Research Note
The Chemoselective Fischer’s Synthesis of Indolenine Derivatives By iso-Butyric Acid As A Weak Organic Acid Catalyst

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Abstract
Iso-butyric acid as a new, simple, and expensive solvent/catalyst was successfully used for the chemoselective Fischer’s synthesis of indolenines derivatives 3a-r by one-pot condensation reaction of various phenylhydrazines 1a-e with the substituted acetophenones 2a-c at reflux conditions. In this protocol, all products 3a-r were obtained in high yields and short reaction time. The structures of the product were established with spectroscopic data of 1H NMR, 13C-NMR, and FT-IR.

Keywords: Fischer’s synthesis; Indolenines; 3H-Indole; Phenylhydrazine; iso-butyric acid.

Introduction
Indolenines are fundamental building blocks in many biologicals, antimigraine drugs, dyes, and natural products [1]. This important ring system continues to fascinate chemists all over the world. A classical synthetic methods for preparation of indolenine derivatives included the reaction of arylhydrazones with the substituted acetophenones in the presence of different acid catalysts [2]. The first Fischer indole synthesis was affected by Emil Fischer and Friedrich Jourdan in 1883 [3]. In recent years, different methodologies have been reported for the synthesis of indolenines in the presence of both protic and Lewis acids to help break the N-N bond in the sigmatropic shift, such as HCl, H2SO4, polyphosphoric acid, p-toluenesulfonic acid, boron trifluoride, ZnCl2, FeCl3, and AlCl3 [4-5]. Due to the significance of indolenines chemistry, chemists are looking for new approaches for the synthesis of indolenines despite the fact that the methodologies for the synthesis of indolenine derivatives are very limited [6-8]. Therefore, providing a simple method seems necessary. Recently, we have reported the use of the citric acid and propanoic acid as acid catalysts for the preparation of indolenine derivatives [9-10]. In continuation of our search for new catalysts [11-18], we are reporting the use of iso-butyric acid as a commercial, inexpensive, and available acid catalyst/solvent for the synthesis of indolenines derivatives.

Materials and Methods
Solvents and reagents used in this work were obtained from Sigma-Aldrich, Fluka or Merck chemical companies and used without further purification. All products are known and are characterized by comparing their spectral (1H NMR and 13C NMR) and physical data.
with that of the authentic samples. The $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) were run on a Bruker Avance DPX-400 FT-NMR spectrometer ($\delta$ in ppm). Monitoring of the reactions and the purity check of the final products were carried out by thin layer chromatography (TLC) using silica gel precoated aluminium sheets (60–120 mesh; Merck) and visualization with ultraviolet light at 365 and 254 nm. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

**General procedure for preparation of indolenines derivatives 3a-r**

A mixture of various phenylhydrazines 1a-e (1.0 mmol) and ketones 2a-c (1.0 mmol) were added to iso-butyric acid (2.0 mL) and, then, was stirred under reflux conditions. Reaction progress was monitored by TLC ($n$-hexane:ethylacetate 4:1). The mixture was cooled and neutralized with 1 M NaOH, diluted with water (100 mL) and extracted with CHCl$_3$ (3×50 mL). The combined organic layer was dried over Na$_2$SO$_4$, and filtered to afford the indolenine which was purified by short silica gel column. A light brown viscous oil of indolenines was obtained in high to excellent yields.

**Results and Discussion**

To extend the scope of our work, the application of iso-butyric acid as an efficient and solvent/catalyst has been reported for the chemoselective Fischer’s synthesis of indolenines derivatives 3a-r by reaction of various phenylhydrazine 1a-f with the substituted acetophenones 2a-c at reflux conditions (Scheme 1).

We selected the reaction of o-methylphenylhydrazines 1a (1 mmol) and 2-methyl cyclohexanone 2b (1 mmol) in the presence of different amounts of iso-butyric acid as a model reaction under reflux and room temperature conditions to provide 3a (Table 1). The results are summarized in Table 1 which shows that the reactions were carried out in the different amounts of iso-butyric acid under reflux and temperature conditions. The best result was obtained when the reaction was carried out in 2 mL of the iso-butyric acid under reflux conditions in 10 min with 92% yield (Table 1, entry 4). The reaction in the absence of iso-butyric at room temperature was without product, and also, under reflux conditions, the reaction has 45% after 24 h (Table 1, entry 1). When 3 and 4 mL of iso-butyric acid was tested, the yield did not increase, while in other cases reaction time was longer (Table 1, entries 5 and 6). Appropriate yields (70-85%) were obtained for the compound 4a for the reaction model at room temperature, but the reaction time was longer (Table 1, entries 2-6). Then, various phenylhydrazines 1a-f (1 mmol) and ketones 2a-c (1 mmol) in the presence of iso-butyric acid under reflux conditions were used with the same procedure as the model reaction in order to provide chemoselective Fischer's synthesis of indolenines derivatives 3a-r. The results are shown in Table 2.

Both the electron-donating (Me and OMe) and electron-withdrawing (Br, Cl, F) substituents on phenylhydrazine precursor afforded the corresponding indolenine derivatives in good to excellent yields.
the reaction between various phenylhydrazines 1a-f and diisopropyl ketone 2c, the reaction time was longer due to steric effect of the ketone. But, the reaction time of isopropylmethyl ketone 2a and 2-methyl cyclohexanone 2b were between 10-20 minutes.

Therefore, these results revealed that this methodology is effective for both phenylhydrazines and aliphatic ketones. Both the electron-donating (Me and
OMe) and electron-withdrawing (Br, Cl, F) substituents on phenylhydrazine precursor afforded the corresponding Indolenine derivatives in good yields.

The structure of the products 3a-r were determined on the basis of their $^1$H NMR, $^{13}$C NMR and IR spectra. For instance, the $^1$H-NMR spectrum of 7-chloro-2,3,3-trimethyl-$3H$-indole 3h in CDCl$_3$ showed two singlets at $\delta = 1.14$ due to two methyl groups and $\delta = 2.16$ due to one methyl group. Also, protons along with signals $\delta = 6.93$-$7.12$ are due to the aromatic protons. The $^{13}$C-NMR spectrum of 7-chloro-2,3,3-trimethyl-$3H$-indole 3h in CDCl$_3$ which showed 10 resonances was in

| Reaction conditions: phenylhydrazines 1a-f (1.0 mmol) and ketone 2a-c (1.0 mmol) in the presence of iso-butyric acid (2.0 mL). | Yield of isolated products. |
|---|---|---|
| 8 | ![Structure 3a](image1) | 00:30 89 |
| 9 | ![Structure 3b](image2) | 26:00 86 |
| 10 | ![Structure 3c](image3) | 00:15 94 |
| 11 | ![Structure 3d](image4) | 00:12 90 |
| 12 | ![Structure 3e](image5) | 26:00 83 |
| 13 | ![Structure 3f](image6) | 00:10 90 |
| 14 | ![Structure 3g](image7) | 00:12 92 |
| 15 | ![Structure 3h](image8) | 24:00 88 |
| 16 | ![Structure 3i](image9) | 00:10 85 |
| 17 | ![Structure 3j](image10) | 00:10 90 |
| 18 | ![Structure 3k](image11) | 18:00 89 |

![Image 1]
![Image 2]
![Image 3]
![Image 4]
![Image 5]
![Image 6]
![Image 7]
![Image 8]
![Image 9]
![Image 10]
![Image 11]
agreement with the proposed structure. IR spectrum shows stretching vibration of $C=N$ at 1706-1716 cm$^{-1}$.

Table 3 shows the comparison of time, temperature, yields, and solvent by this new procedure with those reported in the literature. Table 3 indicates that the new reaction condition is milder with shorter reaction time.

**Conclusion**

In summary, the one-pot condensation reaction of various phenylhydrazines 1a-e with three different ketones 2a-c in the presence of iso-butyric acid as a new and simple catalyst/solvent can be successfully applied for the chemoselective Fischer's synthesis of indolenines derivatives 3a-r. With the obtained experimental results, we can conclude that iso-butyric acid is a versatile and highly efficient catalyst/solvent for indolenine synthesis. It is noteworthy that a wide range of indolenines was obtained in good to excellent yields.

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**References**


