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HOMOALLYLIC SUBSTITUTION REACTION OF PIPERIDINE WITH 1-BROMO-1-CYCLOPROPYLALKANES[1]

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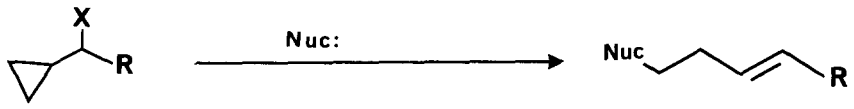
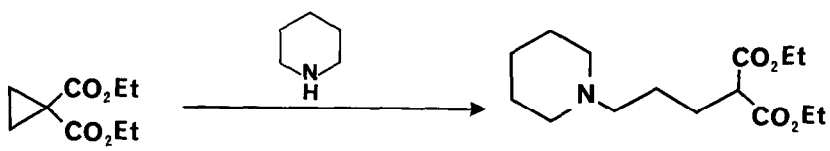
Summary: Reaction of piperidine with 1-bromo-1-cyclopropylalkanes, 7, afforded excellent yields of the homoallylic substitution product, 8, when the bromine-bearing carbon was sufficiently sterically hindered.

Nucleophilic, homoallylic substitution of unactivated cyclopropane rings such as those in cyclopropylcarbinyl halides, 1, under non-cationic conditions, was a process heretofore unknown. Such a reaction would generate alkenes such as 2 and could be classified as the homoallylic



1 2

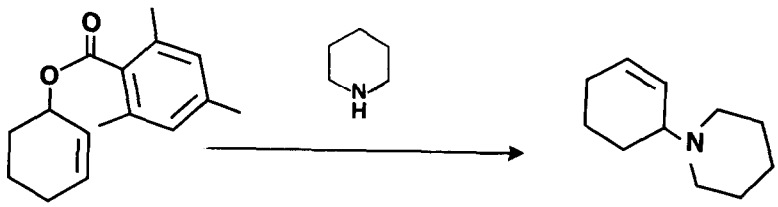
analog of the well-known S_N2' reaction of allylic halides.[2] Although one could envision a simple S_N2 reaction on a homoallylic halide to accomplish the same goal, such halides are generated in strongly acidic media,[3] clearly limiting the utility of the reaction. The one-step conversion of 1 to 2 under the neutral conditions described herein is a potentially superior and more versatile approach, but, the viability of homoallylic substitution on unactivated cyclopropane derivatives remained questionable. It has been shown that cyclopropane rings activated by two electron withdrawing groups, such as 3, undergo facile substitution to compounds such as 4



3 4

in a process which is essentially a Michael reaction.[4] The structural requirements, however, are severe since both electron withdrawing groups must be present for reaction to occur and the plane of the cyclopropane ring should be orthogonal to both carbonyl moieties for optimum reactivity.[5] The proposed homoallylic substitution process should have no such limitations.

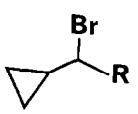
Secondary amines are often utilized in studies of S_N2' reactions and appeared to be an obvious choice for the nucleophilic partner. Piperidine, for example, has been shown to react with mesitoate 5 to give 6 in 92% yield.[6] We therefore anticipated that piperidine, upon reaction

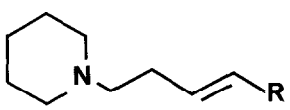


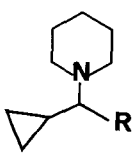
5 6

with compounds such as 1, would give significant amounts of 2 when the alkyl group provided sufficient steric hindrance at the bromine-bearing carbon. Success in these simple models would be a prelude to utilization of cyclopropane derivatives possessing more interesting functionality but without the limitation of two requisite activating groups on the ring.

We first prepared a series of cyclopropylcarbinyl bromides[1-bromo-1-cyclopropylalkanes], 7a-7f, using the general method we described previously for the preparation of 7a.[7] The corresponding alcohol(1, X = OH) was dissolved in a solution of dimethylformamide and triphenylphosphine. Bromine was slowly added at -20°C and the solution stirred for 30 minutes. Flash distillation, in vacuuo, workup and final distillation afforded 7a-7f in 61 - 79% yield, essentially uncontaminated by the corresponding homoallylic halide.[8]



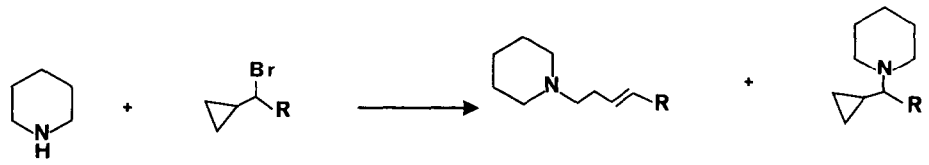




7a	R = Me	8a	R = Me	9a	R = Me
7b	R = Et	8b	R = Et	9b	R = Et
7c	R = n-Pr	8c	R = n-Pr	9c	R = n-Pr
7d	R = n-Bu	8d	R = n-Bu	9d	R = n-Bu
7e	R = iPr	8e	R = iPr	9e	R = iPr
7f	R = t-Bu	8f	R = t-Bu	9f	R = t-Bu

The results of our experiments are summarized in Table 1. We initially examined reaction of the relatively unhindered 7a with piperidine(neat, reflux, 12 hours). Basic workup gave the anticipated direct substitution product, 9a, in 92% yield. We were encouraged, however, by the presence of 8% of the desired homoallylic substitution product, 8a. Extension of the alkyl chain in 7b-7d provided increased steric hindrance and an appropriate increase in the homoallylic products 8b-8d. The relative steric impedance of ethyl, n-propyl and n-butyl was not significantly different and this was reflected in the product distribution. A significant increase in the steric bulk around the bromine-bearing carbon in 7e resulted in a significant increase in the proportion of 8e, to 71%, and the extremely hindered 7f afforded 92% of 8f. Clearly, the

Table 1. Homoallylic Substitution Reaction of 1-Bromo-1-cyclopropylalkanes with Piperidine.



7 8 9

R	% 8 + 9[a]	8 : 9[b]
Me	91	8 : 92
Et	94	36 : 64
n-Pr	98	35 : 65
n-Bu	85	43 : 57
iPr	98	71 : 29
t-Bu	95	92 : 8

[a] isolated yields [b] ratios determined by quantitative vpc analyses

increased proportion of homoallylic substitution products is a function of the steric environment of the bromine-bearing carbon. Reactions of 7a-7f were also carried out at ambient temperatures but the results were virtually identical to those obtained from reflux conditions, except for the much longer reaction times which were required. The products were isolated by distillation or by preparative vpc and were identified by nmr, vpc/ms and vpc analyses with authentic samples.

Our results are analogous to those of S_N2' reactions observed with piperidine in allylic systems.[2,6] The products from reaction of the t-butyl derivative, 7f, however, call into question whether S_N2' is a valid description for conversion of 7 to 8. Clearly, the bromine-bearing carbon of 7f is inaccesible to the nucleophile in a S_N2 attack due to severe steric hindrance, but, 8% of 9f was observed. Indeed, the proportion of the direct substitution product was greater in all cases than that observed in similar S_N2' reactions in allylic halides.[2] This raises the spectre of an ionization pathway either dominating the reaction or competing with direct nucleophilic attack on the cyclopropane ring. The mechanism of S_N2' reactions in general has been the object of intense srcutiny.[2] Bordwell has argued for a nucleophilically assisted heterolysis at the γ-carbon as the most reasonable pathway for S_N2' reactions.[2,9] While this is generally consistent with our results, the relative amount of homoallylic substitution product was greater than expected when compared to allylic systmes. It is well-known that cyclopropylcarbinyl derivatives show a great propensity for solvolysis under cationic, protic conditions.[10] This is usually attributed to the special stability of the cyclopropylcarbinyl cation.[10] Although the amine solvent should preclude formation of carbocations, ion-pair formation may be favorable. The facility of reactions of 7 with piperidine, therefore, is probably the result of facile ion-pair formation induced by the highly reactive bonds of the

cyclopropane ring, followed by trapping of piperidine. Since S_N2' is probably not an appropriate mechanistic description of this reaction, we term it homoallylic substitution.

Our results clearly indicate that homoallylic substitution is a viable process with secondary amines such as piperidine. When the halide possesses a sufficiently large steric impediment, the yield of 8 approaches synthetically useful amounts. This constitutes the first example of nucleophilic attack on an unactivated cyclopropane ring and clearly demonstrates the feasibility of attack without the limiting requirement of activating groups on the ring. The products which are obtained are those which would be produced by nucleophilic substitution on a homoallylic halide but without the necessity of treating the cyclopropyl substrate with acid. These two advantages allow greater flexibility in planning reaction sequences with cyclopropane derivatives and points to the exploration of more sophisticated cyclopropane derivatives in terms of their reactivity with a variety of nucleophiles.

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