Molecular iodine catalyzed synthesis of some biologically active dihydroperimidines

A. Mobinikhaledi[1*], F. Sasani[1], A. Hamta[2], S.M. Shariatzadeh[3]

[1] *Department of Chemistry, Faculty of Science, Arak University, Arak 38156-8-8349, Iran*
[2] *Department of Biology, Faculty of Science, Arak University, Arak 38156-8-8349, Iran*
[3] *Science and Research Branch of Islamic Azad University, Tehran-Iran*

Several perimidines were prepared in good to high yields by reaction of 1,8-diaminonaphthalene and aromatic aldehydes in the presence of molecular iodine as a highly efficient catalyst. This environmentally benign and clean synthetic procedure offers several advantages, such as high yields, short reaction times and easy workup. Antibacterial activity of these compounds was evaluated using Staphylococcus aureus (mm) and E. coli (mm) bacterial strains.

Keywords: Iodine, Catalyst, Perimidine, Antibacterial

INTRODUCTION

There has special interest in the chemistry of perimidines due to a wide range of biological activities exhibited by these compounds [1-5]. Perimidines have also used as intermediates in organic synthesis [6]. Variety methods have been reported for the synthesis of perimidines in literatures [2, 6-15]. The traditionally synthesis of such compounds is still ordinary alongside modern synthesis methods. The general method for the synthesis of perimidines involves the condensation reaction of 1,8-diaminonaphthalene with a carbonyl group in the presence of a Lewis or mineral acid. However, in spite of their potential utility, many of these methods are associated with some limitations and generally need strong acidic conditions, expensive or non-available reagents, prolonged reaction times and high temperatures. Thus, the introduction of new methods and /or further work on technical improvements to overcome these limitations is still needed

The mild Lewis acidity of molecular iodine as a catalyst increased its applications in organic synthesis. It has received substantial attention as a non-toxic and commercially available catalyst for synthesis of benzothiophens [16], bis indoles [17], quinolines [18], esterification [19], phenanthrimidazoles [20] and indazoles [21].

In view of these reports and also due to continuation of our studies on synthesis of perimidines [13,14], we wish to report a simple,

efficient and eco-friendly one pot practical method for the synthesis of perimidines by reaction of 1,8-diaminonaphthalene and aromatic aldehydes in the presence of molecular iodine. We also report the biological activity of these compounds.

EXPERIMENTAL

Firstly, to evaluate the catalytic efficiency of molecular iodine, the reaction of 1,8-diaminonaphthalene and 4-nitrobenzaldehyde was studied by using 2 mol% molecular iodine, as a catalyst, in ethanol at room temperature. For optimization of the amount of catalyst, this reaction was carried out as a model, and different amounts of catalyst were tested to increase the yield of product under the same conditions. The amount of catalyst less than 7 % wt. could catalyze the reaction, but it needed a longer reaction time and yields are low. On the other hand, the amount of catalyst over 7 % wt. did not improve the yield of product (Table 1). To examine the effect of solvent for this model reaction, the reaction was carried out in some organic solvents including C_2H_5OH, CH_3OH, CH_3CN, DMSO and DMF at room temperature with 7 mol% of catalyst for 7 min. As Table 1 shows, the most suitable solvent for this procedure is ethanol.

To examine the generality of this simple procedure, several aromatic aldehydes were treated with 1,8-diaminonaphthalene in the presence of 7 mol% of the molecular iodine as a catalyst (Figure 1).

* To whom all correspondence should be sent:
E-mail: akbar_mobini@yahoo.com

Table 1. Reaction of 1,8-diaminonaphthalene with 4-nitrobenzaldehyde using different amounts of catalyst and solvent at room temperature.

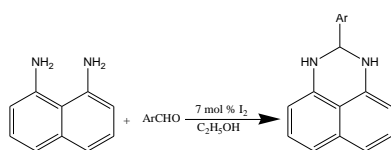| Entry	Catalyst load	Solvent	Time (min)	Yield (%)[a]
1	2	EtOH	25	55
2	3	EtOH	20	77
3	5	EtOH	27	79
4	7	EtOH	7	93
5	10	EtOH	8	80
6	15	EtOH	6	87
7	7	MeOH	7	61
8	7	CH$_3$CN	7	72
9	7	DMSO	7	63
10	7	DMF	7	65

[a] Isolated yield

Fig. 1. The scheme preparation of perimidines.

Table 2. Reaction of 1,8-diaminonaphthalene with aromatic aldehydes prompted by 7 mol% molecular iodine catalyst in C$_2$H$_5$OH.

Compound	Ar	Time (min)	Yield (%)[a]	M.P (°C)
3a	C$_6$H$_5$	40	84	105-106 (101-103)[b]
3b	4-OHC$_6$H$_4$	60	85	162-164 (161-163)[b]
3c	4-OCH$_3$C$_6$H$_4$	20	65	156-158 (151-152)[c]
3d	2-ClC$_6$H$_4$	25	95	115-119 (116-118)[b]
3e	3-ClC$_6$H$_4$	30	80	143-146
3f	3-BrC$_6$H$_4$	20	55	166-168 (165-166)[d]
3g	4-BrC$_6$H$_4$	12	96	115-117 (138-140)[c]
3h	2-NO$_2$C$_6$H$_4$	8	98	183-185 (191-192)[c]
3i	3-NO$_2$C$_6$H$_4$	10	87	180 (188-190)[b]
3j	4-NO$_2$C$_6$H$_4$	7	93	247-249 (>200)[e]
3k	4-FC$_6$H$_4$	20	82	182-183 (180-182)[b]
3l	4-CH$_3$C$_6$H$_4$	7	62	165 (161-163)[b]
3m	2-OH,4-BrC$_6$H$_3$	15	92	112-117 (164-166)[b]
3n	3,4-(OCH$_3$)$_2$ C$_6$H$_3$	45	88	205

a: Isolated yield, b:[ref 13], c:[ref 22], d:[ref 23], d:[ref 24].

The results of this study are presented in Table 2. We were pleased to find that the reaction of different aromatic aldehyses with 1,8-diaminonaphthalene in the presence of molecular iodine afforded corresponding dihydroperimidines **3(a-n)** in good to excellent yields. However, aliphatic aldehydes such as formaldehyde or acetaldehyde were also examined under the same conditions, but the responding products were isolated in low yields (<10%). Almost all synthesized compounds are known and identified using IR and NMR spectroscopy and also by comparison with their authentic samples.

Melting points were determined using an electro thermal digital apparatus and are uncorrected. NMR spectra were recorded on a Brucker 300 MHz spectrometer. IR spectra were performed on a Galaxy FT-IR 5000 spectrophotometer. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III) at the Arak University. The Microanalyses results were agreed favorably with the calculated values. Reaction progress was routinely monitored by thin layer chromatography using silica gel F$_{254}$ aluminum sheets (Merck).

The microbial strains are identified strains and were obtained from the Pasteur Institute of Iran. The bacterial strains studied are Staphylococcus aureus (RTCC, 1885), and Escherichia Coli (ATCC, 35922).

Table 3. Zone inhabitation of dihydroperimidines **(3a-n)**.

E. coli (mm)	Staphylococcus aureus (mm)	Materials
--	9±0.1 mm	3a
--	15±0.2 mm	3b
9±0.1 mm	--	3c
--	--	3d
--	8±0.3 mm	3e
--	--	3f
--	--	3g
--	--	3h
--	--	3i
--	--	3j
--	--	3k
--	--	3l
--	12± 0/2 mm	3m
--	11±0.3 mm	3n
--	--	DMSO
Gentamicin 11 mm	Gentamicin mm 11	Standard drugs

-- indicates resistance of bacteria to compounds. Discs were inculcated with 5 mg of the chemicals dissolved in DMSO. The inhibition zone numbers are the average of three times independent experiments.

Antibacterial activity of synthesized perimidines was tested against Staphylococcus aureus (mm) and E. coli (mm) bacterial strain and the results presented in Table 3. The verification of antibacterial screening data revealed that compounds **3a**, **3b**, **3e**, **3m**, and **3n** have bactericidal properties against Staphylococcus aureus. Also these compounds have bactericidal properties against E. coli as a gram negative. The maximum and minimum antibacterial activities

against Staphylococcus aureus were related to compounds **3b** and **3e**, respectively.

RESULTS AND DISCUSSION

Antibacterial activities

The agar disk diffusion method was used for this purpose. In each test 5mg of chemically synthesized materials was dissolved in 250 µl of DMSO as a solvent and 100 µl of known concentration of the test compounds was introduced onto the disks (0.7 cm) and then allowed to dry. The disk was completely saturated with the test compounds. Then the disk was introduced onto the upper layer of the medium with the bacteria. 100 µl of solvent (DMSO) was added to the blank disk and implanted as a negative control on each plate along with the standard drugs. The plates were incubated overnight at 37°C. The inhibition zones were measured and compared with the controls. The results are given in Table 3.

Typical procedure for preparation of aryldihydroperimidines (3a-n)

To a solution of 1,8-naphthalenediamine (1 mmol) and corresponding aromatic aldehyde (1 mmol) in ethanol (15–20 mL) was added molecular iodine (7 mol %). The reaction mixture was stirred at room temperature for desired time (Table 2). The progress of reaction was monitored by TLC. After completion of reaction, water (15–20 mL) was added to produce the product, which then filtered and washed with cold water and air dried.

Selected spectra data

4-(2,3-Dihydro-1Hperimidine-2-yl)phenol

(3b). IR (KBr): 3396, 3331, 3045, 1600, 1517, 1412 cm^{-1}. ^{1}HNMR (DMSO, 300 MHz): δ 5.23 (s, 1H, CH), 6.45-7.41 (m, 12H, CH$_{arom}$, 2NH), 9.50 (s, 1H, OH). ^{13}CNMR (DMSO, 75 MHz): δ 66.8, 104.7, 112.9, 115.3, 115.6, 127.3, 129.6, 132.4, 134.9, 143.9, 158.2. Anal Calcd for C$_{17}$H$_{14}$N$_2$O: C, 77.84; H, 5.38; N, 10.68%. Found: C, 77.55; H, 5.50; N, 10.64%.

2-(3-Chlorophenyl)-2,3-dihydro-1H-perimidine (3e).

IR (KBr): 3393, 3354, 3045, 2806, 1607, 1416 cm^{-1}. ^{1}HNMR (DMSO, 300 MHz): δ 5.39 (s, 1H, CH), 6.48-7.63 (m, 12H, CH$_{arom}$, 2NH). ^{13}CNMR (DMSO, 75 MHz): δ 65.8, 104.98, 112.9, 116.0, 127.0, 127.4, 128.2, 128.8, 130.6, 133.4, 134.8, 143.1, 145.1. Anal Calcd for C$_{17}$H$_{13}$N$_2$Cl: C, 72.72; H, 4.68; N, 9.98%. Found: C, 72.86; H, 4.51; N, 10.27%.

2-(2-Nitrophenyl)-2,3-dihydro-1H-perimidine

(3h). IR (KBr): 3358, 3231, 2853, 1602, 1519, 1416, 1334 cm^{-1}. ^{1}HNMR (DMSO, 300 MHz): δ 5.82 (s, 1H, CH), 6.51-8.05 (m, 12H, CH$_{arom}$, 2NH). ^{13}CNMR (DMSO, 75 MHz): δ 61.4, 105.2, 112.5, 116.2, 124.6 127.5, 130.0, 130.4, 134.0, 134.7, 136.9, 142.5, 149.4. Anal Calcd for C$_{17}$H$_{13}$N$_3$O$_2$: C, 70.08; H, 4.51; N, 14.43%. Found: C, 69.98; H, 4.59; N, 14.32%.

2-(3-Nitrophenyl)-2,3-dihydro-1H-perimidine

(3i). IR (KBr): 3345, 3227, 1603, 1528, 1416, 1350 cm^{-1}. ^{1}HNMR (DMSO, 300 MHz): δ 5.56 (s, 1H, CH), 6.53-8.45 (m, 12H, CH$_{arom}$, 2NH). ^{13}CNMR (DMSO, 75 MHz): δ 65.3, 105.1, 112.9, 116.1, 123.1, 123.7, 127.4, 130.4, 134.8, 135.1, 142.7, 145.0, 148.1. Anal Calcd for C$_{17}$H$_{13}$N$_3$O$_2$: C, 70.08; H, 4.51; N, 14.43%. Found: C, 70.20; H, 4.53; N, 14.51%.

2-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-perimidine (3n).

IR (KBr): 3350, 2997, 1601, 1416 cm^{-1}. ^{1}HNMR (DMSO, 300 MHz): δ 3.77 (s, 3H, CH$_3$), 3.78 (s, 3H, CH$_3$), 5.29 (s, 1H, CH), 6.47-7.22 (m, 11H, CH$_{arom}$, 2NH). ^{13}CNMR (DMSO, 75 MHz): δ 55.9, 56.5, 68.8, 104.8, 111.7, 113.0, 115.8, 120.7, 127.3, 134.5, 134.9, 143.8, 149.2, 149.59. Anal Calcd for C$_{19}$H$_{18}$N$_2$O$_2$: C, 74.49; H, 5.92; N, 9.14%. Found: C, 74.40; H, 5.99; N, 9.20%.

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СИНТЕЗА НА НЯКОИ БИОЛОГИЧНО-АКТИВНИ ДИХИДРОПЕРИМИДИНИ, КАТАЛИЗИРАНИ ОТ МОЛЕКУЛЕН ЙОД

А. Мобинихаледи[1], М.А. Бодаги Фард[1], Ф. Сасани[2], М.А. Амролахи[3]

[1]Департамент по химия, Научен факултет, Университет в Арак, Арак, Иран
[2]Департамент по химия, Научен факултет, Университет в Язд, Язд, Иран
[3]Научен и изследователски клон на ислямския университет "Азад", Техеран, Иран

(Резюме)

Получени са няколко перимидини с висок добив при реакцията на 1,8-диаминонафтален с ароматни алдехиди в присъствие на молекулен йод като високо-ефективен катализатор. Тази екологично издържана и чиста процедура предлага няколко предимства: висок добив, кратко време за реакция и опростена работа. Оценена е анти-бактериалната активност на тези препарати върху бактериалните щамове *Staphylococcus aureus* (mm) и *Escherichia coli* (mm).