\(^a\) Isolated yields. Figures in parentheses indicate incomplete reactions, and the ratio of starting material to product as judged by \(^\text{1}H\) NMR spectroscopic analysis of the crude reaction mixture. \(^b\) Reaction carried out in Bu\(_2\)O (0.19 M). \(^c\) Reaction carried out in the dark.  

\(^n\) Isolated as a 6 : 1 mixture of 6a : staffane.

![Fig. 2. Synthesis of 1-ido- and 1-bromo-3-substituted BCPs. All reactions performed using 2 equiv. tricyclo[1.1.1.0\textsuperscript{1,3}]pentane (TCP) and 10 mol\% BEt\(_3\) (1 M in hexane) at room temperature, unless indicated otherwise. \(^*\)1 equiv. TCP, 1 mol\% BEt\(_3\), 0 °C. \(^{\circ}\)1.3 equiv. TCP, rt. \(^\circ\)1.3 equiv. TCP, 0 °C. \(^{\circ}\)Co-solvent added to solubilize the substrate: MeOH for 5m, n; CH\(_2\)Cl\(_2\) for 5h, k, r and 6e. \(^{\circ}\)5% staffane observed.](Image)
6) translated smoothly to ethyl difluoroiodoacetate, giving bench-stable BCP 5b in 98% yield,22 incomplete reactions were observed in other cases. To ensure consistency, the substrate screen was therefore conducted using 10 mol% BEt3 and 1.3–2.0 equivalents of TCP at either 0 °C or room temperature, according to the requirements of the substrate. Alkyl iodides showed excellent reactivity, tolerating groups such as hydroxyls and carbamates (5c–e). α-Iodoketones gave high yields across a range of substrates, including heteroaromatics (5f–k). Other electron-withdrawing groups such as amides and sulfones also proved viable (5l–5n),22 including the sensitive but potentially valuable aldehyde 5o. The formation of 5p is particularly notable due to the potential utility of BCP analogues of amino acids,23 no racemization was observed in this reaction. Even chloriodomethane was found to be a suitable substrate, delivering chloromethyl BCP 5q in good yield. Benzyl halides also underwent smooth reaction, providing electron-withdrawing substituents were present on the arene (which presumably accelerates the halide abstraction step from the intermediate BCP radical, 5r–5u).22 The involvement of radical intermediates was supported by the use of (iodomethyl)cyclopropane, which exclusively gave the ring-opened product 5v. Finally, other electron-deficient bromides proved suitable partners, affording products 6c–f in short reaction times; for these substrates, the presence of two electron-withdrawing groups proved essential for efficient bromine atom abstraction.

While the BCP iodide products are stable towards storage at −20 °C (particularly if crystalline), in some cases gradual coloration was observed at ambient temperature. Deiodination was expected to enhance BCP stability, and would simultaneously access the parent phenyl/tert-butyl bioisostere. We questioned whether triethylborane could again be used as initiator for this C–I bond reduction; pleasingly, the use of 1.3 equivalents of tris(trimethylsilyl)silane (TTMSS) as a non-toxic hydrogen atom source24 and 10 mol% BEt3 effected smooth deiodination of various BCP iodides (Scheme 1a), giving amide 9l, a BCP analogue of phenylalanine (9p), and trifluoroacetate salt 9e, the free base of the latter being a BCP equivalent of the monoaminergic neuromodulator phenethylamine. Given the use of the same initiator for both radical processes, a one-pot reaction sequence was also performed in which BCP 9a was prepared directly from 7a in a single operation (64%). Transformation of the iodide into substituents other than hydrogen was also explored (Scheme 1b); lithiation of 5s,10b followed by reaction of the resulting organolithium 10 with benzaldehyde or ethyl formate, gave alcohol 11 and aldehyde 12 respectively. Alternatively, transmetalation to the organozinc and cross-coupling with 2-bromopyridine afforded pyridyl BCP 13 (64%).10a,b Pleasingly, the synthesis of a phenol bioisostere6 (14) could also be accomplished by a borylation quench, followed by oxidation with sodium perborate.

The high functional group tolerance and mild reaction conditions suggested that this methodology could be exploited in the functionalization of more complex organic molecules. For example, 2′-iodouridine derivative 7w (Scheme 2a) underwent successful ATRA reaction to generate 5w (75%, 5 : 1 dr), with deiodination delivering the 2′-deoxy-2′-BCP nucleoside 9w (73%). More generally, the availability of iodides from hydroxyl groups provides a multitude of opportunities for bioisostere installation: Appel reaction of the aspartate–serine dipeptide 15 (Scheme 2b) afforded iodide 5x, which on ATRA reaction and subsequent TTMSS reduction generated BCP-functionalized dipeptide 9x. This sequence corresponds to a three step conversion of a serine residue to a potential phenylalanine
iodide and bromide starting materials. The reaction displays broad substrate scope, and functional group compatibility that is not achievable using other methods, enabling application to the functionalization of complex substrates such as nucleosides, peptides and drug-like molecules. The carbon–halogen bond is easily reduced under similarly mild conditions to reveal the parent bioisostere, or functionalized via methods such as Negishi cross-coupling or oxidation. In addition to offering a new entry to highly-functionalized bicyclopentanes, the C–X bond offers much potential for subsequent transformations; investigations to this end are underway.

Conflicts of interest
There are no conflicts to declare.

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