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Formal Nucleophilic Substitution of Bromocyclopropanes with Azoles

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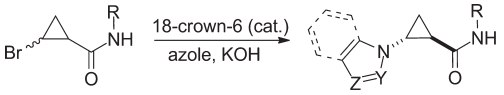
ABSTRACT



12 examples, yields 48-85%, dr >95:5

A highly diastereoselective protocol for the formal nucleophilic substitution of 2-bromocyclopropylcarboxamides with azoles is described. A wide range of azoles, including pyrroles, indoles, benzimidazoles, pyrazoles, and benzotriazoles, can be efficiently employed as pronucleophiles in this transformation, providing expeditious access to *N*-cyclopropyl heterocycles.

Aryl- and hetaryl-substituted cyclopropanes are versatile pharmacophores heavily exploited in drug design.[1] Unusual conformational features arising not only from a rigid strained framework but also from efficient overlap of the cyclopropane's Walsh orbitals with the π-system of the adjacent (hetero)aromatic substituent spurred their growing use as bioisosteres. Thus, arylcyclopropanes efficiently mimic active conformations of the bis-aryl[2] or benzylaryl moieties,[3] resulting in remarkable pharmacological effects.

Current medicinal chemistry literature is overwhelmed by a large number of aryl- and hetarylcyclopropanes with impressive biological profiles, including antimalarial,[4] anticancer,[5] anti-HIV,[6] antidepressant,[7] immunomodulatory,[3] antibiotic,[8] and analgesic[9] properties, to name a few. In addition to well-established cyclopropanations of (het)arylolefins,[10]

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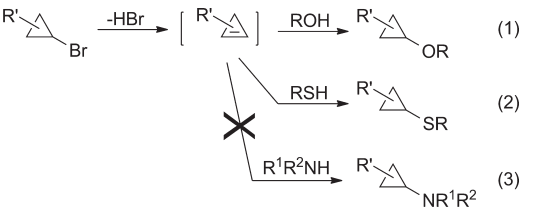
several coupling strategies for direct cyclopropyl-$C_{(Het)Ar}$ bond formation are routinely used for assembly of (het)arylcyclopropanes.[11] At the same time, formation of a cyclopropyl-N_{HetAr} bond represents a more challenging task. Reported examples include only Cu-catalyzed coupling of azoles to cyclopropylboronic acids[12] and cyclopropylbismuth reagents,[13] and the reaction of magnesium cyclopropylidene with *N*-lithioarylamines.[14] As standard substitution protocols employed in larger ring chemistry are prohibitive in cyclopropane analogs due to significant ring strain and high *s*-character, a sequential dehydrobromination/nucleophile addition has served as a nucleophilic substitution surrogate for these strained substrates.[15] This reaction operates via initial base-assisted dehydrobromination, followed by the strain-release-driven addition of a pronucleophile to the double bond of a highly reactive cyclopropene intermediate.[16,17] Our group has previously disclosed efficient, diastereoselective protocols for the formal nucleophilic substitution of structurally diverse bromocyclopropanes with oxygen- (eq 1) and sulfur-based (eq 2) pronucleophiles.[15] At the same time, our attempts to employ amines as nitrogen-based pronucleophiles have failed (eq 3), which was surprising, considering the power and versatility of the analogous aza-Michael reaction.[18]



The lack of reactivity was rationalized by ineffective deprotonation of the N−H bond of 1° or 2° amine function with a relatively weak base typically employed in this reaction (KOH, *t*-BuOK), which renders this moiety less nucleophilic as compared to anionic species derived from more acidic alcohols and thiols.[19] In support of this hypothesis, the reaction of carboxamides, the N−H acidity of which is comparable to that of many *O*-based pronucleophiles,[20] proceeded smoothly giving rise to *trans*-*β*-ACC derivatives.[19] Accordingly, we envisioned that azoles, whose pK_a fall in the same range, could potentially be employed in the formal substitution reaction. It should be mentioned that *N*-alkylation of azoles via formal nucleophilic substitution of bromocyclopropane was previously attempted by other groups, with no or little success.[21] The main problem was the too electron-rich and unstable intermediate—unsubstituted cyclopropene—which undergoes addition of a nucleophile rather slowly resulting in substantial polymerization. Indeed, we have shown earlier that the analogous transformation proceeding via a stable, isolable cyclopropene **2** affords *N*-pyrrolyl cyclopropane **4a** (mode **A**, Scheme 1).[15a] Nucleophilic attack of pyrrole in this case was efficiently directed by carboxamide function producing predominantly *cis*-diastereomer. An alternative approach to enhance the affinity of the cyclopropene intermediate toward soft nucleophiles such as azoles is through conjugation of the strained C=C bond with a suitable electron-withdrawing functionality (mode **B**, Scheme 1). Accordingly, we carried out the 1,2-dehydrobromination of bromocyclopropane **5a** in the presence of pyrrole. The reaction proceeded smoothly to afford the corresponding cyclopropyl pyrrole **7aa** in high yield, but

Scheme 1

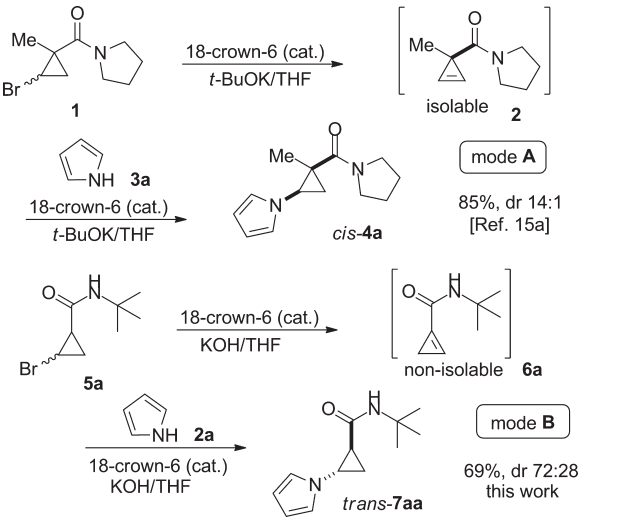


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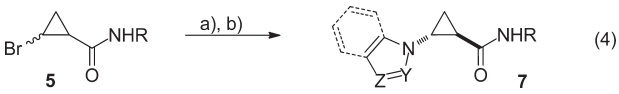
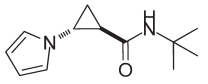
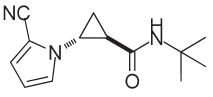
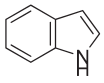
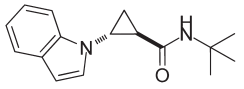
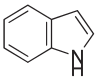
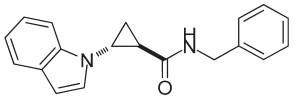
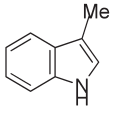
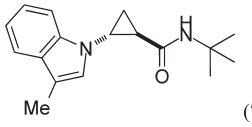
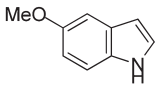
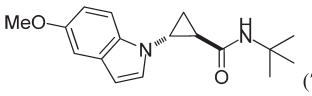
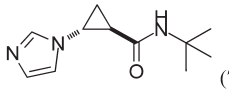
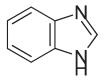
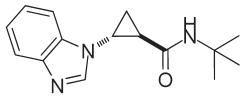
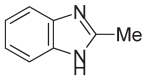
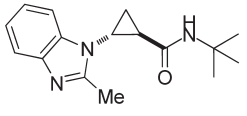
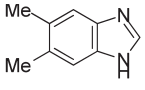
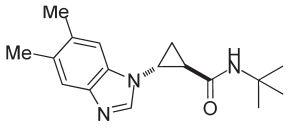
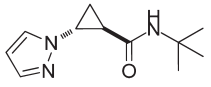
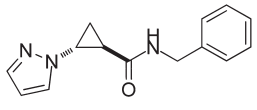
Table 1. Reaction of Bromocyclopropanes with Azoles



(4)

#	R	azole	product[a]	crude dr (trans:cis)[b]	yield, %[c] (dr)[b] after upgrade
1	t-Bu (**5a**)	 (**3a**)	 (**7aa**)	72:28	66 (98:2)
2	t-Bu (**5a**)	 (**3b**)	 (**7ab**)	85:15	82 (95:5)
3	t-Bu (**5a**)	 (**3c**)	 (**7ac**)	73:27	66 (97:3)
4	Bn (**5b**)	 (**3c**)	 (**7bc**)	75:25	48 (97:3)
5	t-Bu (**5a**)	 (**3d**)	 (**7ad**)	75:25	73 (99:1)
6	t-Bu (**5a**)	 (**3e**)	 (**7ae**)	75:25	61 (97:3)
7	t-Bu (**5a**)	 (**3f**)	 (**7af**)	87:13	50 (100:0)[d]
8	t-Bu (**5a**)	 (**3g**)	 (**7ag**)	87:13	66 (100:0)
9	t-Bu (**5a**)	 (**3h**)	 (**7ah**)	93:7	84 (95:5)
10	t-Bu (**5a**)	 (**3i**)	 (**7ai**)	95:5	72 (97:3)
11	t-Bu (**5a**)	 (**3j**)	 (**7aj**)	86:14	85 (99:1)
12	Bn (**5b**)	 (**3j**)	 (**7bj**)	88:12	73 (97:3)

[a] All reactions were performed on 0.25 mmol scale. Reagents and conditions: (a) 18-crown-6 (10 mol %), powdered KOH (3.0 equiv), azole (1.5–2 equiv), bromocyclopropane (1.0 equiv), THF (5 mL), 55 °C, 12–18 h; (b) *t*-BuOK (2–3 equiv), THF (5 mL), 80 °C, 12–18 h. [b] Determined by GC and ^{1}H NMR analysis of crude reaction mixtures. [c] Unless specified otherwise, isolated yields of individual *trans*-isomer purified by column chromatography. [d] NMR yield.

with only marginal diastereoselectivity (Scheme 1). This phenomenon was previously observed in the formal substitution reaction with alkoxides, phenoxides, and thiolates.[15c] Inefficient epimerization was rationalized

by relatively low basicity of non-nucleophilic hydroxide species. This issue was addressed by additional treatment of crude diastereomeric mixtures with a stronger base, *t*-BuOK in the presence of catalytic 18-crown-6.[15c] Gratifyingly, employment of this strategy on cyclopropylpyrrole provided *trans*-**7aa** with a 98:2 selectivity, while maintaining perfect material balance (Scheme 1, Table 1, entry 1). With the optimized conditions in hand, we investigated the scope of azole pronucleophiles (Table 1). Reaction in the presence of 2-cyanopyrrole (**3b**), followed by base-assisted epimerization, afforded the corresponding *trans*-adduct **7ab** in high yield and excellent diastereoselectivity (entry 2). We were happy to find that such problematic nucleophiles such as indoles, known for their susceptibility to Friedel–Crafts alkylation, dimerization, and polymerization,[20b] afforded reasonable isolated yields of corresponding adducts (entries 3–6). As expected, skatole (**3d**), possessing a substituent at the vulnerable C3 position, provided the best yield in the series. When imidazole **3f** was probed as a nucleophilic component, we stumbled upon the isolation issue. Although the corresponding adduct **7af** was produced in reasonable yield (50% as judged by ^{1}H NMR analysis of crude reaction mixture), chromatographic purification of the product proved inefficient due to its partial decomposition on silica gel (27% isolated yield, entry 7). In contrast, reactions in the presence of its fused analogs benzimidazoles **3g**, **3h**, and **3i** proceeded cleanly to afford the corresponding *trans*-products in high yields and excellent diastereoselectivities (entries 8–10). Similarly, pyrazole (**3j**) was engaged in a very efficient transformation with cyclopropylbromides **5a** and **5b**, providing good yields of *N*-cyclopropylpyrazoles **7aj** and **7bj**, respectively (entries 11–12). The *trans*-configuration of the carboxamide and azole substituents was unambiguously confirmed by X-ray analysis of **7bj** (Figure 1).

The present study revealed that the scope of this reaction is limited to poorly acidic azoles (p$K_a \approx 16$–23). However, practical reactivity was also achieved with a more acidic *N*-heterocycle benzotriazole (**3k**, pK_a 11.9). Since benzotriazole exists in solution in two tautomeric forms,[22,23] it produced two regioisomers, **7ak** and **8ak** (Scheme 2). Attempts on the addition of tetrazoles (pK_a 8.2) were unsuccessful, which was expected for such poor aza-Michael donors.[24]

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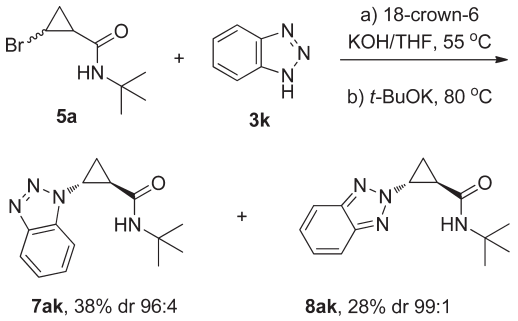
(23) For aza-Michael addition of triazoles, see: (a) Gandelman, M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2393. (b) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Synthesis* **2009**, 1564.

Scheme 2



In conclusion, we have developed an efficient and highly diastereoselective formal substitution of 2-bromocyclopropane carboxamides with azoles leading to *N*-cyclopropyl-substituted aromatic heterocycles. The *trans*-selectivity in this reaction is effectively controlled by a thermodynamically driven base-assisted epimerization.

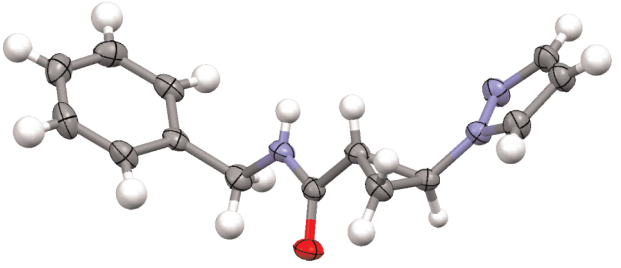


Figure 1. ORTEP drawing of cyclopropylimidazole **6bj** showing 50% probability amplitude displacement ellipsoids.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) (a) Boncel, S.; Mączka, M.; Walczak, K. Z. *Tetrahedron* **2010**, *66*, 8450. (b) Boncel., S.; Saletra, K.; Hefczyc, B.; Walczak, K. Z. *Beilstein J. Org. Chem.* **2011**, *7*, 173.

The authors declare no competing financial interest.