Tetrahedron Letters,Vol.23,No.7,pp 785-788,1982 0040-4039/82/070785-04$03.00/0
Printed in Great Britain

CYCLOPROPANONE EQUIVALENTS FROM 3-CHLOROPROPIONIC ACID 1-PIPERIDINO-1-TRIMETHYLSILYLOXYCYCLOPROPANE

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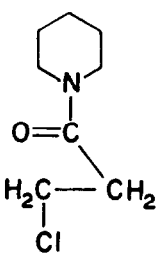
Summary *1-Piperidino-1-trimethylsilyloxycyclopropane and the corresponding 1-hydroxy-1-piperidinocyclopropane are conveniently prepared from the piperidide of 3-chloropropionic acid. Reactions of these cyclopropanone equivalents with various nucleophiles are described*

Because cyclopropanones are so labile and difficult to isolate, the chemistry of this reactive class of ketones has been explored largely through derivatives capable of yielding the parent ketone or an equivalent species in the reaction medium. Reports on the preparation and use of a number of such precursors describe the addition products of alcohols, acids, amines and thiols[1,2,3].

In our earlier studies on the chemistry of cyclopropanones[1b], we have shown that 1-piperidinocyclopropanol (3) may serve as a source of the iminium salt (4) The use of 3 as a cyclopropanone equivalent is, however, limited by the inconvenience of its preparation through the diazomethane-ketene route, and we have therefore sought an alternative preparative method We now report an adaptation of the Ruhlmann procedure[4a], previously used[4b] in the formation of the hemiketal (6), for the convenient synthesis of the carbinol amine (3) and its silyl ether precursor (2) Both of these derivatives may be used for the ready generation of functionalized cyclopropane residues of type (5) when combined with nucleophilic reagents of varied types.



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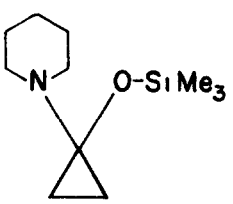

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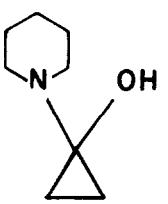

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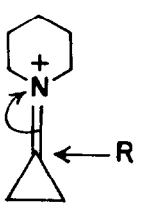

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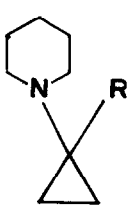

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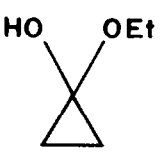

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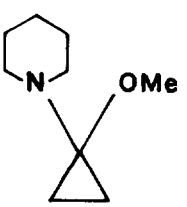

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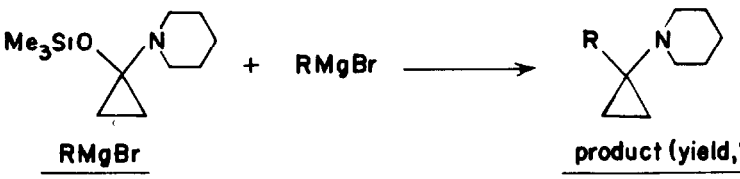
TABLE I



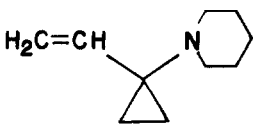
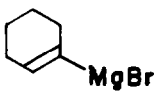
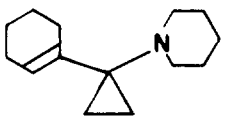
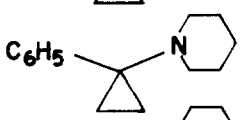
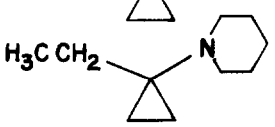
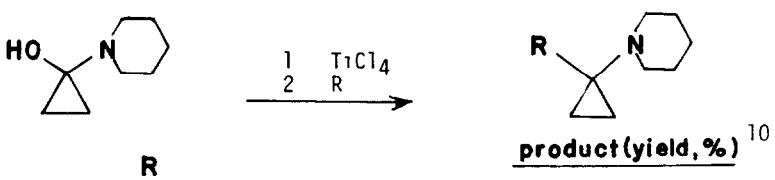
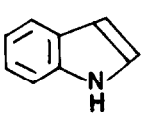
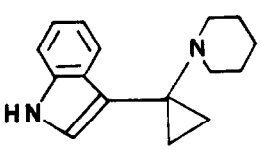
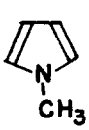
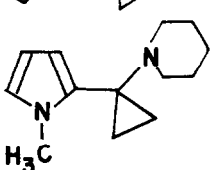
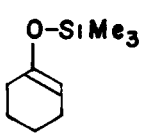
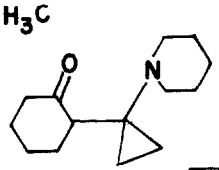
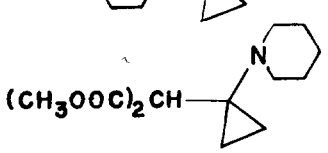
RMgBr	product (yield, %)[10]	
$H_2C{=}CH{-}MgBr$		(67)
		(95)
C_6H_5MgBr		(79)
$H_3C\,CH_2MgBr$		(92)

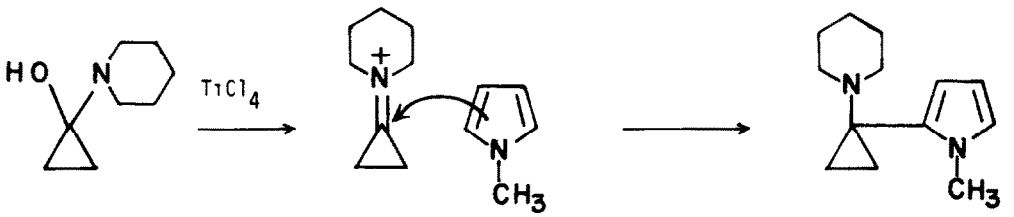
TABLE II



R	product (yield, %)[10]	
		(84)
		(65)
		(63)
$(CH_3OOC)_2CH_2$		(55)

The silyl ether (2) was prepared in one step starting from the piperidide (1)[5] of 3-chloropropionic acid. Reductive cyclization using sodium sand in ether in the presence of trimethylchlorosilane[4] generated 2 in high yield. Conversion of this silyl ether to the known carbinol amine (3)[1b] took place in methanolic tetrabutylammonium fluoride. Details of these procedures are given in the Notes[6,7].

Both 2 and 3 may be used for the ready generation of cyclopropane derivatives corresponding to 5 Thus, the silyl ether (2) can be reacted directly with Grignard reagents to provide cyclopropanated addition products as summarized in Table I[8]. Alternatively, treatment of the carbinol amine (3) with titanium tetrachloride in methylene chloride[9] provides another method for the addition of donor reagents such as indole, N-methylpyrrole, silyl enol ethers and species containing active methylene groups. These results are summarized in Table II. The reaction of 3 with N-methylpyrrole is outlined below as a typical example



3 4 8

The carbinol amine (3) (396 mg, 2 8 mmol) in 50 mL of methylene chloride at -78° under N_2 was treated with $TiCl_4$ (340 µl, 3.1 mmol). To the yellow suspension was added N-methylpyrrole (460 µl, 8.4 mmol) in one portion, and the solution was allowed to warm to 25°. After the solution was stirred overnight, 10 mL of water was added and the aqueous layer was washed with 4 x 40 mL portions of CH_2Cl_2 The organic layers were combined, washed with brine and the solvent was removed in vacuo, providing 859 mg of colorless oil. Purification was accomplished by flash chromatography, yielding 370 mg (65%) of the pyrrole addition product (8). 90 MHz ^1H NMR δ 6.52 (1H,t), 6.04 (2H,m), 3.64 (3H,s), 2.52 (4H, br t), 1.44 (6H br m), 0.96 (2H,t), 0.84 (2H,t), MS m/e(%)204(100)[10]

As has been noted in our earlier work[1b] and in the studies of de Boer[2], the reactions of nucleophilic reagents with 2 and 3 appear to take place by addition to iminium ion intermediates. For example, the iminium salt (4) is most probably involved in the facile conversion of 2 to the methyl ether (7) by the action of methanol and acid We are exploring the use of these procedures as a means of introducing functionalized cyclopropane residues into systems of special interest in synthesis.

Acknowledgments This work was supported in part by N.I.H. Grant GM-07874. We thank Dr. Susan Rottschaefer of Smith Kline Laboratories for help in obtaining high resolution mass spectra. The support of the NSF/NMR Northeast Regional Facility at Yale University (Grant CHE-7916210) is acknowledged.

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b) H H. Wasserman and M S. Baird, *Tetrahedron Lett* , 1729 (1970)

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b) R. Jorritsma, H. Steinberg and Th J de Boer, *Rec. Trav. Chim.*, 100, 184, 194 (1981)

3 For a recent review on cyclopropanones, see H H Wasserman, G C Clark and P C. Turley, *Fortschritte der chemischen Forschung*, 47, 73 (1974)

4 a) K. Ruhlmann, *Synthesis*, 236, (1971). b) J. Salaun, *J. Org. Chem.*, 41 1237 (1976).

5. Prepared from commercially available 3-chloropropionyl chloride Use of other β-chloropropionamides derived from dimethylamine, pyrrolidine or morpholine gave poorer yields of silyloxy derivatives corresponding to 2.

6 1-Piperidino-1-trimethylsilyloxycyclopropane (2). To finely divided sodium, (22 9 g, 996 mmol) in 1500 mL of ether was added 110 mL of trimethylsilyl chloride (TMSCl) under nitrogen To this mixture, the piperidide of β-chloropropionyl chloride (1), (45 g, 260 mmol), in 75 mL of ether was added dropwise with constant vigorous stirring during 5 h The solution was stirred for 24 h at 25° and the solvent carefully decanted The residual solids were washed with 100 mL of Et_2O, the organic layers combined, and excess TMSCl and ether removed by distillation, yielding 47 5 g of compound (2) (87%) as an orange oil. Purification was best accomplished by bulb-to-bulb (Kugelrohr) distillation. IR (neat) 3100, 3000, 2950, 2845, 2800, 1450, 1250, 1205, 1020, 840 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$) δ 2 7 (4H, br s), 1 5 (6H, br s), 0 82 (4H, br s), 0 15 (9H, s) Anal Calcd for $C_{11}H_{23}NOSi$ C, 61 91, H, 10 86, N, 6 56. Found C, 61.86, H, 10 68, N, 6 61

7. 1-Hydroxy-1-piperidinocyclopropane (3). To 160 mL of 1 N tetrabutylammonium fluoride in methanol was added 1-piperidino-1-trimethylsilyloxycyclopropane (2), (32 g, 150 mmol) prepared (undistilled) as described above, and the solution stirred for 1 h at 25°. The solvent was removed in vacuo yielding a viscous orange oil which was partitioned between 750 mL of ether and 750 mL of water The aqueous layer was washed with 2 x 500 mL portions of ether, the organic layers were combined, and the solvent removed in vacuo, yielding an orange crystalline mass (16.4 g). Recrystallization from ether/hexane yielded 6 1 g of 1-hydroxy-1-piperidinocyclopropane (3) mp 80.5-82°, lit[1b] 81-82°. From the mother liquor, an additional 6 g of product could be obtained by evaporation of solvent and flash chromatography of the residue on silica gel. This product was identical (IR, NMR, MS) with the carbinol amine obtained by the diazomethane-ketene-piperidine route[1b].

8 Addition of the silyl ether to a THF solution of the Grignard reagent, followed by workup with 10% NaH_2PO_4 gave the best results

9. For a review of the use of $TiCl_4$ as a Lewis acid, see T. Mukaiyama, *Angew. Chem. Int. Ed Engl.*, 16, 817-826 (1977) and references therein

10. Yields given are for isolated products. All compounds were purified by flash chromatography on silica gel and gave IR, NMR and mass spectra consistent with the assigned structures. Satisfactory C, H and N analyses or high resolution mass spectra were obtained for all new compounds.

(Received in UK 9 December 1981)