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Facile aromatization of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) by iodine

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Abstract

A facile aromatization of 3,4-dihydropyrimidin-2(1*H*)-ones using iodine in dimethyl sulfoxide under microwave irradiation was carried out which is more efficient and gives high yield in less time; presently it is the most important catalyst for dehydrogenation.

Keywords: Dihydropyrimidiones; Iodine; Oxidation; Aromatization

The one-pot three-component Biginelli reaction has been known for more than a century [1], these nonplanar heterocyclic compounds have received considerable attention from the pharmaceutical industry because of their interesting multifaceted pharmacological profiles. These 1,4-dihydropyridines (DHPs) are a class of compounds of NADH coenzyme [2], which have been extensively studied in view of the biological importance of these compounds to the NADH redox process [3]. These compounds have therapeutic functions for treatment of a variety of diseases [4], such as cardiovascular disorders [4a], cancer [4b] and AIDS [4c]. The oxidation of DHPs to the corresponding pyridine derivatives constitutes the principal metabolic route in biological systems, as well as a facile access to the corresponding pyridine derivatives, which show antihypoxic and antiischemic activities [5], from the easily available DHPs [6]. Therefore, oxidative aromatization of DHPs has attracted continuing interests of organic and medicinal chemists and a plethora of protocols has been developed [7].

Until now the aromatization can be carried out by different ways such as HNO_3, $KMnO_4$ and CAN, $PhI(OAc)_2$ and *t*-BuOOH. Recently, attention has been paid to more efficient and environmentally benign methods, such as electrochemical oxidation [8] and catalytic aerobic oxidation using $RuCl_3$ [9], Pd/C [10], activated carbon [11,12] or $Fe(ClO_4)_3$ [13] as the catalyst. By going through the literature, we made our way to the iodine catalyzed aromatization in microwave, as it is easy, efficient and 5–7 min reaction time. Moreover molecular iodine has environmentally benign characteristics [14]; it is inexpensive, non-toxic, insensitive to air and moisture and can be easily removed from

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the reaction mixture. We have exposed the aromatization of 3,4-dihydropyrimidin-2(1*H*)-ones by iodine in DMSO under microwave irradiation.

1. Experimental

The acid-catalyzed cyclo condensation reaction of benzaldehyde (1 mol), ethyl acetoacetate (1 mol) and urea (1 mol) was carried out by refluxing with a catalytic amount of HCl on water bath for 1 h. The completion of reaction was monitored by TLC (ethylacetate:hexane = 60:40). The reaction mixture was poured into crushed ice. The separated solid product was filtered and dried.

Compound (**1a**): White color; IR (KBr, cm^{-1}): 3649.44, 2977.23, 1897.54, 1602.90, 1222.43, ^1H NMR (400 MHz, DMSO-d_6): δ 8.1 (S, 1H), 5.7 (S, 1H), 5.2 (S, 1H), 7.2 (m, 5H) 4.1 (q, 2H), 1.2 (t, 3H), 2.3 (S, 3H).

3,4-Dihydropyrimidin-2(1*H*)-ones and iodine (1:1 mol) were taken in DMSO, and irradiated in microwave reactor at 120 °C for 5 min. The completion of reaction was monitored by TLC (ethylacetate:hexane = 50:50). The brown-red colored reaction mixture was poured into saturated solution of sodium thiosulfate. The separated solid product was filtered, dried and recrystallized from methanol.

Compound (**3a**): Brown color; IR (KBr, cm^{-1}): 3587.72, 3162.40, 1539.73, 1696.93, 1122.67, ^1H NMR (400 MHz, DMSO-d_6): δ 8.5 (S, 1H, exchangeable with D_2O), 7.2–7.9 (m, 5H), 4.3 (q, 2H), 1.4 (t, 3H), 2.1 (S, 3H).

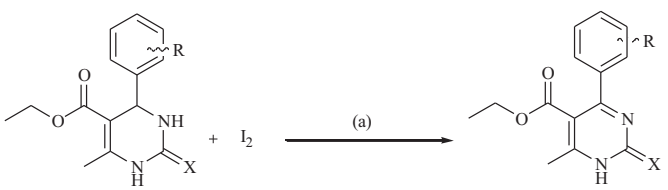
2. Result and discussion

The original Biginelli protocol for the preparation of the DHMPs (**1a–e**, **2a–e**) was followed; *i.e.* the acid-catalyzed cyclo condensation reaction of benzaldehyde, ethyl acetoacetate and urea in presence of catalytic amount of HCl which is depicted in Table 1.

Oxidants such as PCC, $KMnO_4$/clay, DDQ, Chloranil, CAN and $NaNO_2$ are inefficient for the conversion of DHPMs to pyrimidines [15]. There is a report in the literature which describes that the oxidizing properties of iodine. Therefore, we decided to use iodine reagents. A clean and efficient oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones to 1,2-dihydropyrimidines has been achieved using iodine and DMSO (see Scheme 1).

Table 1
Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

Entry	Product	R	X	Time (min)	Yield %	m.p. (°C)
1.	**1a**	H	O	45	90	217–221
2.	**1b**	4-O-CH_3	O	60	80	212–215
3.	**1c**	2,5-O-CH_3	O	65	72	225–227
4.	**1d**	4-OH	O	50	86	238–240
5.	**1e**	4-Cl	O	85	67	249–251
6.	**2a**	H	S	50	70	258–261
7.	**2b**	4-O-CH_3	S	65	71	261–263
8.	**2c**	2,5-O-CH_3	S	65	74	260–263
9.	**2d**	4-OH	S	50	69	252–254
10.	**2e**	4-Cl	S	80	62	272–275

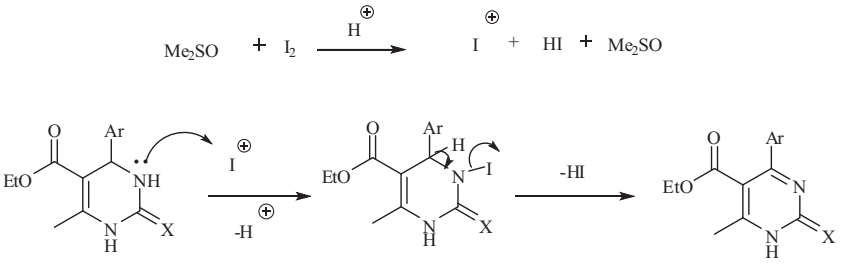


(1a-e, 2a-e) (3a-e, 4a-e)

Scheme 1. Reagent and condition: (a) I_2 (1:1), DMSO, MW, 120 °C.

Table 2
Aromatization of various 3,4-dihydropyrimidin-2(1*H*)-ones.

Entry	Product	R	X	Time (min)	Yield %	m.p. (°C)
11.	**3a**	H	O	5	94	215–217
12.	**3b**	4-O-CH_3	O	5	76	228–230
13.	**3c**	2,5-O-CH_3	O	6	82	191–193
14.	**3d**	4-OH	O	5	90	235–237
15.	**3e**	4-Cl	O	7	68	254–256
16.	**4a**	H	S	5	80	239–241
17.	**4b**	4-O-CH_3	S	5	67	220–223
18.	**4c**	2,5-O-CH_3	S	6	84	247–251
19.	**4d**	4-OH	S	6	76	256–259
20.	**4e**	4-Cl	S	7	69	269–271



Scheme 2. The propose mechanism of the reaction.

Oxidations of several DHPMs with aryl and alkyl substituents at C-4 were carried out. All the reactions were completed in between 5 and 7 min; high yields of the products were obtained. The structures of all the products were established from IR, NMR, and mass spectral analysis. Mild reaction conditions, short reaction times, and easy isolation of the desired product make the present method convenient. The results are summarized in Table 2.

The proposed mechanism (Scheme 2) for the reaction shows the formation of iodonium ion [16] which will catalyze the reaction at 120 °C. The color of the reaction persist till end indicates the regeneration of iodine. The reaction was quenched in dilute HCl.

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