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Taku Shibue, Yasumichi Fukuda

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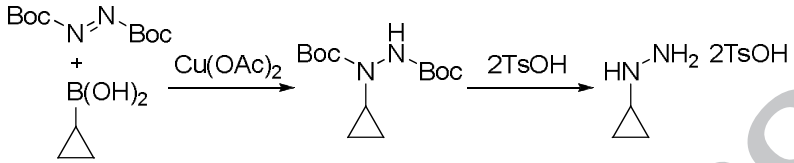

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Efficient Synthesis of Cyclopropylhydrazine Salts

Taku Shibue and Yasumichi Fukuda*

Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd., 2399-1, Nogi, Nogi-Machi, Shimotsuga-Gun, Tochigi, 329-0114, Japan

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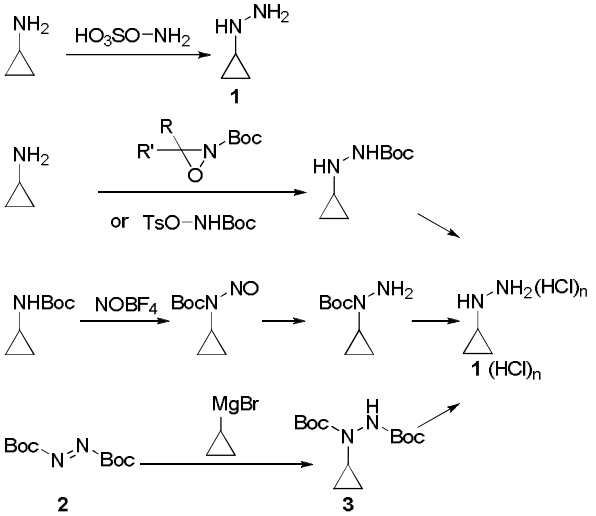
ABSTRACT

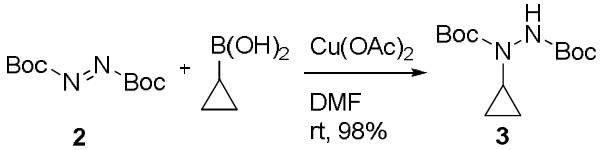
An efficient procedure for the synthesis of cyclopropylhydrazine in the form of its salts is reported. The copper salt-catalyzed addition of cyclopropylboronic acid to the azo group of di-*tert*-butyl azodicarboxylate and subsequent deprotection gave the cyclopropylhydrazine salts in high yields.

Monosubstituted alkyl and arylhydrazines are versatile building blocks for the synthesis of nitrogen-containing heterocycles such as azoles and azines. The synthetic method using monosubstituted hydrazines is a particularly valuable option for the synthesis of *N*-substituted pyrazoles and pyrazole-containing ring systems, which can be easily accessed by the reaction of monosubstituted hydrazines with 1,3-dicarbonyls, β-ketoesters, β-ketoaldehydes or α-chloroacrylonitrile.[1]

During the course of our research, we required an efficient method for synthesizing cyclopropylhydrazine **1** as a component of *N*-cyclopropyl-heterocycles, which are particular interest in the field of pharmaceuticals.[2] The reported synthesis of **1** and its salts employed electrophilic *N*-amination of cyclopropylamine using hydroxylamine-*O*-sulfonic acid,[3] *N*-Boc oxaziridines[4] or *N*-Boc-*O*-tosyl hydroxylamine,[5] and *N*-nitrosation of *N*-Boc cyclopropylamine by nitrosonium tetrafluoroborate[6] (Scheme 1). Although these reported methods are convenient for the provision of small amounts of **1** and its salts, the difficulty in handling the hazardous reagents and *N*-nitroso intermediate made the scale-up laborious and the yields were relatively low. Recently, more effective synthesis of **1** as a hydrochloride was reported by way of *N,N'*-di-Boc-cyclopropylhydrazine **3**, which was prepared by 1,4-addition of cyclopropylmagnesium bromide to di-*tert*-butyl azodicarboxylate **2**.[7] However, the requirement of cryogenic reaction conditions and the disadvantage of low yield still remained for the robust and scalable synthesis of **1**. We describe here an efficient synthesis of **1** in the form of its salts by employing the copper salt-mediated addition of cyclopropylboronic acid to the azo group of **2** under mild conditions in high yield, which would be more safe and scalable (Scheme 2).



Scheme 1. Reported Synthesis of Cyclopropylhydrazine



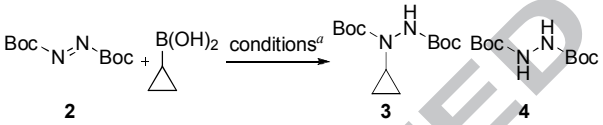
Scheme 2. Copper Catalytic Addition of Cyclopropylboronic Acid to **2**

Previous studies have demonstrated the catalytic addition of arylboronic acids to the azo group of azodicarboxylates using a copper or palladium salt.[8] The copper salt-catalyzed addition

seemed to be more effective because it had less influence on structure of azodicarboxylates. In the above-mentioned study, although styrylboronic acid was added to azodicarboxylate by a copper salt catalyst in a moderate yield, alkylboronic acid did not give the corresponding hydrazine under the same conditions. These observations led us to hypothesize that it would be possible to add cyclopropylboronic acid to the azo group of azodicarboxylate under the same catalytic conditions to give the protected cyclopropylhydrazine because of the olefin-like nature of cyclopropane rings.[9]

Indeed, addition of cyclopropylboronic acid to the azo group of **2** proceeded smoothly with a catalytic amount of copper(II) acetate in DMF to give the desired *N*,*N'*-di-Boc-protected cyclopropylhydrazine **3** in 98% yield (run 1, Table 1).[11] The reaction was incomplete when a shorter reaction time (runs 2 and 3) or equimolar amounts of cyclopropylboronic acid were used (run 6). A higher reaction temperature tended to reduce the reaction time (runs 4 and 7). In contrast to Chatani's report,[8a] a clear difference was observed between the use of DMF and THF as solvents under our reaction conditions. THF failed to generate the desired **3** in a high yield (run 8). Furthermore, methanol, which Mäeorg reported was a suitable solvent for the addition of arylboronic acid to azodicarboxylate,[8b] was not for the production of **3** using our reaction (runs 9 and 10). In this case, a small amount of **4** was the sole detectable product. Among the solvents we investigated as shown in Table 1, DMF gave the best result. These incompatibilities observed about reaction solvents, temperature and time on the addition to the azo group between cyclopropylboronic acid and arylboronic acids would depend on stability and reactivity of cyclopropylboronic acid.[10]

Table 1. Copper Catalytic Addition of Cyclopropylboronic Acid to **2**

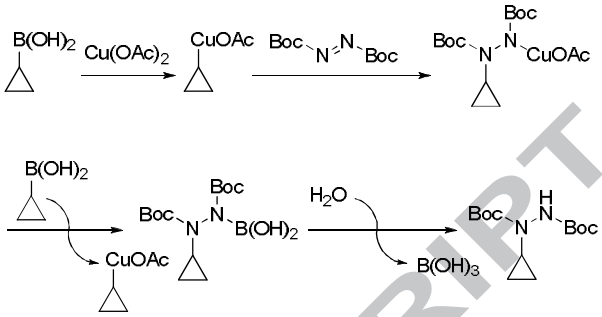


2 **3** **4**

run	catalyst	solvent	temp (°C)	Time (h)	yield (re SM) (%)	**4** (%)
1	$Cu(OAc)_2$	DMF	rt	96	98	
2	$Cu(OAc)_2$	DMF	rt	48	69 (27)	
3	$Cu(OAc)_2 \cdot H_2O$	DMF	rt	48	68	
4	$Cu(OAc)_2$	DMF	50	2	90	
5	$Cu(OAc)_2$[b]	DMF	50	4	90	
6[c]	$Cu(OAc)_2$	DMF	50	3	47(41)	
7	$Cu(OAc)_2$	DMF	80	1	78	11
8	$Cu(OAc)_2$	THF	rt	48	4 (88)	
9	$Cu(OAc)_2 \cdot H_2O$	MeOH	rt	24	N.D.[d]	21
10	$Cu(OAc)_2$	MeOH	rt	24	N.D.	20
11	$Cu(OAc)_2$	CH_3CN	rt	48	8 (61)	
12	$Cu(OAc)_2$	DCE	rt	48	N.D.	
13	$Cu(OAc)_2$	toluene	rt	48	N.D.	

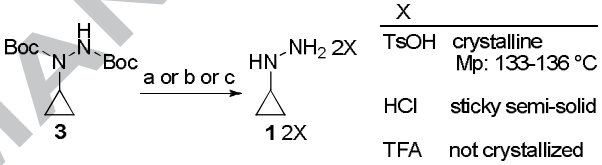
[a]Standard conditions: **2** (0.5 mmol), cyclopropylboronic acid (1 mmol), catalyst (10 mol%) and solvents (1 mL). [b]5 mol%. [c]Cyclopropylboronic acid (0.5 mmol). [d]Not detected by TLC.

Based on the proposed reaction mechanisms of the copper salt-catalyzed addition of arylboronic acid to azodicarboxylate,[8] a possible reaction mechanism would be that shown in Scheme 3.



Scheme 3. Possible Reaction Mechanism

Deprotection of **3** under acidic conditions cleanly provided cyclopropylhydrazine salts in high yields (Scheme 4).[11] We identified the deprotected cyclopropylhydrazine as a ditosylate salt instead of the known hydrochloride due to its hygroscopicity and poor crystallinity. The ditosylate salt of **1** could be stored and was easy to handle.



a: TsOH H_2O, CH_3CN, 60 °C, 5h. *b*: 4M HCl-dioxane. *c*: TFA-DCM.

Scheme 4. Deprotection of **3** to Ditosylate of **1**

In conclusion, we have developed a highly efficient method to synthesize cyclopropylhydrazine salts. The method includes the copper-catalyzed addition of cyclopropylboronic acid to the azo group of azodicarboxylate. Our procedure features cyclopropylhydrazine salts as useful building blocks for the construction of *N*-cyclopropyl group-containing heterocycles.

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11. Experimental procedure of the synthesis of ditosylate of **1**
Step 1. Di-*tert*-butyl 1-cyclopropylhydrazine-1,2-dicarboxylate **3**
To a solution of di-*tert*-butyl azodicarboxylate **2** (23.03 g, 100 mmol) in DMF (200 mL) was added cyclopropylboronic acid monohydrate (20.78 g 200 mmol) and $Cu(OAc)_2$ (1.81 g 10 mmol) at room temperature, and the mixture was stirred at the same temperature for 96 h. After concentration of the resulting mixture in vacuo, flash chromatography (silica gel, hexane:AcOEt = 4:1) of the residue gave **3** (25.32 g, 93%) as a colorless solid. Purification of the product by trituration with hexane provided an analytical sample. Mp: 94–96 °C (colorless solid). ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers at 24°C): δ0.48–0.70 (br, 4H), 1.37 (brs, 9H), 1.39 (brs, 9H), 2.74–2.82 (m, 1H), 8.57 (brs, 0.2H), 8.98 (brs, 0.8H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers at 24°C): δ5.39, 7.40, 27.85, 28.03, 31.43, 79.21, 79.57, 154.93, 155.36. IR (ATR): 3347, 3297, 2978, 1725, 1691, 1498, 1146 cm^{-1}. MS (ESI$^-$) *m/z*: 271 (MH^-). HRMS (ESI$^-$) for $C_{13}H_{23}N_2O_4$ (MH^-): calcd, 271.1658; found, 271.1652.

Step 2. Cyclopropylhydrazine ditosylate **1** 2TsOH
To a solution of **3** (11.0 g, 40.39 mmol) in CH_3CN (160 mL) was added *p*-toluenesulfonic acid monohydrate (30.73 g, 161.56 mmol) at room temperature, and the mixture was stirred at 60 °C for 5 h. After cooling to room temperature, the resulting precipitates were collected by filtration and washed with toluene to give **1** 2TsOH (14.58 g, 87%) as a colorless solid. Mp: 133–136 °C. ^{1}H NMR (400 MHz, CD_3OD): δ0.57–0.62 (m, 2H), 0.64–0.79 (m, 2H), 2.37 (s, 6H), 2.56–2.61 (m, 1H), 7.25 (d, J = 7.9 Hz, 4H), 7.70 (d, J = 7.9 Hz, 4H). ^{13}C NMR (100 MHz, CD_3OD): δ6.11, 21.29, 31.77, 126.96, 129.87, 141.93, 143.17. IR (ATR): 2674, 2578, 1156, 1122 cm^{-1}. MS (CI^+) *m/z*: 73 (MH^+) (as free base). HRMS (CI^+) for $C_3H_9N_2$ (MH^+) (as free base): calcd, 73.0766; found 73.0809. Anal. ($C_3H_8N_2$·2TsOH) C, H, N. calcd: C, 49.02; H, 5.81; N, 6.73. found: C, 48.77; H, 5.77; N, 6.72.