JOC*Note*

Copper-Mediated *N*-Cyclopropylation of Azoles, Amides, and Sulfonamides by Cyclopropylboronic Acid

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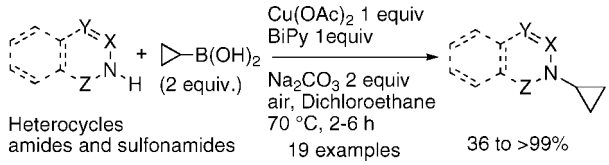
Received May 14, 2008



Reaction of azoles, amides, and sulfonamides in dichloroethane with readily available cyclopropylboronic acid in the presence of copper acetate and sodium carbonate afforded the *N*-cyclopropyl derivatives in good to excellent yields.

The cyclopropyl unit is found in a number of natural products and occupies a central position in pharmaceutical and agrochemical science. Indeed, the unique electronic and geometrical properties[1] associated with its metabolic stability[2] make the cyclopropyl a major structural element in fine-tuning the biological potency of a drug candidate.[3] Since nitrogen-containing molecules are highly represented in bioactive compounds, the development of synthetic methods allowing direct introduction of a *N*-cyclopropyl group is of great importance in medicinal chemistry.[4]

Mainly two strategies have previously been developed for the synthesis of *N*-cyclopropylated molecules: condensation of amines/anilines with cyclopropanone equivalents and functionalization of cyclopropylamines.[5] However, both routes gave generally low yields of desired products and the application scope is rather limited. Very recently, Gagnon and co-workers[6] reported an elegant copper-mediated direct *N*-cyclopropylation of azoles and amides using tricyclopropylbismuth as a donor of cyclopropyl group.[7] Although the reaction proceeded in good to excellent yields with a broad substrate scope, the limited availability and stability of the bismuth reagent leave nevertheless room for improvement.

Transition-metal-catalyzed cross-coupling reactions for the formation of carbon−heteroatom bonds have been a subject of intensive research during the past few years.[8] Among them, the copper-promoted coupling of amines with organoboronic acids has emerged as a powerful tool since the initial report of Chan and Lam[9] and has found wide applications because of the mildness of the reaction conditions.[10] Cyclopropylboronic acids are easily available and are relatively stable to air and water. Although they have been used in palladium-catalyzed reaction to create C−C bonds,[11] cyclopropylboronic acids have not been employed for the formation of C−N bond at the outset of this work.

Despite a reported unsuccessful attempt at coupling of cyclopropylboronc acid and aniline under Chan−Lam conditions,[12] we decided to evaluate in detail the reaction of cyclopropylboronic acid with azoles and amides, reasoning that the increased acidity of NH in these compounds could facilitate the desired transformation. A recent report by Tsuritani[13] on the copper-mediated coupling of cyclopropylboronic acid with indoles and cyclic amides prompted us to report our own results in this Note.

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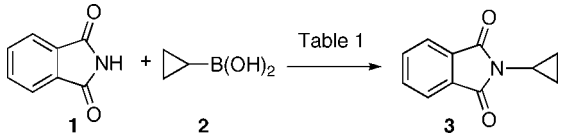
10.1021/jo801033y CCC: $40.75
Published on Web 07/09/2008

TABLE 1. Survey of Reaction Conditions[a]



1 2 3

entry	$Cu(OAc)_2$ (equiv)	solvent	base/ligand (equiv)	temp (°C)	yield (%)[b]
1	1.0	DCE	Et_3N (2.0)	rt	16
2	1.0	DCE	Et_3N (2.0)	50	30
3	1.0	toluene	Py (2.0)	70	70[c]
4	1.0	toluene	Py (2.0)	70	>95[c]
5	0.2	toluene	Na_2CO_3 (2.0) Py (0.4)	70	75[c]
6	0.2	toluene	Na_2CO_3 (2.0) Et_3N (0.4)	70	<10[c]
7	0.2	toluene	Na_2CO_3 (2.0) TMEDA (0.2)	70	60[c]
8	0.2	toluene	Na_2CO_3 (2.0) Phen (0.2)	70	50[c]
9	0.2	toluene	Na_2CO_3 (2.0) BiPy (0.2)	70	80[c]
10	0.2	toluene	$NaHCO_3$ (2.0) BiPy (0.2)	70	80[c]
11	0.2	toluene	K_3PO_4 (2.0) BiPy (0.2)	70	15[c]
12	0.2	toluene	K_2CO_3 (2.0) BiPy (0.2)	70	28[c]
13	0.2	toluene	Cs_2CO_3 (2.0) BiPy (0.2)	70	0[c]
14	0.2	DCE	Na_2CO_3 (2.0) BiPy (0.2)	70	80[c]
15	1.0	DCE	Na_2CO_3 (2.0) BiPy (1.0)	70	100

[a] All reactions were carried out under air atmosphere using 2 equiv of **2**, 0.1 M. [b] Yield after flash column chromatography. [c] Yield estimated by ^1H NMR analysis of the crude product. Abbreviations: Py = pyridine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; Phen = 1,10-phenanthridine, BiPy = 2,2-bipyridine.

Phthalimide **1** was chosen as a model substrate to begin our study because it showed a good behavior in related copper-mediated reactions.[14] We were pleased to find that reaction of **1** with cyclopropylboronic acid (**2**, 2 equiv) furnished the desired *N*-cyclopropylphthalimide **3** in 16% yield under the following conditions: $Cu(OAc)_2$ (1.0 equiv), Et_3N (2.0 equiv), air, in dichloroethane (DCE), room temperature, 24 h (Table 1, entry 1). Upon heating the reaction mixture to 50 °C, the yield of **3** increased to 30% (entry 2). Encouraged by these results, we set out to optimize the reaction conditions by varying the ligand, the base, the reaction temperature, and the solvent. These results are summarized in Table 1.

Carrying out the reaction at 70 °C in toluene in the presence of pyridine afforded compound **3** in 70% yield according to ^1H NMR analysis of the crude product (entry 3). The reaction was very clean since about 30% of the phthalimide (**1**) was recovered under these conditions. Increasing the reaction time or introducing an additional amount of cyclopropylboronic acid failed to increase the conversion. However, we were able to drive the reaction to completion by simply adding 2.0 equiv of Na_2CO_3 under otherwise identical conditions (entry 4).[15]

Interestingly, the coupling reaction worked even under catalytic conditions to afford **3** in about 75% yield (entry 5).[16] Using a catalytic amount of copper acetate (0.2 equiv), the effect of ligand structures and bases was next examined (entries 5−9). From these experimental results, the bipyridine stood out as the ligand of choice in terms of product yield and reaction time, whereas Na_2CO_3 or $NaHCO_3$ was found to produce superior results as a base compared to Et_3N, K_3PO_4, K_2CO_3 and Cs_2CO_3 (entry 9−13). Although both dichloroethane (DCE) and toluene were effective solvents, we found that the reaction performed in the former gave better reproducibility. Finally, we briefly screened other copper sources such as $CuCl_2$ and CuI and found they were less efficient than $Cu(OAc)_2$. Solvent played also an important role and other solvents such as DMSO, methanol, and THF−H_2O were less effective than DCE and toluene. Overall, the best conditions were established as follows: $Cu(OAc)_2$ (0.2 equiv), Bipy (0.2 equiv), Na_2CO_3 (2 equiv), air, in dichloroethane at 70 °C, 6 h (entry 14); or $Cu(OAc)_2$ (1.0 equiv), Bipy (1.0 equiv), Na_2CO_3 (2 equiv), air, in dichloroethane at 70 °C, 3 h (entry 15).

With these optimized conditions in hand, the scope and limitation of this reaction were examined using a stoichiometric amount of copper acetate.[17] Various *N*-heterocycles (imidazole, benzimidazole, 2-acetylpyrrole, benzotriazole, carbazole and oxazolidinone) were successfully transformed to the corresponding cyclopropyl derivatives under standard conditions (Table 2, entry 1−6). It is interesting to note that imidazole failed to undergo *N*-cyclopropylation under Gagnon's conditions. Reaction of thymine with **2** afforded the double *N*-cyclopropylated adduct **5k** in 53% (entry 10). However, when 6-methyluracil was subjected to the established reaction conditions, mono *N*-alkylation occurred predominantly to provide the 3-*N*-cyclopropyl-6-methyl uracil **5i**[18] and the 1,3-dicyclopropyl-6-methyl uracil **5j** in 72% and 7% yields, respectively (entry 9). The observed regioselectivity can be accounted for on the steric ground.

The *N*-cyclopropylation of indoles with different electronic properties was also realized (entry 11−16). The reaction tolerated a variety of functional groups, such as halogen atoms (entries 12 and 18), ester and carbamate (entry 16), ether (entry 14), ketone (entry 15), and nitro (entry 13) groups. Whereas electron-deficient indoles gave excellent results, the electron-rich 5-methoxyindole furnished only 36% yield of **5o**. Interestingly, the yield could be improved to 55% yield when the reaction was carried out under argon atmosphere.

The *N*-cyclopropylation of amides was next investigated. Whereas diflurobenzamide afforded the corresponding **5g** in 59% yield (entry 7), 2-naphthalenacetamide furnished the compound **5h** in a lower yield (36%, entry 8). Sulfonamide can be similarly alkylated to afford the mono- and dicyclopropylated compounds **5t** and **5u** in yields of 66% and 10%, respectively (entry 19). Resubmitting the monocyclopropylated compound **5t** to the reaction conditions afforded the bis-cyclopropylated product **5u** in 61% yield (78% based on conversion). 4-Methoxy-acetanilide was however unreactive under the present reaction conditions (entry 20).[19]

Conversion of the arylboronic acid in the presence of copper catalyst and oxygen to the corresponding phenol has been

(12) Wallace, D. J.; Chen, C.-Y. *Tetrahedron Lett.* **2002**, *43*, 6987–6990.

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(15) Such reaction conditions have been used recently in copper-catalyzed aerobic oxidative amination: Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833–834.

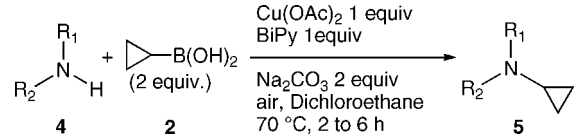
(16) (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233–1236. (b) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418. (c) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528–1531. (d) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077–2079. (e) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397–4400. (f) van Berkel, S. S.; Van den Hoogenband, A.; Terpstra, J. W.; Tromp, M.; Van Leeuwen, P. W. N. M; Van Strijdonck, G. P. F *Tetrahedron Lett.* **2004**, *45*, 7659–7662. (g) Lan, J.-B.; Chen, L.; Yu, X.-Q.; You, J.-S.; Xie, R.-G. *Chem. Commun.* **2004**, 188–189.

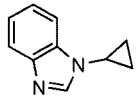
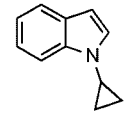
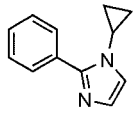
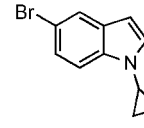
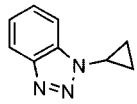
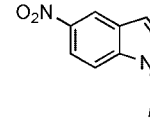
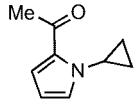
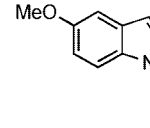
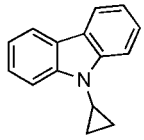
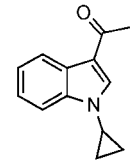
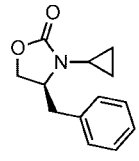
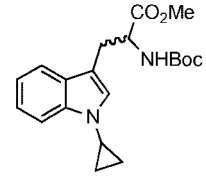
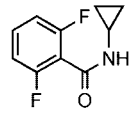
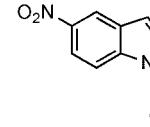
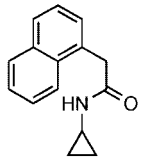
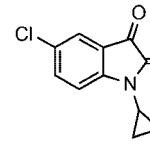
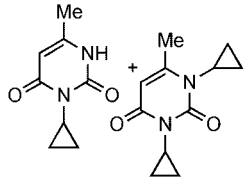
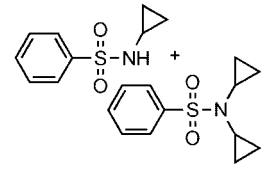
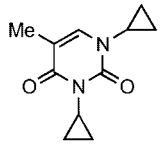
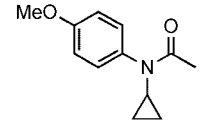
(17) Most of the transformations reported in Table 2 worked in the presence of catalytic amount of copper salt. However, longer reaction time was required with reduced yields of coupling product.

(18) The structure of **5i** was confirmed by NOE experiment.

(19) Preliminary experiments indicate that anilines could be cyclopropylated under established conditions. However, no cyclopropylated product was isolated when *N*-methyl benzylamine was submitted to the identical reaction conditions. We are working towards the optimization of these reactions and the results will be reported in due course.

TABLE 2. Scope of the *N*-Cyclopropylation[a,b,c]



entry	Product	Yield	Entry	Product	Yield[a]
1	 **5a**	75%	11	 **5l**	40%
2	 **5b**	62%	12	 **5m**	75%
3	 **5c**	59%	13	 **5n**	87%
4	 **5d**	74%	14	 **5o**	36% 55%[b]
5	 **5e**	55%	15	 **5p**	87%
6	 **5f**	50%	16	 **5q**[c]	48%
7	 **5g**	59%	17	 **5r**	76%
8	 **5h**	36%	18	 **5s**	61%
9	 **5i, 5j**	72% + 7%	19	 **5t, 5u**	66% + 10%
10	 **5k**	53%	20	 **5v**	0%

[a] Yield after flash column chromatography. [b] Under argon atmosphere. [c] Racemic tryptophane derivative was used. *N*-Cyclopropylation of the carbamate nitrogen was not observed.

observed previously[20] and has been developed for the synthesis of symmetric biaryl ethers.[21] This in part could explain the need of using an excess of cyclopropylboronic acid in the present reaction. It is thus of interest to observe that *N*-cyclopropylation can take place in the argon atmosphere in the presence of stoichiometric amount of copper catalyst.[22]

In conclusion, we have documented a direct copper acetate-mediated *N*-cyclopropylation of nitrogen containing compounds with cyclopropylboronic acid. The method is applicable to a wide range of azoles including imidazole, benzoimidazole, pyrrole, carbazole, oxazolidinone, indole, pyrazole, and cyclic ureas. Primary amides and sulfonamides can be similarly *N*-cyclopropylated.

Experimental Section

General Procedure. To a suspension of cyclopropylboronic acid (51.6 mg, 0.6 mmol), phthalimide (44.0 mg, 0.3 mmol), and Na_2CO_3(63.6 mg, 0.6 mmol) in dichloroethane (1.0 mL) was added a suspension of $Cu(OAc)_2$ (54.5 mg, 0.3 mmol) and bipyridine (46.8 mg, 0.3 mmol) in hot dichloroethane (2.0 mL). The mixture was warmed to 70 °C and stirred for 2 h under air. The resulting mixture was cooled to room temperature, and a saturated aqueous NH_4Cl solution was added, followed by water. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, dichloromethane) afforded the *N*-cyclopropyl phthalimide **3** as a white solid (56.0 mg, quantitative). $R_f = 0.43$ (3:1 heptane/EtOAc). Mp 136 °C. IR (neat, cm^{-1}) ν 3026, 1765, 1710, 1697, 1610, 1462, 1396, 1139, 946, 710. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.82 (m, 2H), 7.69 (m, 2H), 2.71 (m, 1H), 1.01 (m, 4H). ^{13}C NMR ($CDCl_3$, 75,5 MHz) δ 168.9, 134.0, 131.8, 123.1, 20.9, 5.2. HRMS (*m*/*z*) found 242.0798, requires 242.0793 (M + Na + MeOH).

Acknowledgment. Financial support from the CNRS and this institute is gratefully acknowledged.

Supporting Information Available: Physical and spectroscopic data and copies of ^1H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801033Y

(20) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691–1694.

(21) (a) Sagar, A. D.; Tale, R. H.; Adude, R. N. *Tetrahedron Lett.* **2003**, *44*, 7061–7063. (b) For an initial report on copper-mediated C−O bond formation between phenol and arylboronic acid, see: Evans, D. A.; Katz, J. L.; West, T. R *Tetrahedron Lett.* **1998**, *39*, 2937–2940.

(22) One referee pointed out that the presence of a tiny amount of oxygen in the reaction media might serve to oxidize the copper salt. We are working to understand this coupling process. However, we note that the reactions performed under argon atmosphere provided indeed the reproducible results with several different substrates.