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Direct *N*-Cyclopropylation of Cyclic Amides and Azoles Employing a Cyclopropylbismuth Reagent

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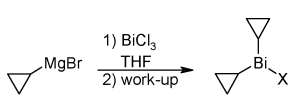
The cyclopropyl group is a privileged unit in medicinal chemistry since it possesses unique spatial and electronic properties[1] in conjunction with high metabolic stability. Therefore, this smallest cycloalkane is often incorporated in biologically relevant compounds in order to fine tune their potency and to reach maximum half-lives in microsomes.[2] These attractive features, combined with the importance of nitrogen-containing molecules in the pharmaceutical industry, make *N*-cyclopropylamides and *N*-cyclopropylazoles extremely valuable compounds. For example, *N*-cyclopropylindoles and *N*-cyclopropylpyrroles have been used as antiviral agents,[3] antitumor agents,[4] and retinoic acid receptor antagonists.[5] Although many methods have been reported to directly arylate indoles, pyrroles, and amides,[6] to our knowledge, there are no procedures allowing the direct transfer of a cyclopropyl fragment to these substrates.[7] Consequently, longer routes have been employed, most of which rely on a condensation step[4b] or an aromatic nucleophilic substitution using cyclopropylamine.[4a,8] Direct *N*-cyclopropylation of azoles and amides would therefore be of great utility, allowing expedient access to these highly contemplated products.

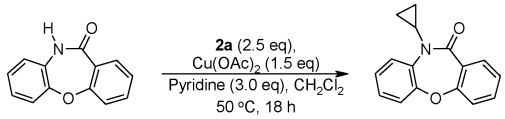
In order to conduct this transformation, we based our strategy on the pioneering work of Barton where the arylation of nitrogenous compounds was accomplished through the use of arylbismuth reagents.[9] Considering the partial sp^2 character of cyclopropyl carbons,[10] we envisaged the transposition of Barton's elegant work for the transfer of cyclopropyl fragments.[11] However, to the best of our knowledge, no report of cyclopropylbismuth compounds could be found, providing us with an impetus to explore the synthesis of these species.[12] Tricyclopropylbismuth **2a** was prepared by the addition of cyclopropyl magnesium bromide **1** to bismuth trichloride (eq 1).[13] Transfer of the reaction mixture over brine and evaporation of the organic layer under argon gave compound **2a** as a colorless oil.[14] Contrary to other alkylbismuth reagents, tricyclopropylbismuth was found to be nonpyrophoric.[15] Therefore, simple workup and trituration in hexanes provided **2a** as a white solid.[16] Mass spectroscopy experiments confirmed the presence of tricyclopropylbismuth. However, the solid contained other minor cyclopropylbismuth species among which **2b** was suspected.[17] For practical reasons, we pursued our investigation with crude **2a**.



1 **2a** : X = *c*-Pr; **2b** : X = Cl (1)

With this reagent in hand, we explored the *N*-cyclopropylation of dihydrodibenzoxazepinone **3** under Barton−Finet−Chan's conditions[18] (Table 1). In the event, heating **3** in dichloromethane at 50 °C for 18 h in the presence of pyridine, copper acetate, and reagent **2a** gave *N*-cyclopropylamide **4** in 63% isolated yield (entry 1).[19]

Table 1. Conditions for the *N*-Cyclopropylation of Amide **3**



3 **4**

entry	change from standard conditions	yield **4** (%)[c]
1	no change[b]	63
2	$CuCl_2$ instead of $Cu(OAc)_2$	0
3	$Cu(OAc)_2$ (0.05 equiv instead of 1.5 equiv)	0
4	Et_3N (3 equiv) instead of pyridine	28
5	Et_3N (3 equiv) as an additive	60
6	Cs_2CO_3 (3 equiv) instead of pyridine	12
7	THF instead of CH_2Cl_2	21

[a] Standard conditions: Amide **3** (0.10 mmol), reagent **2a** (2.5 equiv), $Cu(OAc)_2$ (1.5 equiv), pyridine (3.0 equiv), CH_2Cl_2 (1 mL, 0.1 M), 50 °C (oil bath temperature), 18 h. [b] The number of equivalents for **2a** was calculated based on the molecular weight of tricyclopropylbismuth. [c] Isolated yields.

Among 50 catalysts tested from different metals, only copper acetate was capable of promoting the cyclopropyl transfer. For example, a simple change to copper chloride gave no desired product (entry 2). Moreover, copper acetate could not be used in a substoichiometric amount (entry 3). Changing the base to triethylamine gave a drastic reduction in yield (entry 4), whereas the simultaneous use of this stronger base and pyridine as a copper complexing agent showed no advantage over the standard conditions (entry 5). The use of an inorganic base such as cesium carbonate (entry 6) or replacing the solvent with THF (entry 7) led to a dramatic reduction in the yield.

These optimized conditions were employed to *N*-cyclopropylate a variety of cyclic amides and derivatives (Table 2). For instance, compounds **6a**, **6b**, and **6c** were prepared in modest to excellent yield (entries 1−3). α,β-Unsaturated amides (entry 4) and azabicycloheptenone (entry 5) were also suitable substrates for the *N*-cyclopropyl transfer reaction (**6d** and **6e**). Reagent **2a** was then successfully used to prepare isatin **6f**, oxindole **6g**, and imide **6h** in moderate yields (entries 6−8).[20] Gratifyingly, the method was efficiently extended to the synthesis of *N*-cyclopropyl carbamates **6i** and **6j** (entries 9 and 10).

Due to the ubiquity of heterocycles in medicinal chemistry, we then turned our attention to the *N*-cyclopropylation of azoles (Table 3) and demonstrated that *N*-cyclopropylindoles **8a**−**8i** can be prepared in moderate to excellent yield (entries 1−9). The reaction tolerates numerous functionalities such as nitriles (**8b**, entry 2), aldehydes (**8c**, entry 3), nitro groups (**8d**, entry 4), alcohols (**8e**, entry 5), and benzyl ethers (**8f** and **8g**, entries 6 and 7). Interestingly, a previous synthesis of compound **8b** in a two-step process was reported in an overall yield of 7%.[4a] The procedure reported herein now allows expedient access to this compound in 60% yield from commercially available material.

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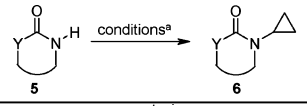
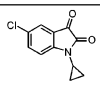
Table 2. *N*-Cyclopropylation of Cyclic Amides and Derivatives

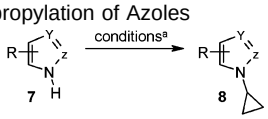


5 6

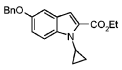
entry	product		yield[b] (%)	entry	product		yield[b] (%)
1		**6a**	97	6		**6f**	44
2		**6b**	65	7		**6g**	38
3		**6c**	37	8		**6h**	47
4		**6d**	70	9		**6i**	87
5		**6e**	60	10		**6j**	87

[a] Standard conditions: See Table 1. [b] Isolated yields.

Table 3. *N*-Cyclopropylation of Azoles



7 8

entry	product		yield[b] (%)	entry	product		yield[b] (%)
1		R=H, **8a**	47				
2		R=CN, **8b**	60	11		**8k**	83
3		R=CHO, **8c**	66				
4		R=NO_2, **8d**	90				
5		R=CH_2OH, **8e**	31	12		**8l**	54
6		R=OBn, **8f**	47				
7		**8g**	35	13		**8m**	83
8		**8h**	98	14		**8n**	53
9		**8i**	58	15		**8o**	56
10		**8j**	30	16		**8p**	38

[a] Standard conditions: See Table 1. [b] Isolated yields.

Electronic effects seem to play an important role in the outcome of the reaction since nitro indole **8d** was obtained in a better yield than the unsubstituted indole **8a** (entry 4 vs entry 1). The reaction also tolerates α-substitution as indicated by the synthesis of compounds **8h** and **8i**. The method was used to prepare *N*-cyclopropyl benzimidazole **8j** (entry 10), albeit in low yield.

In order to further expand the scope of this reaction, we next studied the *N*-cyclopropylation of pyrroles (Table 3). Again, electronic effects were observed as the more electron-deficient pyrrole **8k** (entry 11) was obtained in significantly higher yield than the analogue **8l** (entry 12). Pyrroles **8m**, **8n**, and **8o** were also prepared in modest to good yield (entries 13−15). Finally, the method was applied to the synthesis of *N*-cyclopropylpyrazole in modest yield, as indicated by the synthesis of **8p** (entry 16).[21]

In summary, we have developed a new nonpyrophoric cyclopropylbismuth reagent which is capable of *N*-cyclopropylating cyclic amides, azoles, and related derivatives. The reaction is expedient and simple to operate. Mechanistic studies and transfer of substituted cyclopropyl fragments are underway and will be reported in due course.

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Supporting Information Available: General procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Neutronic activation showed the presence of less than 0.05% magnesium, 0.12% bromine, but also 2.11% chlorine.
(18) Chan, D. M. T. *Tetrahedron Lett.* **1996**, *37*, 9013−9016. Note: The reaction could also be performed under microwave conditions.
(19) The *N*-cyclopropylation reaction of amide **3** failed when reagent **2a** was generated in situ. In a separate experiment, the presence of a large amount of magnesium salts was found to completely shut down the cyclopropyl transfer.
(20) Starting material was completely consumed.
(21) Imidazoles, acyclic amides, and amines did not undergo *N*-cyclopropylation under the conditions reported in this paper.

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