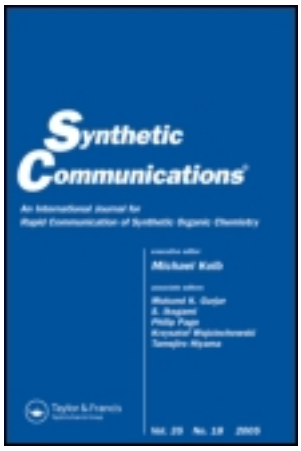

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A SIMPLE AND EFFICIENT PREPARATION OF 3,4-DIALKYLSUBSTITUTED TETRAHYDROISOQUINOLINE USING CYCLOPROPYLETHYLIDEN BENZYLAMINE

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A SIMPLE AND EFFICIENT PREPARATION OF 3,4-DIALKYLSUBSTITUTED TETRAHYDROISOQUINOLINE USING CYCLOPROPYLETHYLIDEN BENZYLAMINE

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ABSTRACT

Intramolecular Friedel–Crafts alkylation of *N*-benzyl-*N*-(1-cyclopropylethyl)acetamide to 3,4-dialkyl substituted tetrahydroisoquinoline by reaction of the acetamide with an excess of PPA is described. The conformational study of intermediates by high resolution NMR analysis is also reported.

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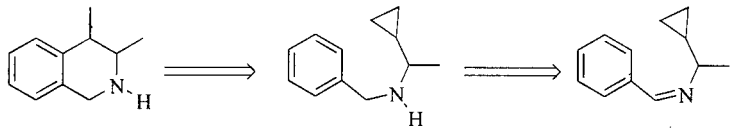


Figure 1.

Isoquinolines as well as 2,3,4,5-tetrahydroisoquinolines have received considerable attention from both theoretical and practical points of view.[1] Tetrahydroisoquinoline core occurs in a large number of alkaloids.[2] Although their methods of preparation have been well-documented, organic and medicinal chemists still continue to develop new approaches to obtain them.

As part of our research program on the preparation of potentially bioactive *N*-heterocycles.[3,4] we recently synthesized new series of 2-benzazepine,[5] quinoline[6] and acridine[7] derivatives using allyl cationic cyclization and now addressed the chemistry of *N*-cyclopropylethyl benzylamine under acidic conditions. Keeping in our minds that cyclopropylimines have proven to be useful building blocks in synthesis of several alkaloids containing pyrrolidine skeleton using, as key step, the intramolecular cyclization process promoted by acids or halide salts,[8] we believed that this type of imines and their derivatives could serve as starting materials in the synthesis of important medicinally 3,4-dialkylsubstituted tetrahydroisoquinolines.

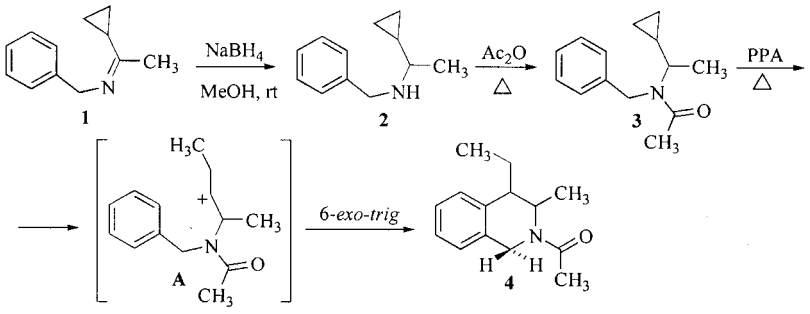
A simple retrosynthetic analysis of disubstituted tetrahydroisoquinoline structure shows that its construction could be realized by electrophilic ring-opening of appropriated cyclopropyl moiety using Brönsted acids (Fig. 1). We report here that reduction of *N*-cyclopropylethyliden benzylamine followed by N-acetylation and subsequent intramolecular Friedel–Crafts ring closure of the corresponding acetamide can be an useful and easy alternative for the preparation of 3,4-dialkylsubstituted tetrahydroisoquinolines. Surprisingly enough, this obvious synthetic strategy has not been used before.

RESULTS AND DISCUSSION

As shown in Sch. 1, the starting imine **1** was obtained by condensation of benzylamine with methyl cyclopropyl ketone in anhydrous benzene at reflux overnight. After distillation in vacuo, the imine **1** immediately was reduced ($NaBH_4$/MeOH/25°C) to secondary benzylamine **2**,[9] that was obtained by silica gel column chromatography as viscous yellow oil with

high yield (92%). To avoid possible decomposition of **2** which can occur under drastic acidic conditions employed, the latter was first reacted with an excess of the acetic anhydride to give the corresponding acetamide **3** in a quantitative yield (96%) as maroon viscous oil after the workup of the reaction mixture with saturated Na_2CO_3 solution, the IR spectrum of which showed a single carbonyl stretching band at 1641 cm^{-1} but no adsorption in the region 3317 cm^{-1} which would be expected for precursor amine.

The structures of compounds **2** and **3** were also confirmed by ^1H and ^{13}C NMR spectroscopy, GC-MS and elemental analysis. The mass spectra of compounds **2** and **3** exhibit low intensity signals of parent ions (3 and 5%, respectively), which agree with the expected molecular mass. High resolution ^1H NMR analysis of both compounds revealed that benzylamine **2** exists as unique conformer **2a**, while acetamide **3** exists as two conformers in 1.8 : 1 ratio (Fig. 2). Major conformationally no restricted acetamide was assigned as conformer **3a** and minor restricted acetamide as conformer **3b**. The results of this analysis are summarized in the Table 1.



Scheme 1.

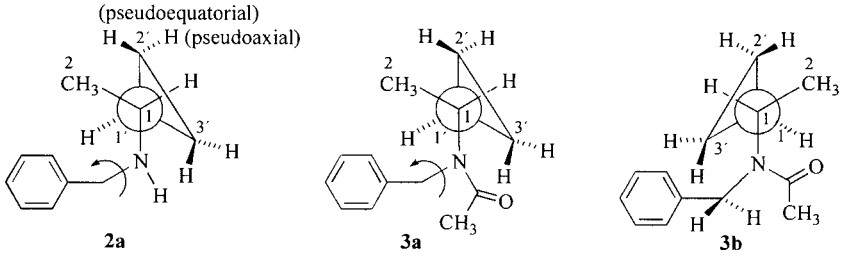


Figure 2.

Because the rotation of benzyl fragment around C–N bond in conformer **3a** is free, the signal of benzylic protons appears as singlet at 4.54 ppm. In contrast, in conformer **3b** the steric effect of cyclopropyl moiety is enough great and hindered the free rotation of benzyl fragment, and by this reason the signal of these protons appears as two doublets at 4.62 and 4.70 ppm with a coupling constant $J = 15.7$ Hz. The ^{1}H NMR spectrum of acetamide also showed that the singlet at 2.26 ppm associated with the NH protons was absent and, instead, a three-proton singlets at 2.01 and 2.14 ppm, and an one-proton multiplets at 3.14 and 3.99 ppm and 0.49

Table 1. The ^{1}H and ^{13}C-NMR Spectral Data of Compounds **2–4**

No.	^{1}H NMR ($CDCl_3$), δ (ppm)	^{13}C NMR ($CDCl_3$), δ (ppm)
2	7.33–7.21 (5H, m, arom.-H), 3.84 (2H, s, benzylic-H), 2.26 (1H, s, N–H), 1.92 (1H, m, 1-CH), 1.20 (3H, d, $J = 6.4$ Hz, 2-CH_3), 0.79 (1H, m, 1′-H), 0.50 (1H, m, 3′-$H_{pseudoeq.}$), 0.43 (1H, m, 3′-$H_{pseudoax.}$), 0.16 (1H, m, 2′-$H_{pseudoeq.}$), 0.07 (1H, m, 2′-$H_{pseudoax.}$)	141.0–128.16 (arom.-C), 58.29 (1-C), 51.54 (benzylic-C), 20.35 (2-C), 17.76 (1′-C), 4.54 (3′-C), 1.93 (2′-C)
3	**3a:** 7.34–7.20 (5H, m, arom.-H), 4.54 (2H, s, benzylic-H), 3.99 (1H, m, 1-CH), 2.01 (3H, s, CH_3–CO), 1.16 (3H, d, $J = 6.8$ Hz, 2-CH_3), 0.49 (1H, m, 1′-H), 0.33–0.21 (4H, m, 2′-H-3′-H)	171.40 (C=O), 138.49 (quaternary-C), 128.53 (*meta*-C), 127.01 (*ortho*-C), 126.04 (*para*-C), 54.98 (1-C), 47.73 (benzylic-C), 22.38 (**C**–CO), 18.22 (2-C), 15.48 (1′-C), 4.48–5.35 (2′-C-3′-C)
	3b: 7.34–7.20 (5H, m, arom.-H), 4.70 (1H, d, $J = 15.6$ Hz, benzylic-H_A), 4.62 (1H, d, $J = 15.7$ Hz, benzylic-H_B), 3.14 (1H, m, 1-CH), 2.14 (3H, s, CH_3–CO), 1.16 (3H, d, $J = 6.8$ Hz, 2-CH_3), 1.16 (1H, m, 1′-H), 0.33–021 (4H, m, 2′-H-3′-H)	170.31 (C=O), 139.62 (quaternary-C), 128.03 (*meta*-C), 127.21 (*ortho*-C), 126.43 (*para*-C), 59.66 (1-C), 44.67 (benzylic-C), 21.89 (**C**–CO), 19.16 (2-C), 16.19 (1′-C), 5.35–4.48 (2′-C-3′-C)
4	7.37–7.18 (4H, m, arom.-H), 4.56 (1H, d, $J = 16.7$ Hz, 1-H_A), 4.46 (1H, d, $J = 17.0$ Hz, 1-H_B), 3.64 (1H, td, $J = 6.8$ and 1.4 Hz, 4-H), 3.51 (1H, q, $J = 7.1$ Hz, 3-H), 1.96 (3H, s, CH_3–CO), 1.40 (2H, m, **CH_2**–CH_3), 1.18 (3H, d, $J = 7.1$ Hz, 3-CH_3), 0.76 (3H, t, $J = 7.4$ Hz, CH_2–**CH_3**)	170.42 (C=O), 138.44–126.56 (arom.-C), 75.80 (4-C), 59.48 (3-C), 53.35 (1-C), 27.77 (**C**–CO), 22.99 (–**C**–CH_3), 10.75 (3-CH_3), 10–42 (CH_2–**C**)

and 1.16 ppm were observed. These data confirmed that the obtained acetamide exists as a mixture of two conformers.

Finally, easily available acetamide **3** underwent an intramolecular electrophilic aromatic alkylation promoted by PPA, in which the cyclopropyl fragment of the acetamide acts as the electrophilic component, giving the tetrahydroisoquinoline **4**, that was obtained by silica gel column chromatography in 80% yield as maroon viscous oil.

The involvement of carbocations in the electrophilic opening of cyclopropyl ring under appropriate acidic conditions has been well established.[10] By this reason, we suppose that under these strongly acidic conditions, initially occurs the cleavage of cyclopropyl ring with the formation of cationic species **A** as unique probably precursor of the formed 2,4-dialkylsubstituted tetrahydroisoquinoline **4** since it corresponds to a secondary, sufficiently stable in situ generated carbocation, which then undergoes intramolecular alkylation by the benzene ring. Other cyclization products have not been detected.

IR spectrum of **4** had carbonyl adsorption band at 1625 cm^{-1}. The mass spectrum of this compound showed a very low intensity (<1%) molecular ion at *m*/*z* 217, and as main fragments the loss of the hydrogen atom, and the subsequent loss of the C_3H_5 (*m*/*z* 176), C_5H_7O (*m*/*z* 134), $C_7H_{11}O$ (*m*/*z* 106) and $C_7H_{12}NO$ (*m*/*z* 91) groups. The ^1H and ^{13}C NMR data allowed us to confirm the expected structure (Table 1). Thus, the presence in ^1H NMR spectrum of one triplet at 0.76 ppm and one multiplet at 1.40 ppm integrated for three methyl and two methylene protons, as well as one triplet of doublets at 3.64 ppm and one quartet at 3.51 ppm integrated for two methyne protons are the best evidences that the cyclization of acetamide take place. Benzylic protons resonated as two doublets at 4.56 and 4.46 ppm.

CONCLUSION

The fast and easy procedure and good yields of the products make our approach a useful addition to the current methodologies. Both building blocks benzylamine and methylcyclopropyl ketone used in this approach as starting materials are commercially available.

EXPERIMENTAL

IR spectra were obtained on a Nicolet Avatar 360-FTIR spectrophotometer as KBr pellets. The ^1H NMR spectra were recorded in $CDCl_3$ solution with TMS as internal standard on Bruker AM-400 spectrometer

(400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR). GC-MS spectra were obtained on a HP-5890A Series II gas chromatograph interfaced to an HP-5972 mass selective detector (MSD) with an HP MS ChemStation Data. The electron beam energy was 70 eV. Elemental analyses were performed on a Leco CHN-600 analyzer. Column chromatography and TLC were carried out using Merck Kieselgel 60 (230–400 mesh) and Silufol UV_{54} chromatoplates. All reagents were purchased from Merck and Aldrich Chemical Co. (p.a. quality). All solvents were used without further purification.

Compounds **1–3** were synthesized according to known methods (**5a**, **9**).

***N*-(1-Cyclopropylethyl)benzylamine, 2:** Viscous oil, n_D^{25} 1.5707; MS *m*/*z* (relative intensity) 175 ($M^{+\cdot}$, 3), 160 (55), 146 (3), 134 (17), 106 (5), 91 (100); Anal. Calcd. for $C_{12}H_{17}N$: C, 82.29; H, 9.71; N, 8.0%. Found: C, 82.10; H, 9.60; N, 8.13%.

***N*-(1-Cyclopropylethyl)benzylacetamide, 3:** Viscous oil, n_D^{25} 1.5208; MS *m*/*z* (relative intensity) 217 (M^+, 5), 202 (1), 188 (18), 174 (9), 160 (21), 148 (35), 134 (9), 126 (8), 106 (55), 91 (100); Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45%. Found: C, 77.51; H, 8.62; N, 6.32%.

Synthesis of *N*-acetyl-4-ethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline 4: A mixture of the acetamide **3** (0.5 g, 2.3 mmol), and PPA (5.0 g) was heated at 70°C for 6 h. After cooling, the reaction mixture was poured into ice (50 g) and neutralized with saturated Na_2CO_3 solution. The organic phase was extracted with dichloromethane (3×30 mL) and dried on anhydrous Na_2SO_4. Evaporation of the solvent leads to a viscous black oil, which is purified by silica gel column chromatography using ethylacetate–heptane (1 : 20) as eluent to give 0.4 g (80% yield) of a viscous maroon oil.

n_D^{25} 1.5209; MS *m*/*z* (relative intensity) 217 (M^+, <1), 216 (<1), 177 (15), 176 (17), 150 (2), 134 (63), 118 (<1), 106 (6), 91 (100); Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45%. Found: C, 77.27; H, 8.90; N, 6.53%.

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