Synthesis of Bicyclo[1.1.0]butanes from Iodo-Bicyclo[1.1.1]pentanes

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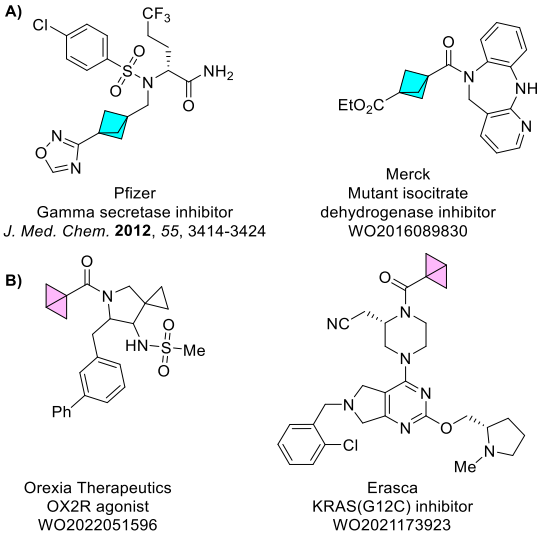
ABSTRACT: We describe a two step process for the synthesis of substituted bicyclo[1.1.0]butanes. A photo-Hunsdiecker reaction generates iodo-bicyclo[1.1.1]pentanes under metal-free conditions at room temperature. These intermediates react with nitrogen and sulfur nucleophiles to afford substituted bicyclo[1.1.0]butane products.

Bicyclo[1.1.1]pentanes (BCPs) are saturated phenyl bioisosteres[1] that have been recently popularized within drug discovery (Scheme 1A).[2] Over the past decade, there have been significant advances in synthetic methods[3] for producing and functionalizing this ring system. Bicyclo[1.1.0]butanes (BCBs), despite being isolated and characterized many decades ago[4], are far less commonly represented in reported bioactive compounds. Reports of bioactive compounds containing BCBs include one biosynthesized fatty acid[5], but primarily include bridgehead-substituted BCBs in which the BCB serves as a pseudo-Michael acceptor for covalent modification by a biological target (Scheme 1B).[6] Curiously, BCBs have less ring strain (64–66 kcal/mol) than BCPs (67–68 kcal/mol).[7] Nevertheless, the high *s*-character of the bridgehead carbons allows BCBs to react with electrophiles, nucleophiles, carbenes, and radicals.[8] BCBs are beginning to be employed more broadly in drug discovery as covalent modulators (Scheme 1B)[9] and as building blocks for the construction of sp^3-rich molecules.[3A, 10] The increased chemical stability of disubstituted BCBs suggests they could be incorporated into final drug molecules. Much of the literature describing the synthesis of BCBs concerns intramolecular substitution reactions of cyclobutyl and cyclopropyl carbanions[4B, 11] or intramolecular [2+1] reactions with carbenes.[12] Synthetic routes to BCBs starting from commercial materials that do not require the preparation of [1.1.1]propellane would be most ideal.

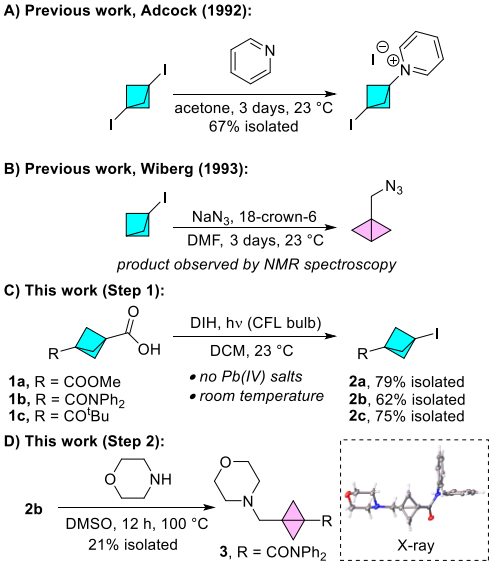
Adcock found that the reaction of pyridine with 1,3-diiodo-BCP formed a substituted BCP pyridinium salt (Scheme 2A)[13] and Wiberg found that C–I bond heterolysis of 1-iodo-BCPs in the presence of NaN_3 yielded a BCB observed by NMR spectroscopy (Scheme 2B).[14] Given the growing commercial availability of BCPs, we wondered if we could expand upon Wiberg's observation and develop a more general intermolecular reaction between iodo-BCPs and nucleophiles to make substituted BCBs.

First, we searched for the simplest way to make iodo-BCPs. We aimed to directly convert commercially-available BCP-1-carboxylic acids to the corresponding iodides as an alternative to strain-release reactions of [1.1.1]propellane[3B, 15] or decarboxylation of redox-active esters.[16]

Scheme 1. Examples of bioactive BCPs[2] and BCBs[9A, 9B].



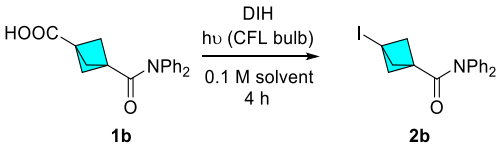
Scheme 2. Substituted BCBs can be prepared in two steps from commercially available BCP carboxylic acids.



Chemists at Enamine solved the longstanding challenge of preparing BCP-1,3-dicarboxylic acid on scale[17], leading to increased commercial availability of **1a**, an intermediate that costs $6.8/mmol.[18] The iodo-BCP **2a** costs $383/mmol (Scheme 2C).[19] **2a** has previously been prepared via stepwise Barton ester formation and decarboxylation[20] or via the Kochi reaction[21], which employs a toxic lead salt. Gandelman reported a mild modification of the photo-Hunsdiecker reaction using diiodohydantoin (DIH) as an iodinating reagent.[22] It was unknown whether these conditions could be extended to BCPs, which were not included in the original substrate scope. When **1a** was treated with 1.0 equiv DIH and light in refluxing 1,2-dichloroethane, evidence of **2a** formation was detected, concomittant with significant side reactions occurring as evidenced by ^{1}H NMR analysis of the crude reaction mixture. Cooling the reaction to room temperature and switching solvents to dichloromethane suppressed the deleterious formation of side products and smoothly afforded the iodinated product **2a** in 79% yield. We characterized the thermal stability of **2a** by differential scanning calorimetry (DSC) due to a recent report[20] on the instability of related compounds (See Supporting Information).[23]

The diphenylamide analog **1b** was selected as a model substrate with a chromophore to aid reaction monitoring for optimization. When **1b** was treated with 0.5 equiv DIH and irradiated for four hours, **2b** was observed to form with 72% conversion. With additional DIH, the conversion increased to >90% (Table 1, Entries 2, 3).

Table 1. Optimization of photo-Hunsdiecker reaction.[a]



1b **2b**

entry	DIH (equiv)	solvent	T (°C)	CFL hν	conversion (%)
1	0.5	DCM	23	+	72
2	1.0	DCM	23	+	92
3	**1.5**	**DCM**	**23**	**+**	**94**
4	2.0	DCM	23	+	90
5	1.0	DCM	23	-	0
6	1.0	MeCN	23	+	32
7	1.0	acetone	23	+	21
8	1.0	DMF	23	+	5
9	1.0	THF	23	+	0
10	1.0	dioxane	23	+	8
11	1.0	DCE	23	+	55

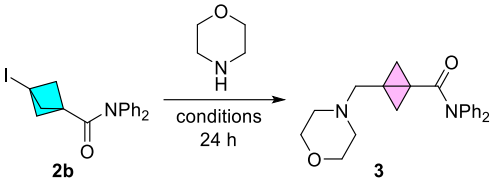
[a]**1b** and 1,3-diiodo-5,5-dimethylhydantoin (DIH) were added to a 4 mL vial equipped with magnetic stirbar and septum. Solvent was added and the reaction was irradiated using a white CFL bulb at 23 °C and monitored by LC/MS. See Supporting Information for experimental details.

With a mild method to access iodo-BCPs **2a-c** in hand, we were intrigued by C–N bond functionalizations based on the results of Adcock[13] and Wiberg (Scheme 2A–B).[24] We hypothesized that we could potentially form amino-substituted BCP products when **2b** is treated with an amine in a polar aprotic solvent. Alternatively, if the rearrangement described by Wiberg[14, 24A] occurred, we could expect a substituted BCB product. The ^{1}H NMR and ^{13}C HSQC spectrum of **3** displayed two singlets corresponding to a pair of magnetically inequivalent protons attached to the same carbon, suggesting the BCB was the product. To confirm, an X-ray crystal structure of **3** was acquired that proved a rearrangement had occurred to the BCB.

We thought this substitution reaction could offer a method for the construction of a diverse array of molecules containing the BCB motif. Optimization of the reaction between morpholine and the iodo-BCP **2b** is described in Table 2. While the reaction tolerated different morpholine loadings (Entries 1–5), we found that the reaction was highly sensitive to solvent and reaction temperature.

Deviating from 80 °C in DMSO led to decreased yields (Entries 6–9). Many solvents were inferior to DMSO (Entries 10–17). Hexafluoroisopropanol (HFIP)[25] and 2,2,2-trifluoroethanol (TFE), which are low-nucleophilic, carbocation-stabilizing solvents, decomposed the starting material and only provided trace yields of the product (Entries 10–11). In contrast, the reaction performed in NMP at 80 °C was sluggish, and the remainder of the mass balance was mostly leftover starting material (Entry 13).

Table 2. Optimization of the iodo-BCP substitution reaction.[a]



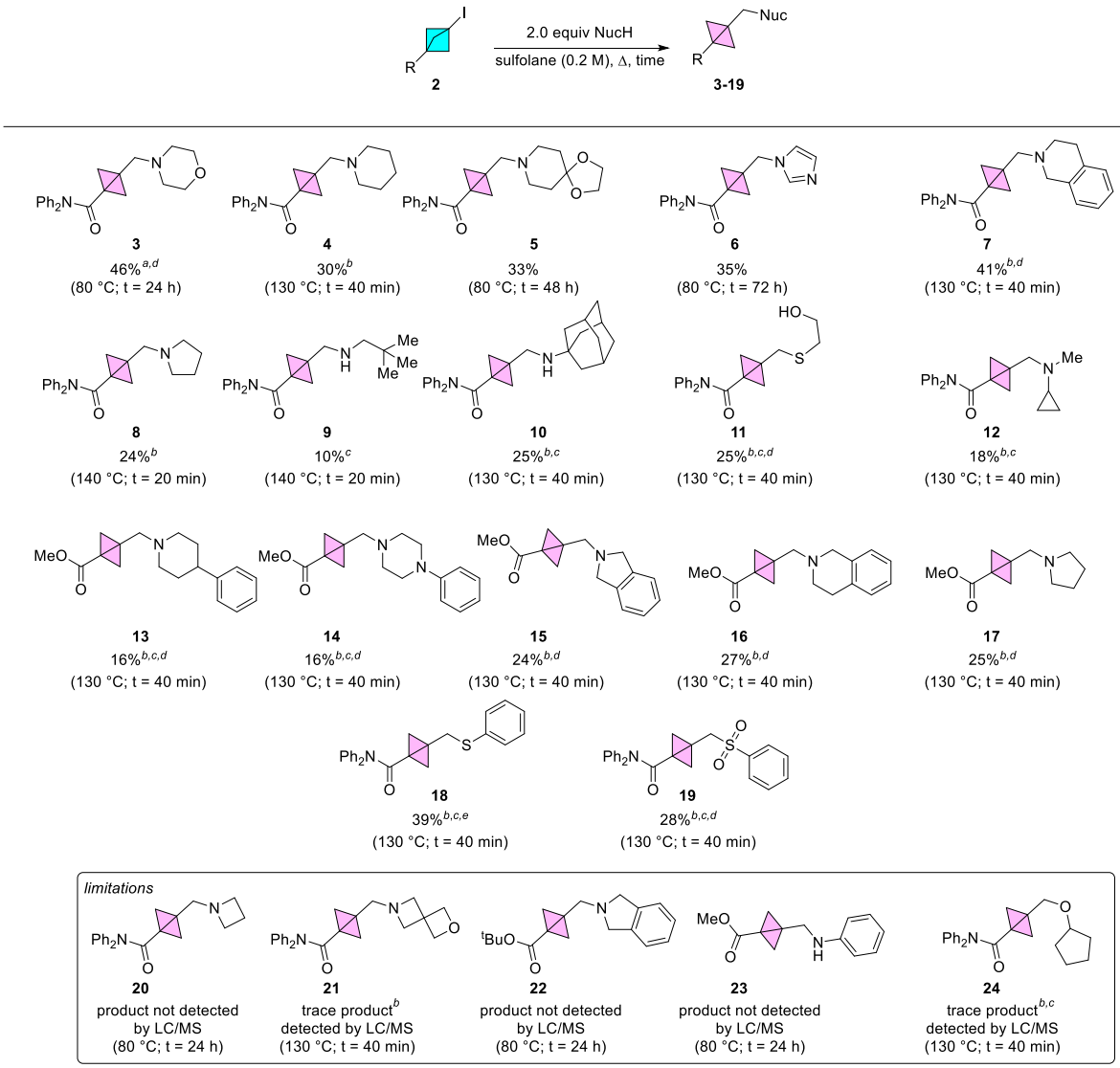
2b **3**

entry	morpholine (equiv)	solvent	T (°C)	yield (%)[b]
1	1.0	DMSO	80	17
2	1.5	DMSO	80	18
3	2.0	DMSO	80	20 (21)
4	5.0	DMSO	80	19
5	10.0	DMSO	80	17
6	2.0	DMSO	100	18
7	2.0	DMSO	60	5
8	2.0	DMSO	40	4
9	2.0	DMSO	23	2
10	2.0	TFE	80	13
11	2.0	HFIP	80	6
12	2.0	DMF	80	13
13	2.0	NMP	80	4
14	2.0	AcOH	80	0
15	2.0	MeOH	80	13
16	2.0	acetone	80	0
17	2.0	DMPU	80	6
18	2.0	sulfolane	60	3
19	**2.0**	**sulfolane**	**80**	**32 (37)**
20	2.0	sulfolane	100	24
21	2.0	sulfolane	120	0
22	2.0	sulfolane	150	0
23	2.0	sulfolane	80	5[c]
24	2.0	sulfolane	80	21[d]

[a]Stock solutions of **2b** and morpholine were combined in a 4 mL vial equipped with a magnetic stir bar. The vials were sealed and heated for 24 h and then a stock solution of 5,6-dibromobenzo[d][1,3]dioxole (0.1 M, $CDCl_3$) was added as an internal standard. An aliquot was removed and then analyzed by ^{1}H NMR spectroscopy. [b]NMR yields. Isolated yields in parentheses. [c]10 equiv. Ag_2O added. [d]10 equiv. ZnO added.

Sulfolane[26] was found to be an improvement over DMSO (Entry 19); however, temperatures higher than 80 °C for 24 h led to decomposition (Entries 20–22). Decreasing the temperature to 60 °C led to a ten-fold decrease in NMR yield (Entry 18). Metal additives known to promote carbocation formation from alkyl halides,[27] such as silver oxide and zinc oxide[28] were tested and resulted in lower analytical yields than did additive-free conditions (Entries 23–24).

Scheme 3. Substrate scope of BCP to BCB substitution reaction.



All yields are isolated yields. [a]1.0 mmol scale. [b]Microwave reaction. [c]4.0 equiv DIPEA added. [d]Purified by reverse-phase HPLC. [e]1.0 equiv thiol and 2.0 equiv DIPEA used.

We further examined the substrate scope of the BCP to BCB reaction in sulfolane (Scheme 3). Secondary amine nucleophiles commonly employed in medicinal chemistry were tolerated such as morpholine (**3**), piperidine (**4**), and a ketal-protected piperidone (**5**). Imidazole delivered **6** in 35% isolated yield after 3 days of heating in sulfolane at 80 °C. 1,2,3,4-tetrahydroisoquinoline afforded **7** in 41% yield after a short microwave reaction. We found that microwave heating can quickly probe whether the reaction will be successful, and in many cases isolated yields were comparable to those of conventional heating (See Table S1–S2). For the preparation of compound **11**, microwave heating gave better performance. Either normal- or reverse-phase chromatography can be used to purify the products. In the former case, sulfolane must first be removed by aqueous workup (e.g. with methyl tert-butyl ether[26]). In the latter case, the sulfolane solution can be directly injected into a reverse-phase HPLC column.

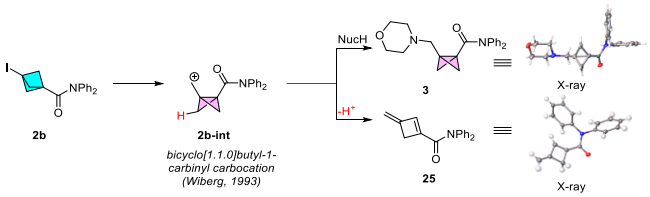
Substitution with pyrrolidine gave **8** in 24% yield. The bulky primary neopentylamine and 1-adamantylamine afforded **9** and **10** respectively, albeit in lower yields. Aliphatic alcohols did not give isolable products, but the more nucleophilic thiol 2-mercaptoethanol afforded **11** in 25% isolated yield. The methyl iodo-BCP carboxylate ester **2a** was also a competent electrophile (**13**–**17**). Thiophenol and phenylsulfinate yielded the thioether **18** and sulfone **19** respectively.

Limitations included four-membered ring amine nucleophiles that did not lead to significant product formation (**20**–**21**); instead, the starting material decomposed. Unfortunately, the tert-butyl ester **2c** did not yield substituted BCB product **22** and instead decomposed upon heating. Aniline did not afford **23** and cyclopentanol gave only trace amounts of **24**.

In all substitution reactions with **2b**, the desired product formed concomitantly with an elimination product that was isolated and characterized as the 3-methylene-1-cyclobutene **25** by X-ray crystallography (Scheme 4). We obtained higher yields of **25** and lower yields of **3** when microwaving at higher temperatures for shorter times. We hypothesize the BCP to

BCB substitution reaction occurs via an S_N1/E1-type mechanism involving the intermediacy of the bicyclo[1.1.0]butyl-1-carbinyl carbocation proposed by Wiberg.[14, 24A] We cannot rule out a carbanionic or concerted mechanism as proposed by Della and coworkers.[29] In our hands, sulfolane was the optimal solvent for this reaction, and while aprotic solvents are not usually associated with promoting S_N1/E1 reactions, it is reported that sulfolane is capable of strongly solvating cations due to its high dipole moment (4.7 D).[26]

Scheme 4. Mechanistic proposal for BCP to BCB conversion.



Since monosubstituted BCBs have been employed as covalent modifiers (Scheme 1B), we subjected compound **3** to a glutathione (GSH) stability assay. We found no GSH conjugation upon incubation at 37 °C with NADPH (see Supporting Information).[30]

We have demonstrated a convenient two-step procedure for the synthesis of substituted BCBs from commercially available starting materials. First, 1-iodo-3-substituted-BCPs are generated by a mild decarboxylative iodination reaction promoted by simple CFL irradiation at ambient temperature. The corresponding iodo-BCPs can then be transformed to substituted BCBs upon reaction with primary and secondary amines or aliphatic thiols in sulfolane. Microwave heating at high temperatures (130–140 °C) for less than 1 hour affords substituted BCB products in similar yields as heat block reactions at 80 °C for several days. We hope that this transformation can be used to expand the collection of BCB derivatives as sp^3-rich carbocyclic cores.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

General experimental procedures and spectroscopic data for all new compounds. X-ray crystal structures of **3** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

ACCESSION CODES

CCDC 2259736 and 2259735 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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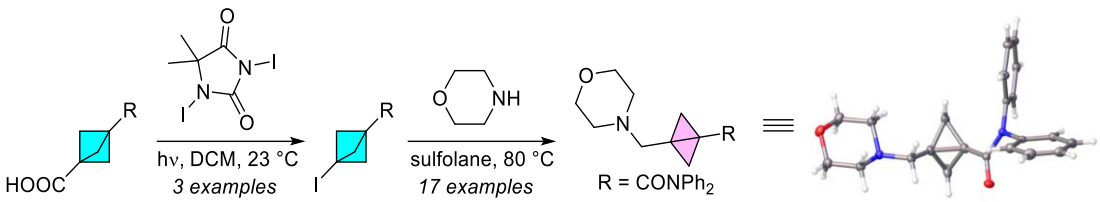
HOOC
R
hν, DCM, 23 °C
3 examples
I
R
sulfolane, 80 °C
17 examples
O
NH
O
N
R
R = CONPh2