REARRANGEMENT OF 1-PIPERIDINOCYCLOPROPYL KETIMINES. A SYNTHESIS OF 2-SUBSTITUTED PYRROLES

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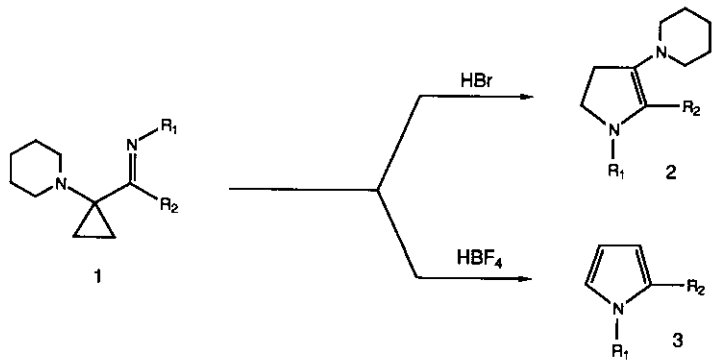
Abstract- On heating 1-(N-piperidino)cyclopropyl ketimines with HBF_4, rearrangement to 2-substituted pyrroles takes place.

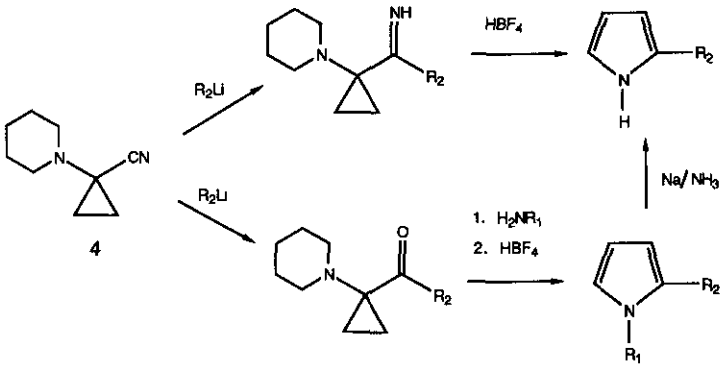
We have previously reported that cyclopropyl ketimines having a piperidino group at the 1-position, as in **1**, undergo rearrangement in the presence of HBr forming 2-pyrrolines **2**.[1] This ring-enlargement is analogous to the cyclopropyl imine rearrangements reported earlier by Stevens.[2,3] When the acid-catalyzed process takes place in the presence of a non-nucleophilic counterion, the reaction follows a different course. Under these circumstances (use of HBF_4·OMe_2), pyrrole formation (**3**) is the predominant event.[1]

We have now found that the rearrangement of these cyclopropyl ketimines with HBF_4 may serve as a general synthetic route to 2-substituted pyrroles. Whereas most procedures for functionalizing pyrroles rely on electrophilic substitution of the heterocyclic ring, the sequence outlined below (Scheme 1) is unusual in that the substituent is introduced in a nucleophilic process.

The starting cyclopropyl ketimines are conveniently prepared by addition of an organolithiate to 1-cyano-1-piperidinocyclopropane (**4**), which is readily available from the



Dedicated with best wishes to Professor Sir Derek Barton on the occasion of his 70th birthday.



SCHEME 1

corresponding β-chloropropionamide, as described in an earlier communication.[1] Table 1 lists the imine substrates investigated and the corresponding products formed with HBF_4. In this first phase of our work, the yields of the pyrroles were moderate, since the N-unsubstituted pyrroles are prone to decomposition under the reaction conditions. We therefore modified the reaction sequence so as to minimize the acid-catalyzed pyrrole breakdown, by the formation of the more stable N-benzyl pyrroles as intermediates.

Table 1

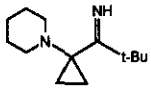
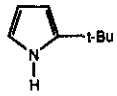
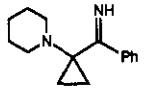
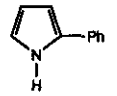
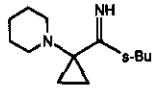
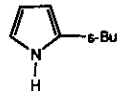
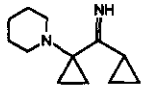
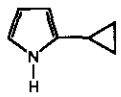
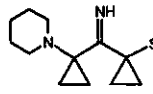
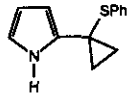
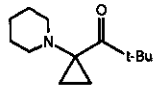
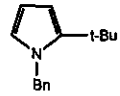
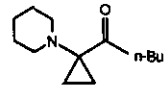
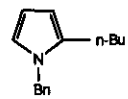
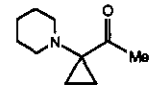
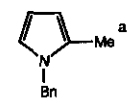
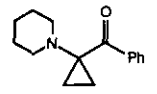
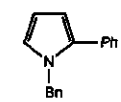
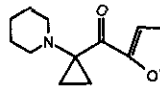
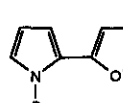
Imine	Product	Yield
		41%
		51%
		22%
		32%[1]
		42%[1]

Table 2

Ketone	Product	Yield
		41%
		80%[a]
		63%[a]
		66%
		78%

a) With the N-unsubstituted pyrroles, the yields of the corresponding 2-n-butyl and 2-methyl derivatives were 16 and 10% respectively.

In the modified procedure, we used the cyclopropyl ketones shown in Table 2 as starting materials. These were treated with benzylamine and the substituted cyclopropyl imines allowed to react with $HBF_4 \cdot OMe_2$. The rearrangement which followed furnished N-benzyl-2-substituted pyrroles in improved yields. Generation of the N-unsubstituted pyrroles readily takes place on reduction with sodium in liquid ammonia by Albrecht's method[5].

A typical procedure for pyrrole formation is provided below:

1-Benzyl-2-methylpyrrole

The cyclopropyl nitrile (200 mg, 2.00 mmol) in 2 ml of dry THF was added to a solution of MeLi (1.6 M, 2.50 ml, 4.00 mmol) in 10 ml of THF at –78°C, the mixture warmed to 0°C and *stirred for 0.5 h. After quenching with ca.* 1 g $Na_2SO_4 \cdot 10H_2O$, the reaction mixture was stirred at 0°C for 30 min, after which the solid material was filtered through celite and washed with Et_2O. The solvent was removed *in vacuo* and the resulting yellow oil was stirred with *20 ml of wet* Et_2O *containing 10 mg of p-TsOH. After 24 h the* Et_2O was removed and methyl 1-piperidinocycloprop-1-yl ketone isolated by flash chromatography[6] using 10% Et_2O/pentane, 327 mg (98%).

The methyl cyclopropyl ketone (81 mg, 0.53 mmol), in 1 ml of dry xylenes, was stirred with benzyl amine (85 mg, 0.79 mmol) for 12 h over 4Å molecular sieves. Addition of 0.10 ml of $HBF_4 \cdot OMe_2$ and refluxing for 15 min, followed by flash chromatography, yielded 1-benzyl-2-methylpyrrole (63%). ^1H Nmr (90 MHz, $CDCl_3$) δ 7.33-7.10 (m, 3H), 7.05-6.85 (m, 2H), 6.55 (m,1H), 6.05 (m,1H), 5.90 (m, 1H), 4.97 (s,2H), 2.15 (s, 3H). MS-EI m/z (%) (20 ev) 171 (73.2), 91 (100.0), 81 (1.3), 65 (1.8); IR (CCl_4) 2890, 2950 cm^{-1}. HRMS Calcd. for $C_{12}H_{13}N$: 171.1049; Found: 171.1044.

We plan to report on the mechanism of the HBF_4–promoted rearrangement in a future communication.[7]

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