Gabriel Synthesis of Aminomethyl-Bicyclo[1.1.0]butanes

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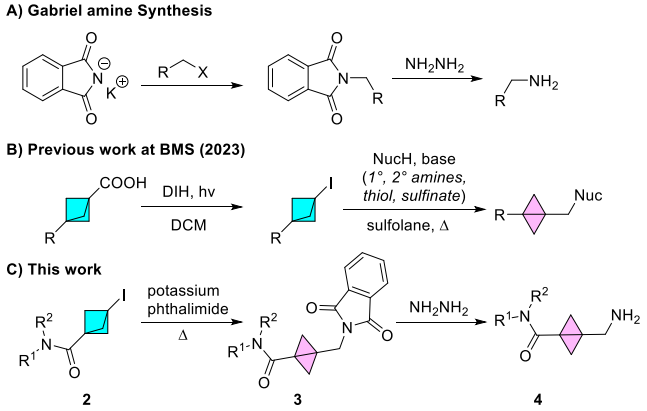
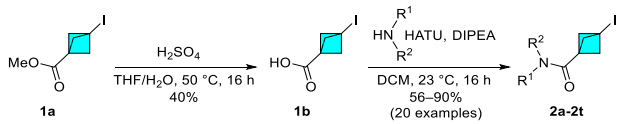
ABSTRACT: The reaction of iodo-bicyclo[1.1.1]pentanes with potassium phthalimide yields phthalimide-substituted bicyclo[1.1.0]butanes (BCBs), which upon hydrazinolysis afford the corresponding aminomethyl-BCB products.

The Gabriel amine synthesis is a classic method for the preparation of primary amines.[1] In this textbook reaction, potassium phthalimide reacts with alkyl halides to afford *N*-alkylphthalimides, which can be hydrolyzed or hydrazinolyzed to primary amines (Scheme 1A). Among the medicinal chemistry community, there is a widespread interest in the synthesis of bioisosteres incorporating higher fraction sp^3-character.[2] Bicyclo[1.1.0]butanes (BCBs) have emerged from obscurity as strained laboratory curiosities[3] to the limelight as versatile linchpins for the construction of sp^3-rich molecules.[4] Moreover, BCBs have been used as covalent reactive groups in biochemical tool compounds.[5] Recently, we disclosed a general reaction between iodo-bicyclo[1.1.1]pentanes (BCPs) and nucleophiles to yield substituted BCBs[6], building from a prior observation by Wiberg.[7] Such iodo-BCPs can be prepared in one step from commercial acid-BCPs by a modification of the Gandelman photo-Hunsdiecker reaction.[8] Under thermal conditions, iodo-BCPs react with primary and secondary amines, thiols, and sulfinates as nucleophiles to afford substituted BCB compounds (Scheme 2B). Distal to the iodide, a bridgehead electron-withdrawing group such as carboxamide or ester seems to be required.[9] Herein, we disclose that potassium phthalimide reacts with iodo-BCPs **2** in polar aprotic solvents to form aminomethyl-BCBs **3**. Hydrazinolysis of **3** leads to primary amines **4** (Scheme 2C).

Scheme 1. Gabriel amine synthesis applied to BCP to BCB transformation.

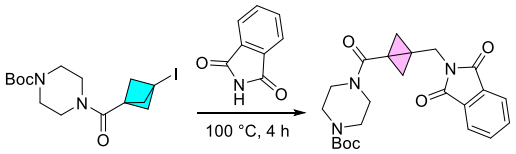


Scheme 2. Synthesis of iodo-BCP-amides **2**[a]



Twenty iodo-BCP-amides **2** were prepared by HATU-mediated coupling of iodo-BCP-COOH **1b** and amines (Scheme 2). We reasoned that amides would be more resilient than esters during the BCP to BCB rearrangement reaction and subsequent hydrazinolysis. Next, we heated **2q** and phthalimide with a variety of bases in sulfolane, a high-boiling aprotic solvent[10] (Table 1, Entries 1–6). Although DBU appeared to provide BCB **3q** in 20% NMR yield, we found that the conjugate base of phthalimide (Table 1, Entry 7), afforded modest improvement in yield together with operational simplicity. Other solvents were not found to improve the yield (Table 1, Entries 8–16).

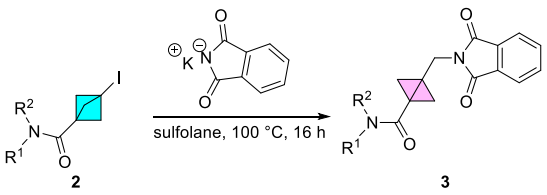
Table 1. Optimization of iodo-BCP-amide substitution reaction[a]



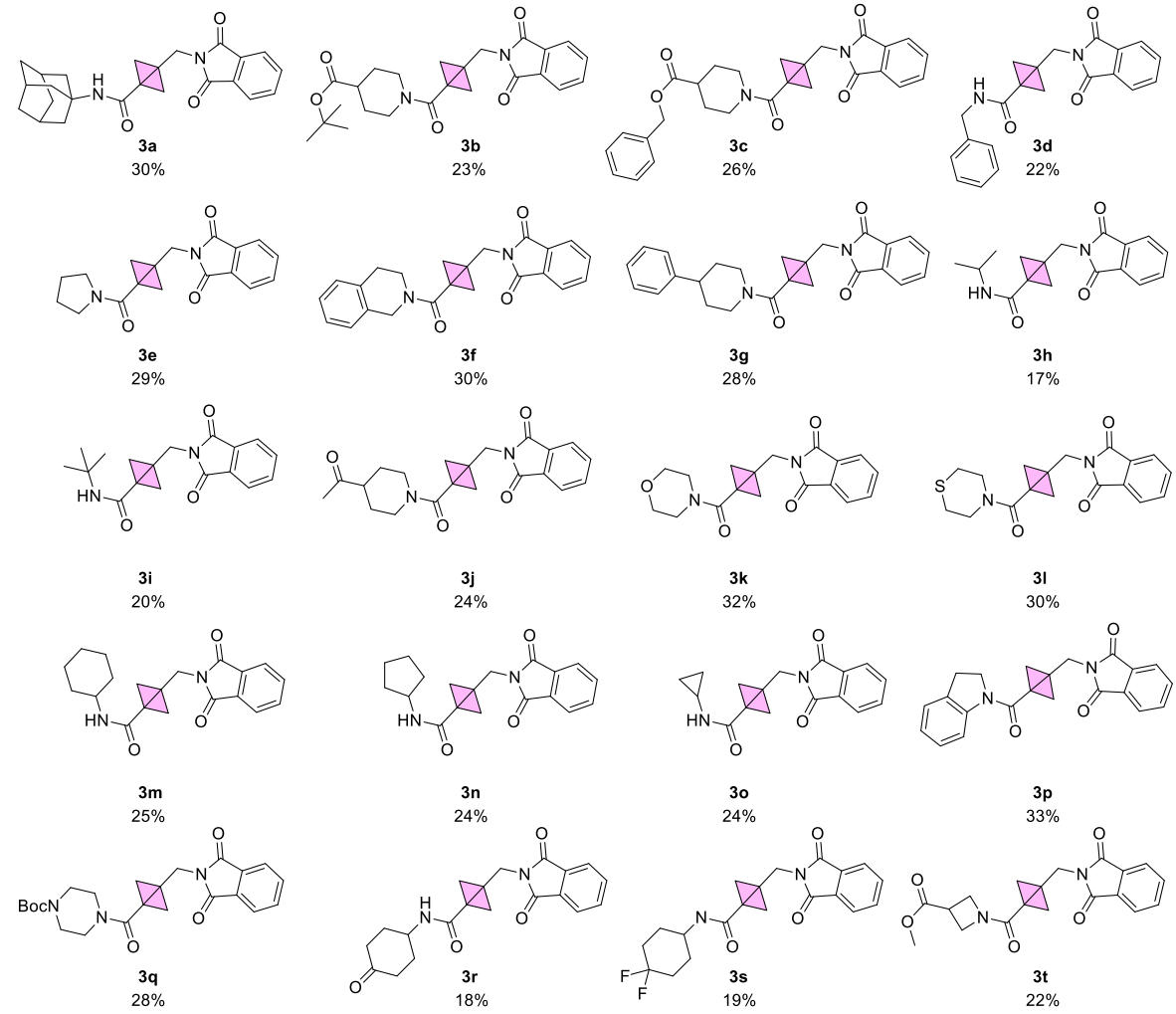
entry	solvent	base (equiv)	NMR yield (%)[b]
1	sulfolane	pyridine (1.0)	0
2	sulfolane	DIPEA (1.0)	<5
3	sulfolane	DBU (1.0)	20
4	sulfolane	Cs_2CO_3 (1.0)	16
5	sulfolane	K_2CO_3 (1.0)	0
6	sulfolane	K_3PO_4 (1.0)	<5
7	**sulfolane**	**--**	**30[c]**
8	DMSO	--	21[c]
9	EtOH	--	<5[c]
10	nBuOH	--	<5[c]
11	HFIP	--	0[c]
12	THF	--	0[c]
13	NMP	--	9[c,d]
14	DMF	--	7[c,d]
15	AcOH	--	0[c]
16	Cyrene	--	0[c]

[a]**2q** (1.0 equiv), phthalimide (1.2 equiv), and base (1.2 equiv) were heated to 100 °C in solvent (0.1 M final concentration) for 4 h unless otherwise noted. [b]NMR yields using 1,2,4,5-tetramethylbenzene as an internal standard. [c]Potassium phthalimide used. [d]16 h reaction time.

Scheme 3. Substrate scope of BCB-phthalimides **3**[a]



2 **3**

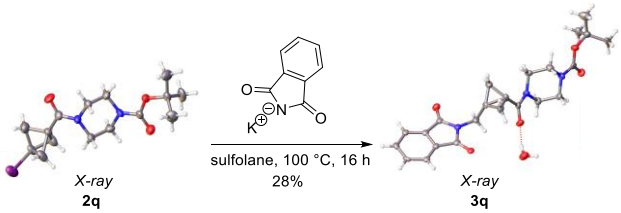


[a]Isolated yields following silica gel chromatography. BCP iodide **2** (1.0 equiv), potassium phthalimide (1.2 equiv), and sulfolane (0.1 M final concentration) were stirred at 100 °C for 16 h. See Supporting Information for full experimental details.

We previously found that these rearrangement reactions suffer from a competition between conversion to desired product and undesirable elimination side-products.[6] While we were not able to improve the yield of the reaction beyond 30%, we used our best conditions from **Table 1** to probe the scope of the thermal phthalimide and BCP-I reaction.

Twenty iodo-BCP amides **2a**–**t** were converted to the corresponding BCB-phthalimides **3a**–**t** (Scheme 3). After verifying the heat stable adamantyl amide **3a** could be prepared, we prepared tert-butyl ester **3b** and benzyl ester **3c**, which were tolerated in the reaction. Heterocyclic amides such as pyrrolidine-derived **3e**, tetrahydroisoquinoline-derived **3f**, and phenylpiperidine-derived **3g** were all tolerated. Ketones **3j** and **3r**, which are susceptible to both enolization and nucleophilic attack, were isolated in 24% and 18% yield respectively. Single-crystal X-ray diffraction analysis confirmed the structural assignment of the BCB skeleton with Boc-protected piperazine **3q** (Scheme 4).

Scheme 4. X-ray structures of iodo-BCP-amide **2q** and BCB-phthalimide **3q**



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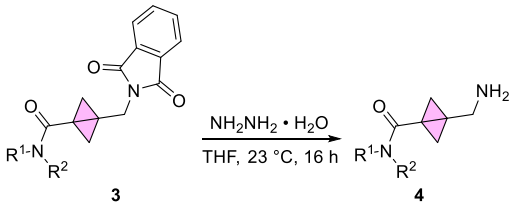
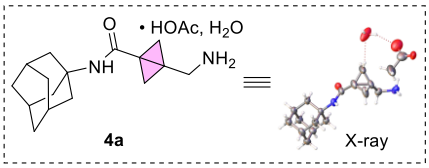
Finally, we attempted the conversion of BCB-phthalimides **3** to aminomethyl-BCBs **4**. We expected this might be challenging due to the highly reactive nature of the BCB central C–C σ bond.[3A] Out of the twenty BCB-phthalimides **3a-t**, we were able to isolate 13 aminomethyl-BCBs **4** following treatment with hydrazine (Table 2).[11] Each compound was purified by reverse-phase HPLC with ammonium acetate buffer and isolated as the acetate salt. An X-ray crystal structure of **4a** confirmed the ionic bond along with a bound water molecule (Table 2).

Table 2. Hydrazinolysis of BCB-phthalimides **3** to aminomethyl-BCBs **4**[a]



entry	3	4 (yield, %)[b]
1	**3a**	**4a** (80%)
2	**3c**	**4c** (76%)
3	**3d**	**4d** (70%)
4	**3e**	**4e** (77%)
5	**3h**	**4h** (64%)
6	**3i**	**4i** (65%)
7	**3k**	**4k** (67%)
8	**3l**	**4l** (82%)
9	**3m**	**4m** (80%)
10	**3n**	**4n** (73%)
11	**3o**	**4o** (80%)
12	**3p**	**4p** (75%)
13	**3q**	**4q** (77%)



[a]**3** (1.0 equiv) and hydrazine hydrate (5.0 equiv) were stirred in THF (0.1 M final concentration) at 23 °C for 16 h. [b]Isolated yields after reverse-phase HPLC.

We demonstrated an application of the classic Gabriel synthesis to form BCBs bearing a primary amine handle. Traditionally, the Gabriel sequence is performed with primary alkyl halides, while secondary/tertiary alkyl halides are not well tolerated. Iodo-BCPs are a special kind of tertiary alkyl halide that undergo substitution accompanied by skeletal rearrangement when they are heated with a nucleophile. We expanded our scope of nucleophiles (1°, 2° amines, thiols, and sulfinates)[6] to include phthalimide, which has important utility as an amine precursor.

The process we describe in this paper to make aminomethyl-BCBs uses no organometallic reagents or transition metals. Moreover, the starting material iodo-BCPs are readily synthesized from commercially-available and inexpensive acid-BCPs. Despite these advantages, our current sequence is limited by low yields of the **2** to **3** rearrangement reaction, which deserves further investigation and optimization. Currently we are working to try and improve the conversion and suppress decomposition pathways. Ultimately, we hope to be able to expand upon library compound collections by adding amine-functionalized BCB reagents with this chemistry.

ASSOCIATED CONTENT

Supporting Information

General experimental procedures and spectroscopic data for all new compounds. X-ray crystal structures of **2q**, **3q**, **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

ACCESSION CODES

CCDC 2315016, 2336718, 2336719 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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