Original research paper

Synthesis and Characterization of n-(4-(tert-butyl) benzyl)-1-(4-tert-butyl) phenyl)-n-methyl methanaminium chloride from Tert-butyl benzyl derivatives

ABSTRACT

Aims: To synthesize N-(4-(tert-butyl) benzyl)-1-(4-tert-butyl) phenyl)-N-methyl methanaminium chloride, a butenafine analogue from tert-butyl benzyl derivative, and to compare the solvent action of Tetrahydrofuran (THF), acetonitrile, methanol and 1,2-dichloroethane (DCE), and the reducing efficiency of $NaBH_4$ and sodium triacetoxyborohydride (STAB) during the synthesis.

Study design: The study involved laboratory experiments leading to the synthesis of the target compound by varying the solvents used, the reducing agent and the temperature of operation in the presence or absence of a catalyst.

Place and Duration of Study: M.Sc. Access controlled Teaching Laboratory, School of Chemistry, Newcastle University, Newcastle upon Tyne, United Kingdom between June and August, 2012.

Methodology: Reductive amination was carried out by reacting 4-tert-butylbenzaldehyde and 4-tert-butylbenzylamine, using the direct then the indirect approaches. This was followed by methylation using Eschweiler-Clarke reaction in each of the two approaches. The time taken by each reaction was monitored and the product of each approach was characterized by EIS-MS, ^{1}H NMR, ^{13}C NMR and FTIR.

Results: 1,2-dichloroethane gave the best solvent action at 40 ^{o}C (Yield: 75%) and $NaBH_4$ gave the best reducing action in the presence of silica chloride at room temperature (Yield: 50%). In all products obtained at the end of each synthesis, ^{1}H NMR spectrum showed a singlet peak of 18 hydrogen atoms with a chemical shift at 1.3 -1.5 ppm for the presence of 6 methyl groups in the two tert-butyl substituents, the ^{13}C NMR spectrum also indicated the presence of the two tert-butyl substituents by the peak with a chemical shift at 31-32 ppm, for the six methyl carbon atoms, the FTIR spectrum indicated the presence of a tertiary ammonium ion by a strong band at 2460 cm^{-1} and finally the EIS-MS confirmed the molar mass of the compound by a mass to charge ratio of 324.2693.

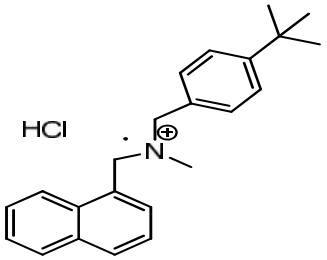
Conclusion: The target compound can be sythesised by both direct and the indirect approaches of reductive amination in any of the solvents tested with/without a catalyst at room or elevated temperature using $NaBH_4$ or STAB as a reducing agent but the best solvent action can be achieved with DCE at 40 ^{o}C and the best reducing action can be achieved with $NaBH_4$ in the presence of silica chloride.

Keywords: Antifungal agents; structure-activity properties; Butenafine; reducing agents; pharmacological activity; reductive amination; methylation.

1. INTRODUCTION

Butenafine chloride, which is simply referred to as Butenafine is an antifungal agent belonging to benzylamine group. Over the years, studies have shown the high potency of Butenafine in treating mycoses (fungal infections) caused by dermatophytes, aspergilli, dimorphic fungi and damatiaceous fungi [1]. Butenafine was reported to exhibit excellent pharmacological activity over Clortrimazol, Naftifine, Terbinafine and bifonazole,against 87 strains of dermatophytes (Minimum Inhibition Concentration, MIC = 0.0015 - 0.05 µg cm^{-3}), 15 strains of Aspergillus (MIC = 0.025-0.78 µg cm^{-3}), 4 strains of *Cryptococcus neoformans* (MIC = 0.78 -1.56 µg cm^{-3}) and 67 strains of *candida spp* (MIC = 3.13->100 µgcm^{-3}) [2].

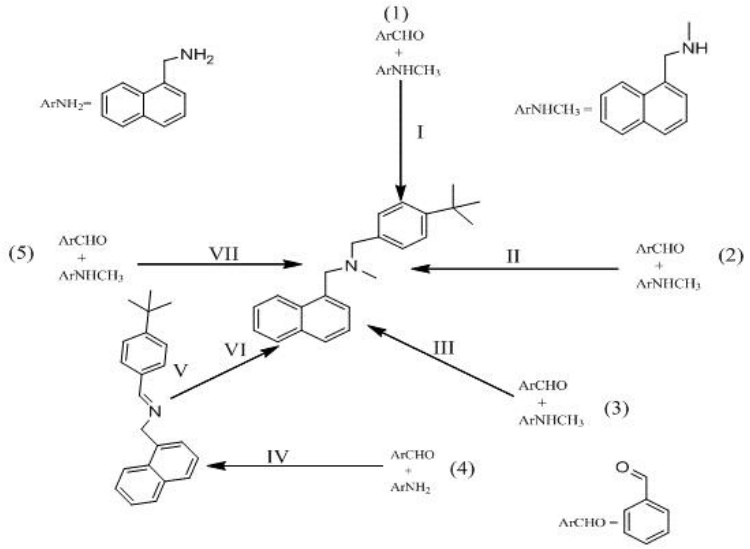
Butenafine is composed of a central nitrogen atom, to which a methyl group, a tert-butyl benzyl group and a methyl naphthalene group are attached. It is synthesised and crystallised as hydrochloride salt, as shown below [2]:



N-4-tert-butylbenzyl-N-methyl-1-naphthylenemethylaminehydrochloride

Fig. 1: The structure of Butenafine

Most of the syntheses of Butenafine reported in the literature adopted reductive amination, using sodium cyanoborohydride ($NaBH_3CN$) as the reducing agent in methanol, with approximately 50 - 95 % yield [2]-[5]. However, there exist other approaches that employed the use of different reagents. The following scheme summarised few of the approaches to the synthesis of Butenafine from its major precursors [2]-[7]:



Key:

(I) 0.3 eq. $B_{10}H_{14}$, MeOH, r.t, 05-12h

(II) 3eq. $NaBH_3CN$, sat. NH_4OAC in EtOH/30% aq. NH_3 (5:2), reflux, 18h

(III) 1.2 eq.$NaBH_4$, 2,2,2-trifluoroethanol, 40^{o}C,1-30 min.

(IV) MeOH, r.t., ~3h, 1.6 eq. $NaBH_4$, 10-15 min.

(V) 1.3-1.6 eq, $NaBH(OAc)_3$, 1-2eq. ACOH, DCE or THF, r.t., 0.5-75h

Fig. 2: Synthesis of Butenafine by various approaches of reductive amination

Approach 2 was reported more often in the literature and the reasons given for this choice were its simplicity and high yield (ca.95%) [2]-[4]. However, the $NaBH_3CN$ used in the approach is very toxic; it releases toxic gases, such as HCN to the surrounding and above all, it has the risk of contaminating the product with cyanides. In addition, the approach is time consuming, when compared to approach 4 [5]. Owing to the reagents in the process, approach 4 may be simpler, cheaper, safer and even faster.

Over the years researchers have been exerting efforts on the structure-activity properties of Butenafine in relation to other antifungal agents; however, only little or no effort was recorded on the substituents attached to the aromatic systems in the drug.

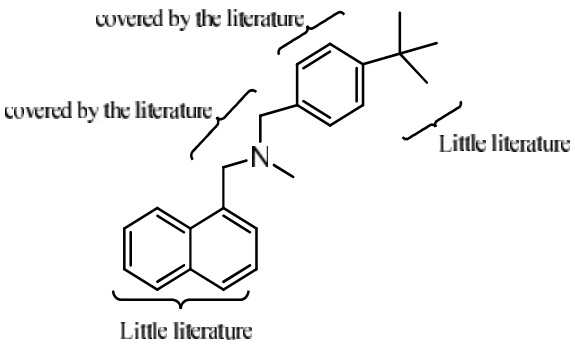


Fig. 3: Parts of Butenafine covered by literature

The researches carried out so far on the pharmacological activity of Butenafine indicated that it is potent over a wide range of fungal infections; however, its activity towards *candida spp.* is very weak [8]. Production of Butenafine, with an improved activity, by substituting the 3-phenyl-2-propenyl moiety in Naftefine with 4-tert-butyl benzyl group is an important indicator of the importance of this benzyl group in Butenafine [8]; changing it may lead to loss of activity. Other researches stressed on the importance of the methyl group on the central nitrogen atom as well as the importance of the hydrogen atoms within the vicinity of the central nitrogen [2], [3].

In this research, the naphthalene derivative of the drug is substituted with benzyl derivative so that the potency of the resulting analogue can be tested by future researchers. Alongside the synthesis, the use of sodium borohydride ($NaBH_4$) as a reducing agent was compared to the use of sodium triacetoxyborohydride (STAB) in reductive amination. Various solvents were usesssd for the synthesis to identify the one that gives a product with high purity and a better yield.

2. EXPERIMENTAL DETAILS

2.1 General Comment

All chemicals were purchased from Sigma Aldrich, Acros Organics, Alfa Aesar or Fluka Chemicals and they were used as supplied by these commercial sources. All reactions were carried out under nitrogen environment, because of the high affinity of amines to moisture and the hygroscopic property of sodium triacetoxyborohydride [9]. Except otherwise stated, all the reactions were monitored by Thin Layer Chromatography; TLC (Petrol/Ether 9:1, visualised in UV light). Melting points were determined by Stuart Hawkesworth melting point machine and were uncorrected. Both proton and carbon-13 NMR were recorded on Bruker 300 or JNM-ECS-400 in a solution phase, using $CDCl_3$ or DMSO-d_6 as a solvent and Infrared spectra were recorded on Varian 800 FT-IR Scimitar series spectrophotometer, using KBr optics.

2.2 General Procedure for Reductive Amination of Aldehydes

2.2.1 The Direct Approach

***2.2.1.1 Method I: Preparation of N-(4-tert-butyl) benzyl)-1-(naphthalen-1-yl) methanamine (3a) and bis(4-(tert-butyl) benzyl) amine(4a)* [5]:**

Tetrahydrofuran (40 cm^3) was added to a well stirred mixture of the aldehyde (10 mmol) and the primary amine (10 mmol), followed by sodium triacetoxyborohydride (3.0 g, 14 mmol) in a round bottom flask (250 cm^3). The resulting milky mixture was stirred at 70 ^oC for 24 hours; the TLC showed no trace of the reactants. The reaction was quenched with saturated $NaHCO_3$ and the product was extracted with EtOAc (3 X 15 cm^3).The combined organic extracts were dried ($MgSO_4$) for 20 minutes. The solvent was evaporated and the products were recrystallized from ethanol as white prismatic crystals.

***2.2.1.2 Method II: Preparation of N-(4-tert-butyl) benzyl)-1-(naphthalen-1-yl) methanamine (3b) and bis(4-(tert-butyl) benzyl) amine (4b)* [5]:**

The procedure and the substrates were same as in method I but the solvent used was acetonitrile. The reaction was completed in 5 hours in respect of product 3b and 4 hours with respect to product 4b. The products were obtained as white powders.

2.2.1.3 Method III: Preparation of N-(4-tert-butyl) benzyl)-1-(naphthalen-1-yl) methanamine (3c) and bis(4-(tert-butyl) benzyl) amine(4c) **[5]:**
The substrates and procedure were same as in Method I except for the use 1, 2- dichloroethane (DCE) as a solvent. Reaction with respect to 3c was completed in 4 hours, whereas the reaction that resulted in 4c lasted for 3 hours. The products were as described in Method II.

2.2.1.4 Method IV: Preparation of bis (4-(tert-butyl) benzyl) amine (4d) **[5]:**
The procedure and the substrates used were as mentioned in the reaction for the formation of 4c, using 1 mmol each of the substrates at 40 ^{o}C, in 4 cm^3 of DCE and the reaction went into completion in 3 hours. The product was as described in Method II.

2.2.1.5 Method V: Preparation of bis (4-(tert-butyl) benzyl) amine (4e) **[10]:**
To a well stirred mixture of the aldehyde (10 mmol) and the amine (10 mmol) was added THF (40 cm^3) followed by sodium borohydride (0.4g, 10 mmol) and silica chloride (5.0 g) in a round bottom flask (250 cm^3). The resulting milky liquid mixture was stirred at room temperature and the reaction was completed in 25 minutes, as indicated by TLC. The catalyst was filtered off. The residue was washed with dichloromethane (2 X 10 cm^3) to extract more of the product. The organic layers were combined and the mixture was concentrated under reduced pressure. The crude (light brown liquid) was purified by column chromatography on silica gel (Petrol/EtOAc, 7:3). The Product obtained was as described in Method I.

2.2.2 The Indirect Approach: Preparation of 3s$^{1\&2}$ and 4s$^{1\&2}$

2.2.2.1 Step I: Preparation of 1-(4-tert-butylphenyl)-1-(naphthalene-1-yl)methanamine (3s^1) and N-(4-tert-butyl benzylidene)-1-(4-(tert-butyl)phenyl-N- methylmathanamine (4s^1) **[5]:**

To a well stirred mixture of the primary amine (10 mmol) and the aldehyde (10 mmol) was added methanol (40 cm^3) in a round bottom flask (250 cm^3) and the mixture was stirred under reflux at 60 ^{o}C for 3 hours. The TLC did not show any trace of the starting materials. 3Å molecular sieves were added to dry the product for 1 hour. The solvent was evaporated in vacuo to give the required aldimine.

2.2.2.2 Step II: Preparation of N-(4-tert-butyl)benzyl)-1-(naphthalene-1-yl)methanamine (3s^2) and bis (4-(tert-butyl) benzyl) amine(4s^2) **[5]*:***

To the product of step 1 (5 mmol) in a round bottom flask (250 cm^3) was added anhydrous methanol (20 cm^3), followed by sodium borohydride; $NaBH_4$ (0.9 g, 24 mmol) and the mixture was stirred at room temperature for 15 minutes. The TLC showed complete conversion of imine to the corresponding amine. The reaction was quenched with 1 moldm^{-3} Sodium hydroxide and the product was extracted from ether (3 X 15 cm^3). The solvent was evaporated under a reduced pressure [1] and all Products were obtained as described in Method I.

2.3 General Procedure for Methylation of Amines: Eschweiler-Clarke Reaction [11]:

To a round bottom flask (25 cm^3), was added the amine (0.5 mmol), the flask was cooled in an ice bath and 88% methanoic acid (0.06 cm^3, 0.07 g, 1.5 mmol) was added slowly, followed by 36% methanal (1.3 mmol, 0.04 g, 0.04 cm^3) and the resulting colourless mixture was stirred under reflux at 80 ^{o}C for 24 hours. 6 moldm^{-3} HCl (0.15 cm^3) was added and the resulting colourless mixture was extracted with ether (5 cm^3). The resulting white precipitate formed in the ether layer which gradually settled in the aqueous layer was filtered off. The white solid product was recrystallized from ether/ethanol (4:2).

3. RESULTS AND DISCUSSION

3.1 Results

The target compound, N-(4-(tert-butyl) benzyl)-1-(4-tert-butyl) phenyl)-N-methyl methanaminium chloride was synthesised from tert-butyl benzyl derivatives in a quantitative yield by reductive amination, followed by methylation of the resulting secondary amine and finally the reaction of the tertiary amine with hydrochloric acid.

Two approaches were used to carry out the reductive amination: the direct approach and the stepwise approach. In each case, the familiar compound (**3**) was synthesised and the observations made

during the process of its synthesis and characterisation were used as precautions in the synthesis of the target compound (**4**). The results obtained from the synthesis of (**3**) and (**4**) are summarised in table 1-4 and those of their characterization are detailed below:

3.1.1 Characterization of the Compounds

N-(4-(tert-butyl)benzyl)-1-(naphthalen-1-yl)methanamine (3): R_f: 0.7; mp: 136-140 ^oC; 'HNMR (300 MHz, $CDCl_3$) δ_H 8.05 (d, 1H, naphthyl-H), 7.85 (d, 1H, naphthyl-H), 7.80 (d, 1H, naphthyl-H), 7.55 (m, 3H, naphthyl-H), 7.50 (d, 1H, naphthyl-H), 7.37 (m, 3H, phenyl-H), 7.35 (m, 2H, phenyl-H), 4.3 (d, 2H, CH_2), 4.0 (d, 2H, CH_2), 2.7 (s, 1H, NH), 1.3 (s, 9H, t-butyl-H); ^{13}C NMR (400MHz, $CDCl_3$) δ_c 151 (Ar), 136 (Ar), 135.5 (Ar), 135 (Ar), 131 (Ar), 129 (Ar), 128 (Ar), 127 (Ar), 126 (Ar), 125.42 (Ar), 125.34 (Ar), 124 (Ar), 52.10 (CH_2), 49.29 (CH_2), 34 (C), 31.33 (t-butyl-CH_3); IR: v_{max} cm^{-1} 2960 (m,C-H), 1518 (s, Ar-C=C), 1396 (s, Ar-C-N), 903 (s), 774 (s), 608 (s); HRMS (ESI) calcd for $[C_{22}H_{25}N+H]^+$ 304.2065, obsd 304.2054.

N-(4-tert-butyl benzyl)-1-(naphthalene-1-yl)methanamine (3s[1]): R_f: 0.5; mp: 65-70 ^oC; 'HNMR (300MHz, $CDCl_3$) δ_H 9.09 (s, 1H, N=C-H) 9.00 (d, J=6, 1H, naphthyl-H), 8.00 (d, 1H, naphthyl-H), 7.95 (t, 3H, naphthyl-H), 7.65 (d, 2H, naphthyl-H), 7.65 (d, 2H, phenyl-H), 7.55 (m, 2H, phenyll-H), 7.37 (m, 1H, phenyl-H), 5.0 (s, 2H, CH_2), 1.36 (s, 9H, t-butyl-H); ^{13}C NMR (MHz 400, $CDCl_3$) δ_c 161.4 (C=N), 149.75 (Ar), 134 (Ar), 131.5 (Ar), 131 (Ar), 129 (Ar), 128(Ar), 127.5(Ar), 127.1 (Ar), 125.4 (Ar), 125.1(Ar), 66. (CH_2), 34 .4 (C), 31.33 (3XCH_3); IR: v_{max} cm^{-1} 2964 (m, N=C-H), 1641 (s,C=N), 1514 (s, Ar-C=C), 1396 (s, Ar-C-N), 774 (s), 578 (s).

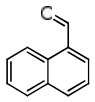
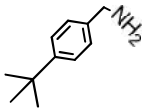
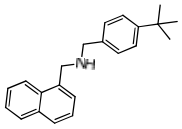
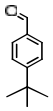
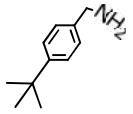
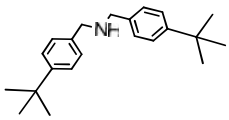
N-(4-(tert-butyl)benzyl)-N-methyl-1-(naphthalen-1-yl)methanaminium (3EW): Yield: 98%; R_f: 0.8; mp: 207-210 ^oC; 'HNMR (300MHz, $CDCl_3$) δ_H 8.05 (d, 1H, naphthyl-H), 7.85 (d, 1H, naphthyl-H), 7.80 (d, 1H, naphthyl-H), 7.55 (m, 3H, naphthyl-H), 7.50 (d, 1H, naphthyl-H), 7.37 (m, 2H, phenyl-H), 7.35 (m, 2H, phenyl-H) , 4.8 (dd, J=3, 1H, CH_2), 4.6 (dd, J=3, 1H, CH_2), 4.3 (dd, J=3, 1H, CH_2), 4.0 (dd, J=3, 2H, CH_2), 2.54 (s, 3H, N-CH_3), 1.3 (s, 9H, t-butyl-H); ^{13}C NMR(400MHz, $CDCl_3$) δ_c 153 (Ar), 134 (Ar), 132 (Ar), 131 (Ar), 130.5 (Ar), 129 (Ar), 128 (Ar), 127 (Ar), 126 (Ar), 125.42 (Ar), 125.34 (Ar), 124 (Ar), 59.80 (CH_2),54.00 (CH_2), 38 (N-C), 34 (C), 31.33 (t-butyl-CH_3); IR: v_{max} cm^{-1} 2964 (m,C-H), 2534 (m.b.p, NH^+), 1473(s, Ar-C=C), 908 (s), 798 (s), 575 (s); HRMS (ESI) calcd for $[C_{23}H_{27}N+H]^+$ 318.2222, obsd 318.2220.

Bis(4-(tert-butyl) benzyl)amine (4): R_f: 0.9; mp: 180-182 ^oC; 'HNMR (300MHz, $CDCl_3$) δ_H 7.40-7.50 (m, J=15, 8H, Ar-H) ,3.6 (s, 4H, CH_2), 2 (s, 1H, NH), 1.3 (s, 18H, t-butyl-H); ^{13}C NMR(400 mhz, $CDCl_3$) δ_c 149 (Ar), 136.8 (Ar), 128.2 (Ar), 125 (Ar), 57.5 (CH_2), 34.41 (C), 31.3 (t-butyl-C); IR: v_{max} cm^{-1} 2958 (m,C-H), 1512 (s, Ar-C=C), 905 (s), 816 (s), 722 (s); HRMS (ESI) calcd for $[C_{22}H_{31}N+H]^+$ 310.2535, obsd 310.2522.

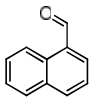
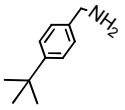
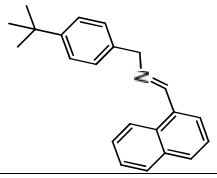
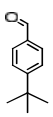
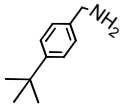
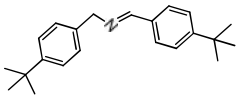
N-(4-tert-butyl) benzylidene)-1-(4-(tert-butyl)phenyl) methanamine (4s[1]): R_f :0.9; mp: 77-80 ^oC; 'HNMR (300MHz, $CDCl_3$) δ_H 8.39 (s, H-C=N), 7.75 (d, J=(15, 2H, Ar-H), 7.50 (d, J=15, 2H, Ar-H), 7.40 (d, J=15, 2H, Ar-H) , 7.3 (d, J=15, 2H, Ar-H), 4.85 (s, 2H, CH_2), 1.35 (s, 9H, t-butyl-H), 1.33 (s, 9H, t-butyl-H); ^{13}C NMR (400MHz, $CDCl_3$) δ_c 161.7 (C=N), 153 (Ar), 149.7 (Ar) 136.4 (Ar), 133.5 (Ar), 128.0 (Ar), 127.6 (Ar), 125.4 (Ar), 125.3 (Ar), 64.74 (CH_2), 34.86 (C) 34.42 (C), 31.35 (t-butyl-C), 31.19 (t-butyl-C); IR: v_{max} cm^{-1} 2963 (m, C-H), 1642 (s, C=N), 1501 (s, Ar-C=C), 829 (s), 643 (s), 559 (s); HRMS (ESI) calcd for $[C_{22}H_{30}N+H]^+$ 308.2378, obsd 308.2367.

N-(4-(tert-butyl) benzyl)-1-(4-tert-butyl) phenyl)-N-methyl methanaminium (4EW): Yield: 75%; R_f: 0.9; mp: 180-182^oC; 'HNMR (300MHz, $CDCl_3$) δ_H 7.40-7.50 (m, J=15, 8H, Ar-H), 4.2 (s, 4H, CH_2), 1.7 (s, 1H, N-CH_3), 1.3 (s, 18H, t-butyl-H); ^{13}C NMR (400MHz, $CDCl_3$) δ_c 153 (Ar), 131 (Ar), 127 (Ar), 126 (Ar), 56 (CH_2), 35 (C), 31.17 (t-butyl-C); IR: v_{max} cm^{-1} 2958 (m,C-H), 2460 (m.b.p, NH^+), 1513 (s, Ar-C=C), 1224 (s, C-N), 931 (s), 817(s); HRMS (ESI) calcd for $[C_{23}H_{33}N+H]^+$ 324.2691, obsd 324.2693.

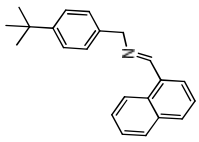
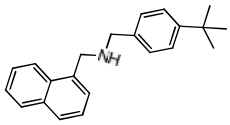
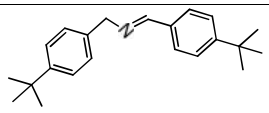
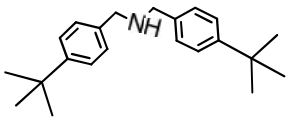
227 **Table 1. Reductive Amination (Direct Approach)**

Entry	Reactants		Product (Secondary Amine)	Colour and Physical State	Method	Time, hrs	Yield, %
	Aldehyde	Primary Amine					
3a				White solid	I	24	13
3b					II	05	24
3c					III	04	29
4a				White solid	I	24	09
4b					II	04	19
4c					III	03	23
4d					IV	03	75
4e					V	0.4	50

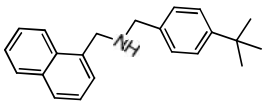
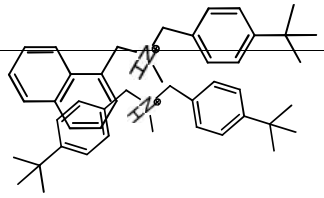
228
229
230 **Table 2. Preparation of Imines in Methanol (Step I)**

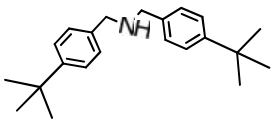
Entry	Reactants		Product (Imine)	Colour and Physical State	Time, hrs	Yield, %
	Aldehyde	Primary Amine				
$3s^1$				Yellow oil	03	73
$4s^1$				Brown solid	02	62

231
232 **Table 3. Reduction of Imines to Amines by Sodiumborohydride (Step II)**

Entry	Reactant (Imine)	Product (Secondary Amine)	Colour and Physical State	Time, hrs	Yield, %
$3s^2$			White solid	03	73
$4s^2$			White solid	02	99

233
234 **Table 4. Methylation of the Secondary Amines by Eschweiler-Clarke Reaction**

Entry	Substrates		Product (Methanaminium derivative)	Time, hrs	Yield, %
	Aldehyde	Amine (Secondary Amine)			
3EW				24.5	98

	CH_2O				
4EW	CH_2O			24.5	75

3.2 Discussion

3.2.1 Reductive Amination (The Direct Approach)

This involves *in situ* reduction of an aldehyde by reacting with a primary amine in the presence of a reducing agent in the same reaction vessel [5].

Despite that the three polar aprotic solvents used in carrying out the reactions are all inert towards the substrates; it could be argued that reductive amination is faster in DCE, with a better yield than in acetonitrile, which appeared with a better result than THF, although the yields were generally poor.

Considering the condition for these reactions, the reason for good solvent activity of DCE might be attributed to its good azeotropic property with water (68% by weight at 70 ^{o}C), which is a good property in driving off water during imine formation and as such, contribute in driving the reaction to completion [12]. Acetonitrile also possesses this azeotropic property with water, but the temperature and percentage by weight of its azeotropic property are 76 ^{o}C and 83.7% respectively [13]. Tetrahydrofuran (THF) on the other hand, possesses this property at 63 ^{o} C but with the highest weight percentage (95%) [14].

Since the volumes of the three solvents used were uniform in each case, the differences in the rate of their azeotropic properties, particularly the percentage composition, could be the reason for the faster reaction and higher yield associated with the use of DCE.

In an attempt to improve the yield, after varying the substrates, the temperature, as well as the solvents, the idea that STAB decomposes at 50 ^{o}C brought about a concern for reducing the temperature to 40 ^{o}C. This gave a better yield without affecting the reaction time. This suggests that at temperatures higher than 50 ^{o}C, as a result of STAB decomposition, side reaction occurs, instead of reductive amination of the targeted substrates, as illustrated (Fig. 4) below:

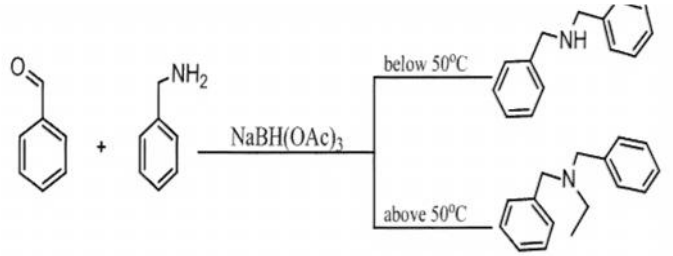


Fig. 4. Side reaction by decomposition of sodium triacetoxyborohydride at temperatures above 50 ^{o}C

The need for a faster reaction brought about the direct approach, using $NaBH_4$ (see entry **4e**). The reaction was carried out using the same concentration of substrates as in all other entries, in the presence of silica chloride as a catalyst, at room temperature [10]. The reaction went into completion in 25 minutes, as indicated by the TLC and the yield was not too poor (50%). As a surface active agent, the silica chloride might have sped up the reaction as follows (Fig. 5):

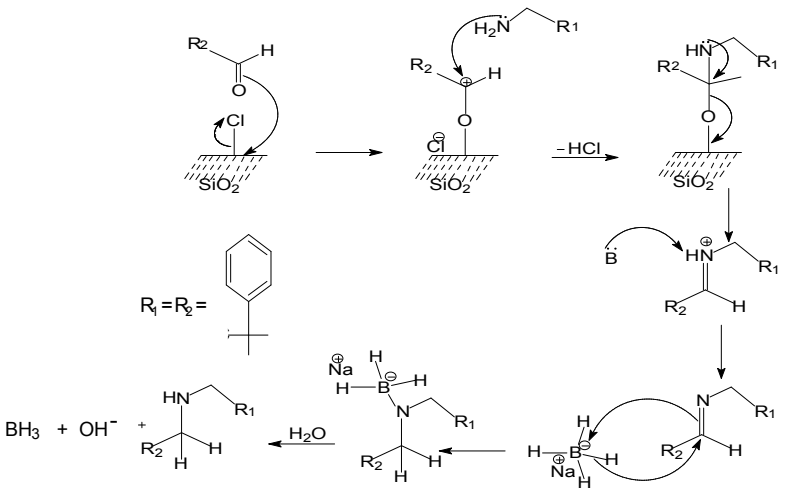


Fig. 5. Mechanism for silica chloride catalysed reductive amination

3.2.2 The Step-wise Approach

This involves reaction of aldehyde and amine in a suitable solvent, such as methanol to form imine followed by the reduction of the imine using a suitable reducing agent, such as $NaBH_4$ to give an amine.

In most cases the reaction is *in situ*, because of the difficulties involved in isolating the imine. Therefore the reaction involves two steps that can be carried out separately, in the same vessel.

3.2.2.1 Step I

This reaction was carried out in methanol under reflux at 60 ^{o}C for 3 hours not the room temperature proposed by Abdel-Magid and co-workers [5]. This is to drive the reaction to completion in favour of imine. 3Å molecular sieves were applied to remove water, so as to prevent the reverse reaction.

The reaction of the substrates in entry **4s**[1] appeared to be faster than substrates in entry **3s**[1]. This may likely be brought about by the activation property of the tertiary butyl group attached to the ring at the *para* position of benzaldehyde. Due to the ability of the tertiary carbon atom to be involved in hyper conjugation with the adjacent carbon in the ring, it reduces electron density on the carbonyl carbon and hence increases its δ+ and therefore speed up the nucleophilic attack that comes from the amine group. This factor could be responsible for driving the reaction faster, in entry **4s**[1].

Characterisation of the resulting products in table 2 actually indicated the presence of the imine functionality. The proton NMR of all the products obtained, showed peaks with chemical shifts between 8.45 and 9.0 ppm (s, H-C=N) with the corresponding deshielding of one of the two CH_2 and the loss of the peaks of the other in compound **3**. The target molecule being symmetrical with the peaks of all tertiary butyl protons as well as the aromatic protons having almost the same chemical shifts in its amine form, appeared with slightly different chemical shifts in product **4s**[1], with the groups adjacent to the imine (C=N) in the downfield because they have become more desheilded, whilst the other protons maintained their initial positions.

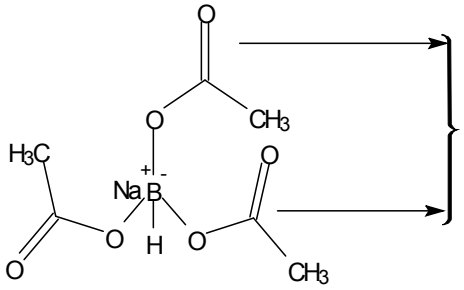
The ^{13}CNMR spectrum of **4s**[1] shows additional peak with a chemical shift around 161 ppm in addition to the first peak in the aromatic region of its amine form. This is a good example of the existence of sp^2 hybridised carbon, adjacent a more electronegative element, such as nitrogen.

The IR spectra of all the products obtained in table 2 above have strong peaks at wave number 1642 to 1645 cm^{-1}, indicating C=N bend in addition to the peak at 2962 to 2965 cm^{-1} (s, H-C=N stretch). This is another supporting evidence for the existence of imine functional group. Furthermore, the EIS-MS of all the imine products obtained above indicated the presence of the imine functional group by having a 2 units decrease in m/z with the corresponding increase in the double bond equivalence (DBE) by 1unit.

3.2.2.2 Step II

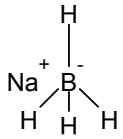
The excellent reducing property of sodium borohydride was clearly shown in the reduction of amines in this step, although in the presence of residual aldehyde, a mixture of alcohols and amine are obtained as products. As a result of this, for the *in situ* process of this indirect approach, complete conversion of the aldehydes must be ensured before introducing sodium borohydride into the reaction vessel.

This excellent reducing property of $NaBH_4$ can be attributed to possession of strong hydride ion in the absence of a species that may share the electron density on the hydride, as it is the case with $NaBH_3CN$ and $NaBH(OAc)_3$ (fig. 6a-b).



These groups make it a selective and a milder reducing agent by the virtue of their electronic and stearic effects.

(a) $NaBH(OAC)_3$: Sodium triacetoxyborohydride



No group that may reduce the nucleophilicity of the hydride

(b) $NaBH_4$: Sodium borohydride

Fig. 6: Selectivity in Sodium triacetoxyborohydride

From the results above (Table 3), $NaBH_4$ can be regarded as a convenient reducing agent for reductive amination. Its reaction occurs in a shorter time with a higher yield. In each case, the products were extracted accordingly; the NMR, the IR and the HRM (ESI) spectra indicated the presence of compounds **3** and **4.** The aromatic peaks were observed as multiplets at chemical shift (7.50-7.40 ppm), with the peak for the CH_2 (X2) appearing as singlet (exactly at 4.2 ppm). This is a good indication for the presence of symmetrical molecule and deshielded C-H protons. The presence of the N-H can be seen by the peak with a chemical shift 1.7 ppm (br, s), which is almost agreeing with 1.76 ppm reported by Yu et al [15]. The IR spectrum U_{max} 2958, 1513 and 1224 cm^{-1} for C-H stretch, aromatic C=C bend and C-N bend respectively and the m/z: 324.2693 recorded by EIS-MS supported the NMR in respect of the target compound (4EW).

3.2.3 Methylation of Amines (Eschweiler-Clarke reaction)

Characterisation of the products obtained in table 4 gave clear indications for the presence of the targeted compounds. A new peak was observed between chemical shift1.5 to 2.5 ppm in the proton NMR spectra of the methylated products, which was not there before methylation. This is a clear indication of the presence of such methyl group on the central nitrogen atom.

The carbon-13 NMR spectra of all the products in table IV indicated an increase in the number of the types of carbon atoms by one, which was clearly visible between chemical shifts 36 and 39.0 ppm.

The IR spectra of all these products (table 4) indicate the presence of this methyl group by the presence of an additional strong peak of C-H stretch around wave number 2958 to 2962cm^{-1}, in addition to a very strong broad peak (multiple band peak) for the presence of ammonium ion (i.e.-NH^{+}) appearing with a wave number between 2400 to 2500 cm^{-1}. The EIS-MS m/z of all these products indicated the presence of this methyl group by having a difference of 14 from the ones found in their corresponding non methylated analogues.

4. CONCLUSION

This research indicated that N-(4-(tert-butyl) benzyl)-1-(4-tert-butyl) phenyl)-N-methyl methanaminium chloride, a butenafine analogue can be synthesised from tert-butyl benzyl derivatives in a good yield by reductive amination that is followed by Eschweiler-Clarke-methylation reaction. With respect to the atmospheric condition at hand during the research, this work has indicated that reductive amination (direct approach) gives a better yield in a shorter time with DCE at 40 ^{o}C than with other solvents tested (Table 1). It was obvious that sodium borohydride as a reducing agent used in the step wise approach gives a better yield, with high purity in a shorter time than sodium triacetoxyborohydride, despite its selectivity (Table 3). It has also become apparent that substituting one of the rings in naphthaldehyde by a tert-butyl group increases the reactivity of the molecule, because doing so reduces the extent of conjugation. Although the yield is good and the reaction is clean, there is need for alternative to Eschweiler-Clarke, because the traditional method is too time consuming.

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