

## Synthesis of Some Capsaicin Analogues Using Fatty and Benzoic Acid- Chlorides

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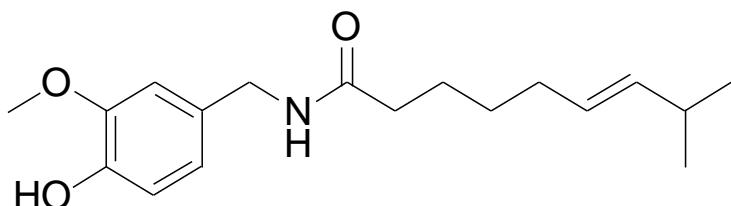
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**Abstract:** Oleoyl, palmitoyl and benzoyl analogues of capsaicin were prepared by coupling the respective acid chlorides with vanillin amine prepared through vanillin-vanillin oxime route. Good yields of between 65-72% were obtained. Products were characterized with the aid of FTIR and GC/MS spectroscopy.

**Keywords:** Synthesis, Capsaicin, analogues, fattyacid, benzoyl

### 1. INTRODUCTION

Capsaicin is a naturally occurring alkaloid found in peppers. It causes a burning sensation when eaten as it activates the TRPV1 protein which occurs throughout the mammalian body [1] and [2].



Capsaicin has three distinct functional groups. The substituted benzene ring (the polar group), the amide group and the hydrophobic chain. The length of the hydrophobic chain alters the pungency of the molecule. The longer the chain the more potent the burning sensation, though there is an optimum length of carbon atom chains beyond which there is no additional potency. Research has indicated that capsaicin has wide ranging biological and physiological activity. Capsaicin and its analogues have antioxidant and anticarcinogenic properties. They are also known for promotion of energy metabolism, suppression of fat accumulation and analgesic properties [2].

However, capsaicin and capsaicinoids possess extensive neurological toxicity and direct irritant effects on skin and mucous membrane [3], hence the need to search for analogues with less undesirable effects. We chose to introduce C-16 and C-18 fragments of palmitic and oleic acid fragments as the hydrophobic chain in our target molecule as opposed to C-9 in capsaicin.

We report here the synthesis of some analogues of capsaicin starting with vanillin conversion to vanillin oxime. Subsequent reduction to vanillin amine with zinc dust and acetic acid and coupling with the acid chlorides of oleic acid, palmitic acid and benzoic acid to yield the respective analogues of capsaicin. To the best of our knowledge, this is the first time that fatty acid analogues of capsaicin were prepared.

### 2. MATERIALS AND METHODS

The infrared spectra were recorded on Shimadzu FTIR-8400S Fourier transform infrared spectrophotometer. The GC/MS were run on Shimadzu GCMS-QP2010-Plus. All liquid chemical compounds used were redistilled before use, but all solid reagents were used with melting points uncorrected. FTIR and GCMS are available if required.

## 2.1. Vanillin Oxime

Hydroxylamine hydrochloride (4.75 g, 0.065mol) and sodium hydroxide (2.60 g, 0.065 mol) was dissolved in 30 mL of 95% ethanol in a 250mL round bottom flask equipped with a reflux condenser. Vanillin (10.00 g, 0.065 mol) was added and the mixture and refluxed for 1hour. A rotary evaporator was used to reduce the volume of the mixture to half its original volume. The resulting solution was allowed to cool to room temperature. The crude crystals formed were filtered and washed with 2 x 5 mL of cold water. The crystals were recrystallized from ethanol. The yield of the vanillin oxime is 9.1g (82.82%), m.p.:118 – 120 °C.

## 2.2. Vanillyl Amine

Vanillyl oxime (10.00g, 0.0598 mol) was dissolved in 10 mL of acetic acid in a 250mL conical flask. The solution was cooled to 15°C in an ice bath and zinc dust (15.7 g, 0.0598 mol) added. The resulting mixture was stirred and allowed to warm to room temperature over 3 hours. Excess zinc was filtered and the filtrate carefully neutralized with ammonia solution. The formed solid was vacuum filtered and washed with 2 x 5mL cold water. The yield of the vanillyl amine is 7.2g (78.57%).

## 2.3. Preparation of Vanillyl Amides

### 2.3.1. Oleoyl Vanillyl Amide

1g (0.006mol) of vanillyl amine was dissolved in 10mL of 10% sodium hydroxide solution (0.28g, 0.007mol) in a 250ml conical flask. 2.15g (2.36mL, 0.007mol) of oleoyl chloride was added about 0.5ml at a time, with constant shaking and cooling in water. The mixture was shaken vigorously for about 8 minutes. The oleoyl chloride derivative was separated from the mixture by adding 10mL of cold water in a separatory funnel. The lower layer was decanted off and the upper layer (the oleoyl vanillyl amide was then washed with 2 x 5 mL of cold water and then 5mL of Sodium sulphate solution. The yield for oleoyl vanillyl amide is 2.2mL (81%). FTIR ( $\text{cm}^{-1}$ , neat): 3300-3400, 2904.89, 1707.06.

### 2.3.2. Benzoyl Vanillyl Amide

Dissolve 1g (0.006mol) of vanillyl amine was dissolved in 10mL of 10% sodium hydroxide solution (0.28g, 0.007mol) in a 250ml conical flask. 0.9839g (0.8132mL, 0.007mol) of Benzoyl chloride was added about 0.5ml at a time, with constant shaking and cooling in a water bath. The shaking was continued vigorously for about 8 minutes. The mixture was filtered and the residue, solid benzoyl chloride derivative, washed with 2 x 5mL of cold water (1.354g, 80.64%, m.p. 54-58°C). After recrystallization from 95% ethanol to give benzoyl vanillyl amide, 1.24g (73.64%), m.p.: 54-56 °C. FTIR ( $\text{cm}^{-1}$ ,  $\text{CHCl}_3$  film) 3390, 1658.84.

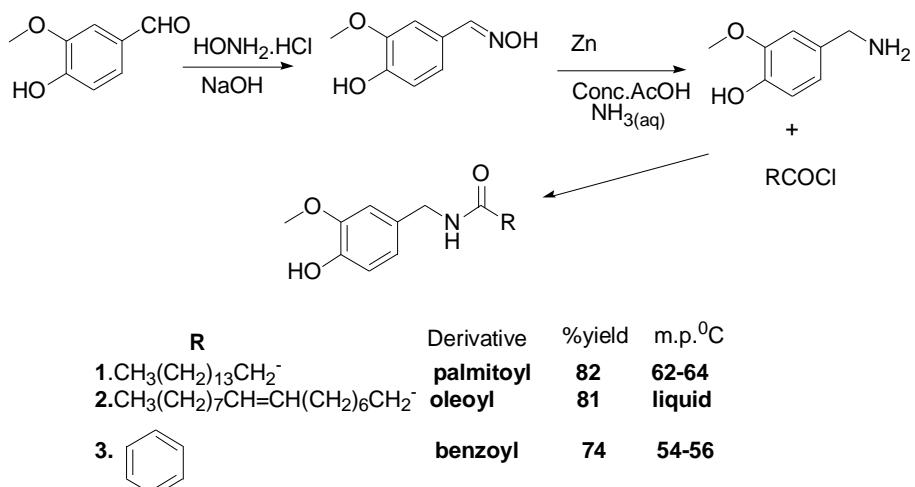
### 2.3.3. Palmitoyl Vanillyl Amide

1g (0.006mol) of vanillyl amine was dissolved in 10ml of 10% sodium hydroxide solution (0.28g, 0.007mol) in a 250ml conical flask. 1.92g (2.11mL, 0.007mol) of palmitoyl chloride was added about 0.5ml at a time, with constant shaking and cooling in a water bath. The resulting mixture was shaken vigorously for about 8 minutes. The mixture was filtered, and the residue washed with cold water (2 x 5mL). Crude yield: (2.34g, 91.39%, m.p 62-66°C). After recrystallization with 95% ethanol: palmitoyl vanillyl amide is 2.10g (82%), m. p. 62-64°C. FTIR ( $\text{cm}^{-1}$ , KBr) 3400, 2900,1650.

## 3. RESULTS AND DISCUSSION

The synthesis of some fatty acyl and benzoyl amide analogues of capsaicin was achieved with good yields (74 – 82%). The oxime was prepared by the reaction of the aldehyde with hydroxylamine hydrochloride in the presence of sodium hydroxide [4]. Zinc dust used for the conversion of oxime to vanillyl amine must be freshly opened or reactivated for the conversion to succeed.

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Abiraj *et al* [5], were the first to report a rapid, selective and simple reduction of oximes to corresponding primary amines using low cost zinc dust and ammonium formate. The conversion was achieved previously with systems like ammonium formate and palladium catalyst systems, but these systems are expensive, dangerous and require long reaction times with low yields [5]. The Schotten-Baumann reaction conditions of amide synthesis that makes use of aqueous sodium or potassium hydroxide solution was employed. Since the acyl chlorides used in this reaction are high molecular weight (long chain) and aromatic, they are suitable for this procedure because they are insoluble in water and do not hydrolyse easily; a slight excess of the acyl chloride is used to compensate for the loss through hydrolysis.

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