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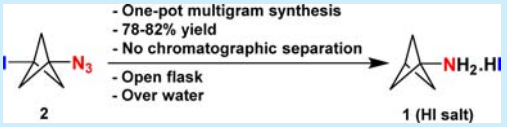
A New Route to Bicyclo[1.1.1]pentan-1-amine from 1-Azido-3-iodobicyclo[1.1.1]pentane

Yi Ling Goh, Eric K.W. Tam, Paul H. Bernardo, Choon Boon Cheong, Charles W. Johannes, Anthony D. William, and Vikrant A. Adsool*

Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology, and Research (A*STAR), 11 Biopolis Way, Helios Block, #03-08, Singapore 138667, Singapore

Supporting Information

ABSTRACT: From a medicinal chemistry perspective, bicyclo[1.1.1]-pentan-1-amine (**1**) has served as a unique and important moiety. Synthetically, however, this compound has received little attention, and only one scalable route to this amine has been demonstrated. Reduction of an easily available and potentially versatile intermediate, 1-azido-3-iodobicyclo[1.1.1]pentane (**2**), can offer both a flexible and scalable alternative to this target. Herein, we describe our scrutiny of this reportedly elusive transformation and report our ensuing success with this endeavor.



In the modern practice of medicinal chemistry, tactical application of bioisosteres has, on several occasions, provided an efficient solution to issues related to design and development of drug candidates. Not surprisingly, synthesis and application of new bioisosteres continue to be of considerable interest.[1] Contemporaneously, exploration of novel chemical space has attracted significant attention from medicinal chemists.[2] A combination of these two concepts can expedite generation of new lead compounds with enhanced druglike properties and can also be employed as a strategy to secure novel intellectual property. Nontraditional sp^3-rich building blocks such as bicyclo[1.1.1]pentane (BCP) derivatives have offered one such opportunity.[2a,3] In fact, bicyclo[1.1.1]pentan-1-amine (**1**) has served as a showcase example of the applicability of these 3D structures in bioactive compounds (Figure 1).[4,5] Indeed, more than a decade after the initial report by Barbachyn and co-workers on the application of **1** as a bioisosteric replacement of the *tert*-butyl group,[4] a renewed interest in its use has been evident in recent times.[5]

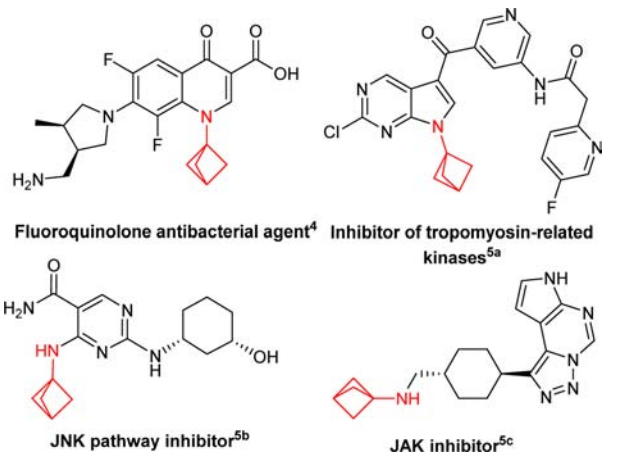


Figure 1. Selected bioactive compounds containing bicyclo[1.1.1]-pentane scaffold.

In the context of an ongoing medicinal chemistry effort, we were interested in examining the utility of BCP compounds such as **1**, and other 1-*N* substituted BCP analogues, as bioisosteric replacements for phenyl and aryl groups.[6] This ambition warranted an efficient access to these targets. To our surprise, a literature survey indicated a scarcity of such protocols, a fact that has perhaps resulted in their limited use. Thus, despite more than four decades of attention by the synthetic community, only a few rather inefficient routes to **1** existed until recently.[7] In 2011, Bunker and co-workers[8] reported an elegant synthesis of **1** by cleverly applying the Carreira hydrohydrazination protocol.[9] However, this approach lacked the desired versatility that was necessary to tackle our aforementioned objectives. From a synthesis perspective, a direct access to **1** via the known compound **2**[10a] seemed to be a more convenient tactic, especially since the latter could also serve as point of divergence to other useful BCP derivatives.[6] Surprisingly, this seemingly simple and straightforward transformation had discouraging literature precedence. Thus, on the sidelines of their successful synthesis of **1**, Bunker and co-workers also reported their failure to efficiently reduce the iodo azide **2** (Scheme 1).[8] Prior to this, similar unsuccessful reduction attempts on **2** were reported by Hossain and Timberlake.[11]

Intrigued by this synthetic impasse and propelled by a necessity to establish a diversifiable route, we decided to invest our efforts in deciphering the reduction of **2**. Herein, we report our success with this endeavor.

We commenced our synthetic efforts on the conversion of **2** (three steps, 52% overall yield)[10] to **1** by attempting some of the reported failed efforts so as to comprehend the problem in

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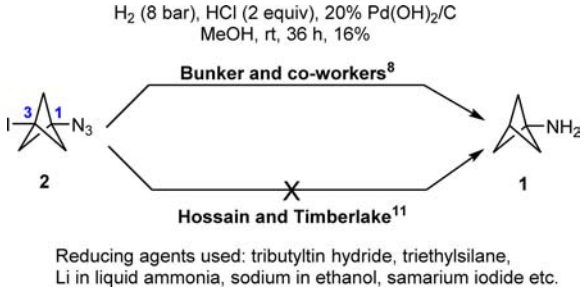
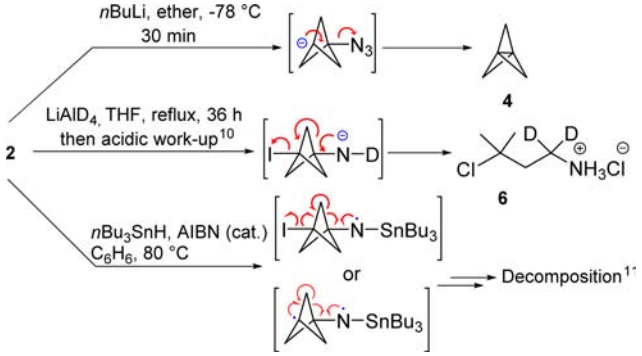
Scheme 1. Previous Efforts on the Reduction of 2 to 1



a more fundamental fashion. A selected set of these experiments and the potential causes behind their failure are worth mentioning. Thus, an attempt to effect a dehalogenation−protonation maneuver at the C-3 carbon (for numbering, see Scheme 1) via *n*-BuLi-induced metal−halogen exchange resulted in the formation of propellane (**4**) (Scheme 2). The

Scheme 2. Action of Selected Reagents on 2

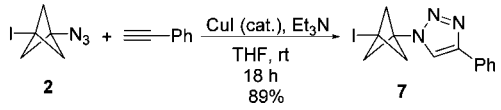


cause for this detriment could be related to the unusual proximity between C-1 and C-3 positions of **2**.[12] At the other end, Timberlake has shown that attempts to selectively reduce the azide at C-1 with LAH results in the opening of the BCP scaffold to yield **6**.[11] Such a dismantling event was proposed to be initiated by a negatively charged nitrogen atom at C-1.[11,13] Lastly, based on the failure of SmI_2 or tributyltin hydride (TBTH) to effect desired reduction, we opined that a ring-opening phenomenon, similar to the one proposed by Timberlake,[11] may also be instigated by a nitrogen radical as shown in Scheme 2. Thus, to reiterate, we concluded that a radical or an anionic nitrogen atom at the C-1 or a carbanion at C-3 was detrimental for the reduction of **2**.[14]

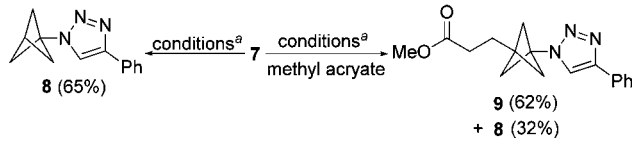
Based on our above analysis, we envisaged that a selective and radical-based reduction at C-3 of **2** may establish a solid foundation for reduction at C-1. More specifically, we hoped that installation of a stronger C−H bond at C-3 would allow an uneventful reduction of the azide. Before we embarked on this hypothesis, however, we sought some clarity on the stability of the anticipated radical at C-3 of **2**, assuming that we could keep the pendant azide dormant. To gain such evidence, we planned to model this study by transforming the azide in **2** to more tolerant triazole functionality. Synthetic exploration on this front commenced with a smooth conversion of **2** to the 1,2,3-triazole **7** (89%, Scheme 3a).[15] We then attempted the reduction at the C-3 of **7** by employing TBTH as a reducing agent. Indeed, this radical-based approach afforded the reduced product **8** in a good yield (65%, Scheme 3b).[6] Furthermore, in

Scheme 3

a: Synthesis of 7 from 2



b: Reduction and functionalization of 7



[a] nBu$_3$SnH, AIBN (cat.), C_6H_6, reflux.

the presence of a commonly employed radical trap such as methyl acrylate, under otherwise similar reaction conditions, we could partly capture the BCP-based tertiary radical to afford the bis-functionalized product **9**.[16] Overall, these observations indicated that a radical at C-3 of **7** may be a relatively stable species with no perceptible tendency to initiate or participate in undesired decomposition pathways.

Having gained some confidence in our hypothesis we decided to proceed with the daunting challenge of a selective reduction at C-3 of **2**. We hypothesized that this objective could be achieved by influencing the formation of key reaction intermediates during the azide reduction at C-1 via the deployment of a bulkier radical-based reducing agent in place of TBTH. Chatgilialoglu's reagent, tris(trimethylsilyl)silane (TTMSS), seemed to be a suitable choice.[17] We anticipated that the use of this sterically demanding reducing reagent[18] would kinetically favor the formation of intermediate **II** over the competing intermediate **I** and thus effect the desired chemoselective reduction (Figure 2). Moreover, we were also cognizant of the reported preference of TTMSS toward the reduction of alkyl halides over the azide functionality.[19]

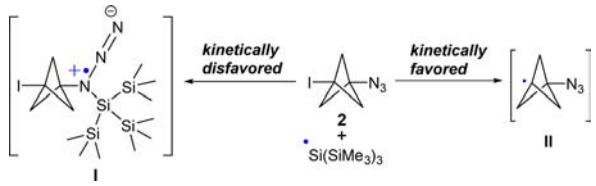


Figure 2. Anticipated bias between intermediates **I** and **II**.

We commenced the exploration of our hypothesis by allowing **2** to react with TTMSS at ambient temperature and under the action of atmospheric oxygen as a radical initiator.[20] Encouragingly, a rapid and a clean conversion of **2** was observed, by NMR, to a compound that we hoped to be our desired azide **10**. However, despite several efforts, we could not isolate **10** in a pure form. Fortunately, we could address this ambiguity by converting **10** to the 1,2,3-triazole **11** in an excellent yield (91%, Scheme 4).[21]

Having secured an easy access to the partially reduced compound **10**, we directed our efforts to reduce its azide function. Most gratifyingly, preliminary exploratory results hinted at the formation of the target compound **1** upon prolonged reaction of **2** with 2 equiv of TTMSS. This breakthrough was explored further and a selected set of these efforts is depicted in Table 1. Thus, after 18 h, the reaction of **2**

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Scheme 4. Selective Reduction at C-3 of 2

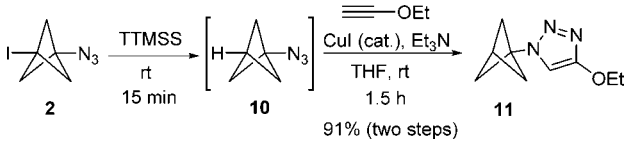
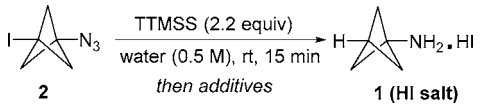


Table 1. Selected Optimization Results for the Reduction of 2 with TTMSS[a]



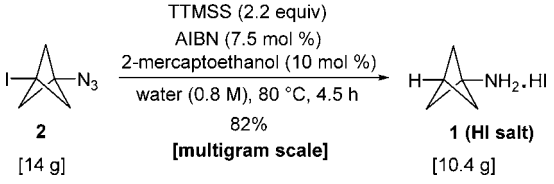
entry	additives[d]	time (h)	temp (°C)	yield,[b] (%)
1		18	rt	27[c]
2		3.5	80	33
3	AIBN	3.5	80	68
4	AIBN, 2-mercaptoethanol	3.5	80	**80**
5	2-mercaptoethanol	18	rt	13[c]
6	2-mercaptoethanol	18	80	61

[a]All optimization studies were done on 1.3 mmol of **2**. [b]Isolated yields. [c]Yields were observed to be inconsistent. [d]AIBN (10 mol %), 2-mercaptoethanol (15 mol %).

with TTMSS at room temperature furnished the target amine in a low yield (27%, entry 1). Allowing the reaction to continue beyond the said duration afforded no apparent gain in its yield. Next, we observed that elevation of the reaction temperature to 80 °C reduced the reaction time considerably and afforded a modest increment in the reaction yield (33%, entry 2). In the subsequent attempt, with the aim of reinforcing the initiation and propagation steps of the radical process, we deployed catalytic amounts of AIBN, at 80 °C, as an "additional" radical initiator. This modification afforded an explicit improvement in the yield (68%, entry 3). Furthermore, in order to achieve further enhancement of the reaction yields, we decided to explore the application of the TTMSS/thiol couple in our reaction.[22,23] Indeed, the best results, with regard to both the yields and consistency were obtained when the reaction shown in entry 3 was repeated with inclusion of 2-mercaptoethanol (80%, entry 4).[24] Interestingly, the presence of 2-mercaptoethanol as a sole additive, at room temperature, seemed to have a depreciating effect on the yield (13%, entry 5) when referenced against the reaction as shown in entry 1. At the same time, a similar reaction with the thiol additive, at 80 °C, gave a better yield (61%, entry 6) than its counterpart shown in entry 2.

With the optimized conditions at hand, we then explored the practicality of the protocol on multigram scales, and consistent outcomes were obtained in all cases (78−82%).[25] A representative example of this effort is illustrated in Scheme 5. It is worth mentioning that, in addition to the convenience of a rather simple experimental setup, the reaction protocol offers

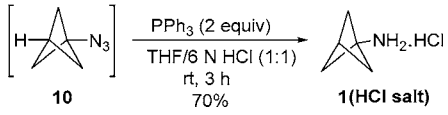
Scheme 5. Multigram-Scale Reduction of 2



expedient product isolation. Thus, upon completion of the reaction, the reaction mixture was cooled to room temperature, and the aqueous layer was separated and evaporated in vacuo to yield a yellow amorphous solid. This crude product was then washed with ethyl acetate to yield the pure compound as an off-white solid, thus evading the need for a chromatographic or chemical purification. Furthermore, no external addition of acid is necessary as the hydroiodic acid generated during the first step is well-utilized in the formation of the ammonium salt. Overall, the sequence provided a very easy and efficient access to **1**.[26]

In further support of our hypothesis, we could reduce the azide in **10** by performing the traditional Staudinger reaction and isolating the product as its hydrochloride salt in a decent yield of 70% (unoptimized, Scheme 6).[13,27] This protocol can serve as an alternative to the above-described reduction with TTMSS.

Scheme 6. Reduction of 10 under Staudinger Reaction Conditions



It is worth mentioning that, originating from the same starting material **3** (see ref 10c for the synthetic scheme), our route offers more flexibility by the virtue of its intermediates as compared to the methods described by Bunker[8] and others.[7] Indeed, intermediates **5** and **2**, have served as a starting point for other BCP derivatives.[28,21] Also, as an added advantage of our procedure, we could evade the need to distill **4** by quenching this rather unstable intermediate in situ to generate **5**. This subtle improvement renders the process more compatible for continuous synthesis of intermediates such as **5** or **2**,[11] and we are currently exploring these alternatives. Admittedly, however, at the current state of optimization, our route offers a lower overall yield (42%) than the one reported by Bunker (62%).[8]

To summarize, we have successfully identified and resolved the problems pertaining to the direct reduction of **2** and revealed a new, scalable, and diversifiable route to **1**. We believe that this work will further encourage the application of **1** in lead compounds and also in drug candidates. Also, apart from the displayed exemplifications, the understanding of the reactivity of the azide **2** revealed in this work may facilitate its use as a versatile intermediate in the synthesis of several other 1-*N*-substituted-3-functionalized BCP derivatives. Current efforts in our laboratory include the further optimization of the reported synthesis of **1**, especially from a process-scale perspective. Simultaneously, we are also developing practical synthetic routes to novel BCP derivatives that may be of interest in medicinal chemistry. These results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

*Email: vikrant_adsool@ices.a-star.edu.sg.

Notes

The authors declare no competing financial interest.

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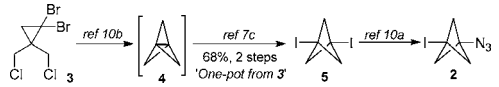

(d) We have successfully synthesized >20 g of **2** in a single batch without any untoward incident. However, precaution should be taken when working with azides due to their potentially explosive nature.

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(13) Use of Staudinger conditions to reduce the azide in **2** failed to yield the desired product and resulted in a complex mixture of unknown compounds. This failure can also be explained by the described mechanistic rationale.

(14) A successful selective reduction of the azide in **2** has been reported by employing BH_3–THF as a reducing agent.[11] Unfortunately, in our hands, we could not repeat the reported result.

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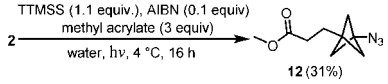
(21) We could also successfully trap the incipient radical **II** with methyl acrylate to afford **12**. The scope of this work will be reported separately.



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(24) The reaction performed under neat conditions gave comparable yields (after aqueous workup); however, the isolated product seemed to retain significant coloration (brown to yellow). Moreover, from the scalability (and safety) perspective, the presence of water was preferred since it was beneficial in dissipation of heat during the initial exothermic reaction (reaction temperature = 45 °C).

(25) The reaction has been repeated >10 times on scales ranging from 5 to 14 g. See the Supporting Information.

(26) See the Supporting Information.

(27) Initial exploratory results on the reduction of **10** by catalytic hydrogenation protocols gave very low yields (<10%).

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