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Original article

Three-component synthesis and antibacterial evaluation of some novel 1,2-dihydroisoquinoline derivatives

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ABSTRACT

Isoquinoline reacts with dialkyl acetylenedicarboxylates in the presence of kojic acid or 8-hydroxyquinoline to generate 1,2-dihydroisoquinoline derivatives. The simplicity, mild reaction conditions and high yields of products make it an interesting process compared to other approaches. The compounds have been analyzed for antibacterial activity against Gram negative and Gram positive bacteria. The results indicated that 1,2-dihydroisoquinolines derived from kojic acid are effective against all of the studied bacteria especially against *Bacillus subtilis*, while the products obtained from 8-hydroxyquinoline are active only against Gram positive bacteria.

1. Introduction

The isoquinolines are of great importance to humanity because of their biological and medicinal activities [1]. In particular, 1,2-dihydroisoquinolines exhibit antidepressant [2], sedative [3], antitumor and antimicrobial activities [4]. Recently, the 1,4-dipolar intermediates generated by reacting isoquinoline with acetylenic esters were trapped by NH-acids such as indoles [5,6] and amides [7] and CH-acids like phenyl acetylene [8], β-diketones [9–11] and β-nitro ketones [12] as well as OH-acids, such as 6-hydroxy1-benzofuran [13]. On the other hand, the interest in biological substances involving kojic acid and 8-hydroxyquinoline increased. Kojic acid, 8-hydroxyquinoline and their derivatives have shown to possess various bioactivities such as antimicrobial [14–16], antitumor [17,18], antioxidant [19], antibacterial [20–22]. On the basis of these reports, we were encouraged to synthesize novel 1,2-dihydroisoquinolines, including kojic acid or 8-hydroxyquinoline moieties within their structures.

We herein report the reactions of isoquinoline and acetylenic esters **1a–e** with kojic acid **2** or 8-hydroxyquinolone **3** as OH-acids to synthesize 1,2-dihydroisoquinolines 4**a–e** and **5a**, **5d–e**, respectively (Scheme 1).

2. Experimental

Pyridine, isoquinoline, kojic acid, 8-hydroxy quinoline and electron-deficient acetylenic esters were obtained from Fluka (Buchs, Switzerland) and Merck (Germany) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. The IR spectra were recorded on a FT-IR Bruker Vector 22 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker DRX-400 AVANCE spectrometer at 400.13 MHz and 100.6 MHz, respectively. Mass spectra were measured on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 30 eV.

2.1. General procedure for synthesis of compound 4

To a mixture of kojic acid (2 mmol) and acetylenic esters (2 mmol) in THF (10 mL), was added isoquinoline (2 mmol). The reaction mixture was stirred for 2 h at room temperature for

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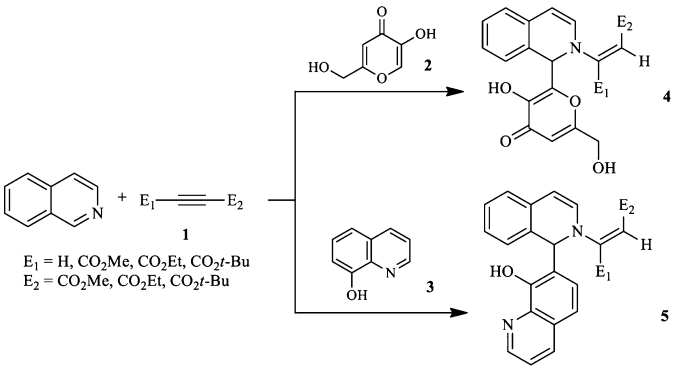

Scheme 1. Reactions of isoquinoline and acetylenic esters **1** with kojic acid **2** or 8-hydroxyquinolone **3** as OH-acids.

dialkyl acetylenedicarboxylates or 7–8 h at 60 °C for alkyl acetylenecarboxylates. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane:ethyl acetate = 1:4, v:v) the products **4a–e** were obtained in good to high yields (58%–80%) as white or yellow powders.

Dimethyl (2*Z*)-2-[1-[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]isoquinolin-2(1*H*)-yl]but-2-enedioate (**4a**): Yellow powder, yield: 80% mp 112–114 °C. IR (KBr, cm^{-1}): υ_{max} 3422 (OH), 1739 and 1701 (2C=O). ^1H NMR (400.1 MHz, DMSO-d_6): δ 3.56 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.09 and 4.13 (AB quartet and doublet, 2H, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 6.4 Hz, OCH_2), 5.24 (s, 1H, N–C=CH), 5.60 (t, 1H, $^3J_{HH}$ = 6.4 Hz, OH), 5.95 (d, 1H, $^3J_{HH}$ = 8.0 Hz, =CH), 6.26 (s, 1H, NCH), 6.43 (s, 1H, CH), 6.50 (d, 1H, $^3J_{HH}$ = 8.0 Hz, =CH), 7.17 (d, 1H, $^3J_{HH}$ = 7.2 Hz, $CH_{aromatic}$), 7.20–7.28 (m, 3H, $3CH_{aromatic}$), 10.06 (s, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 51.5 and 53.7 ($2OCH_3$), 53.8 (NCH), 59.8 (OCH_2), 90.4 (CH), 107.8 (CH), 109.6 (O–C=*CH*), 125.4, 126.6, 127.3 and 128.1 (4CH), 128.6 (Cq), 129.3 (CH), 129.6, 139.7, 147.2, 149.6 and 164.6 (5Cq), 166.6 and 168.4 (2C=O, esters), 173.8 (C=O, pyrone). MS (*m*/*z* %): 413 (M^+, 5), 382 (M^+-OCH_3, 2), 354 (M^+-CO_2Me, 26), 322 [$M^+-(CO_2Me+OMe+H)$, 5], 272 ($M^+-C_6H_5O_4$, 12), 252 [$M^+-(2OMe+C_4H_3O_3)$, 13], 225 [$M^++1-(CO_2Me+OMe+C_4H_3O_3)$, 24], 167 ($C_7H_5NO_4^+$, 9), 129 ($C_9H_7N^+$, 100), 102 ($C_8H_6^+$, 26).

2.2. General procedure for synthesis of compound *5*

To a mixture of 8-hydroxy quinoline (2 mmol) and acetylenic esters (2 mmol) in dichloromethane (10 mL), was added isoquinoline (2 mmol). The reaction mixture was stirred for 30 min at room temperature for dialkyl acetylenedicarboxylates or 1 h at room temperature for alkyl acetylenecarboxylate. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The solid residue was purified and washed further with diethyl ether and products **5a** and **5d–e** were obtained in high yields (62%–94%) as yellow powders.

2.3. General procedure for evaluation of antibacterial activity

In vitro antibacterial activity of the compounds **4a**, **4d–e**, **5a** and **5d–e** was assayed using the disc diffusion method with determination of inhibition zones [36]. The Gram negative and Gram positive test organisms were used as follows: *Escherichia coli* PTCC 1330, *Pseudomonas aeruginosa* PTCC 1074, *Staphylococcus aureus* ATCC 35923 and *Bacillus subtilis* PTCC 1023 [37]. The late exponential phases of the bacteria were standardized with a final cell density of approximately 10^8 cfu/mL. Muller-Hinton agar (Merck) were prepared and inoculated from the standardized cultures of the test organisms, then spread as uniformly as possible throughout the entire media. Sterile paper discs (6 mm diameter, Padtan, Iran) were impregnated with 20 μL of the compound solution (20 mg/mL in DMSO) then placed on the upper layer of the seeded agar plate and incubated at 37 °C for 24 h. The antibacterial activities of the compounds **4a**, **4d–e**, **5a** and **5d–e** were compared with known antibiotic gentamicin (10 μg/disc) and chloramphenicol (30 μg/disc) as positive control and DMSO (20 μL/disc) as negative control. Antibacterial activity was evaluated by measuring the diameter of inhibition zone (mm) on the surface of plates and the results reported as mean ± SD after three repeats.

3. Results and discussion

3.1. Chemistry

The reaction of kojic acid and dimethyl acetylenedicarboxylate (DMAD) with isoquinoline at room temperature afforded compound **4a** in good yield (80%). Similarly, 8-hydroxyquinoline reacted smoothly with dimethyl acetylenedicarboxylate (DMAD) and isoquinoline to give the desired 1,2-dihydroisoquinoline **5a** in high yield (95%). In order to examine the scope and limitations of this reaction, we extended our study to the other acetylenic diesters and monoesters and the results are shown in Table 1. When the reaction was performed with alkyl acetylenecarboxylate, instead of dialkyl acetylenedicarboxylate, with only one electron-withdrawing substituent (CO_2R), the yield of the corresponding product was decreased (Table 1, comparing entries 1 with 4, entries 6 with 7 and 2 with 5). This might probably be due to the lower electrophilicity of the β-carbon of monoesters. Interestingly, sterically hindered diesters, such as di-*tert*-butyl acetylenedicarboxylate reacted with kojic acid to produce the corresponding 1,2-dihydroisoquinoline **4c** in good yield (73%).

It is noteworthy to mention that when pyridine was used instead of isoquinoline in reactions with kojic acid in the presence of acetylenic esters under the same reaction conditions, the corresponding C-vinylated products of kojic acid were obtained as reported previously (Scheme 2) [23].

When quinoline was used in this reaction, in all cases a complex mixture was obtained, which could not be identified.

A proposed mechanism for the reactions is shown in Scheme 3. On the basis of the well-established chemistry of *N*-heterocyclic nucleophiles [24–35], it is reasonable to assume that the 1:1

Table 1
Reaction of isoquinoline, kojic acid, 8-hydroxyquinoline and acetylenic esters.

Entry	Compounds	OH-acid	E_1	E_2	Temperature	Time (h)	Yield (%)
1	**4a**	Kojic acid	CO_2Me	CO_2Me	r.t.	2	80
2	**4b**	Kojic acid	CO_2Et	CO_2Et	r.t.	2	78
3	**4c**	Kojic acid	$CO_2{}^t$-Bu	$CO_2{}^t$-Bu	r.t.	2	73
4	**4d**	Kojic acid	H	CO_2Me	70 °C	7	62
5	**4e**	Kojic acid	H	CO_2Et	70 °C	8	58
6	**5a**	8-Hydroxy quinoline	CO_2Me	CO_2Me	r.t.	0.5	94
7	**5d**	8-Hydroxy quinoline	H	CO_2Me	r.t.	1	65
8	**5e**	8-Hydroxy quinoline	H	CO_2Et	r.t.	1	62