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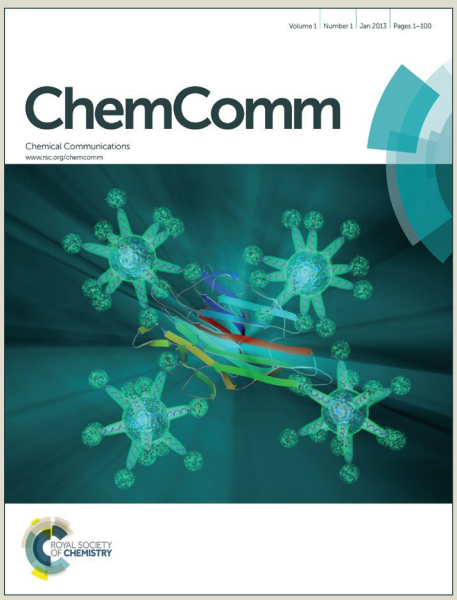

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ARTICLE TYPE

Expedient synthesis of 3-phenylbicyclo[1.1.1]pentan-1-amine via metal-free homolytic aromatic alkylation of benzene.

Navanita T. Thirumoorthi,[a] Chew Jia Shen[a] and Vikrant A. Adsool,*[a]

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Recently, the potential utility of the BCP motif, as a contemporary lead optimization tactic, has generated substantial interest in medicinal chemistry. To facilitate this inquisitiveness, concomitant development of efficient synthetic protocols is crucial. The following work discloses a new, expedient and versatile approach to one such potentially useful BCP derivative.

In the contemporary practice of medicinal chemistry, strategic deployment of bioisosteres has often served as an effective tool to outwit issues related to design and development of drug candidates. Not surprisingly, synthesis and application of new molecular entities that may serve as bioisosteres, is of substantial interest in the pharmaceutical industry.[1] This seemingly fundamental endeavor, if aimed at appropriate targets, and traversed by exploiting novel chemical space, can result in a powerful approach to expedite generation of new lead compounds and to secure new intellectual property domains. On that note, the ubiquitous aryl rings serve as an intriguing target for bioisosteric manipulation.[1] Thus, whereas the use of these aromatic moieties is often considered to be indispensible due to their unique shape and rigidity, their presence is also known to be one of the leading causes of compound attrition in drug discovery.[2] Interestingly however, despite of this understanding, a paucity of new bioisosteric alternatives to aryl rings has prevailed for a long time.

During a medicinal chemistry effort in our laboratory, we comprehended both the need and the challenge behind the scarcity of aryl mimics. Specifically, our lead-optimization attempts of replacing the ring B (Figure 1a) of an aryl ring system **1**, with traditional bioisosteres (Figure 1b) seemed to be ineffective.

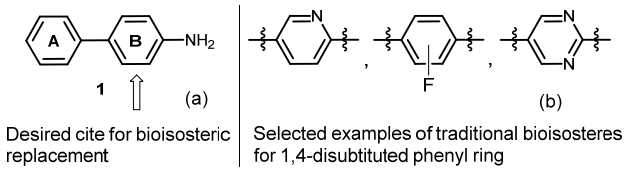


Fig. 1 Biaryl ring for bioisosteric manipulation and known alternatives

At that point, the structurally atypical, and sp^3-rich, bicyclo[1.1.1]pentane (BCP) motif attracted our attention. Two rather sporadic, but nevertheless seminal, reports provided support to the use of this 3D moiety as a replacement for 1,4-disubstituted phenyl rings.[3] Thus in 1996, Pelliciari and co-workers, in their study on MGluR receptors, had demonstrated the use of the BCP moiety as a 'spacer' to replace an aryl ring in a known MGluR1 antagonist **2** to generate a potent and structurally diverse analogue **3** (Figure 2a).[3a] More recently, in 2012, Stepan and co-workers[3b] disclosed the equipotency of a BCP derivative **5** relative to the clinical candidate for γ-secretase inhibitor,[3c] **4** (Figure 2b). In doing so, they offered the first compelling, and well-supported, evidence of the use of a BCP moiety as a phenyl replacement. Given the encouraging parallels between these reports to our aforementioned intentions, we were intrigued on the prospects of employing **6** as a bioisosteric alternative to **1** (see Figure 2c).

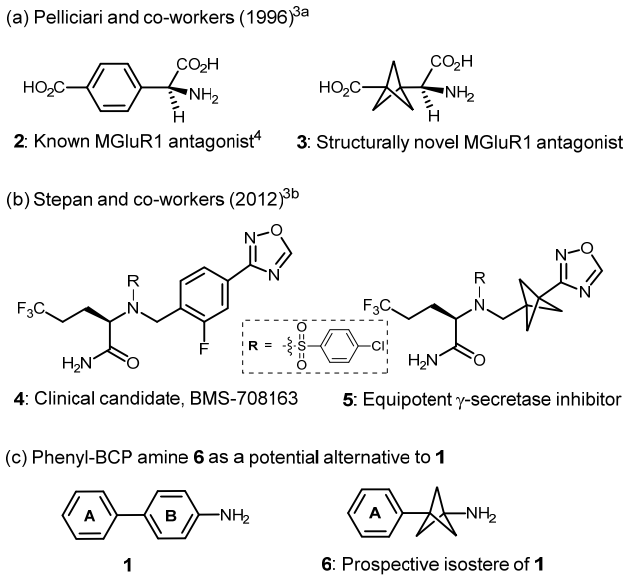
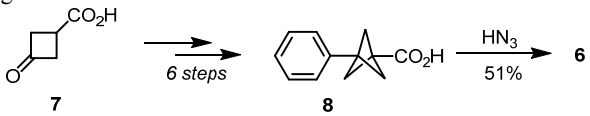


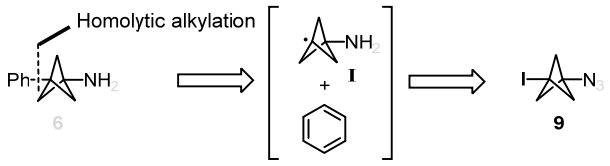
Fig. 2 Literature precedents and our proposed use of BCP moiety.

Having ascertained the use of the BCP derivative **6** in our lead optimization effort, we now targeted the synthesis of this amine. Surprisingly, our literature survey revealed that only one synthetic route to this compound had been reported (Scheme 1).[5] Moreover, the synthetic prolixity[6], and the use of the perilous hydrazoic acid (extremely toxic and explosive) in the key step (**8**→**6**, Scheme 1) of this sequence rendered it undesirable for general use.



Scheme 1 Known synthesis of the BCP derivative **6**.[5]

Given the recent interest in the BCP compounds, we believed that this rather primordial route warranted an expedient alternative that would be compliant with the contemporary trends in organic synthesis. This perspective motivated us to target the rather ambitious retrosynthetic dissection across the phenyl-BCP bond of **6** (Scheme 2). In the forward sense, our theoretical plan could be envisioned to originate from an alkyl radical species such as **I** and benzene, and proceed via an alkyl homolytic aromatic substitution (HAS) mechanism. Moreover, from our previous work, the radical synthon **I** could be unambiguously proposed to be derived from an easily available starting material **9** (three steps from commercially available starting materials, 52% overall yield).[7] In this Letter, we narrate our studies and the ensuing success in achieving the synthesis of **6** in a convenient, concise and versatile fashion.

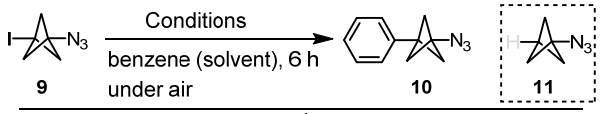


Scheme 2 Retrosynthetic approach

From a general perspective, HAS with alkyl radicals finds two negative preludes in the literature. Firstly, aromatic compounds are not considered to be ideal substrates for homolytic alkylation since the rates of addition of alkyl radicals onto arenes are generally too slow to be of synthetic application.[8,9a] Secondly, such alkylations with alkyl halides have much shorter kinetic (radical) chain length than their organometallic counterparts such as alkylmercury halides, thus suggesting the use of metals to be rather inevitable.[9,10] Given our intention to comply with the current-day synthesis requisites, we were reluctant to employ toxic metals in our approach. Despite this disappointing prologue, we were keen in embarking on this approach based on our earlier studies with **9**.[7c] Thus, we had previously demonstrated generation of the radical from iodide **9** by using Chatgilialoglu's reagent, tris(trimethylsilyl)silane (TTMSS).[7c] This experience in conjunction with Minisci's[11a] and Togo's[11b] work on homolytic alkylations with TTMSS provided a good rationale to deploy efforts towards our aforementioned plans.

A succinct representation of our attempts to use TTMSS as a radical mediator is shown in Table 1. Our studies started on an

Table 1 Studies with TTMSS as a radical mediator.

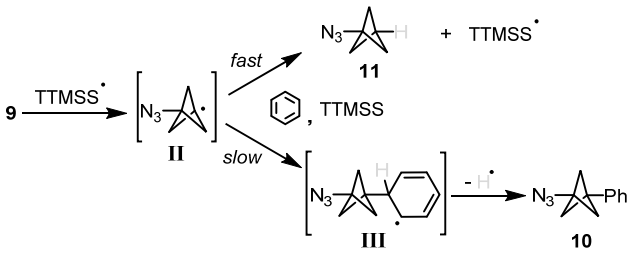


Entry	Conditions[a,b]	Temp. (ºC)	Yield (%Y)
1	hν, TTMSS	4	<10[c]
2	hν, TTMSS	rt	<10[c]
3	hν, AIBN, (0.1), TTMSS	4	12[d]
4	hν, AIBN, (0.1), TTMSS	rt	15[d]
5	hν, AIBN, (1.1), TTMSS	rt	13[d]
6	Δ, AIBN (1.1), TTMSS	80	17[d]

[a]All optimization studies were done on 0.1 mmol of **9** with 1 equivalent of TTMSS in 1.5 mL benzene. Equivalents of AIBN are denoted in the brackets. [b] hν = 254 nm, pyrex tube, air balloon. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Isolated yields. [e]^{1}H NMR analysis of the reaction mixture showed incomplete reaction, and reduced compound **11** as the major constituent, in all the depicted cases.

encouraging note, wherein, the product formation was detectable (<10% by ^{1}H NMR, entry 1 and 2) during the reaction of the iodide **9** with TTMSS under photolytic conditions (UV = 254λ) at both 4 ºC and room temperature.[12d] Addition of catalytic amounts of AIBN furnished, albeit modest, an increment in the yields that allowed product isolation at both the temperature variations (12% and 15% for entries 3 and 4 respectively). However, these seemingly favorable outcomes were marred by incomplete reaction and predominant formation of the reduction by-product **11**[7c] was apparent from ^{1}H NMR analysis of the crude reaction mixture. Furthermore, in spite of several optimization attempts including the use of stoichiometric amounts of AIBN (13%, entry 5),[12] and elevation in the reaction temperature to reflux conditions (17%, entry 6), we failed to secure selective formation of **10** over the undesired side-product **11**. In short, although our studies with TTMSS had afforded the proof-of-concept of our planned homolytic alkylation contrive, the daunting challenge of demonstrating its synthetic utility remained impervious.

Analysis of the mechanistic aspects of this reaction was deemed necessary to chart the further course of action (Scheme 3). Our desired pathway would encompass the formation of radical intermediate **II** and its addition onto the benzene molecule. Aromatization of the resulting cyclohexadienyl radical intermediate **III** would then afford **10**. However, based on our observations (Table 1) it seemed that the expected addition of the alkyl radical **II** to benzene may have been either completely, or partially, overtaken by the competing reduction of **II** to **11**.



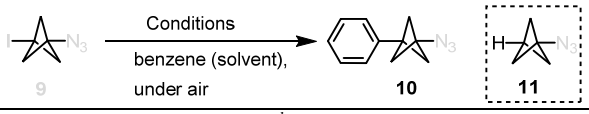
Scheme 3 Mechanistic interpretation of the reaction of **9** with TTMSS.

The above scrutiny was particularly intimidating since it rhymed with the aforesaid literature opinion on the synthetic utility of HAS of alkyl radicals.[8,9] However, from a different perspective, our analysis (Scheme 3) also suggested that the replacement of TTMSS with a radical mediator having lesser inclination towards the unwanted reduction would offer a potential tilt in the favor of our HAS contrive. Gratefully, Ryu's recent work on a borohydride reagent, tetrabutylammonium cyanoborohydride (TBACB), appeared to fit this criteria.[13] In a series of elegant studies, Ryu has shown TBACB to act as an efficient radical mediator with a much reduced tendency to donate its hydride payload.[13g]

To validate our hypothesis we undertook an extensive effort to test the application of TBACB in our case, and a pertinent set of this work is depicted in Table 2. The attempt to react **9** in presence of only TBACB in excess benzene under photoirradiation afforded poor conversion (<10%, entry 1). However, this observation was a rather assuring outcome in that no reduction of **9** was observed. Also, this result was indicative of a chain termination event, perhaps led by the cyclohexadienyl radical intermediate.[12c] In order to investigate this assumption, we repeated these reaction conditions with stoichiometric amounts of

AIBN with the expectation that this reagent will play the dual role of a radical initiator and also that of an oxidant.[12] Unfortunately, no major increment in the product formation was observed (<10%, entry 2). In our next optimization maneuver we swapped the photoirradiation-based activation with thermal conditions, in an otherwise identical setting. This modification led to a small but noticeable change in the product formation (~20 %, entry 3). Several ensuing attempts to optimize these conditions (not shown) failed in furnishing **10** in decent yields suggesting that AIBN was only of partial help. Uncertain of the cause of the assumed radical chain termination, we decided to provide a continuous supply of oxygen to the reaction mixture in order to aid the conversion of the proposed intermediate **II** to **10** (see Scheme 3). Accordingly, we repeated the reaction conditions shown in entry 3 (Table 2) by bubbling air through the mixture. A major increase in the reaction product formation was observed (32%, entry 4). It was imperative to note that the presence of both AIBN and air passage through the reaction mixture was essential and the absence of the former resulted in no reaction (entry 5). Subsequently, under the influence of both AIBN and air, we examined the presence of additional reducing agent on the desired reaction. Gratifyingly, a significant improvement in the reaction yields was noted when the amount of TBACB was doubled (55%, entry 6). Resultant studies furnished our best reaction conditions; wherein, the periodic addition of 4 equivalents of TBACB to the reaction mixture gave a very good and reproducible conversion of **9** to **10** (65%, entry 7). Gratifyingly, only 13% of the reduced compound **11**[7c] was observed by ^{1}H NMR.

Table 2 Studies with TBACB as a radical mediator.

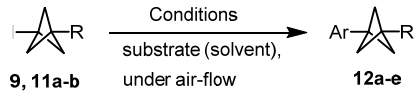


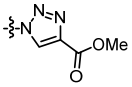
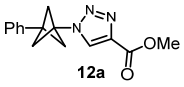
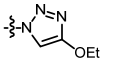
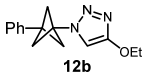
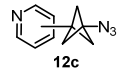
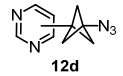
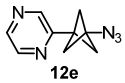
Entry	Conditions[a,b]	Time (h)	Temp. (ºC)	Yield (%Y)
1	hν, TBACB(1)	4	rt	<10[c]
2	hν, AIBN (1.1), TBACB(1)	4	rt	<10[c]
3	AIBN (1.1), TBACB (1)	4	100	<20[c]
4	AIBN (1.1), TBACB (1), air flow[d]	5	100	32[e]
5	Δ, TBACB (1.5), air flow[d]	3	100	0[c]
6	AIBN (1.1), TBACB (2), air flow[d]	2	100	55[e]
7	AIBN (1.1), TBACB (4), air flow[d]	2.5	100	65[e]

[a]All optimization studies were done on 0.2 mmol of **9** in 3.75 mL of benzene. [b]hν = 254 nm, pyrex tube, air balloon. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Under continuous air flow through the reaction mixture. [e]Isolated yield. [f]Equivalents are indicated in brackets.

Encouraged by our success, we were intrigued by the prospect of applying our newly-discovered protocol for the synthesis of other compounds. Indeed, our preliminary results (un-optimized) indicate that a series of BCP compounds are accessible by the said procedure (Table 3). Thus, triazoles **11a**[7d] and **11b**[7c] reacted efficiently to generate the corresponding phenyl-BCP derivatives **12a** (67%, entry 1) and **12b** (72%, entry 2). Electron deficient substrates such as pyridine, pyrimidine and pyrazine also afforded the desired products **12c** (38%, entry 3), **12d** (24%, entry 4) and **12e** (24%, entry 5); with the former two compounds generating regioisomeric mixtures favouring the ortho products. Further optimization of the reaction conditions for the depicted substrates is apparent.[14]

Table 3 Preliminary results with selected substrates.



Entry	R[a]	Substrate	Product	Yield[b,c] (%)
1			 12a	67
2			 12b	72
3			 12c	38[d]
4			 12d	24[e]
5			 12e	24

[a]All optimization studies were done on 0.2 mmol of **11** unless indicated otherwise. [b]Un-optimized yields. [c]Isolated yields. [d]Ratio of substitution at position 2/6:3/5:4 = 1:0.6:0.4. [e]Ratio of substitution at position 2: 4/6: 5 = 1:0.8:0.3.

Our postulated mechanism of the TBACB mediated homolytic alkylation is shown in figure 3. We propose that the radical chain may initiate with the addition of **II** on the benzene to generate the cyclohexadienyl radical **III**. Aromatization of **III,** in-principle, could occur with the aid of either AIBN or that of the molecular oxygen. However, based on our observations, in our case both these reagents seemed necessary to furnish **10** in a decent yield.

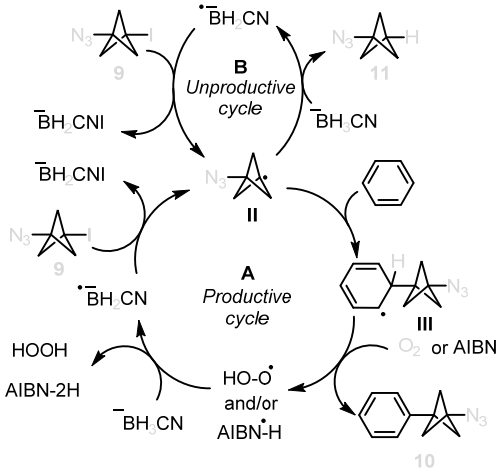
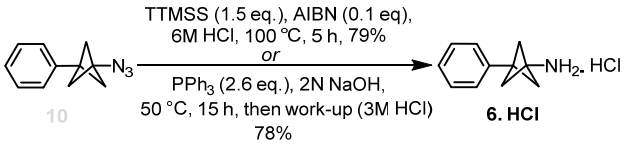


Fig 3 Postulated radical chain events during the formation of **10** and **11**.

Further on, the resulting hydroperoxide or the AIBN radicals may propagate the chain by activating the cyanoborohydride reagent,

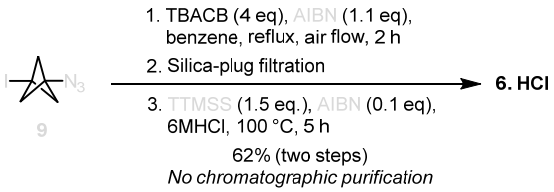
which in turn would abstract the iodide from **9** to yield **II**. Importantly, as per the plot, the competing undesired radical chain reaction B was seen to be slower thus generating lesser amounts of the reduced product **11**.

With the optimized conditions in hand, we now focused on the reduction of the azide **10** to the desired amine **6**. This goal could be secured uneventfully by using either Staudinger conditions (78%, Scheme 4) or by using the TTMSS (79%) as a reducing agent in an excellent yield.[7c]



Scheme 4 Reduction of the **10** to **6**.

In addition to the described success of our approach to secure **6**, the practicality of our protocol deserves a mention. Thus, we could telescope the synthesis of **6** from **9** by carrying forward the crude azide **10** after subjecting it to a simple short-bed silica filtration (Scheme 5).[15] This material was reduced with TTMSS in presence of catalytic amounts of AIBN. Upon completion of the said reduction, the amine **6** could be isolated by chemical separation thus circumventing the need for a chromatographic purification (62%, over two steps, Scheme 5).



Scheme 5 Convenient synthesis of **6** from **9**.

Conclusions

In response to an apparent synthesis-based paucity of a BCP compound **6**, we have disclosed a new, concise, and convenient access to this target (five steps, 32% overall yield) from commercially available starting materials. The described method can serve as an efficient alternative to the existing route[5] (seven steps, ~14% overall yield, Scheme 1) and also helps evade the use of an unsafe reagent such as hydrazoic acid. The said objective was secured via a novel, potentially versatile, metal-free homolytic alkylation protocol. This study may provide further impetus to the use of BCP compounds in drug discovery. Furthermore, the described application of Ryu's reagent[13] can provide an encouraging precedence for metal-free homolytic alkylation reactions. A detailed account of this work, along with further studies on the disclosed preliminary results, will be reported in due course.

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[a] *11 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). Fax: (65) 6874 5870; Tel; (65) 6799 8503; E-mail: vikrant_adsool@ices.a-star.edu.sg.*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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14 This study (Table 3) deserves further investigation and will be duly reported in the detailed account of this work. Our intention of disclosing the said results at this point is to provide a tentative procedure, or a starting point, for synthesis of novel BCP compounds such as **12a-e**.

15 See the supporting information