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Research Note

Citric acid as an efficient and trifunctional organo catalyst for one-pot synthesis of new indolenines by Fischer's method at reflux condition in ethanol

M.A. Zolfigol[a,*], S. Sajjadifar[b,*], Gh. Chehardoli[c] and N. Javaherneshan[a,b]

a. *Faculty of Chemistry, Bu-Ali Sina University, Hamedan, P.O. Box 6517838683, Iran.*
b. *Department of Chemistry, Payame Noor University, Tehran, P.O. Box 19395-4697, Iran.*
c. *Department of Medicinal Chemistry, School of Pharmacy, Hamadan University of Medical Sciences, Zip Code 65178, Hamadan, Iran.*

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KEYWORDS
3H-indole;
Indolenine;
Fischer's reaction;
Citric acid;
Green synthesis.

Abstract. New indolenines **I(1-18)** were prepared by Fischer indole synthetic reaction of hydrazines derivatives **H(1-6)** with isoproylmethylketone **K1**, 2-methylcyclohexanone **K2** and diisopropyl ketone **K3** in presence of citric acid as a new catalyst at reflux condition in high yield.

1. Introduction

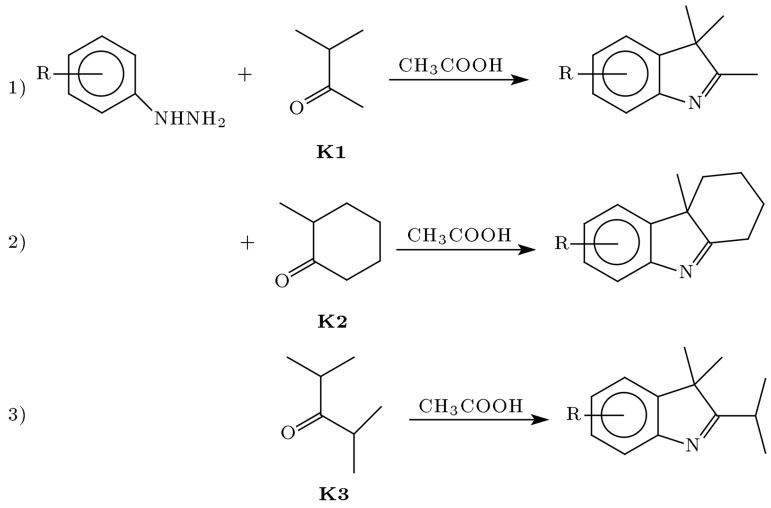
The Fischer indole synthesis is a chemical reaction which produces the aromatic heterocyclic indole from a substituted or unsubstituted phenylhydrazines and aldehydes or various ketones under acidic conditions. This reaction was discovered in 1883 by Fischer and Jourdan [1]. Today antimigraine drugs of the triptan class are often synthesized by this method [2]. The choice of acid catalyst is very important. Bronsted acids such as HCl, H_2SO_4, polyphosphoric acid and p-toluenesulfonic acid have been used successfully. Lewis acids such as boron trifluoride, zinc chloride, iron chloride, and aluminium chloride would also be regarded as useful catalysts [2,3]. The mechanism of Fischer indole synthetic reaction has been suggested by Robinson [4-6].

Miller and Neal Schinske [7] have examined the effects of acid catalysts and temperature in the uncatalyzed reaction on the direction of cyclization of unsymmetrical ketone phenylhydrazones in the Fischer indole synthesis. Higher acidity, as previously reported, and higher temperature in the thermal process cause cyclization toward the less substituted position. The observations are considered in terms of a refined version of the first two stages of the mechanism of the reaction.

A perplexing aspect of the Fischer indole synthesis has been reported as its cyclization of phenylhydrazones of unsymmetrical ketones to form two possible indoles. The early generalizations of Plancher [5] suggesting that the course of the reaction depends only on the structure of the ketone moiety of the phenylhydrazone, have not been sustained by more recent investigations [8-10]. In the mentioned investigations the ratio of the products has been found to vary with the nature of the acid used as the catalyst, its concentration, or its absence in a thermal cyclization.

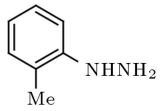
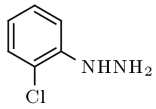
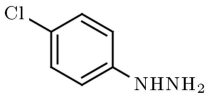
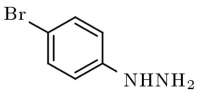
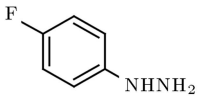
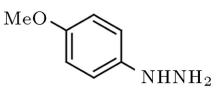
Previously, we examined indolenine synthesis in presence of excess acetic acid [11] and propanoic acid as weak organo acid catalyst and solvent. Then, we studied Fischer's method for indolenine synthesis in presence of citric acid as an organo catalyst and ethanol as a solvent.

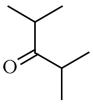
*. *Corresponding authors. Tel.: +98 841 2228316; Fax: +98 841 2221053*
E-mail addresses: zolfi@basu.ac.ir (M.A. Zolfigol); ss_sajjadifar@yahoo.com (S. Sajjadifar)

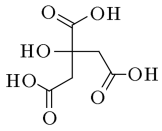


Scheme 1. Preparation of indolenines by reaction of substituted phenylhydrazins with isopropyl methyl ketone **K1**, 2-methyl cyclohexanone **K2** and diisopropyl ketone **K3**.

Table 1. Structures of hydrazines and ketones used in this research.

					
H1	**H2**	**H3**	**H4**	**H5**	**H6**

		
K1	**K2**	**K3**



Citric acid
(or 2-hydroxypropane-1,2,3-tricarboxylic acid)

2. Result and discussion

As mentioned in the introduction, the presence of different ketone for indole synthesis has been investigated, but, the application of substituent group's effects on benzene in phenylhydrazine for Fischer indole synthesis has not been yet reported. For this purpose, we studied m,p-methylphenylhydrazines and o,p-nitrophenylhydrazines in indolenine synthesis [11]. In this research, we studied methoxy, chloro, bromo and fluoro groups in different situation connected with phenylhydrazine **H(1-6)** in reaction with isopropyl methyl ketone **K1**, 2-methyl cyclohexanone **K2**, and diisopropyl ketone **K3** and corresponding indolenines **I(1-18)** were obtained (Scheme 1).

We had previously reported the synthesis of new 3H-indoles [11], and synthesized the methyl and nitro 3H-indoles. In this research, we used methyl, chloro, boromo, methoxyhydrazines and isoproylmethylketone **K1**, methylcyclohexanone **K2** and diisopropyl ketone (Table 1). For choosing a better solvent, we examined various solvents and ethanol was the best solvent for this reaction (Table 2). The optimum yields of the products were obtained when 50 mol% of citric acid (0.5 mmol) was used (Table 3).

Table 2. Optimization of solvent (5 mL) in presence of citric acid (50 mol%).

Entry	Solvent	Time (h)	Yield %
1	H_2O	6	50
2	CH_3CH_2OH	6	80
3	CH_2Cl_2	6	45
4	CH_3CN	6	40
5	CH_3COOEt	6	40
6	n-C_6H_{14}	6	25
7	C_3H_6O	6	40

As mentioned before, in this method the product concentration is significantly high (85-98%). It is mainly regarded as a mono product, and is also carried

out in easy conditions. Thus, in this regard, our research proves to be remarkable.

In the presence of various strong acids, both the indole or indolenine were produced. This results in indole as the main product (Table 4). But in the presence of propanoic acid and citric acid, only 3H-indole was produced (Scheme 2).

Phenylhydrazines **H(1-6)** reacted with isopropylmethyl ketone **K1** and produced the corresponding indolenines **I(1, 4, 7, 10, 13, 16)** with high yield (85-95%). ^{1}H NMR spectrum of these indolenines revealed singlet signal of two methyl groups at $\delta = 1.1$ ppm, and singlet signal of methyl group C-2 at $\delta = 2.05$. IR spectrum indicated a stretching vibration C=N at 1690 cm^{-1}.

Phenylhydrazines **H(1-6)** reacted with 2-methyl cyclohexanone **K2** and produced indolenines **I(2, 5, 8, 11, 14, 17)** with high yield (83-85%). ^{1}H NMR spectrum of **I-2** as a model for these indolenines showed 0.80 (t, $J = 11.74$ HZ, 1H), 0.94(s, 3H, CH_3), 1.10(t, $J = 13.2$ HZ, 1H), 1.25-1.46(m, 2H), 1.86(t, $J = 13.74$ HZ, 2H), 2.19-2.30(m, 1H), 2.36(s, 3H, CH_3) 2.63(d, $J = 12.74$ HZ, 1H), and 6.79(s, 3H, Ar-H). Figure 1 shows the ^{1}H NMR of aliphatic region. The IR spectrum indicated stretching vibration C=N at 1706-1716 cm^{-1}.

Phenylhydrazines **H(1-6)** reacted with diisopropyl ketone **k3**, and indolenines **I(3, 6, 9, 12, 15, 18)** were produced with moderate yield (55-75%). ^{1}H NMR spectrum of **I-3** were noticed as doublet signal of two methyl groups at $\delta = 1.52$, singlet signal of two methyl groups at $\delta = 1.64$ and multiplet signal of CH at $\delta = 2.17 - 2.29$ ppm. IR spectrum indicated a stretching vibration C=N at 1706-1716 cm^{-1}.

Table 3. Optimization of citric acid.

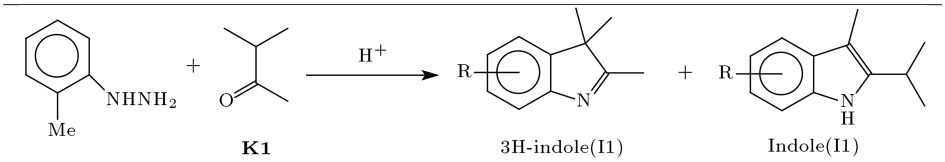
Entry	Citric acid (mmol)	Time (h)	Yield%
1	0.1	6	60
2	0.3	6	75
3	0.5	6	80
4	0.8	6	80
5	1	6	78

3. Experimental

3.1. General

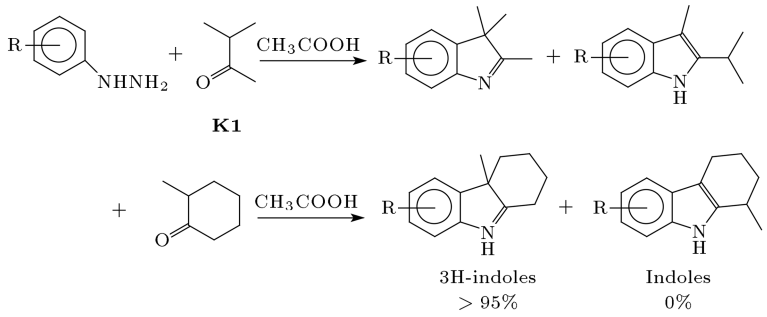
All chemicals were purchased from either Merck or Fluka Chemical Companies. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. IR spectra were run on a Shimadzu FTIR-

Table 4. Use of different acids for comparing production of 3H-idole and indole.



Entry	Acid	Condition	Time (h:min)	Yield %[a] 3H-indole(I1)	Yield %[a] Indole(I1)
1	HCl	RT	1:30	30	70
2	HNO_3	RT	1:30	30	70
3	H_2SO_4	RT	1:30	20	80
4	H_3PO_4	RT	1:30	45	55
5	HBr	RT	1:30	30	70
6	Acetic acid	RT	1:30	> 89	0
7	Propanoic acid	RT	1:30	> 90	0

[a] By using TLC.



Scheme 2. Selective synthesis of 3H-indoles in presence of citric acid.

8300 spectrophotometer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were run on a Bruker Avance DPX. FT-NMR spectrometer (ppm). Chemical shift δ were measured in parts per million (ppm) in $CDCl_3$ as solvent and relative to TMS as the internal standard. Melting points were recorded on a Bü chi B-545 apparatus in open capillary tubes. Optical rotations were measured in spectral grade solvents using a Perkin-Elmer 341 polarimeter. Infrared spectra were recorded on a Thermodicolet-Nexus 670 FTIR instrument and elemental analyses were carried out on an Exeter analytical model CE440 C, H and N elemental analyzer.

3.2. General procedure for 3H-indole synthesis

Hydrazines **H(1-6)** (1 mmol), isoproylmethylketone **K1**/2-methylcyclohexanone **K2**/diisopropyl ketone **K3** (1 mmol) and citric acid (0.1 g, 0.5 mmol) were added to ethanol (5 mL) at reflux condition. The mixture was refluxed for appropriate time (Table 5) with stirring. TLC indicated the end of the reaction

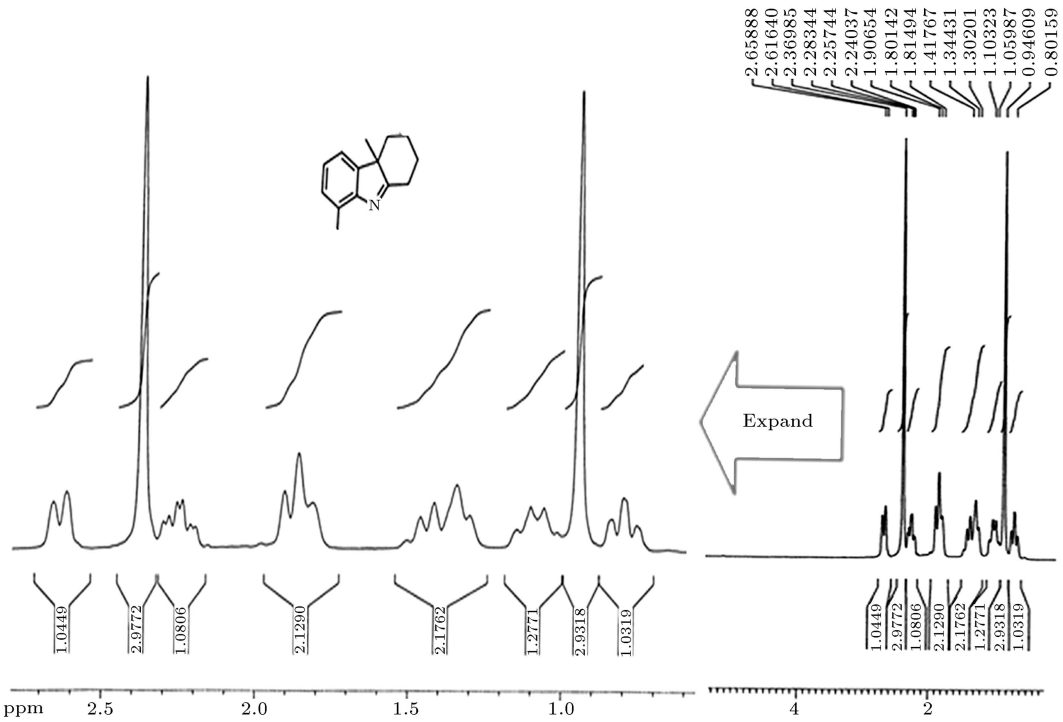


Figure 1. ^{1}H NMR spectrum of aliphatic cyclic in 5,6,7,8-tetrahydro-1,4b-dimethyl-4bH-carbazole (**I-2**).

Table 5. Indolenines synthesis by using citric acid as a new catalysts.

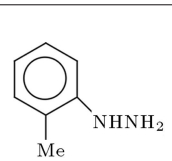
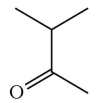
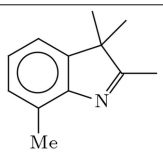
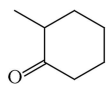
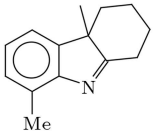
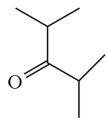
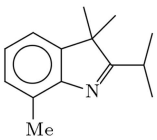
Entry	Hydrazine	Ketone	Product	Condition time (h)	Yield%[a]
1	 **H1**	 **K1**	 **I1**	6	95
2		 **K2**	 **I2**	5	83
3		 **K3**	 **I3**	24	75

Table 5. Indolenines synthesis by using citric acid as a new catalysts (continued).

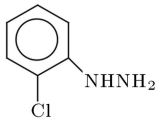
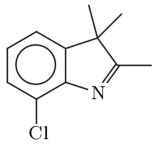
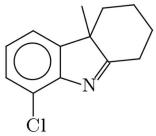
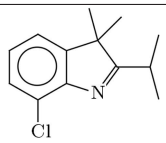
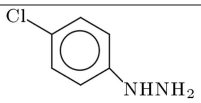
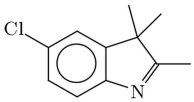
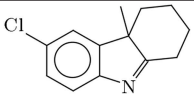
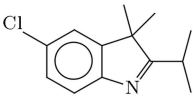
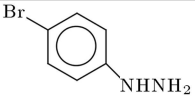
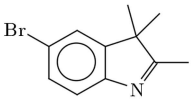
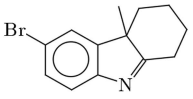
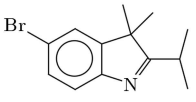
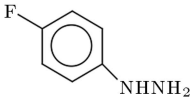
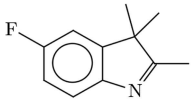
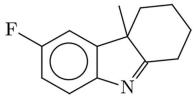
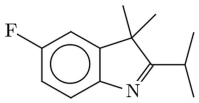
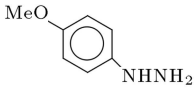
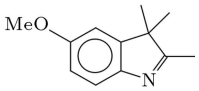
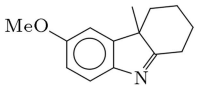
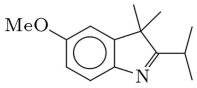
Entry	Hydrazine	Ketone	Product	Condition time(h)	Yield%[a]
4	 **H2**	**K1**	 **I4**	8	80
5		**K2**	 **I5**	24	84
6		**K3**	 **I6**	24	62
7	 **H3**	**K1**	 **I7**	9	82
8		**K2**	 **I8**	8	85
9		**K3**	 **I9**	9	65
10	 **H4**	**K1**	 **I10**	9	82
11		**K2**	 **I11**	8	85
12		**K3**	 **I12**	24	66
13	 **H5**	**K1**	 **I13**	18	81
14		**K2**	 **I14**	12	84

Table 5. Indolenines synthesis by using citric acid as a new catalysts (continued).

Entry	Hydrazine	Ketone	Product	Condition time(h)	Yield%
15		**K3**	 **I15**	24	55
16	 **H6**	**K1**	 **I16**	6	80
17		**K2**	 **I17**	5	85
18		**K3**	 **I18**	18	70

and formation of the product. The mixture was cooled and neutralized with 1 M NaOH then diluted with water (100 mL) and extracted with $CDCl_3$ (3×50 mL). Organic layer dried with Na_2SO_4, the solvent was removed by means of evaporation and the residue was passed through a short silica gel column for further purification. A light brown viscous oil of indolenines **I(1-18)** was obtained in high yield (85-98%).

4. Conclusion

As it was mentioned before, similar to the acetic and propanoic acids, the yield of indolenine synthesis increased when we used citric acid as a steric hindrance catalyst for Fisher's indole synthesis. Moreover, in the indolenine synthesis mechanism, the steric hindrance of catalyst can be seen as the main originator of such an orientation.

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References

1. Fischer, E. and Jourdan, F. "Indole synthesis", *Ber.*, **16**, pp. 2241-2245 (1883).
2. Fischer, E. and Hess, O. "The Fischer indole synthesis", *Ber.*, **17**, pp. 559-568 (1884).
3. Robinson, B. "Studies on the Fischer indole synthesis", *Chem. Rev.*, **69**, pp. 227-250 (1969).
4. Van Orden, R.B. and Lindwell, H.G. "Indole", *Chem. Rev.*, **30**, pp. 69-96 (1942).
5. Lyle, R.E. and Skarlos, L. "Direction of cyclization of unsymmetrical ketone phenyl hydrazones in the Fischer indole synthesis", *Chem. Comm.*, pp. 644-646 (1966).
6. Allen, C.F.H. and Wilson, C.V. "The use of ^{15}N as a tracer element in chemical reactions. The mechanism of the Fischer indole synthesis", *J. Am. Chem. Soc.*, **65**, pp. 611-612 (1943).
7. Miller, F.M. and Neal Schinske, W. "Direction of cyclization in the Fischer indole synthesis. Mechanistic considerations", *J. Org. Chem.*, **43**, pp. 3384-3388 (1978).
8. Pausacker, K.H. "The Fischer indole synthesis. Part III. The cyclisation of the phenylhydrazones of some 2-substituted cyclohexanones", *J. Chem. Soc.*, pp. 621-624 (1950).
9. Lily, H. and Funderburk, L. "Fischer indole synthesis. Direction of cyclization of isopropylmethyl ketone phenylhydrazone", *J. Org. Chem.*, **33**, pp. 4283-4285 (1968).
10. Palmer, M.H. and Mclntyre, P.S. "Fischer indole synthesis on unsymmetrical ketones. The effect of the acid catalyst", *J. Chem. Soc. B*, pp. 446-449 (1969).
11. Sajjadifar, S., Vahedi, H., Massoudi, A. and Louie, O. "3H-Indole synthesis by Fischer's method. Part I", *Molecules*, **15**, pp. 2491-2498 (2010).

Biographies

Mohammad Ali Zolfigol was born in 1966 in Iran. He obtained his BS degree from Arak University, Iran, his MS from Isfahan University of Technology, Iran, and his PhD from Shiraz University, Iran. He became a faculty member of Bu-Ali Sina University in 1997 and Professor in 2005. In 2003, he was selected as distinguished researcher by the Ministry of Science, Research and Technology of Iran. He was also awarded at the Khwarizmi International Festival and at COMSTEC, in 2008. His research interests include: the discovery and development of new synthetic methods by the synthesis and application of new solid-supported reagents, especially silica-based resins.

Sami Sajjadifar was born in Malekshahi-Ilam, Iran in 1973. He studied chemistry at the University of Shahid Chamran, Ahvaz, Iran and received his MSc degree in organic chemistry from Urmia University in 2000 and PhD degree in organic chemistry from Bu-Ali Sina University and Payame Noor University (PNU) of Mashhad in 2012. He focused his doctoral thesis on the application of Boron Sulfonic Acid (BSA) catalyst in organic synthesis. His research interests focus on the application of new reagents in organic reactions, the synthesis of different types of organic compounds, design and study of novel solid acid catalyst and organic reaction.

Gholamabbas Chehardoli was born in Iran in 1973. He received his BS degree in Chemistry from Bu-Ali Sina University, Iran, in 1998, and MS and PhD degrees in Organic Chemistry from the same university in 2000 and 2006, respectively. He is currently teaching Organic Chemistry in the School of Pharmacy at Hamedan University of Medical Sciences, I.R. Iran. His research fields include: methodology in organic chemistry.

Nematollah Javaherneshan was born in Iran in 1973. He received his B.S. degree in Chemistry from Bu-Ali Sina University, Iran, in 1998, and his M.S. degree in Organic Chemistry, from Payame Noor University (PNU) of Hamedan, Iran, in 2013. His research interests include: Fischer's synthesis, applications of ionic liquids, solvent-free conditions in organic synthesis, and synthesis and application of acidic catalysts in organic reactions.