Bulgarian Chemical Communications, Volume 45, Number 3 (353 – 356) 2013

Molecular iodine catalyzed synthesis of some biologically active dihydroperimidines

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Received March 27, 2012; Revised February 7, 2013

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 Escherichia 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] A 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 commercially available catalyst for synthesis of benzothiophens, [16] bis indoles, [17] quinolines, [18] esterification, [19] phenan-thrimidazoles [20] and indazoles.[21]

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

RESULTS AND DISCUSSION

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 mol% 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 mol% 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).

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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	93
6	15	EtOH	6	87
7	7	MeOH	7	61
8	7	CH_3CN	7	72
9	7	DMSO	7	63
10	7	DMF	7	65

[a] Isolated yield

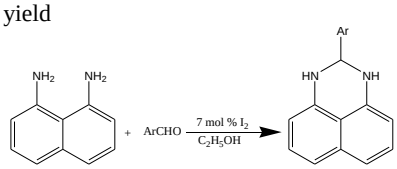

Fig. 1. The scheme preparation of perimidines.

The results of this study are presented in Table 2. We were pleased to find that the reaction of different aromatic aldehydes 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.

Table 2. Reaction of 1,8-diaminonaphthalene with aromatic aldehydes prompted by 7 mol% molecular iodine catalyst in C_2H_5OH.

Compound	Ar	Time (min)	Yield (%)[a]	M.P (°C)
3a	C_6H_5	40	84	105-106 (101-103)[b]
3b	4-OHC_6H_4	60	85	162-164 (161-163)[b]
3c	4-$OCH_3C_6H_4$	20	65	156-158 (151-152)[c]
3d	2-ClC_6H_4	25	95	115-119 (116-118)[b]
3e	3-ClC_6H_4	30	80	143-146 (144-146)[d]
3f	3-BrC_6H_4	20	55	166-168 (165-166)[d]
3g	4-BrC_6H_4	12	96	135-137 (138-140)[c]
3h	2-$NO_2C_6H_4$	8	98	190-192 (191-193)[d]
3i	3-$NO_2C_6H_4$	10	87	185-187 (188-190)[b]
3j	4-$NO_2C_6H_4$	7	93	247-249 (>200)[e]
3k	4-FC_6H_4	20	82	182-183 (180-182)[b]
3l	4-$CH_3C_6H_4$	7	62	165 (161-163)[b]
3m	2-OH,5-BrC_6H_3	15	92	164-166 (165-166)[d]
3n	3,4-$(OCH_3)_2$ C_6H_3	45	88	205 (206-207)[d]

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

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 study

Antibacterial activity of synthesized perimidines was tested against *Staphylococcus aureus* (mm) and *Escherichia 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 *Escherichia coli* as a gram negative. The maximum and minimum antibacterial activities against *Staphylococcus aureus* were related to compounds **3b** and **3e**, respectively. As Table 3 shows the compounds having more electron releasing groups specially OH and OMe groups exert more antibacterial activity compared to others.

EXPERIMENTAL

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 F254 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).

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-1H-perimidine-2-yl)phenol (3b). IR (KBr): 3396, 3331, 3045, 1600, 1517, 1412 cm-1. 1HNMR (DMSO, 300 MHz): δ 5.23 (s, 1H, CH), 6.45-7.41 (m, 12H, CH_{arom}, 2NH), 9.50 (s, 1H, OH). 13CNMR (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 C17H14N2O: 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-1*H*-perimidine (3e). IR (KBr): 3393, 3354, 3045, 2806, 1607, 1416 cm-1. 1HNMR (DMSO, 300 MHz): δ 5.39 (s, 1H, CH), 6.48-7.63 (m, 12H, CH_{arom}, 2NH). 13CNMR (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 C17H13N2Cl: 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-1*H*-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 $C_{17}H_{13}N_3O_2$: 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-1*H*-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 $C_{17}H_{13}N_3O_2$: 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-1*H*-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 $C_{19}H_{18}N_2O_2$: 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

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Постъпила на 27 март, 2012 г.; коригирана на 7 февруари, 2013 г.

(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).