A New Method for the Preparation of 2,2-Dialkylcyclopropylamines

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2,2-Dialkylcyclopropylamines have been prepared by a new synthetic method involving base-induced cyclization of β-chloroimines and subsequent hydrolysis.

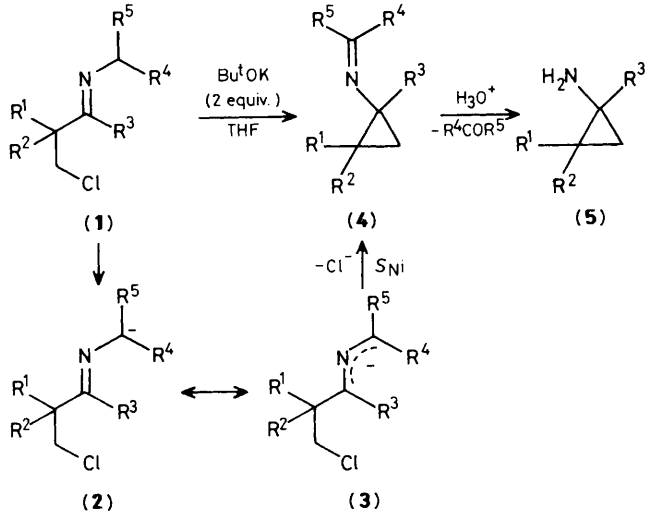
Cyclopropylamines are a well known class of compounds which can be prepared by Hofmann or Curtius rearrangement of the corresponding acid derivatives (cyclopropane carboxamides and cyclopropane carbonyl azides) and by Beckmann rearrangement of the oximes derived from cyclopropyl ketones.[1,2] Certain tertiary cyclopropylamines could be prepared in variable yields by addition of carbenes across enamines[3,4] and on reaction of nucleophiles (such as hydride) with certain β-aminoallylic halides.[5,6] Here we report a simple synthesis of primary 2,2-dialkylcyclopropylamines (**5**) by base induced cyclization of β-chloroimines (**1**)[7] (Scheme 1).

This cyclopropanation requires a suitable active nitrogen substituent and the use of a non-nucleophilic strong base. These conditions were met with *N*-benzyl-, *N*-α-methylbenzyl-, and *N*-(methoxycarbonyl)methyl-imines (**1**) using potassium t-butoxide as base in tetrahydrofuran (THF). Subsequent hydrolysis of the resulting benzylidenecyclopropylamines (**4**) (and analogues; Table 1; 82—97%) provided cyclopropylamines (**5**) in high yields. If nucleophilic reaction conditions are employed (*e.g.* NaOMe or NaCN in methanol) no cyclopropanation is observed owing to competitive azetidine formation resulting from nucleophilic addition across the imino bond and subsequent intramolecular nucleophilic chloride ion displacement.[8]

The formation of cyclopropylamines (**5**) can be interpreted as originating from an initial deprotonation at the activated α-carbon atom of the nitrogen substituent, resulting in the anion (**2**). This deprotonation only takes place if R^4 or R^5 is an 'activating' group, capable of enhancing the acidity of the α-hydrogens of the N-substituent (*e.g.* Ph or ester). The anion (**2**) is mesomeric with the delocalized carbanion (**3**), which easily undergoes intramolecular nucleophilic substitution with expulsion of chloride anion.

The possible 5-*exo*-*tet*-process, *i.e.* intramolecular nucleophilic substitution of anion (**2**) onto the chlorinated carbon, leading to 4,5-dihydro-3*H*-pyrroles, was not observed at all.

If R^2 = Me, R^1 = Et (entry **g**) a mixture of *cis*- and *trans*-isomers (**4**) was found in a 1 : 1 ratio (capillary g.l.c.). All benzylidenecyclopropylamines (**4a—g, i**) and the *N*-cyclopropylimine (**4h**) possess the *E*-configuration exclusively (^{1}H n.m.r.), and were easily hydrolysed with oxalic acid (5 equiv.) in 20% aqueous methanol to afford the cyclopropylamines (**5**)



Scheme 1

Table 1. Preparation of N-cyclopropylimines (**4**).[a]

	R^1	R^2	R^3	R^4	R^5	Reaction time[b,c]	% Yield of (**4**)
(**4a**)	Me	Me	Me	Ph	H	Δ 2 h	95[d]
(**4b**)	Me	Me	Ph	Ph	H	Δ 3 h	92[d,e]
(**4c**)	Me	Me	H	Ph	H	Δ 2 h	93[d]
(**4d**)	Me	Me	H	Ph	Me	RT 3 d	83[f]
(**4e**)	Me	Me	*p*-MeC_6H_4	Ph	H	RT 1 d	95[d]
(**4f**)	Et	Et	H	Ph	H	RT 2 d	97[d]
(**4g**)	Et	Me	H	Ph	H	RT 1 d	90[d]
(**4h**)	Me	Me	H	CO_2Me	H	RT 12 h	82[f]
(**4i**)	$-[CH_2]_5-$		Me	Ph	H	RT 3 d	96[d]

[a] All compounds (**4**) gave spectral (^{1}H and ^{13}C n.m.r., i.r., mass) data and microanalytical data in agreement with the proposed structures. [b] Δ = reflux; RT = room temperature; d = day. [c] Reaction conditions: Bu^{t}OK (2 equiv.) in tetrahydrofuran. [d] Crude reaction mixture (purity >97%; checked by g.l.c. and ^{1}H n.m.r.). [e] Spectral data for (**4b**): i.r. (NaCl): $\nu_{C=N}$ 1640 cm^{-1}; ^{1}H n.m.r. (C_6D_6) δ 0.94 (3H, s, Me), 1.28 and 1.44 (2H, ABq, *J* 4.4 Hz, CH_2), 1.70 (3H, s, Me), 7.00—7.80 (5H, m, Ph C=N), 7.22 (5H, s, Ph), and 7.87 (1H, s, CH=N); *m/z* (%): 249 (M^+, 10), 234(12), 194(20), 193(100), 192(12), 166(7), 165(15), 146(6), 120(6), 119(4), 116(5), 115(5), 107(5), 105(11), 104(9), 103(9), 91(30), 90(35), 89(40), 77(13), 65(7), 64(6), 63(8), 56(7), 51(10), 44(20), and 41(11); ^{13}C n.m.r. ($CDCl_3$) δ 156.78 (d, CH=N), 138.53 (s, quat. C), 137.29 (s, quat. C), 131.23, 129.66, 128.29, 128.03, 127.54, 127.00 (6 × d, 2 × *o*-, *m*-, and *p*-C), 58.73 (s, N–C), 28.82 (t, CH_2), 27.09 (s, CMe_2), and 24.94 and 21.29 (2 × q, Me_2). [f] Isolated pure by g.l.c. because of the presence of small amounts of unidentified products.

Table 2. Synthesis of cyclopropylamines (**5**).

Starting material	Product	R^1	R^2	R^3	% Yield of (**5**) from (**1**)
(**4a**)	(**5a**)	Me	Me	Me	92[a,b]
(**4b**)	(**5b**)	Me	Me	Ph	90[a,b,c]
(**4e**)	(**5c**)	Me	Me	p-MeC_6H_4	82[b,d]
(**4c**)	(**5d**)	Me	Me	H	70[e]
(**4i**)	(**5e**)	$-[CH_2]_5-$		Me	91[a,b]

[a] Yield of crude reaction mixture (purity >97%, checked by g.l.c. and ^1H n.m.r.). [b] All compounds gave spectral data (^1H and ^{13}C n.m.r., i.r., and mass) in agreement with their structures and satisfactory analytical data. [c] Spectral data of (**5b**): i.r. (NaCl): $\nu(NH_2)$ 3380 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.65 and 1.01 (2H, ABq, J 4.5 Hz, CH_2), 0.78 (3H, s, Me), 1.44 (3H, s, Me), 1.75 (2H, br. s, NH_2), and 7.40 (5H, s, Ph); m/z (%): 161 (M^+, 34), 160(72), 147(12), 146(100), 145(6), 144(7), 143(5), 131(6), 130(8), 129(25), 128(14), 127(6), 119(5), 106(11), 105(45), 104(92), 103(8), 91(12), 84(5), 78(8), 77(43), 76(6), 65(16), 51(6), 50(21), 49(6), 44(16), 42(9), 41(18), 40(8), and 39(11); ^{13}C n.m.r. ($CDCl_3$) δ 145.39 (q, quat. C), 128.26 (2 × C) and 126.29 (3 × d, *o*-, *m*-, and *p*-C), 45.82 (s, *C*Ph), 25.66 (t, CH_2), 24.18 and 20.63 (2 × q, Me_2), and 22.83 (s, *C*Me_2). [d] B.p. 50—52 °C at 0.7 mmHg. [e] Purity 85% (g.l.c., ^1H n.m.r.), b.p. 85—86 °C.[9]

and the corresponding carbonyl compounds (benzaldehyde in most cases). Both products were separated by acid (carbonyl compound) followed by basic (cyclopropylamine) extractive work-up (Table 2). The reaction mixtures of all products were free of side products (checked by g.l.c. and ^1H n.m.r.) except for (**4d, h**) and (**5d**). In these cases g.l.c. was used to isolate the pure products. All cyclopropylamines (**5**) and benzylidene-cyclopropylamines (**4**) [in addition to ester (**4h**)] are new compounds except for (**5d**).[9] Some related *N*-benzylidene-cyclopropylamines have been reported.[10—15]

In conclusion the synthesis using β-chloroimines (**1**) provides a new elegant approach to cyclopropylamines which have already been shown to be physiologically active compounds, some being monoamine oxidase inhibitors.[16]

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