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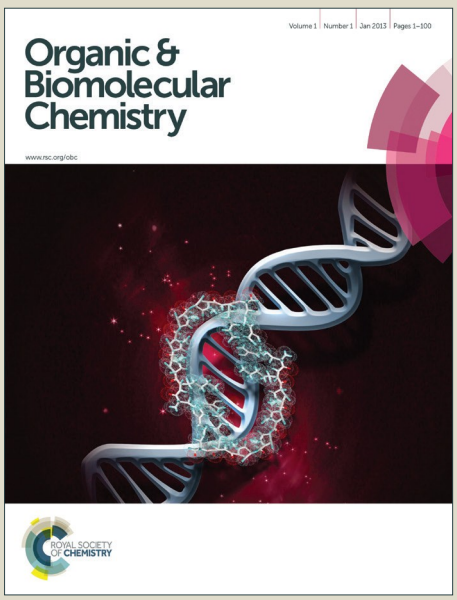

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Radical fluorination powered expedient synthesis of 3-fluorobicyclo[1.1.1]pentan-1-amine

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Exploration of novel chemical space, a modern trend in medicinal chemistry, is heavily reliant on the synthetic access to new and interesting building blocks. In this direction, the following work describes an expedient synthesis of one such moiety, 3-fluorobicyclo[1.1.1]pentan-1-amine, by employing radical fluorination.

From the perspective of modern medicinal chemistry, strategic installation of new building-blocks into lead compounds can serve as a powerful approach to enhance their drug-like properties and to secure relevant intellectual property space.[1] Despite this cogency, initiatives to instil structural novelty in bioactive compounds often fail to garner traction due to the lack of robust and convenient synthetic access to the desired molecular components.

The bicyclo[1.1.1]pentane (BCP) motif can serve as an excellent example of the above-mentioned notions. Thus, while a few reports have hinted the BCP scaffold to be of broader use in medicinal chemistry, the use of this moiety has been hampered by the paucity of relevant synthetic know-how.[2] The apparent synthetic impasse, at least in part, is an outcome of the highly strained and unique shape of the BCP motif. The exceptional structural traits often render the BCP scaffold immune to generic functionalization strategies, and warrant development of customized alternatives.[3,4]

Recently, we have actively pursued the application of the BCP moiety in our programs.[4] In particular, we have been interested in the synthesis of 1-*N* substituted BCP analogues such as the bicyclo[1.1.1]pentan-1-amine, **1** (Fig. 1).[4a] Interestingly however, we noticed that although the use of **1** has been relatively well-reported[5] in the medicinal chemistry literature the application of its potential bioisosteric contender, fluoride **2** (Fig. 1), has been surprisingly absent. Additionally, the growing use and effectiveness of fluorine compounds in pharmaceuticals also made **2** an attractive target[6] and we were eager to investigate the use of the amine, **2**, in our program. Encouragingly, our primary analysis suggested that, although no explicit synthesis of **2** has been reported in the literature,[7] the task of securing this fluoride would be rather straightforward via Schmidt rearrangement on the known acid **3** (Scheme 1).

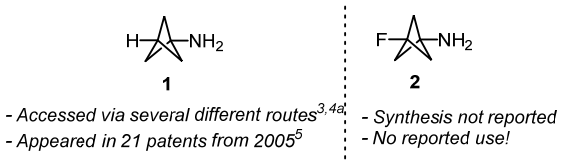
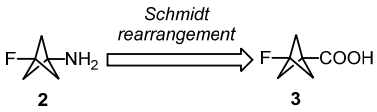


Fig. 1 A comparison between BCP amine **1** and its fluoro analogue **2**.

Unfortunately, a more detailed scrutiny of the situation revealed that prevailing synthetic routes to the acid **3** were inconvenient and inefficient (Scheme 2). Thus, in his 1995 report,[8a] Adcock reported the synthesis of **3** from the intermediate **5** (synthesized in 9 steps from **4**).[8b] This sequence, apart from its synthetic prolixity, generated an inseparable mixture of the desired product, **3**, and the reduced side product, **7**, thus diminishing its synthetic utility. In 1999, as a sequel to his previous studies, Adcock reported an alternative synthesis of **3** from **6** (synthesized in 6 steps from **4**).[8c] Unfortunately, while this route furnished **3** in pure form, it suffered from tedious purification procedures and very low yields (5% overall yield). Interestingly, on the sidelines of his latter study, Adcock also addressed the challenge of separating **3** from **7**. Thus, he revealed that treatment of the mixture with either $AgNO_3/(NH_4)_2S_2O_4$ or XeF_2 resulted in the decomposition of the reduced product and allowed isolation of **3** in a pure form (Scheme 3).[8c]

In our opinion, for meaningful use and exploration of **2**, the prevailing state of the art in its synthesis deserved a robust and efficient alternative. We also recognised the need to protract our original plan, and first target an efficient synthesis of the acid **3**. In this Letter we report our success in these aims.



Scheme 1 Our original plan to generate **2** from the known acid, **3**.

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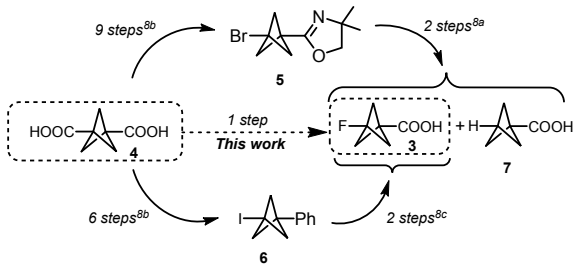
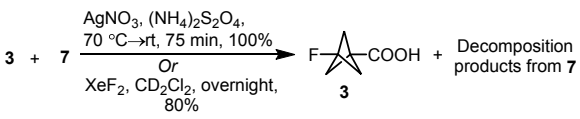


Scheme 2 Known syntheses of **3**.

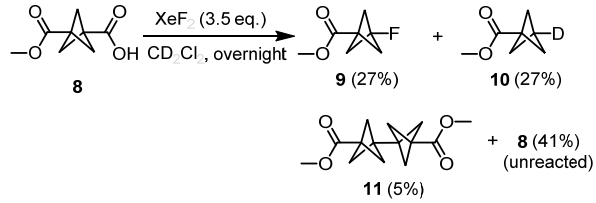


Scheme 3 Adcock's protocol to secure pure **3** via decomposition of **7**.

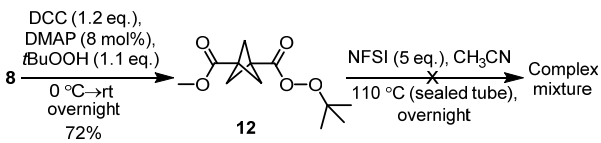
Based on our previous experience with the functionalization of the BCP scaffold, we were biased towards employing a radical-mediated fluorination strategy.[4a,b] In this regard, Adcock's synthesis of the fluoride **9** by reacting the acid **8** with XeF_2 seemed relevant (Scheme 4).[8c] By itself, this reaction suffered serious limitation by the virtue of the cost of XeF_2. Moreover, generation of unwanted by-products, **10** and **11**, further downgraded the prospective synthetic utility of this transformation.[8d] However, to us, this result served as an encouraging proof-of-concept for our radical-mediated fluorination strategy. Explicitly, we were keen to explore the contemporary developments in radical fluorination to eliminate the use of XeF_2.

In accord with our plans, we first investigated the conditions described in the seminal report by Sammis and co-workers for fluorination of alkyl radicals using SELECTFLUOR®.[9a] The relevant starting material, perester **12**, was synthesized uneventfully from **8**. However, the reported conditions failed to yield the product and a complex mixture of the reaction products was obtained (Scheme 5).[9b] It is likely that the rather harsh conditions employed for the decomposition of the perester **12** results in an array of radical events leading to the observed outcome.

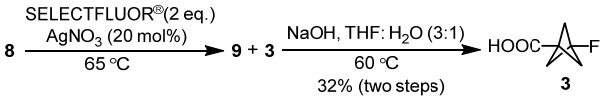
Next, we assessed the Li decarboxylative fluorination method.[10] This protocol allowed us the direct use of acid **8** as a starting material. To our delight, application of Li's conditions (SELECTFLUOR®, $AgNO_3$ (cat.)) to **8**, furnished a mixture of **9** and the



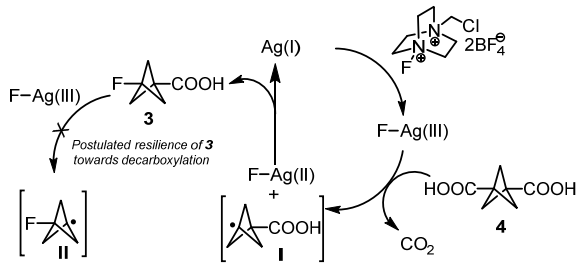
Scheme 4 Adcock's NMR tube experiment with XeF_2.



Scheme 5 Attempted decarboxylative fluorination by the Sammis protocol



Scheme 6 Application of Li's protocol for radical fluorination of **8**.



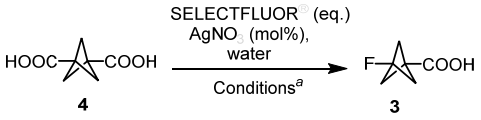
Scheme 7 Possible pathway for silver-catalysed decarboxylative fluorination of **4**

hydrolyzed product **3** (Scheme 6). Given our interest in the latter, we performed a base hydrolysis on this mixture to converge on the desired intermediate **3** in 32% yield. Disappointingly, our attempts to build on this early success were unfruitful and we also realized two previously imperceptible issues embedded in our approach. First, our current choice of starting material, **8**, is derived from an easily available and cheap bis acid **4**,[11] in a couple of rudimentary but low-yielding transformations.[11a] Secondly, our protocol necessitated chromatographic separation of the intermediates. Taken together, these traits had the potential to dampen our claim for an efficient synthesis of acid **3** and hence amine **2**.

We attacked the issue at its core by evaluating the prospects of employing the bis acid, **4**, as the starting material. It is generally reasonable to assume that given the degenerate nature of the carboxylic acid groups in **4**, a decarboxylation event would lead to an unproductive bis-decarboxylation at some stage of the reaction. Counterintuitive to this rationale, Adcock and co-workers, in their studies with XeF_2 mediated decarboxylative fluorinations, had demonstrated and explained the resilience of **3** towards decarboxylation (see Scheme 3).[8c] Extrapolating the gist of this study to Li's proposed mechanism of decarboxylative fluorination, we envisaged that the reaction of the bis acid, **4**, under Li's conditions, would be arrested at the mono-fluorination stage and thus result in the predominant formation of our desired intermediate, **3** (Scheme 7). Clearly, our approach hinged on both the rapid fluorination of intermediate **I**, and the apparent resistance displayed by **3** to decarboxylate to the radical intermediate **II**.

Indeed, to our satisfaction, good conversion of **4** to the desired intermediate, **3**, was achieved in a single step (56% yield, Table 1, entry 1). Extensive optimization studies, partially depicted in Table 1, allowed fine-tuning of the reaction conditions. To start with, we ascertained that the best outcomes were obtained when the reaction was allowed to continue overnight (16 hours). Furthermore, reaction temperatures higher or lower than 65 °C resulted in lower yields (entry 2 and 3 respectively). Lowering the amount of SELECTFLUOR® was detrimental to the reaction yield (entry 4). An increase in the catalyst amount beyond 10 mol% appeared to be inconsequential to the reaction outcome (entry 5). Use of 2.5 equivalents of SELECTFLUOR® was found to be optimal (entry 6). Lowering the catalyst loading to 5 mol% gave low yields

Table 1 Optimization of conditions for direct synthesis of **3** from **4.**



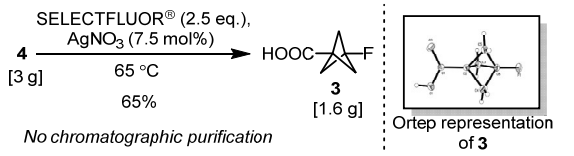
Entry	SELECTFLUOR® (eq.)	$AgNO_3$ (mol%)	Temp. (°C)	Yield (%)	Recovered 4 (%)
1	1.8	10	65	56	~2
2	1.8	10	90	47	0
3	1.8	10	50	56	4
4	1.3	10	65	49	18
5	1.8	20	65	50	4
6	2.5	10	65	63	4
7	2.5	5.0	65	50	27
8	2.5	7.5	65	67	5

[a] *All reactions were performed with 100 mg of starting material and 3.2 mL (0.2 M) of the solvent.*

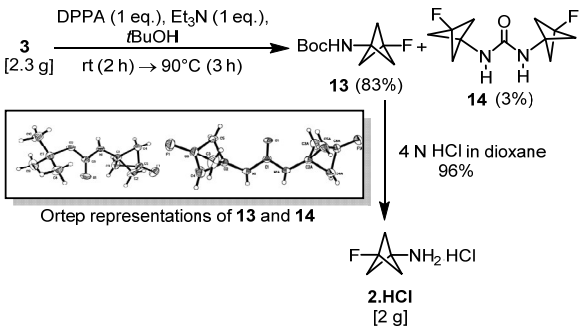
and poor conversion (entry 7). Finally, consolidation of the above intelligence delivered the best outcome wherein with 2.5 equivalents of SELECTFLUOR® and 7.5 mol% of the catalyst at 65 °C gave the product in a consistent yield of 67% (entry 8).[12]

Further in our optimization studies, we also discovered that the desired product could be isolated in a very pure form (>98%) via simple extraction of the reaction mixture, thus eliminating the need for chromatographic purification. Thus, with the combination of features such as low catalyst loading, mild reaction conditions, moderate temperature etc., we could expediently perform the reaction on a multi-gram (3 gram) scale to isolate the product in 65% yield (Scheme 8). This effort enabled us to isolate crystalline **3** suitable for X-ray crystallography.[13]

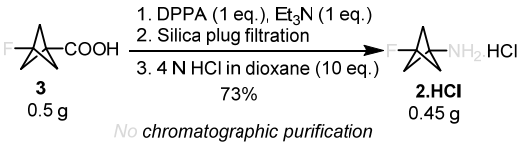
Having secured a reliable and scalable access to **3**, our advance to the final target, **2**, was simplified. Thus, reaction of the carboxylic acid **3** with a mild reagent such as diphenylphosphoryl azide (DPPA) afforded the 'Boc' protected amine, **13**, in an excellent yield after chromatographic isolation (83%), along with a small amount (~3%)



Scheme 8 Multi-gram synthesis of **3** from **4**



Scheme 9 Gram-scale synthesis of **2** from **3**



Scheme 10 Convenient synthesis of **2** from **3**

of urea **14** as a by-product. We confirmed the structure of these intermediates by X-ray crystallography (Scheme 9).[14] Finally, acid induced deprotection gave the desired product, **2**, in 96% yield.

Furthermore, we could demonstrate the convenience of this method by telescoping the products from the Schmidt rearrangement, after a quick silica-plug filtration, to the acid mediated deprotection step (Scheme 10). The overall yield (73%) for this consolidated sequence, over two steps, was in good agreement to the yields obtained from its two-step counterpart.

Conclusions

A tactical combination of insights from both past[8c] and modern[10] studies in radical fluorination allowed us to gain a concise, robust and convenient synthesis of **2** (three steps, 48% overall yield, no chromatographic purification) via another crucial intermediate **3** (one step, 67% overall yield, no chromatographic purification). Moreover, the reported syntheses originate from an easily available starting material **4**.[11] We believe that this work will facilitate both the synthetic and commercial availability of these compounds and thus allow for a realistic opportunity for their evaluation and application in pharmaceutical and other fields. From a synthetic chemistry perspective, our route illustrates the application of modern radical-based fluorination methods.

Notes and references

‡ This work was performed in collaboration with GSK, Singapore. The authors would like to thank, Dr. N Paul King (GSK) for his help to enable this work. Authors also acknowledge Dr. King's help in proof-reading the manuscript of this document. The authors would also like to thank Dr. Rakesh Ganguly and Dr. Li Yongxin of Nanyang Technological University, for X-ray structures of compounds **3**, **13** and **14**. We are grateful to Ms. Triana Reyastuty Bte Mohd Kamil (ICES, A*STAR) and Mr. Ng Kang Wei Jeffrey (ICES, A*STAR) for their help with DSC and HRMS analysis respectively.

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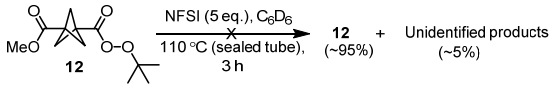

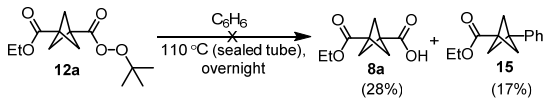

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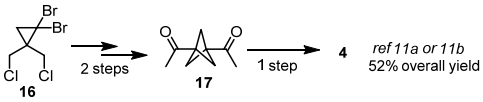

(d) For a flow photochemistry based multi-gram synthesis of **17** see: L. D. Elliott, *et al. Chem. Eur. J.,* 2014, **20**, 15226. (e) Bis acid **4** was sourced from TCG Lifesciences (~$150/gram). Also, according to SciFinder®, bis acid **4** is commercially available from ~40 chemical suppliers.

12 The success of the Li protocol, as compared to the decarboxylative fluorination with XeF_2 (Scheme 4), in delivering a smooth and a more exclusive transformation to the fluoride product **3** may perhaps be attributed to the proximity of F-Ag(II) intermediate to the intermediate **I** (Scheme 7) after the decarboxylation event by F-Ag(III). It is also likely that the proposed mechanism for Li's fluorination protocol is more complicated than our above hypothesis.

13 The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, reference number CDCC1411982 (**3**).

14 The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, reference number CCDC1421038 (**13**) and CCDC 1421039 (**14**).