Synthesis of 1,3-disubstituted bicyclo-[1.1.1]-pentane (BCP) salts: arylsulfonium, arylpyridinium and arylammonium isosteres

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Abstract: Herein, we describe the synthesis of pyridinium, sulfonium and ammonium bicyclo-[1.1.1]-pentane salts as potential aryl isosteres. Arylsulfonium, ammonium and pyridinium salts are central motifs in several natural products, pharmaceuticals, and high value commodities within the industrial chemical sector. The reaction proceeds by a nucleophilic substitution on a bench stable precursor 1,3-diodobicyclo-[1.1.1]-pentane (DIBCP). The transformation displays broad substrate scope, good to excellent yield profile, with several of the BCP products being fully characterised by single crystal X-ray crystallography, highlighting the unique 3-dimensional structure of these potential isosteres. Finally, the pyridinium and quinolinium BCP salts can be cleanly converted into piperidinone and quinolone BCP analogues.

Arylsulfonium, arylammonium and arylpyridinium salts are core motifs found in several natural product and pharmaceutical classes, as well as being highly significant to the industrial sector as surfactants, antistatic agents, antibacterial agents, herbicides and ionic liquids (fig. 1A).[1] Ammonium and pyridinium salts (fig. 1B) are broad-spectrum antibacterial agents,[2] universally applied in medical, industrial and household settings as well as the agrochemical industry.[3],[4] The sulfonium salt methyl methionine is a known precursor to natural odor agents;[5] salacinol, kotalonal and derivatives are natural products from the genus *Salacia* used to treat type 2 diabetes mellitus;[6,7] and ammonium and pyridinium salts are found in several natural product families (fig. 1C).[8,9] Furthermore, the synthetic utility of ammonium, pyridinium and sulfonium salts has recently flourished.[8,10–13] They have been used as radical sources in several cross-coupling reactions protocols and are now *established* key precursors in natural product synthesis and drug discovery.

Over the past decade bicyclo-[1.1.1]-pentanes (BCPs) (Scheme 1A, **4**) have developed into an exciting class of small cage molecules. They have found application in the materials sector,[14] as well as impacting drug discovery as plausible bioisosteres for the *t*butyl group,[15,16] internal alkynes,[17] and disubstituted arenes (scheme 1A and B).[18–23] The attractiveness of BCPs lies in its core which is comprised solely of sp^3 carbons. This provides a unique 3-dimensional structure with an increased fraction of sp^3-hybridised carbons (Fsp^3)[24] compared to traditional flatland motifs, and it is this 3-dimensionality that has become increasingly desirable in drug development.[25,26] This impact has been driven by the rapid expansion of new synthetic strategies that has enabled access to multi-substituted BCPs.[27,28]

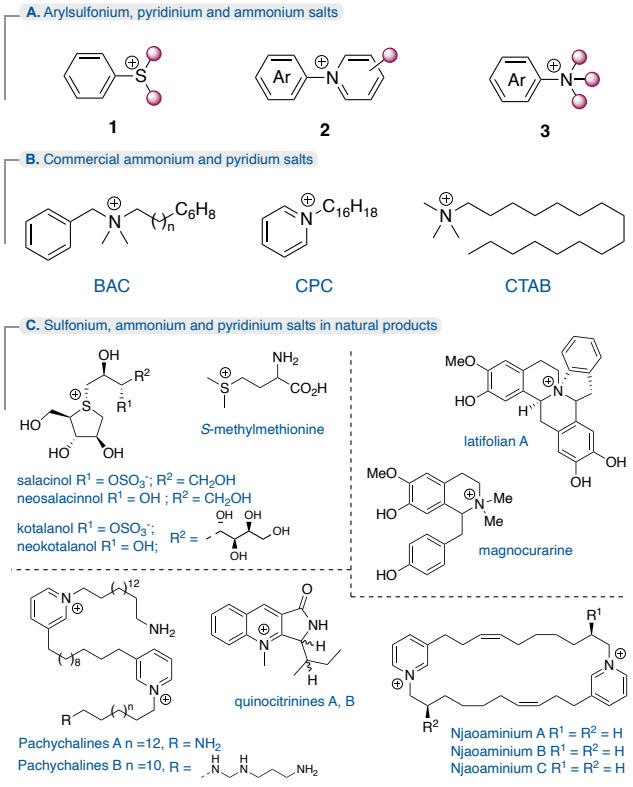
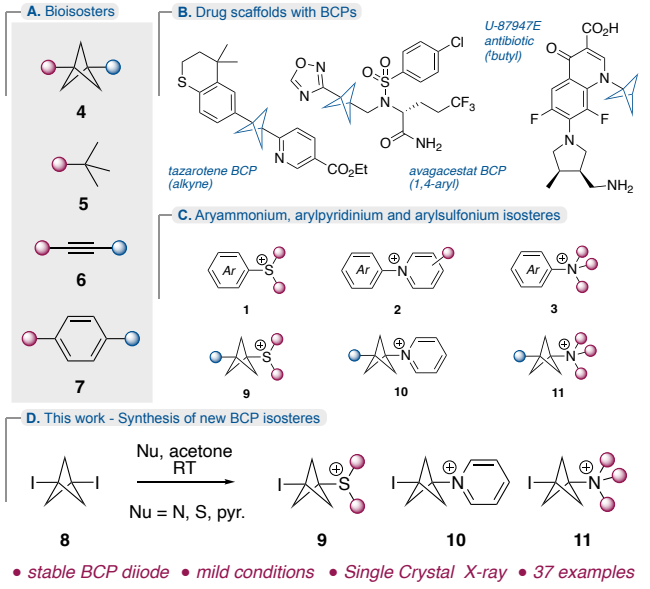


Figure 1. A). Structures of arysulfonium, arylpyridinium and arylammonium salts; B). Representative examples of historic commercially available ammonium and pyridinium salts; C). Representative examples of sulfonium, ammonium, and pyridinium motifs in natural products.

In contrast, there have been no developments of ammonium, pyridinium and sulfonium functionalized BCPs, beyond their initial report by Wiberg and co-workers[29] and Adcock and co-workers[30,31] nearly 30 years ago (scheme 1C). This is despite the

impact that BCPs have made in medicinal chemistry, drug discovery, materials chemistry, and the patent literature. The incorporation of the BCP framework into the bipyridyl framework of paraquat, a highly toxic agrochemical, may provide novel herbicides with reduced toxicity; a BCP within the carbon chain of CPC could modulate its antibacterial activity; and the ammonium, pyridinium or sulfonium functional group could provide a useful synthetic handle for the synthesis of novel BCP scaffolds.

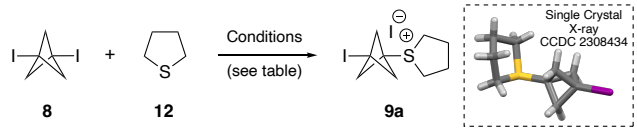


Scheme 1. A) The BCP framework as a bioisostere for a ᵗbutyl group, 1,3-alkyne and para-disubstituted benzene; B) Current BCP containing drugs; C) Potential use of sulfonium, pyridinium and ammonium BCP salts as isosteres; D) The work described within this disclosure.

Herein, we report the synthesis of BCP isosteres of arylammonium, pyridinium and sulfonium salts (scheme 1D). Unlike conventional BCP syntheses that use [1.1.1]-propellane, this approach uses the bench-stable 1,3-diiodobicyclo-[1.1.1]-pentane (**8**, DIBCP),[29-31] a stable crystalline BCP which results from the treatment of [1.1.1]-propellane with iodine. It is principally seen as an unwanted by-product, whose formation is keenly suppressed in the synthesis of BCPs. Surprisingly, since the re-emergence of BCPs over the past decade, the synthetic utility of **8** has been largely overlooked, with recent notable exceptions by Zarate and co-workers[32] and Aïssa and co-workers.[33,34] The synthesis of these isosteres proceeds under mild conditions, providing a large scope of arylammonium, pyridinium and sulfonium salts, with broad functional group tolerance. We provide a synthesis of several BCP analogues that have potential to be used in natural products, agrochemicals, and as odor agents. Additionally, the pyridinium salts can undergo further synthetic manipulation affording piperidinone and quinolinone substituted BCPs that cannot be accessed by current synthetic methodology.

We first studied the reaction of **8** with tetrahydrothiophene (THT, **12**) (scheme 2). The starting DIBCP (**8**) was synthesized by treatment of [1.1.1]-propellane with iodine. We began by using the conditions first reported by Adcock and co-workers,[30,31] in the addition of pyridine to **8**. This involved stirring THT in excess (10 equiv.), with DIBCP (**8**) in acetone for 3 days. After simple trituration with diethyl ether and subsequent filtration this provided the tetrahydrothiophenium salt **9a** in 47% isolated yield. All physical data confirmed the product and fortunately we were able to unambiguously assign the structure using single crystal X-ray analysis (scheme 2).[35] Next, a solvent screen was examined, with acetonitrile giving no conversion to **9a**, with only starting material being detected after 3 days (entry 2). Several solvents were also trialed including DMF, THF, ethyl acetate and 1,4-dioxane, but all solvents, apart from acetone, gave little or no conversion.[36] An examination of concentration followed, and we found that reducing the concentration of the reaction mixture reduced the yield of **9a** (entry 3), while increasing concentration improved overall yield (entry 4). When this was combined with a reduction of equivalents of THT (**12**) from 10 to 5, the yield further improved to 75% (entry 6). However, with further increases in concentration, while maintaining the equivalents of **12** at 5, we observed gradual erosion in yield of **9a** (entries 7 and 8, respectively). Finally, we attempted the reaction of **8** in neat THT, but this provided **9a** in a poor 17% yield (entry 9).

Table 1 and scheme 2. Reaction optimisation for the formation of **9a**.[a]



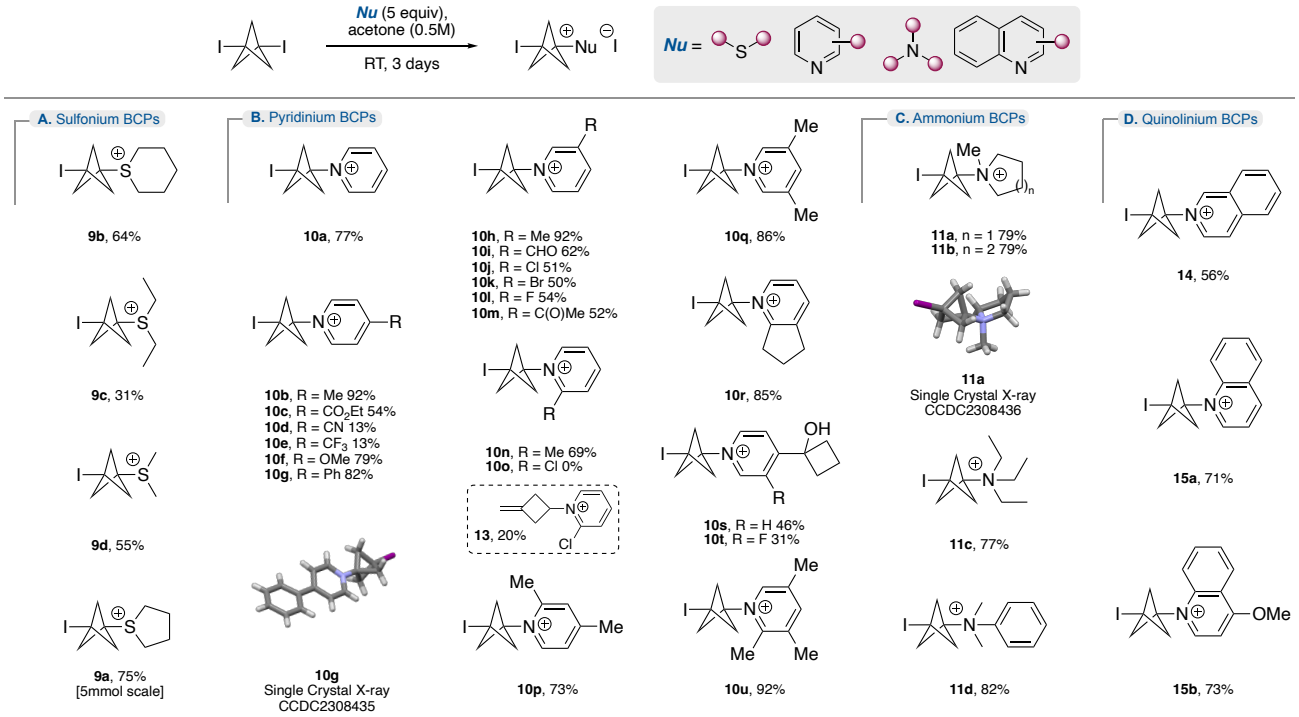
8 **12** **9a**

entry	solvent	Conc.[M]	equiv. **12**	Yield **9a** [%][c]
1[b]	acetone	0.15	10	47
2	acetonitrile	0.15	10	-
3	acetone	0.10	10	35
4	acetone	0.25	10	43
5	acetone	0.5	5	75
6	acetone	0.75	5	66
7	acetone	1.00	5	41
8	-	-	10	17

[a] Performed on 0.2mmol of **8** for 3 days unless otherwise stated; Table footnote. [b] Performed on 1.0 mmol of **8**; [c] isolated yields.

With optimal conditions found we then examined reaction scope, firstly with sulfur nucleophiles (scheme 3A). Reaction of **8** with tetrahydrothiopyran provided the salt **9b** salt in a good yield of 64%. The diethyl sulfide BCP salt **9c** proved problematic to isolated, and it could only be isolated in a modest yield of 31%; however, the dimethyl salt **9c** was obtained in an improved isolated yield of 55%. The THT salt **9a** could also be synthesized on a 5mmol scale without any depreciable erosion in isolated yield (ca. 75%).

Our attention then turned to pyridyl nucleophiles given the importance of such salts as antibacterial agents, both commercially and in combatting antimicrobial resistance (scheme 3B).[3,4,37] Pyridine reacted well with **8** to give the pyridinium salt **10a** in 77% isolated yield, again an improvement on the current literature.[30,31] Substitution at the 4-position of the pyridine ring followed the expected reactivity profile. Electron donating groups methyl, methoxy and phenyl providing the salts **10b**, **10f** and **10g** in good to excellent isolated yields. The structure of the 4-phenyl

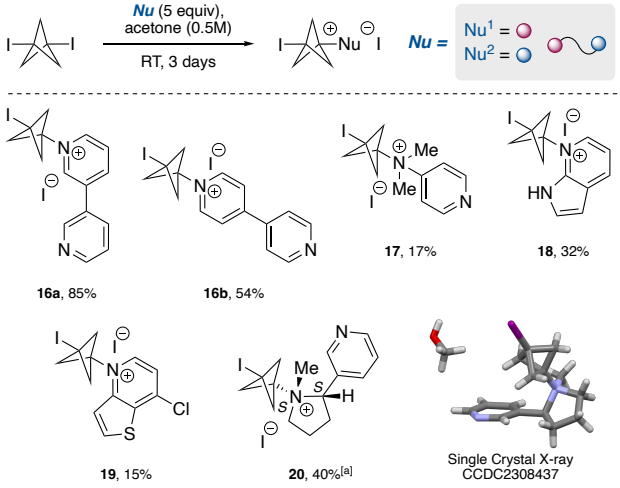


Scheme 3. Substrate scope for nucleophile addition to 8; A) Sulfur; B) Pyridines; C) tertiary amines; and D) isoquinoline and quinolines. The iodide counteranion has been omitted in each structure for clarity.

pyridinium BCP salt **10g** was confirmed by single crystal X-ray analysis.[35] Electron withdrawing groups at the 4-position of the pyridine ring such as carboxyethyl, nitrile and trifluoromethyl all provided the pyridinium BCP salts **10c**, **10d** and **10e**, but in modest isolated yields. Our reaction condition proved very accepting of substitution at the 3-position of the pyridine ring, with electron donating and withdrawing groups being tolerated, with pyridinium salts **10h-m** being isolated in good to excellent isolated yields. 2-Methylpyridine provided the salts **10n** in 69% yield; however, 2-chloropyridine failed to deliver the anticipated salt (**10o**) but instead an unknown product was isolated in a poor 20% yield. Through analysis of the ^{1}H and ^{13}C NMR we have *tentatively* assigned this structure as the cyclobutene **13**, which may result from opening of the propellane ring system as initially reported by Wiberg and co-workers[38,39] and more recently by Mandler and co-workers.[40] Disubstituted pyridines were well tolerated; with 2,4-lutidine and 3,5-lutidine giving the pyridinium BCP salts **10p** and **10q** in 73% and 86% yield, respectively. This also extended to the 2,3-cyclopentenopyridine giving the pyridinium BCP salt **10r** in excellent isolated yields. However, 2,6-lutidine failed to add to **8**, with only starting material being observed after 3 days. This is likely due to adverse steric interactions from the flanking methyl groups, preventing addition. Finally, to complete this pyridyl screen, 2,3,5-trimethyl pyridine was added to **8**, providing the pyridinium salt **10u** in an excellent 92% isolated yield.

The reaction of **8** with tertiary amines was next explored, with *N*-methylpyrrolidine giving **11a** in 79% yield and *N*-methylpiperidine providing **11b** also in 79% isolated yield (scheme 3C). The stability of **11a** proved challenging when assigning the ^{1}H NMR; however, we were able to confirm its structure through single crystal X-ray analysis.[35] Triethyl amine reacted with **8** cleanly to give the salt **11c** in 77% isolated yield, an improvement on the existing method,[30,31] while *N*, *N*-dimethylaniline also gave the corresponding BCP **11d** in an excellent yield of 82%.

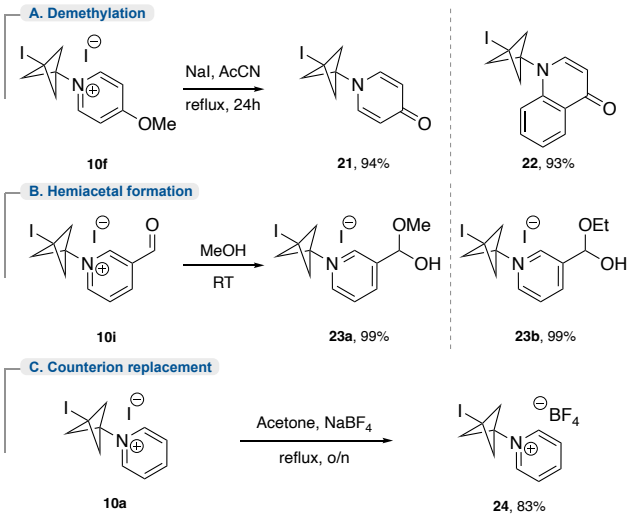
Finally, we examined quinoline nucleophiles and observed, broadly, the same reactivity as with the substituted pyridines (scheme 3). Using the optimized conditions from table 1, isoquinoline and quinoline added to 8 giving the novel isoquinolinium salt **14** and **15a** in 55% and 71% yields, respectively. 4-Methoxyquinoline also provided the quinolinium salts **15b** in 73% isolated yield. The reactivity of each nucleophile in the addition to **8** prompted us to investigate substrates possessing two, reaction compatible, heteroatoms (scheme 4).



Scheme 4. The behaviour of several *bis*-nucleophiles in the addition to DIBCP (**8**). [a]

We first investigated 3,3- and 4,4-bipyridine, which under the optimized conditions with **8** gave exclusively the mono BCP salts **16a** and **16b**, respectively. This observation is most likely a result of the insolubility of the mono BCP salt instead of any intrinsic substrate selectivity but does provide a convenient method for monoalkylation of bipyridyl substrates. The reaction of DMAP with **8** gave the BCP salt **17** in 17%, where alkylation occurs on the tertiary nitrogen, exclusively. Two heterocycles, 7-azaindole and 7-chlorothienopyridine, gave alkylation exclusively through the pyridine nitrogen giving **18** and **19** in 32% and 15%, respectively. Finally, the reaction of (-)-nicotine with **8** provided the salt **20**. The ^{1}H and ^{13}C NMR of this structure proved extremely difficult to attain, given the instability of the salt in the NMR solvent. However, analysis of the crystalline solid did provide data for single crystal X-ray analysis which confirmed the structure given in scheme 4.[35] Recently, quaternary ammonium salts of nicotine have found use as antimicrobial agents[37] and as phase transfer catalysts.[41]

Our focus then moved to exploring the potential synthetic utility of these pyridinium BCP salts, particularly the 4-methoxy pyridinium **10f**, as this was of interest given limited synthetic access to piperidinone BCPs. Pleasingly, we discovered treatment of **10f** with NaI[42] cleanly produced the piperidinone **21** in an excellent 94% isolated yield (scheme 5A). This reactivity was mirrored for 4-methoxy quinolinium **15c**, providing the 4-quinolone **22** in an excellent yield of 93%. This transformation now reveals a unique synthetic route to *N*-BCP quinolone derivatives, and the opportunity to access novel quinoline antimicrobial agents.[43] Given the ability to access aldehyde **10i**, we were able to cleanly form the hemiacetal **23a** and **23b**, which opens the door to using these novel BCP-salts as odor delivery agents (scheme 4B).[44] Finally, were able to exchange the iodide counterion ion in **10a**, to give the tetrafluoroborate salt **24** in 83% yield, with a peaks of -147.9 ppm and -148.0 ppm, respectively in the ^{19}F NMR confirming salt formation (scheme 5C).



Scheme 5. The synthetic utility of the pyridinium and quinolinium BCP salts

In conclusion, we have demonstrated an improved methodology for the formation of isosteres for arylsulfonium, arylpyridinium and arylammonium salts. The reaction conditions are extremely mild, with the desired BCP sulfonium, pyridinium and ammonium salts being obtained through simple trituration and filtration, with recrystallisation required in some instances. The pyridinium substrate scope is extensive, and in several cases the unique structure of these BCP salts has been determined through single crystal X-ray crystallography. The synthetic potential of our synthesized pyridinium BCP isosteres has been briefly explored, by providing an expedient synthetic route to piperidone BCP analogues, as well as *N*-BCP quinolone analogues that could be used to access novel quinolone antibiotics. Additionally, the formation of the hemiacetal BCP-pyridinium isosteres, suggests a role for these isosteres as odor delivery agents. Finally, we hope that this disclosure demonstrates the potential of the BCP motif as potential isosteres for the arylsulfonium, arylpyridinium and arylammonium salts.

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Keywords: Isostere • bicyclo-[1.1.1]-pentane • pyridinium • ammonium • sulfonium

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[35] Deposition numbers CCDC2308434 (for **9a**), CCDC2308435 (for **10g**), CCDC2308436 (for **11a**) and CCDC2308437 (for **20**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

[36] Please see the Supporting Information.

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