INTRODUCTION

Compounds containing the imine group (–C=N–) are usually called Schiff bases.1 Aliphatic aldimines, contrary to their aromatic counterparts,2 are reported to be usually unstable and susceptible to self-condensation or polymerization under different reaction conditions.2 However, aldimines can be stored for long periods under anhydrous conditions in an oxygen-free atmosphere.4

The formation of imines may lack efficiency because of their low stability.3 The instability of aliphatic imidines in acetic medium has been attributed to polymerization of the carbodiimide intermediate formed in the reaction of aliphatic aldehydes with primary aliphatic amines. The low yields of aldimines have also been attributed to polymerization of the aldehyde substrate under acidic conditions.1 This polymerization competes with the formation of aldimines.6 Aldimines are normally less reactive electrophiles than the corresponding aldehydes.2 It has been demonstrated that the aldimines are stable under certain experimental conditions in which imine-enamine tautomerism is not favored. The tautomeric equilibrium is normally shifted toward the imine form except when the enamines result from the condensation of aldehydes with unsubstituted amines.4 Low temperatures and active nucleophiles have been used to prevent the decomposition of imines in acetic media.6

Although the properties and reactivities of the aliphatic aldimines are well-known, the structure of the decomposition products were not described in detail in the literature until the early 1990s.13 In fact, unidentified products were reported during the formation of imines using titanium tetrachloride as the catalyst.11 The literature also reports that unidentified products may be obtained during the synthesis of aldimines that bear alpha hydrogen atoms for the imino group.12 Although aromatic aldimines without an alpha hydrogen are stable in acetic medium,13 the presence of a methylene group between the ring and the imino group resulted in significant alterations in the ultraviolet spectrum,14 and unidentified decomposition products have been produced under these conditions.15

Few studies have been performed to characterize the products formed from self-condensation of imines in acetic medium.16 Imines undergo Mannich-type reactions in the presence of a catalytic amount of metal complexes,17 and it has been suggested that these reactions occur under free radical conditions.18 The condensation of N-unsubstituted aromatic aldimines yields imine products,19 while aldimines obtained from aliphatic aldehydes and primary amines provide polymers.20 Dimetile products named enamines (αβ-unsubstituted imines) were identified among the products obtained from the reaction of N-alkyl aldimines.21 There is some experimental evidence suggesting that the mechanism of deamination catalyzed by samarium complexes occurs through the homo-condensation of imines to furnish enamines in which the E-isomers predominate.22 Enamines are also obtained from reactions between imines and alkenes catalyzed by metal complexes.23 Another method of obtaining enamines involves the reaction between amines and αβ-unsubstituted aldehydes or ketones, but this method furnishes low yields of enamines.24 When self-condensation products are identified in the literature, their configurations tend not to be specified.25 In those cases where configuration had been specified, only the E-isomer was mentioned.29

In view of the scarcity of information about the structure of the condensation products obtained from aldimines in acetic medium, an alternative and simple method by which enamines are formed by self-condensation of aldimines without catalysts by metal complexes is described in this work. A self-condensation mechanism was proposed with N-valeryl benzalmine (1) as the starting material (Scheme 1). Moreover, the nucleophilic attack of the enamine tautomer (2) on an imine was proposed as the first step of the reaction to furnish an aminoimine intermediate (3). This intermediate underwent deamination to yield the corresponding αβ-unsubstituted imines – E-4 and Z-ename (5) with different configurations for the substituents on the terminal sp2 carbon, as shown in Scheme 1. The present study was mainly based on NMR (1D and 2D) and mass spectral analyses, followed by DFT theoretical investigations.

RESULTS AND DISCUSSION

The GC chromatogram of the distilled product exhibited peaks at RT = 9.880 and 10.165 min, respectively, with a mass spectrum
characteristic of both enamine isomers (4 and 5). The peak at \( \delta = 167 \) in the mass spectrum was attributed to the molecular ion. The peak at \( \delta = 138 \) was attributed to the loss of an ethyl radical. The base peak at \( \delta = 124 \) corresponds to the loss of a propyl radical.

The \( ^1H \) and \( ^13C \) NMR spectra of the distilled product indicated the presence of two different groups of signals. The high-intensity signals in the 2D NMR experimental data were first analyzed as follows. The hydrogen signal at \( \delta = 7.07 \) (H-1) showed an HSQC correlation with the carbon signal at \( \delta = 163.7 \) (C-1) and HMBC correlations with carbon signals at \( \delta = 141.9 \) (C-2), 139.9 (C-3), 63.0 (C-4), and 18.5 (C-5). The hydrogen signal at \( \delta = 4.50 \) (H-3) showed an HSQC correlation with the carbon signal at \( \delta = 153.9 \) (C-3) and HMBC correlations with carbon signals at \( \delta = 163.7 \) (C-1), 141.9 (C-2), 29.8 (C-4), 22.1 (C-5), and 18.5 (C-1). The hydrogen signal at \( \delta = 3.38 \) (H-1') showed an HSQC correlation with the carbon signal at \( \delta = 65.0 \) (C-1') and HMBC correlations with carbon signals at \( \delta = 163.7 \) (C-1), 23.5 (C-2'), and 11.0 (C-3'). The hydrogen signal at \( \delta = 2.38 \) (H-1') showed an HSQC correlation with the carbon signal at \( \delta = 18.5 \) (C-1') and HMBC correlations with carbon signals at \( \delta = 163.7 \) (C-1), 141.9 (C-2), 139.9 (C-3), and 13.6 (C-2'). The hydrogen signal at \( \delta = 2.20 \) (H-1') showed correlations with the carbon signals at \( \delta = 65.0 \) (C-1') and \( \delta = 11.0 \) (C-3'), the hydrogen signal at \( \delta = 1.48 \) (H-5) showed correlations with signals at \( \delta = 2.20 \) (H-1') and 0.94 (H-6); the hydrogen signal at \( \delta = 1.01 \) (H-2') showed correlations with signals at \( \delta = 3.38 \) (H-1') and 0.87 (H-3'); and the hydrogen signal at \( \delta = 2.38 \) (H-1') showed correlations with the signals at \( \delta = 1.04 \) (H-2'). These NMR data are in agreement with the corresponding data of an N-propyl-2-ethylhexyl-2-enzyme. The configuration was determined to be that of the E-isomer 4 because of the NOESY correlation of the signal at \( \delta = 7.07 \) (H-1) with the signal at \( \delta = 5.07 \) (H-3).

The low-intensity signals in the 2D NMR data showed a correlation pattern (COSY, HSQC, HMBC) similar to that observed for the E-isomer 4. This low-intensity pattern was assigned to the Z-isomer 5. The hydrogen signal at \( \delta = 8.27 \), attributed to H-1 of the Z-isomer 5, is more highly shielded than that of the same hydrogen in 4 (\( \delta = 7.07 \)); \( \Delta \delta = \delta_5 - \delta_1 \), of 4 (\( \Delta \delta = 0.60 \) ppm). The calculated hydrogen chemical shift difference between the corresponding hydrogen 1 of 4 and 5 is in accord with the experimental data, i.e., \( \Delta \delta = \delta_5 - \delta_1 \), of 4 (\( \Delta \delta = 0.87 \) ppm) by BLYP/6-31G* and B3LYP/6-31G* calculations, respectively. In addition, other comparisons between experimental and calculated chemical shifts confirm the structural characterization of 4 and 5. Thus, \( \Delta \delta_1 = 0.08 \) ppm and \( \Delta \delta_5 = 0.13 \) ppm (by BLYP/6-31G* calculations) and \( \Delta \delta_1 = 0.31 \) ppm (by B3LYP/6-31G* calculations) for the respective hydrogen chemical shifts, while the values for the corresponding carbon chemical shifts were \( \Delta \delta_1 = -4.40 \) ppm and \( \Delta \delta_5 = -8.88 \) ppm (by BLYP/6-31G* calculations) and \( \Delta \delta_1 = -4.39 \) ppm (by B3LYP/6-31G* calculations).

The formation of 4 and 5 may be explained by deamination of 3 (Scheme 1). In turn, the latter may be formed by condensation of 1 with 2 (Scheme 1). Enamines have higher energies than the corresponding imines and, for this reason, are not experimentally observed. The first step in the formation of an enamine occurs through nucelophilic attack of the enamine on the carbon of the imino group. Similar to the case of enaminoesters, the reactivity of enaminoesters towards electrophilic reactants is enhanced on C-2. In fact, N-ethylbutyl-2,2-dichlorobutanimine, which has no hydrogen bound to the carbon alpha for the imino group, was obtained via the reaction between N-ethylbutyltrimine and N-chlorosuccinimide. The NMR signal at \( \delta = 7.64 \) attributed to the imine hydrogen of N-ethylbutyl-2,2-dichlorobutanimine, remained unaltered for two months following the addition of a catalytic quantity of butanoic acid.

The mass spectrum of the distilled product did not exhibit a peak at \( \delta = 226 \) that might be attributed to the molecular ion of the imineamine intermediate 3. In addition, the \( ^1H \) and \( ^13C \) NMR spectra and DEPT 135° subspectrum of the distilled product and residue did not show signs that might be attributed to 3.

Decomposition of 3 was investigated by theoretical calculations using the BLYP/6-31G* level. A lower energy was obtained for the Z-isomer than for the E-isomer (\( \Delta \delta = \Delta \delta_5 - \Delta \delta_1 = 2.22 \) kcal/mol by BLYP/6-31G* and 3.05 kcal/mol by B3LYP/6-31G*), suggesting that the formation of 5 is thermodynamically controlled. In spite of this fact, the E-isomer 4 was the principal product obtained. Only two configurations were considered for imineamine 3—the pro-Enamine (C-2 and C-3) and the pro-Z-enamine (both C-2 and C-3 having the S configuration). Other possibilities for the configurations at C-2 and C-3 correspond to the enantiomers of these structures. The Newman projections of the pro-Enamine and pro-Z-enamine are shown in Scheme 2. BLYP/6-31G* geometry optimizations indicated a lower energy for the pro-Z-enamine than for the pro-Enamine, but the energy difference is small (\( \Delta \delta = 0.58 \) kcal/mol) and does not explain the higher proportion of 4 than 5 in the distilled product.

The transition states for pro-Enamine and pro-Z-enamine formation were investigated using the BLYP/6-31G* level and furnished the ET-pro-E and ET-pro-Z optimized geometries, respectively. The theoretical calculations indicated a lower energy for ET-pro-E than for ET-pro-Z (\( \Delta \delta = 0.74 \) kcal/mol). Although the energy difference is small, the high-intensity signals in the NMR experiments for the distilled product must certainly be related to 4. Because of this small energy difference, the formation of 4 must be kinetically controlled. In fact, the self-condensations of 1 in the presence of a catalytic quantity of butanoic acid in DMF were performed at different temperatures during a 24-h period. The effect of temperature on the E/Z isomer ratio was verified for reactions at 25, 80, and 180 °C. An increase in temperature lead to a higher proportion of Z-isomer (0.15, 0.22, and 0.41, respectively). The E/Z isomer ratio in the reaction mixture was determined by integration of the imino hydrogen signals registered in the \( ^1H \) NMR spectrum.
(δH, 8.27 for 5 and δC, 7.67 for 4). As a consequence, the decrease in relative intensity of the signal at δH, 6.77 (H-1 of 4) may also be a result of decomposition of this compound.

On the other hand, the mass spectrum of the residue from the distillation exhibited a peak at m/z 280 that may be attributed to the molecular ion of the iminonitrile (Scheme 3). This compound was formed by condensation of enamine 2 with enamine 4 or 5. In fact, the 1H NMR spectrum of the residue presented a low-intensity doublet at δH, 7.50 (J = 6.0 Hz) and a singlet at δH, 5.68 that may be attributed to H-5 and H-1 of 6, respectively. Moreover, the 13C NMR spectrum and DEPT 135° sub-spectrum of the residue also present low-intensity signals at δC, 167.2, 131.2, 113.6, 63.9, and 50.9 that, based on calculated chemical shift calculations, were attributed to C-5, C-1, C-2, C-1', and C-1", respectively, of 6.

Scheme 3. Chemical structures proposed after MS and NMR analyses of the residue obtained from self-condensation of imine 1.

The GC/MS chromatogram of the residue also contained a peak at m/z 221 in the mass spectrum that may be attributed to the molecular ion of the dienamine. This by-product can be formed from cyclization of 6 as is shown in Scheme 3. The 13C NMR spectrum and DEPT 135° sub-spectrum of this residue also present low-intensity signals at δC, 126.6 and 108.3 that, based on calculated carbon chemical shifts, may be attributed to C-1/C-5 and C-2/C-4, respectively, of 7.

**EXPERIMENTAL**

**General**

IR spectra were recorded on a FTIR Perkin Elmer Spectrum 200 spectrometer in KBr pellets. The 1H and 13C NMR spectra at 400.129 and 100.613 MHz, respectively, as well as the 1H-1H COSY (J1H2, J1H3, and J1H4), 1H-13C HMBC (J1C3, 2H, 3H, and 4H), 1H-13C HMOC (J1C4, 3H, and 4H), and 1H-13C HSQC (J1C2, 3H, and 4H) experiments were performed on a Bruker DRX 400 A VANCE spectrometer, using CDCl₃ as the solvent, with direct or inverse probes and a field gradient. The chemical shifts were registered in ppm (δ) relative to TMS as the internal standard. The coupling constants (J) were registered in Hertz. Experiments were performed using the pulse sequence and programs provided by the manufacturer. 1H and 13C NMR spectra were acquired under standard conditions by using a direct detection 5-mm 1H/13C dual probe. Standard pulse sequences were used for 2D homonuclear and heteronuclear shift correlation techniques by employing a multinuclear inverse detection 5-mm probe with a field gradient at the z-axis. Three delays for the evolution of long-range coupling [1J(1H, 13C)] in 65, 125, and 130 ms were used for 1H-13C HMBC experiments. For the 1H-1H NOESY experiment, two mixing times (350 and 700 ms) were pre-optimized by a specific Bruker computer program.

Mass spectra (MS) by electron impact at 70 eV were obtained on a Shimadzu QP 5050-A gas chromatograph-mass spectrometer (GC/MS) (JF). Chromatographic separations were performed on a PTE®-5 (Supelco, USA) column (30 m x 0.25 mm i. d. x 0.25 μm film) with helium as the mobile phase at a flow rate of 56.5 μL/min. The carrier gas pressure was 120 kPa. One microliter of sample solution (10 μg/100 μL of hexane) was injected using a 1:20 split; the injector temperature was 240 °C. The column temperature was programmed with an initial temperature of 60 °C and heated to 150 °C at a rate of 5 °C/min, followed by heating to 250 °C at a rate of 20 °C/min. Retention time (RT) is given in minutes. The mass range was 40 to 500 με at a rate of five scans per second. Data acquisition and handling was performed with CLASS 5000 Shimadzu software. Raw data files were analyzed by the automated mass deconvolution and identification system (AMDIS) software, version 2.1, supplied by the National Institute of Standards and Technology (NIST, USA). The identification of the components was achieved using the Nist Mass Spectral Search Program for the NIST/EPA/NIH Mass Spectral Library, version 2002, upgraded to 2006 (NIST, USA).

**Procedure for the synthesis of N-propylbutanamine (1)**

A solution of 0.20 mol of butanol in 50 mL of dichloromethane was added to a solution of 0.20 mol of propylyamine in 100 mL of dichloromethane in a three-neck, round-bottom flask equipped with an addition funnel, Dean-Stark apparatus, and condenser with a calcium chloride drying tube, over a 15-min period while stirring in an ice bath. The mixture was heated under reflux for 4 h and dried over magnesium sulfate. The solvent was removed at atmospheric pressure, and the product was distilled under reduced pressure to afford (92%) yield as a yellow oil.

**N-propylbutanamine (1); bp 28 °C/26 mmHg; IR (KBr; cm−1) v 2990-2820, 1670, 1400, 1210, and 1100; 1H NMR (400 MHz, CDCl₃ ppm) δH, 7.60 (t, J = 4.4 Hz; H-1), 3.30 (t, J = 6.8 Hz; H-1'), 2.14-2.17 (m; H-2), 1.62-1.51 (m; H-3 and H-4'), 0.96-0.93 (t, J = 7.6 Hz; H-4), and 0.90-0.88 (t, J = 7.8 Hz; H-3'); 13C NMR (100 MHz, CDCl₃ ppm) δC, 161.7 (C-1), 61.0 (C-1'), 35.9 (C-2), 22.4 (C-2'), 17.9 (C-3), 11.8 (C-4), and 9.5 (C-3').**

**Procedure for the synthesis of (E)- and (Z)-N-propyl-2-ethylhex-2-enamines**

Butanoic acid (0.02 mol) in 50 mL of pentane was added dropwise over a period of 15 min to a stirred solution of 0.20 mol of aldime 1 in 100 mL of pentane in an ice bath. The reaction mixture was stirred at room temperature for 36 h and then dried over magnesium sulfate. The pentane was removed under atmospheric pressure, and the products were distilled under reduced pressure to furnish the distilled product (59.3%) yield of enamine 4 and 5 and a monomethyl residue. The EI/MS isomer ratio (0.89:0.11) in the distilled product was calculated by integration of the ion and fragment ions signals recorded in the 1H NMR spectrum. The physical data for the Z-isomer are only partially described here because of the predominance of the E-isomer in the distilled product.

**E-N-Propyl-2-ethylhex-2-enamine (4); IR (KBr; cm−1) v 2950-2850, 1670, 1665, 1645, 1625, 1460, 1450, 1380, 1320, 1220, 1150, 1085, 1065, and 970; 1H NMR (400 MHz, CDCl₃ ppm) δH, 7.65 (s, H-1), 5.70 (t, J = 7.6 Hz; H-3), 3.38 (t, J = 6.8 Hz; H-1'), 2.38 (q, J = 7.6 Hz; H-1), 2.20 (q, J = 7.6 Hz; H-1), 1.61 (sextet, J = 7.6 Hz; H-2'), 1.48 (sixtet, J = 7.6 Hz; H-1), 1.04 (t, J = 7.6 Hz; H-2'), 0.94 (t, J = 7.6 Hz; H-6), and 0.87 (t, J = 7.6 Hz; H-3'); 13C NMR (100 MHz, CDCl₃ ppm) δC, 163.7 (C-1), 141.9 (C-2), 139.9 (C-3), 63.0 (C-1'), 29.8 (C-4), 23.5 (C-5), 22.1 (C-6), 18.5 (C-1'), 13.8 (C-6'), 13.6 (C-2'), and 11.0 (C-3'); GC/MS m/z 101 (base peak), 99, 98, 82, 81, 80, 79, 68, 67, 56, and 53.**

**Z-N-Propyl-2-ethylhex-2-enamine (5); 1H NMR (400 MHz, CDCl₃ ppm) δH, 8.27 (s, H-1); 5.78 (t, J = 7.6 Hz; H-3), and 3.45 (t, J = 6.8 Hz; H-4'); 13C NMR (100 MHz, CDCl₃ ppm) δC, 157.9 (C-1), 139.2 (C-2), 135.7 (C-3), 63.5 (C-1'), 28.5 (C-4), 23.4 (C-5), 18.9 (C-1'), 13.8 (C-6), 13.6 (C-2'), and 11.0 (C-3').**
Theoretical method

Theoretical studies were performed using the Gaussian03 software package. Spatial arrangements determined from NMR data were used as initial models for geometry optimizations of 4 and 5. DFT geometry optimizations were performed using the geometries previously obtained by the PM3 semi-empirical method. The BLYP and B3LYP6-31G° functionals with standard Pople's split valence 6-31G° base set were used for DFT calculations. The optimized geometries were characterized as true minima on the potential energy surface (PES) when all harmonic frequencies were real. The BLYP6-31G° and B3LYP6-31G° calculations have been efficiently employed to investigate chemical properties of other organic compounds containing carbon–nitrogen bonds. This fact justifies the use of these calculations for amine and imine derivatives.

The electron-nuclear energies (E) were calculated by DFT methods. BLYP6-31G° and B3LYP6-31G° optimized geometries were used in carbon chemical shift calculations at the same level of theory. Carbon chemical shifts (ΔδC) were calculated relative to the corresponding value for tetramethylsilane using BLYP6-31G° (ΔδC 32.14 and ΔδC 180.02) and B3LYP6-31G° (ΔδC 32.18 and ΔδC 189.06) calculations. Correlations between the ΔδC values and experimental carbon chemical shifts (ΔδC) were obtained using the Origin® Standard 7.5 software package. The ΔδC and ΔδC values were plotted on x- and y-axes, respectively. Correlation curves were given as linear fits with correlation coefficients (R) furnished by the program.

CONCLUSION

In conclusion, an efficient method for the specific synthesis of α,β-unsaturated imines without catalysis by metal complexes was developed. Aliphatic aldimines bearing α,β-hydrogen are not stable in acidic medium, and the imine-enamine tautomerism is favored. The nucleophilic attack of the enamine tautomer on the corresponding imine furnishes an intramolecular intermediate with two different configurations (pro-Enamine and pro-Z-Enamine). BLYP6-31G° calculations showed that the transition state for the pro-Enamine had a lower energy than the transition state for the pro-Z-Enamine, but the intermediate pro-Z-Enamine had a lower energy than the pro-Enamine. Considering that the Z-Enamine had a lower energy than the Enamine, the former was the principal product, the self-condensation of N-propylbutanmine must be kinetically controlled. An increase in temperature produced a higher proportion of the Z-isomer.

ACKNOWLEDGEMENTS

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), the Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) for financial support.

REFERENCES AND NOTES
