# New Synthesis of *N*-Alkyl 2,2-Dialkylcyclopropylamines *via* α-Chloro Imines

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2,2-Dialkylcyclopropylamines have been prepared by a new synthetic method involving cyclopropanation of α-chloro imines and reductive demethoxylation of the resulting 1-methoxycyclopropylamines.

Cyclopropylamines belong to an important class of physiologically active compounds[1] which are mostly prepared from cyclopropyl-substituted precursors, *e.g.* cyclopropanecarboxylic acid derivatives (Hofmann and Curtius rearrangement) or cyclopropyl ketone oximes (Beckmann rearrangement).[2] A recent report disclosed a novel *N*-cyclopropanation of aromatic amines involving substitution of 1-bromo-1-ethoxycyclopropane with the aromatic amine and $BF_3$-assisted reductive removal of the ethoxy moiety in the resulting 1-ethoxy-(*N*-aryl)cyclopropylamine.[3] This method started

from a cyclopropane substrate and was not applicable to the synthesis of *N*-alkylcyclopropylamines. Here we report an easy synthesis of *N*-alkyl-2,2-dialkylcyclopropylamines (**6**) from α-chloro imines (**2**), which are readily accessible from ketones (**8**) and primary amines.

The cyclopropanation reaction of α-halogeno imines with sodium methoxide is limited to tertiary substrates; primary and secondary α-halogeno imines show a pronounced tendency for nucleophilic substitution and rearrangement *via* α-methoxyaziridines, respectively.[4,5] The Favorskii rearrangement of α-chloro imines with potassium t-butoxide does not stop at the stage of the cyclopropane derivatives but affords rearranged carboxylic amides.[5] However, tertiary α-chloro imines (**2**) have been reported to yield geminally substituted cyclopropanes (**4**) upon methanolysis in the presence of nitrogen bases, but the final products were contaminated with substantial amounts of substitution products (α-methoxy imines) and rearranged α-amino acetals.[4] We have found now that these side reactions can be nearly completely circumvented by the use of a much stronger base, *i.e.* 1 M sodium methoxide (1.1 equiv.). In this way, the solvolysis of α-chloro imines (**2**) *via* 2-(*N*-alkylamino) allylic carbenium ions is replaced by a base-induced Favorskii-derived 1,3-dehydrochlorination[5] to yield cyclopropylideneamines (**3**), which are trapped by the solvent to yield geminally substituted cyclopropanes (**4**).

A range of concentrations of sodium methoxide in methanol was evaluated for the cyclopropanation of α-chloro imines (**2**), and 1 M sodium methoxide in methanol gave the best results (80—92%) (Table 1). Lower concentrations gave solvolysis products (α-methoxy imines or rearranged α-amino acetals), and at higher concentrations 1,2-dehydrochlorination to afford α,β-unsaturated imines became important. The requisite tertiary α-chloro imines (**2**) were obtained by regiospecific alkylation of secondary α-chloro imines (**1**)[6] with lithium di-isopropylamide as base (THF; 0 °C; 1—2 h) and alkyl bromides or iodides as electrophiles.[7] Reactions of methoxylated cyclopropylamines (**4**) with sodium borohydride in alcohols (methanol or ethanol) did not lead to cyclopropylamines (**6**). The reaction conditions used in the recent communication,[3] *i.e.* demethoxylation of *N*-aryl-1-methoxycyclopropylamines with sodium borohydride in tetrahydrofuran in the presence of boron trifluoride–ether complex, either did not afford cyclopropylamines (**6**) at all, or yielded a complex mixture.

The conversion of geminally functionalized cyclopropanes (**4**) into cyclopropylamines (**6**) *via* iminium species (**5**) could be accomplished by Lewis-acid-assisted reaction with lithium aluminium hydride in ether under reflux overnight. Depending on the quality of the lithium aluminium hydride used, some substrates required a shorter reaction time. However, the longer reaction times which were used did not lead to base-induced ring opening of cyclopropylamines (resulting in aliphatic secondary amines). This result is surprising in view of

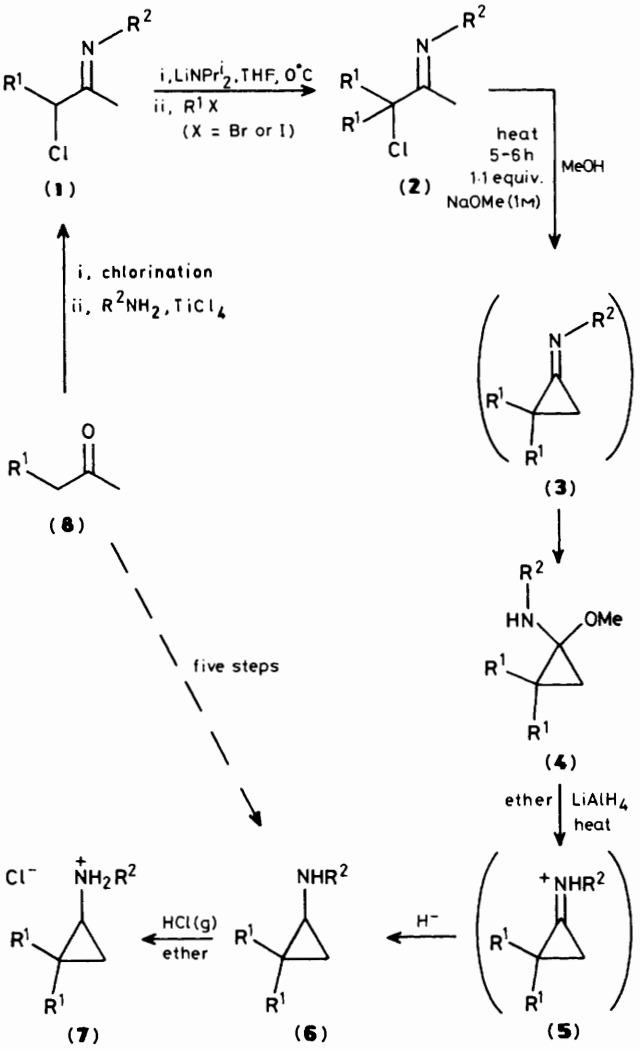


**Table 1.** Preparation of cyclopropanes (**4**) and cyclopropylamines (**6**).

| | R$^1$ | R$^2$ | Yield of (**4**)[a] (%) | B.p. of (**4**) (°C/Torr) | Reaction time[b] of (**4**) (h) | Yield of (**6**) (%) | Hydrochloride (**7**)[c] Yield (%) | Hydrochloride (**7**)[c] M.p. (°C) |
|---|---|---|---|---|---|---|---|---|
| **a** | Me | Pr$^i$ | 80 | 52—56/11 | 17 | 68 | | |
| **b** | Me | Bu$^t$ | 86 | 66—68/11 | 18 | 83 | 82 | 170 |
| **c** | Et | Bu$^t$ | 85 | 36—42/0.05 | 17.5 | 80 | 85 | 206 (Subl. from 175) |
| **d** | Pr | Bu$^t$ | 92 | 46—49/0.05 | 19.5 | 86 | 75 | 137 |
| **e** | Bu | Bu$^t$ | 84 | 99—109/0.1 | 18 | 78 | 80 | 159 |

[a] Reaction of α-chloro imines (**2**) with 1 M NaOMe/MeOH (1.1 equiv.) for 5.5 h under reflux. All cyclopropanes (**4**) gave correct elemental analyses. [b] Reaction of 1-methoxy-(*N*-alkyl)-2,2-dialkylcyclopropylamines (**4**) with $LiAlH_4$ (8 mol. equiv.) in ether (heated). All cyclopropylamines (**6**) gave correct elemental analyses. [c] Reaction of cyclopropylamines (**6**) with dry hydrogen chloride in ether at room temperature.

previous reports on the reactivity of cyclopropylamines towards bases, but can probably be explained in terms of steric hindrance in the substrates (**6**) and the absence of carbanion-stabilizing groups on the three-membered ring.[8]

The cyclopropylamines (**6**) are stable colourless liquids, easily converted into their hydrochlorides (**7**) by treatment with dry hydrogen chloride gas in ether. These white crystalline salts are the preferred form for storage and easily liberate the free bases on treatment with aqueous alkali.

All the methoxylated cyclopropylamines (**4**) were characterized by full spectral analysis (i.r., mass, and $^1H$ and $^{13}C$ n.m.r.). In particular, the typical AB system ($J$ 4.6 Hz) of the cyclopropane protons ($^1H$ n.m.r.) was indicative of the structure. In a similar way, the cyclopropylamines (**6**) showed a typical ABX system ($^1H$ n.m.r.) for the cyclopropane protons ($J_{AB}$ 4.4, $J_{BC}$ 7.1—7.4, $J_{AC}$ 4.0—4.2 Hz).

In conclusion, a convenient and straightforward synthesis of *N*-alkyl-2,2-dialkylcyclopropylamines (**6**) has been developed starting from simple ketones (**8**) and primary amines, *via* Favorskii-type cyclopropanation of α-chloro imines (**2**). The reductive demethoxylation of the resulting 1-methoxy-(*N*-alkyl)cyclopropylamines (**4**) by lithium aluminium hydride is in sharp contrast with the Lewis-acid-catalysed reduction of the corresponding *N*-aryl derivatives by sodium borohydride.[3]

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