

Research Note

The Chemoselective Fischer's Synthesis of Indolenine Derivatives By *iso*-Butyric Acid As A Weak Organic Acid Catalyst

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Received: 18 October 2017 / Revised: 26 September 2018 / Accepted: 8 April 2019

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; 3*H*-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 arylhydrazone 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

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with that of the authentic samples. The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were run on a Bruker Avance DPX-400 FT-NMR spectrometer (δ 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_2SO_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.

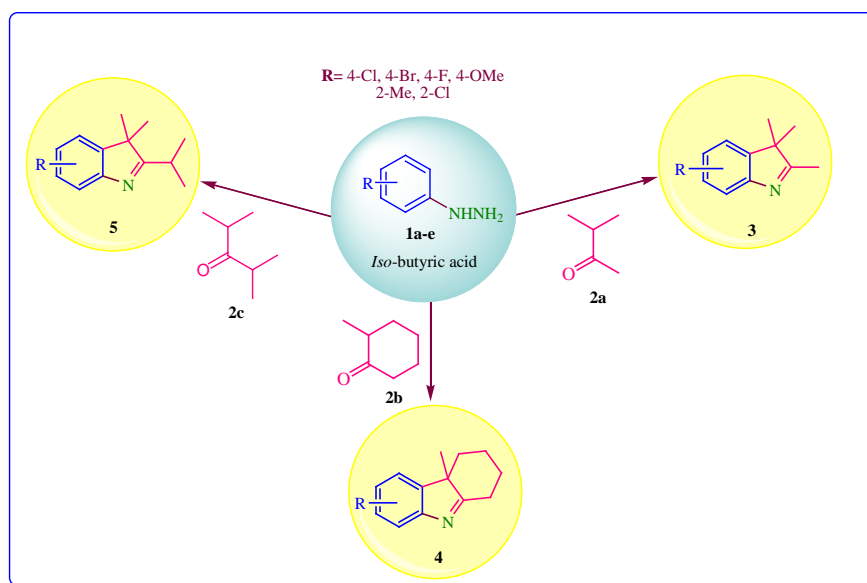
Results and Discussion

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. In

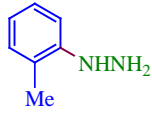
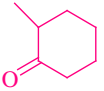
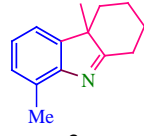
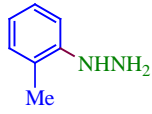
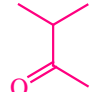
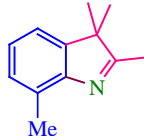
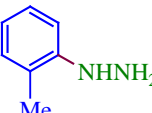
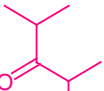
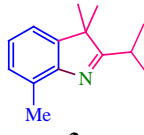
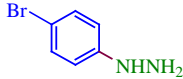
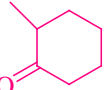
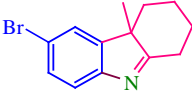
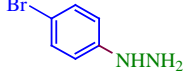
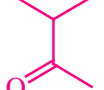
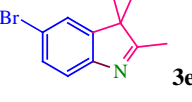
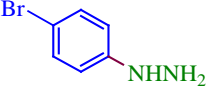
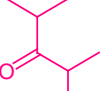
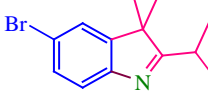
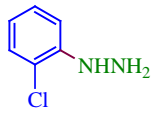
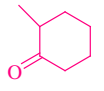
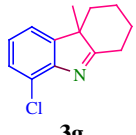


Scheme 1. Synthesis of indolenine derivatives using *iso*-butiric acid at reflux conditions.

Table 1. The synthesis of compound **3a** under different amounts of catalyst under reflux and room temperature conditions.

Entry	<i>iso</i> -butyric acid (mL)	Reflux		Room temperature	
		Time (h:min)	Yield (%) ^a	Time (h:min)	Yield (%) ^a
1	None	24:00	45	24:00	-
2	0.5	00:35	75	18:00	70
3	1	00:20	88	18:00	80
4	2	00:10	95	18:00	85
5	3	00:15	90	18:00	85
6	4	00:15	83	18:00	76

^a Yield of isolated products.**Table 2.** Synthesis of indolenine derivatives using *iso*-butyric acid at reflux conditions^a.

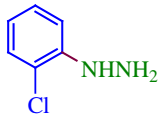

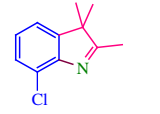
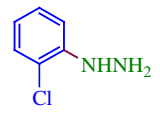

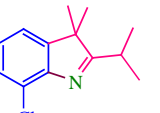
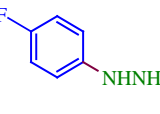

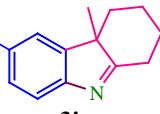
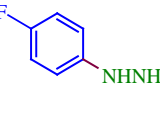

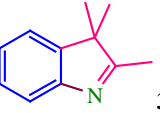
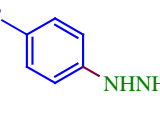

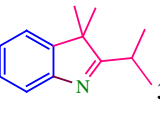
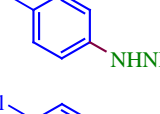


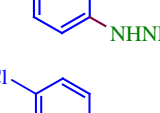

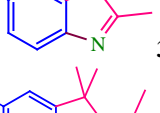
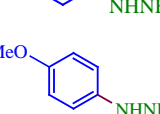

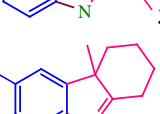
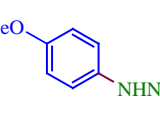

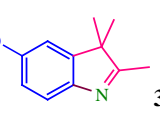
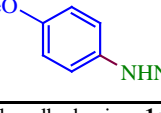

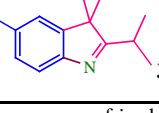
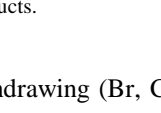

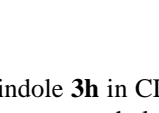
Entry	Phenylhydrazine	Ketone	Product	Time (h:min)	Yield (%) ^b
1			 3a	00:10	95
2			 3b	00:10	90
3			 3c	12:00	85
4			 3d	00:10	94
5			 3e	00:15	92
6			 3f	28:00	88
7			 3g	00:20	93

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

Table 2. Ctd

8				00:30	89
9				26:00	86
10				00:15	94
11				00:12	90
12				26:00	83
13				00:10	90
14				00:12	92
15				24:00	88
16				00:10	85
17				00:10	90
18				18:00	89

^aReaction conditions: phenylhydrazines **1a-f** (1.0 mmol) and ketone **2a-c** (1.0 mmol) in the presence of *iso*-butyric acid (2.0 mL).

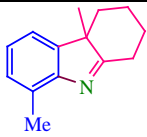
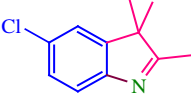
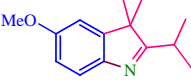
^bYield of isolated products.

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 ¹H NMR, ¹³C NMR and IR spectra. For instance, the ¹H-NMR spectrum of 7-chloro-2,3,3-

trimethyl-3*H*-indole **3h** in CDCl₃ 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 ¹³C-NMR spectrum of 7-chloro-2,3,3-trimethyl-3*H*-indole **3h** in CDCl₃ which showed 10 resonances was in

Table 3. Comparison of the results of the synthesis of compound **3a**, **3n**, and **3r** catalyzed by our new catalyst with those obtained by the recently reported catalysts.

Entry	Product	Catalyst	Cocditions	Time (h:min)	Yield (%)
1		Acetic acid	Reflux ^a	-	-
		Propanoic acid	Reflux ^b	00:15	86
		Citric acid	Reflux, EtOH	05:00	83
		<i>iso</i> -butyric acid	Reflux ^c	00:10	95
2		Acetic acid	Reflux	00:30	90
		Propanoic acid	Reflux	00:45	93
		Citric acid	Reflux, EtOH	09:00	82
		<i>iso</i> -butyric acid	Reflux	00:12	92
3		Acetic acid	Reflux	-	-
		Propanoic acid	Reflux	18:00	83
		Citric acid	Reflux, EtOH	18:00	70
		<i>iso</i> -butyric acid	Reflux	18:00	89

^a At reflux conditions (118.1 °C)^b At reflux conditions (141.2 °C)^c At reflux conditions (155 °C)

agreement with the proposed structure. IR spectrum shows stretching vibration of C=N at 17061716 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.

Acknowledgments

The authors gratefully acknowledge partial support of this study by the Payame Noor University (PNU) of Ilam, I.R. Iran.

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