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Orginal Research Article

Synthesis of *N*-formyl morpholine as green solvent in the synthesis of organic compounds

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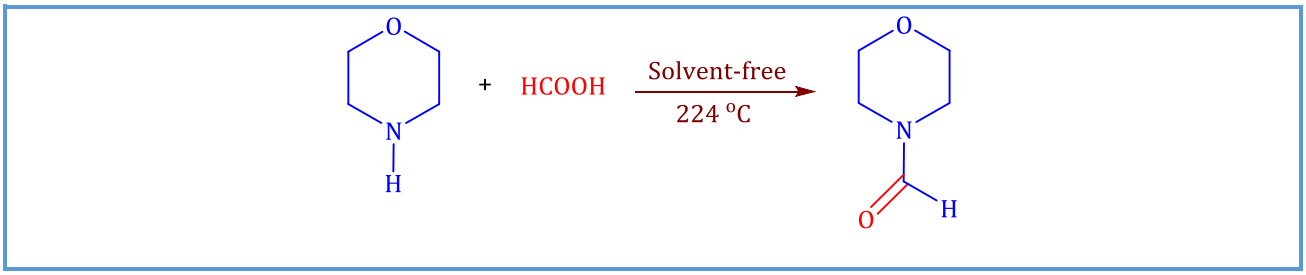
ABSTRACT

Formamides, an important class of the amine derivatives, have widely used in the synthesis of the pharmaceutically valuable compounds. The *N*-formylmorpholine is chemically stable, non-toxic, and non-corrosive, due to its unique structure, aliphatic hydrocarbons, aromatic hydrocarbon and water compatibility, and the dissolved aromatics which greatly reduces the relative volatility of the aromatics. In this research, we evaluate the synthesis of the *N*-formylmorpholine as green solvent from the reaction of the morpholine and formic acid under optimization conditions (Pressure=1 atmosphere and temperature=224 °C) in high yields. This compound was used as the green solvent for synthesis of the heterocyclic compounds.

Graphical Abstract



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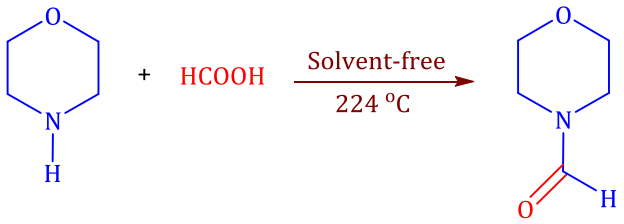
Introduction

Over the last decade, agreat number of pharmaceutical and chemical industries strived to eliminate, replace, recycle or minimize the use of solvents. This effort has been driven by the desire to reduce the human health impacts, process safety risks, and multiple impacts to the environment [1, 2]. The idea of using ‘‘green’’ solvents is the goal to minimize the environmental impact resulting from their use in chemical production and the bio-solvents derived from the renewable resources. Therefore, substitution of the hazardous solvents with the green solvents would be beneficial for the both environment and human [3, 4]. The amide linkage is one of the most significant functional groups in the contemporary chemistry. It is essential to sustain the life, making up the peptide bonds in the proteins and enzymes. It is found in many natural products and in the modern pharmaceutical molecules [5]. Formamides have extensively used in the synthesis of the pharmaceutically valuable compounds such as fluroquinolones [6], substituted aryl imidazoles [7], 1,2-dihydroquinolines [8], nitrogen-bridged heterocycles [9] oxazolidinones [10] and cancer chemotherapeutic agents [11]. They also constitute important precursors in the synthesis of the fungicides and herbicides. Furthermore, *N*-formyl compounds are Lewis bases, which are known as catalyze allylation [12] and hydrosilylation [13] of the carbonyl compounds. The formyl group in combination with a tert-butyl ester group is useful in preparing the highly functionalized peptide derivatives [14]. Variety kinds of methods are available in literature for synthesis of the *N*-formylated product [15–33]. In this study, the *N*-formyl morpholine was synthesized from the reaction of morpholine and the formic acid under the solvent-free conditions at 224 °C (Scheme 1).



Scheme 1. Synthesis of *N*-formylmorpholine

Experimental

Matreials and methods

IR spectra were recorded on a FT-IR spectrometer. IR spectra of the NFM were recorded in thin plates. Solvents, reagents and chemicals were purchased from Aldrich, Fluka and Merck. Also, morpholine was distilled before use.

First procedure for N-formyl morpholine

The procedure for synthesis of *N*-formylmorpholine is three steps as following:

I) The purity of morpholine is recorded 95.34% with GC spectroscopy. The purity of formic acid is 86.4% that was determined via titration with NaOH. To a stirred morpholine 91.38 g (95.34%), was added 63.93 g (86.4%) dropwise in silicon oil bath at 50 °C (Figure 1). After adding all of the formic acid, the mixture was connected to distillation system and increased temperature slowly (Figure 2). The distillation of first drop was occurred at 96 °C and continued until the temperature reached 120 °C. In the first step, the container containing the sample, which contains water and a little bit of unreacted formic acid, is weighed to 33.44 g. materials, was not distilled at this stage.

II) In the second step, the sample container is placed on a hot air bath and we raise it to a range of 198-210 °C and collect the second product, which contains some excess of acid and excess of some morpholin, as well as some NFM product. The second product weight is 17.85 g.

III) In the third step, the temperature increased up to 224-225 °C and the pure NFM product was collected. The product weighed 82.46 g and the pH of the product was neutral and no acid has entered the final product.

The yield of *N*-formyl morpholine is calculated as following:

Considering the total weight of the input materials (Containing 91.38 g of morpholine and 63.93 g of formic acid), a total of 155.31 g of the substance was introduced. The system output consists of 33.44 g (First product) +17.85 g (Second product) +82.46 g (Third product) and totally 133.75 g. Therefore, the amount of waste of the system is equal to:

$$155.31\text{-}133.75=21.56 \text{ g}$$

Because pure NFM is obtained at 82.46 g, and on the other hand, a morpholine mole is removed, so the percentage is equal to:

$$\frac{82.46}{87.12} \times 100 = 94.65\%$$

Figure 1. Mixing stage diagram

Figure 2. Disstilation stage diagram.

Second procedure for N-formyl morpholine

The purity of morpholine is recorded 95.34% with GC spectroscopy. The purity of formic acid is 86.4% that was determined via titration with NaOH. To a stirred morpholine 91.38 g (95.34%), was added 63.93 g (86.4%) dropwise at 50 °C for 2 hours (Figure 3). After addition of the acid, the 10 mL (11.15 g) of mixture was used for the determination of water and acid by GC analyzing. The density of this solution is 1.115 g/mL. After installing the reflux system, the mixture of reaction was heated slowly. The reaction mixture was refluxed at 112 °C. It was then sampled at intervals of one hour and at three points. To prevent the oxygen from being entered to the system, the upper part of the reflux condenser was sealedby an elastic ballon (Industrial nitrogen can be used on a scale) (Table 1).

Figure 3. Reaction stage diagram

Table 1. The collected samples

Sample	Sample description	Density D=g/mL	Sample weight withdrawn from /g the reactor	Amount of water (%)
Sample 1	After completion of adding acid	1.115	11.15	8.84
Sample 2	After completion of adding acid	1.079	10.79	18.27
Sample 3	After completion of adding acid	1.07	10.7	17.67
Sample 4	After completion of adding acid	1.080	10.80	17.68

When the density of the mixture in two sequential sampling is identical, the reaction is completed. In other words, the density of sample 3 (1.07 g/cm^3) and sample density 4 (1.08 g/cm^3) are the same, so it can be concluded that the reaction is completed after 3 h of reflux. At the distillation stage, we raise the temperature gently. Distillation of the first drop occurred at 96 °C. The appropriate temperature to compelet the water distillation, and remove the additional formic acid and non-reacted morpholine and NFM was 210 °C. The distilled compounds weight at this stage was 32.49 g. The pure NFM product was distilled at 200 °C. The weight of the distilled compounds at of 210 °C was 81.82 g. We then distilled it at 224 °C to obtain a pure NFM product. The net weight of the NFM was 79.98 g and the distilled impurities content of 1.78 g were measured.

Figure 4. Reaction and distillation setup

Results and discussion

The *N*-formylmorpholine is a colorless and odorless liquid with chemical formula ($C_5H_9NO_2$), which is mainly used as a solvent for the synthesis of organic matter and as a solvent extraction agent in aromatic units. Under optimal condition, formic acid and morpholine are reacted together with the molar ratio, atmospheric pressure and maximum temperature (224 °C) and *N*-formylmorpholine was produced and purified more than 99.5% after separation and purification. The result of this reaction is given in Table 2. Also, the purity of product is measured by GC spectrum (Figure 5–9).

Table 2. Synthesis of *N*-formylmorpholine under optimal conditions

Essential point	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5 (Product)
Amount of water (%)	8.8387	18.2710	17.6740	17.6794	-
MP (%)	36	2.977	1.436	0.81	0.1281
AF (Titration method)	16.51%	4.26 %	3.116%	1.9%	0.21%
GC (Acid) (%)	23.82	2.419	3.844	2.65	0.2191
NFM (%)	31.09	76.33	76.72	78.28	99.6528
Unknoun (%)	0.2513	0.003	0.0326	0.58	0.00

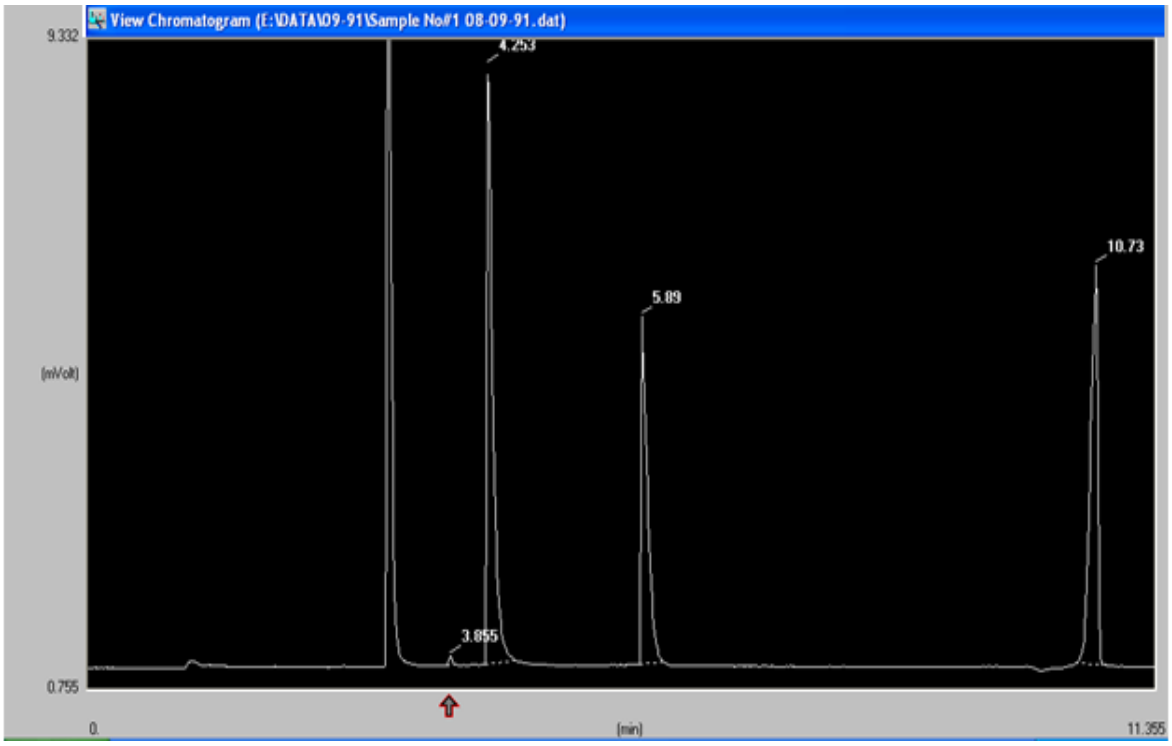


Figure 5. GC spectrum for sample 1

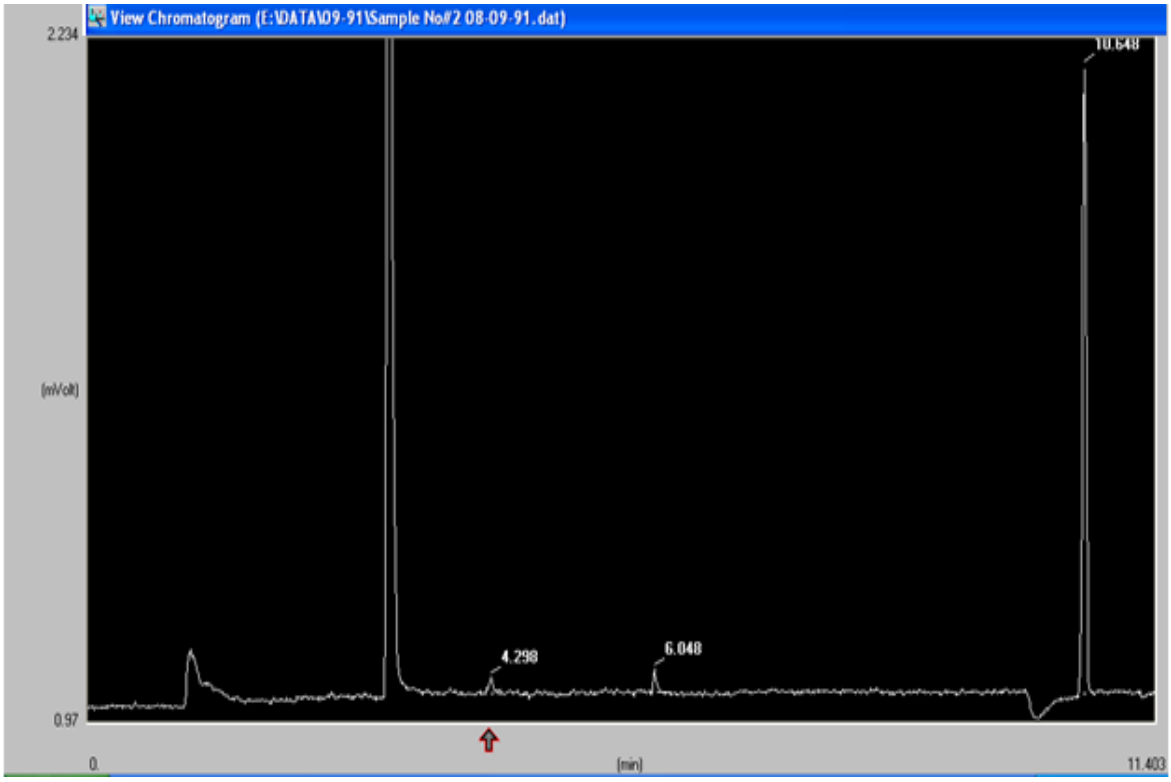


Figure 6. GC spectrum for sample 2

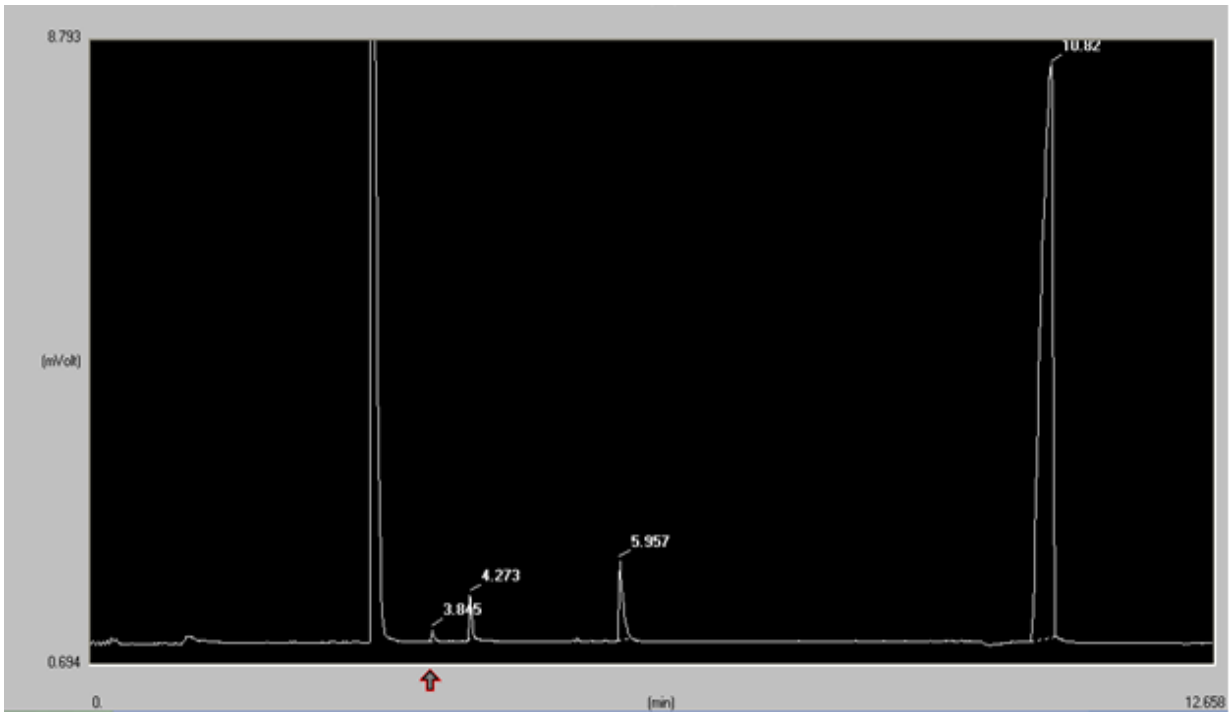


Figure 7. GC spectrum for sample 3

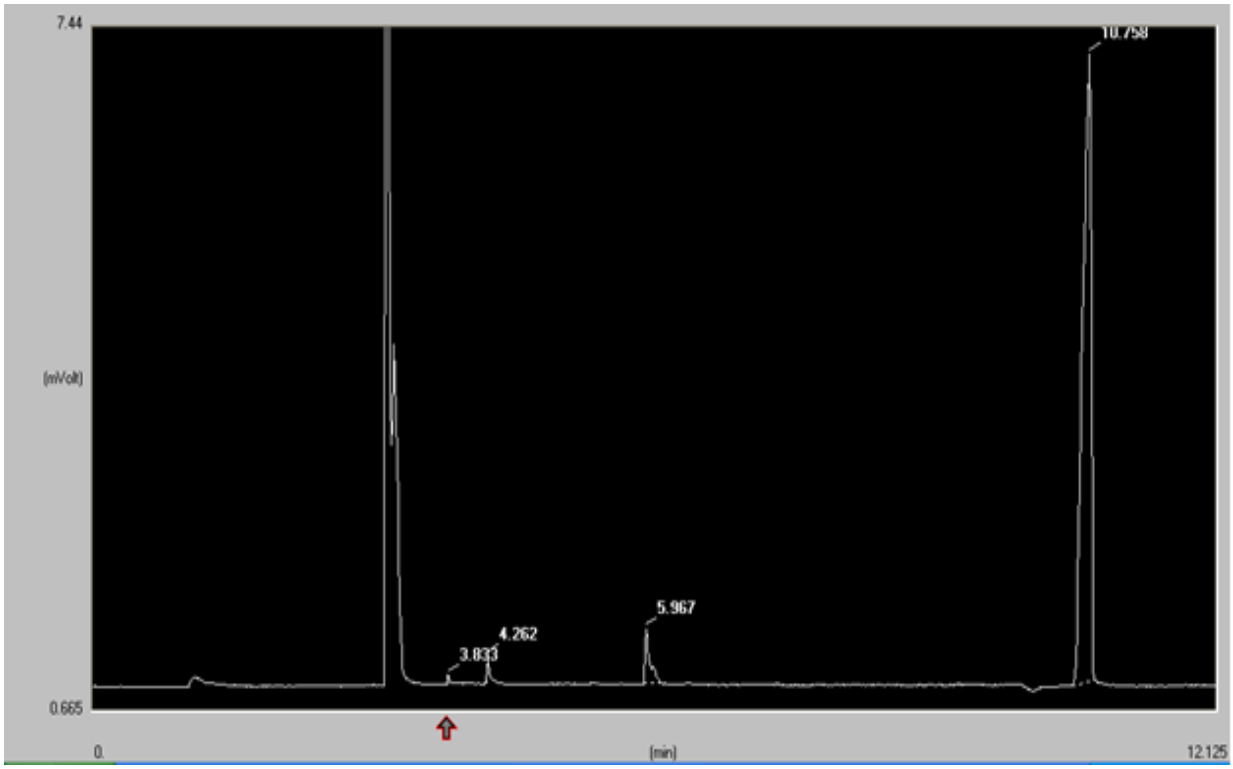


Figure 8. GC spectrum for sample 4

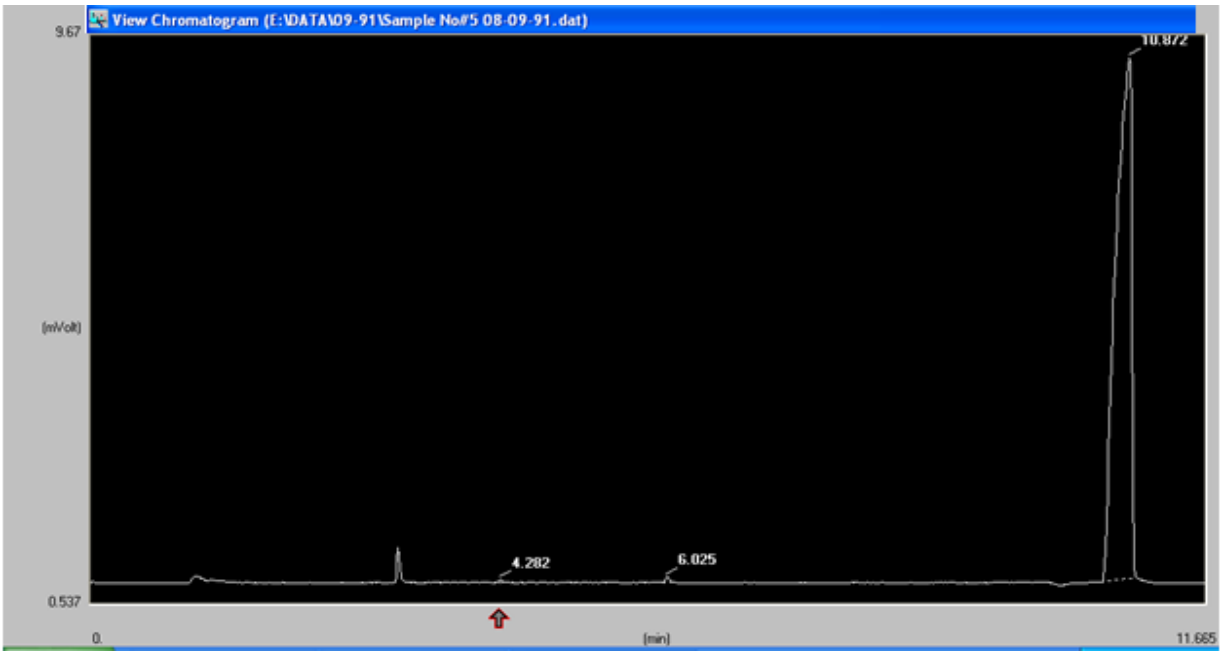


Figure 9. GC spectrum for sample 5

Conclusion

We can conclude that our developed methodology is a remarkably simple and highly efficient. Operational simplicity, solvent and catalyst-free media, mild reaction conditions, environmentally friendly reaction conditions, the compatibility with various functional groups are the main advantages of the procedure. To the best of our knowledge, our observation is the first report of *N*-formylation with formic acid without any catalyst and solvent. We believe that this will present a better and more practical alternative to the existing methodologies for the *N*-formylation of amines.

Orcid

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