Reaction Parameters for the Synthesis of $N,N$-Dimethyl Fatty Hydrazides from Oil

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Abstract: Hydrazide derivatives have been synthesized from methyl esters, hydrazones and vegetable oils. They are important due to their diverse applications in pharmaceutical products, detergents as well as in oil and gas industries. The chemical synthesis of fatty hydrazides is well-established; however, only a few publications described the synthesis of fatty hydrazide derivatives, particularly, when produced from refined, bleached and deodorized palm olein. Here, the synthesis and characterization of $N,N$-dimethyl fatty hydrazides are reported. The $N,N$-dimethyl fatty hydrazides was successfully synthesized from fatty hydrazides and dimethyl sulfate in the presence of potassium hydroxide with the molar ratio of 1:1:1, 6 hours reaction time and 80°C reaction temperature in ethanol. The product yield and purity were 22% and 89%, respectively. The fatty hydrazides used were synthesized from refined, bleached and deodorized palm olein with hydrazine monohydrate at pH 12 by enzymatic route. Fourier transform infrared, gas chromatography and nuclear magnetic resonance (NMR) spectroscopy techniques were used to determine the chemical composition of $N,N$-dimethyl fatty hydrazides. Proton NMR confirmed the product obtained were $N,N$-dimethyl fatty hydrazides.

Key words: fatty hydrazides, $N,N$-dimethyl fatty hydrazides, dimethyl sulfate and potassium hydroxide

1 INTRODUCTION

Hydrazides, R-CO-NHNH$_2$ are the acylated derivatives of hydrazine which possess a nitrogen functional group attached to a nitrogen covalent bond tied together with an acyl group. Hydrazides were first mentioned in the literature in 1895. To date, many methods have been developed for preparation of hydrazides. There are several reports highlighting hydrazides prepared by chemical route from methyl esters, hydrazones and nontraditional oils such as neem oil, rice bran oil and karanja oil. In addition, many studies have shown that hydrazides can also be prepared by enzymatic route such as from benzoic acid, palm oil, fatty acid methyl esters as well as directly from vegetable oils i.e., olive oil, sesame oil and corn oil. Hydrazides are important starting materials as well as intermediates in organic synthesis due to their high reactivity.

Many N-alkylation methods have been reported by Salvatore and co-workers, 2001. $N$-methylated amines hold critical importance in amine chemistry. Recently, Badr and co-workers (2010) reported direct $N$-methylation of primary amines using dimethyl sulfate with 80% yield. They used methyl ester as a starting material to prepare the hydrazide. Then, $N,N$-dimethyl acyl hydrazide was synthesized as intermediate in preparation of cationic gemini surfactants.

Dimethyl sulfate or Me$_2$SO$_4$ has been produced commercially since 1920s. It is used mainly as a methylating agent for converting active-hydrogen compounds such as phenols, amines and thiols to the corresponding methyl derivatives. It has also been used in the production of pharmaceuticals and as a quaternizing agent in dyestuffs manufacture. By using dimethyl sulfate, methyl transfer is occurring via an $S_n2$ reaction. Methyl sulfate is preferred because of its low cost and high reactivity compared to methyl halides, for instance methyl iodide.

This paper focuses on the synthesis of $N,N$-dimethyl fatty hydrazides from fatty hydrazides. To obtain the...
product, several parameters such as effect of potassium hydroxide (KOH) loading, temperature, reaction period and solvent were studied.

2 MATERIALS AND METHODS

2.1 Materials

Fatty hydrazides were obtained from Malaysian Palm Oil Board. The fatty hydrazides used were synthesized from refined, bleached and deodorized palm olein with hydrazine monohydrate at pH 12 by enzymatic route (15). The compositions of the fatty hydrazides were palmitic acid, stearic acid, palmitoyl hydrazide, oleyl hydrazide and stearyl hydrazide. Dimethyl sulfate and KOH were purchased from Merck, Germany. Dioxane was obtained from Fluka, Switzerland. Absolute ethanol was purchased from John Kollin Corporation, United Kingdom. Chloroform was obtained from Fisher Scientific, United Kingdom. All solvents used in this study were of analytical grade with 99.5% purity.

2.2 Synthesis of N,N-dimethyl fatty hydrazides

Fatty hydrazides (2.8 g, 0.01 mol) and dioxane (20 mL) were placed into a 250 mL reaction vessel, stirred and heated under reflux to dissolve the fatty hydrazides. Then, dimethyl sulfate (0.95 mL, 0.01 mol) was added gradually into the reaction vessel. After 10 minutes of stirring, KOH (0.56 g, 0.01 mol) was added into the mixture. The reaction mixture was stirred and heated under reflux condition at 100°C for 6 hours. The product was washed with water (100 mL) and filtered. Then the product was dissolved in absolute ethanol (100 mL) at 80°C and left at room temperature (25°C) for precipitation process. This procedure was repeated twice. The mixture was filtered off using vacuum filter. The white solid product (22% yield) was kept dry in a desiccator over silica gel to avoid further moisture absorption. Scheme 1 shows the equation of reaction.

2.3 Characterization

2.3.1 Fourier Transform Infrared (FTIR) Spectroscopy

Nicolet Magna-IR 550 spectrometer series II FTIR by Nicolet Instrument Corporation, USA was used to record the FTIR spectra in the range of 650 - 4000 cm⁻¹, using 64 scans with a resolution of 6 cm⁻¹. The spectra were used to identify the presence of functional groups and the structural characteristics of all compounds produced. Samples were analyzed by grinding with potassium bromide (KBr) powder and pressing into a disc prior to the analysis.

2.3.2 Gas Chromatography (GC)

GC analyses were performed using HP5890 Series II equipped with 7673 Series autoinjector from Hewlett-Packard, USA. Chromatography separation was achieved with the aid of Phenomenex ZB-HT5 Zebron inferno column (30 m × 0.25 mm × 0.25 μm). The GC was operated in the split injection mode using a 50:1 split ratio while maintaining the injector temperature of 350°C. In order to improve the volatility, selectivity, sensitivity and separation of the amines, silylation technique was used according to Kataoka (1996). In this study, N,O-bistrifluoroacetamide was the silylating agent whereby hydrogen of the carboxylic acid, amide and amine groups were replaced with tri-methylsilyl group. The sample was dissolved in dichloromethane, dimethyl formamide and N,O-bistrifluoroacetamide. Then, 1 μL of the mixture was injected into the GC column with initial oven temperature of 170°C. The oven temperature was programmed at 6°C/min until 350°C. Flow rate of the carrier gas helium was 0.8 mL/min. The temperature of flame ionization detector was set at 380°C.

2.3.3 Nuclear Magnetic Resonance (NMR) Spectroscopy

1H NMR spectra of N,N-dimethyl fatty hydrazides was recorded using FT-NMR spectrometer model JMT-500/54/SS from JEOL USA, Inc at 500 MHz using pyridine as a solvent.

3 RESULTS AND DISCUSSION

3.1 Effect of KOH loading

The reaction of fatty hydrazides and dimethyl sulphate was carried out at 100°C in dioxane under reflux for 6 hours in the presence of various amounts of KOH i.e., 0.000, 0.003, 0.005, 0.010 and 0.020 mol, respectively.

3.1.1 FTIR analysis

Figure 1 shows the effect of KOH on the formation of N,N-dimethyl fatty hydrazides. The FTIR spectrum of fatty hydrazides shows absorption bands for the primary amine N-H stretching at 3318.8 and 3291.2 cm⁻¹ wavenumbers, while at 3180.4 cm⁻¹ wavenumbers, the absorption band of secondary amine N-H stretching was observed. The absorption bands of the amide carbonyl C=O stretching and the

$\text{N}(1)$ \hspace{1cm} $\text{N}(2)$

R-C-NH$_2$ + (CH$_3$)$_2$SO$_4$ + KOH $\xrightarrow{\Delta}$ R-C-NH-N(CH$_3$)$_2$ + KHSO$_4$ + H$_2$O

Scheme 1 Synthesis of N,N-dimethyl fatty hydrazides.
primary amine N-H bending appeared at 1630.8 and 1537.0 cm\(^{-1}\) wavenumbers respectively. The formation of \(N,N\)-dimethyl fatty hydrazides was monitored by the presence of N-H stretching for the secondary amide at frequency of 3226-3230 cm\(^{-1}\) wavenumbers, amide carbonyl C=O stretching at frequency 1600 cm\(^{-1}\) wavenumbers and C-N stretching of amine at a frequency in the region of 1032-1120 cm\(^{-1}\) wavenumbers. In addition primary amine N-H stretching and N-H bending disappeared after formation of the desired product. The FTIR spectrum of \(N,N\)-dimethyl fatty hydrazides prepared in the absence of KOH shows a weak absorption band of primary amine N-H stretching at 3344.0 and 3304.1 cm\(^{-1}\) wavenumbers and absorption band for secondary amide N-H stretching at 3211.0 cm\(^{-1}\). The absorption band for the amide carbonyl C=O stretching was at 1606.6 cm\(^{-1}\) wavenumbers. However, the absorption band for the amine C-N stretching was observed at 1031.3 cm\(^{-1}\) wavenumbers.

The disappearance of absorption bands of the primary amine N-H stretching and N-H bending indicated that the reaction occurred at the NH\(_2\) group. However, a weak absorption band of primary amine N-H stretching was observed with 0.003 mol KOH at frequencies 3343.2 and 3293.2 cm\(^{-1}\) wavenumbers. This could indicate that the reaction was not completed with 0.003 mol of KOH and also without KOH. FTIR spectra of \(N,N\)-dimethyl fatty hydrazides prepared with 0.005, 0.010 and 0.020 mol of KOH show the absorption bands of the secondary amide N-H stretching at 3226.2, 3227.5, 3230.0 and 3228.2 cm\(^{-1}\) wavenumbers, respectively. Absorption bands for both stretching and bending of primary amine were not observed. The presence of these absorption bands indicated that the reaction may occur at NH\(_2\). In addition, the absorption bands of C=O stretching of amide carbonyl were observed at 1600.8, 1600.4, 1599.9 and 1600.4 cm\(^{-1}\) wavenumbers. While absorption bands of the amine C-N stretching were observed at 1032.4, 1106.6, 1116.9 and 1120.6 cm\(^{-1}\) wavenumbers.

3.1.2 GC Analysis

GC analysis was used to monitor the formation of the synthesized compound. Standard fatty acids were injected and the fatty acid peaks \textit{i.e.}, caprylic (C8), capric (C10), lauric (C12), myristic (C14), palmitic (C16), oleic (C18:1) and stearic (C18:0) were observed at retention time of 1.39, 1.90, 2.88, 4.50, 5.66, 8.78 and 9.11 min respectively. Figure 2 shows the chromatograms for standard fatty acids, fatty hydrazides and \(N,N\)-dimethyl fatty hydrazides produced using different amounts of KOH. It was observed that the peaks for fatty hydrazides appeared at the retention times of 6.68 to 14.72 min. The five peaks and GC composition of fatty hydrazides at retention times 6.68, 9.14, 9.92, 12.39 and 14.72 were referred to palmitic acid.
Fig. 2  GC chromatograms of (a) standard fatty acids (C8 to C18:0) and C18:1, (b) fatty hydrazides, (ci-ciii) mixtures of fatty hydrazides and N,N-dimethyl fatty hydrazides and (civ-cv) N,N-dimethyl fatty hydrazides. Product produced with molar ratio fatty hydrazides: dimethyl sulfate of 1:1 in dioxane at 100°C for 6 hours.

By increasing the amount of KOH to 0.010 and 0.020 mol, it was observed that fatty hydrazide peaks fully disappeared from the chromatogram. These results showed that 0.010 mol of KOH was sufficient to obtain the required product. There were three peaks for N,N-dimethyl fatty hydrazides which may indicated that dimethylation occurred at palmityl hydrazide, oleyl hydrazide and stearyl hydrazide.

(5.11 %), stearic acid (6.29 %), palmityl hydrazide (32.35 %), oleyl hydrazide (46.88 %) and stearyl hydrazide (9.37 %). While peaks for N,N-dimethyl fatty hydrazides were observed at retention times of between 24.68 and 28.18 min. As the amount of KOH increased, the intensity of the fatty hydrazide peaks decreased indicating diminishing of starting material.
Reaction Parameters for the Synthesis of N,N-Dimethyl Fatty Hydrazides from Oil

J. Oleo Sci. 64, (1) 41-49 (2015)

The result is in agreement with a previous study carried out by Badr et al. (2010) in which the synthesis of N,N-dimethyl fatty hydrazides was carried out in the presence of KOH. Moreover, the reaction requires a stoichiometric amount of a base and produces a stoichiometric amount of inorganic salt which need to be disposed of. In this study, the amount of KOH required was the same as the amount of fatty hydrazides and dimethyl sulphate which was at 0.010 mol. Based on these observations, the reaction with 0.010 mol of KOH was used to further investigate the effect of other parameters in order to optimize the reaction.

3.2 Effect of temperature

In order to study the optimum reaction temperature in synthesizing the N,N-dimethyl fatty hydrazides, reactions were carried out in temperatures between 80°C and 100°C for 6 hours.

3.2.1 FTIR analysis

Figure 3 shows the effect of increasing temperature on the formation of the desired product. For reactions carried out at 80 and 90°C, there is an absorption band observed at about 3345.0 cm⁻¹ and 3344.0 cm⁻¹ wavenumbers, which corresponds to the N-H stretching of a primary amine. This single absorption band may indicate that the reaction was incomplete. In addition, the absorption band of the secondary amide N-H stretching was observed at about 3227 to 3230 cm⁻¹ wavenumbers at all temperatures 80, 90 and 100°C. However, at 100°C, only a single absorption band of the secondary amide N-H stretching was observed. This result indicated that complete formation of the product was achieved at the reaction temperature of 100°C.

3.2.2 GC analysis

GC analysis was used to monitor the effects of temperature on the formation of the desired product. Figure 4 shows the chromatograms for fatty hydrazides and N,N-dimethyl fatty hydrazides produced at different reaction temperatures. The GC results showed that at temperatures below 100°C, there were still unreacted fatty hydrazides left in the product as indicated by the presence of peaks at retention time of 6.69 to 14.73 min. However, these peaks were not observed in the product produced at 100°C. The product shows peaks in the GC at retention times between 23.87 and 28.20 min. Therefore, the best reaction temperature to produce the desired product was 100°C.

3.3 Effect of reaction time

By using fatty hydrazides and 0.010 mol dimethyl sulphate, the optimum KOH loading and temperature to produce N,N-dimethyl fatty hydrazides was 0.010 mol of KOH at 100°C for 6 hours. Another study was carried out to determine the effect of reaction time by reducing the reaction time from 6 to 3 hours.

3.3.1 FTIR analysis

The effects of reaction time on the reaction between fatty hydrazides, dimethyl sulfate and KOH with the molar...
ratio 1:1:1 at 100°C is depicted in Fig. 5. It was observed that the FTIR spectra for \textit{N,N}-dimethyl fatty hydrazides prepared at reaction times from 3 to 6 hours show absorption bands of the secondary amide N-H stretching, the amide carbonyl C=O stretching and the amine C-N stretching. GC analysis was used to determine the optimum reaction time to produce the desired product.

3.3.2 GC analysis

Based on GC analysis as illustrated in Fig. 6, it was observed that peaks for fatty hydrazides fully disappeared at the reaction period of 6 hours. While at the reaction period less than 6 hours, there were several peaks for fatty hydrazides at retention time 6.67, 9.11, 12.28 and 14.69 min. It can be concluded that the reaction has to be carried out at 100°C for 6 hours in order to complete the reaction.

3.4 Effect of solvent

The use of aprotic solvents for \textit{N}-alkylations has received considerable attention because of the interesting level of chemoselectivity and environmental compatibility as well as the simplicity of the procedure\textsuperscript{18, 19}. In this study, three solvents with different polarity were used to synthesize
Reaction Parameters for the Synthesis of N,N-Dimethyl Fatty Hydrazides from Oil

The chosen solvents were dioxane (polar aprotic), chloroform (moderately polar) and ethanol (polar protic). The reactions were carried out at the molar ratio of 1:1:1 of fatty hydrazides, dimethyl sulphate and KOH at boiling temperatures of the respective solvents for 6 hours i.e., 100°C in dioxane, 61°C in chloroform and 80°C in ethanol.

FTIR and GC analysis were carried out for the products prepared in those three solvents. FTIR results showed that the products have similar absorption bands. GC results also indicated that all products showed the presence of peaks at similar retention times. Therefore it can be concluded that the N,N-dimethyl fatty hydrazides can be prepared either in dioxane, chloroform and ethanol. However, the preferred solvents were chloroform and ethanol as dioxane is a toxic chemical. According to US Environmental Protection Agency and International Agency for Research on Cancer, dioxane is classified as a carcinogenic compound and it is a potential carcinogen to human.

The result obtained for product prepared in ethanol is in agreement with the work by Khan et al. (2002) which showed that alkylation of hydrazides at the N(1) or N(2) atom strongly dependent on the nature of the solvent. In neutral medium, terminal N(2) atom is alkylated whereas, in the presence of a strong base such as sodium or sodium methoxide, alkylation at the internal N(1) atom is favored in aprotic solvents such as ether and benzene, while protic solvents such as ethanol will lead to N(2) substitution. Khan and co-workers had synthesized 2-(2-cyanoethyl)hydrazides from the reaction of hydrazides and acrylonitrile in ethanol for 48 hours.

3.5 1H NMR analysis

Chemical shift for proton NMR (500 MHz) of N,N-dimethyl fatty hydrazides (product produced with molar ratio fatty hydrazides: dimethyl sulphate: KOH of 1:1:1) in pyridine- d5 at 60°C is presented in Fig. 7. Solvent peaks were observed at δ 7.22, 7.59 and 8.73. Proton NMR spectrum of fatty hydrazides showed chemical shift at δ 0.91 (t, CH3), 1.28 (t, -(CH2)2-), 1.86 (t, -CH2-CH2-CONH-), 2.49 (t, -CH2-CONH-), 4.56 (s, -N-(CH3)2) and 10.82 (s, -CONH-).

The peak of two methyl groups at the terminal nitrogen of N,N-dimethyl fatty hydrazides was observed at δ 4.56. Thus, it was confirmed that methylation occurred at terminal nitrogen (N2) of the hydrazides.

4 CONCLUSIONS

N,N-dimethyl fatty hydrazides have been successfully synthesized from fatty hydrazides and dimethyl sulfate, in the presence of KOH. The optimum molar ratio of fatty hydrazides, dimethyl sulphate and KOH was 1:1:1. The complete formation of the product was achieved either in dioxane, chloroform or ethanol at 100°C, 61°C and 80°C respectively for 6 hours of reaction time. However, chloroform and ethanol were preferred to dioxane due to safety.
The disappearance of N-H stretching and N-H bending absorption bands for primary amines in FTIR results showed the formation of the hydrazide derivatives. GC chromatogram of \(N,N\)-dimethyl fatty hydrazides showed three peaks. This result indicated that the \(N,N\)-dimethyl fatty hydrazides may contain a mixture of hydrazide derivatives *i.e.* \(N,N\)-dimethyl palmityl hydrazide, \(N,N\)-dimethyl oleyl hydrazide and \(N,N\)-dimethyl stearyl hydrazide. Proton NMR confirmed the presence of two methyl groups at terminal nitrogen of \(N,N\)-dimethyl fatty hydrazides.

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Reaction Parameters for the Synthesis of N,N-Dimethyl Fatty Hydrazides from Oil

Fig. 7 Proton chemical shift of N,N-dimethyl fatty hydrazides (product produced with molar ratio fatty hydrazides: dimethyl sulfate: KOH of 1:1:1 in ethanol at 80°C for 6 hours).

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