Synthesis of pyrimidines, aromatic and heteroaromatic acids as Biginelli reaction catalysts

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Síntesis de pirimidinas y ácidos aromáticos y heteroaromáticos como catalizadores de la reacción de Biginelli

Síntesi de pirimidines i àcids aromàtics y heteroaromàtics com a catalitzadors de la reacció de Biginelli

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RESUMEN

Se ha hallado que ácidos aromáticos y heteroaromáticos son catalizadores excelentes de la síntesis de dihidropirimidonas mediante la reacción de tres componentes de Biginelli. Para este propósito pueden utilizarse ácido benzoico, ácidos benzoicos substituidos, o ácidos heterocíclicos de 5 y 6 miembros.

Palabras clave: Reacciones multicomponente, Pirimidinas, Urea, Tiourea

SUMMARY

Aromatic as well as heteroaromatic acids were found to be excellent catalysts for the Biginelli three component synthesis of dihydropyrimidinones. Benzoic acid, substituted benzoic acids, five- and six- membered heterocyclic acids can be used for this purpose.

Key words: Multiple component reactions, Pyrimidines, Urea, Thiourea.

RESUM

S'ha trobat que els àcids aromàtics i heteroaromàtics son excel·lents catalitzadors de la síntesis de dihidropirimidones mitjançant la reacció de tres components de Biginelli. Amb aquest objectiu es poden utilitzar àcid benzoic, àcids benzoics substituïts, o àcids heterocíclics de 5 y 6 membres.

Mots clau: Reaccions multicomponent, Pirimidines, Urea, Tiourea

INTRODUCTION

The Biginelli reaction is one of the important multicomponent reactions (MCRs) which results in affording dihydropyrimid-2-ones and 2-thiones[1,2].These pyrimidines are interesting potential scaffolds for the preparation of a large number of heterocyclic molecules with useful biological activities of which calcium channel blockers are already in clinical use[3].Biginelli reaction has recently been reviewed encompassing various aspects of the reaction[4]. A number of catalysts have found to be effective in promoting the reaction and the list is ever expanding. Our own interest in this reaction has led us to the use of novel catalysts/ conditions in these reactions with competitive if not higher yields of the products. We have already reported the use of copper salts[5], high boiling alcohols[6] and amino acids[7], among others, under investigations. The original Biginelli reaction was conducted with acid catalysis [1]. The scope was increased by involving a series of aliphatic carboxylic acids[8]. While contemplating to explore the usefulness of aromatic carboxylic acid as catalysts in this reaction, we were constrained to go ahead in view of the findings of Feng *et al*.[9] who reported high enantioselectivity (up to 98% in the cyclocondensation of various aldehydes, ethyl acetoacetate and urea by a "dual activation" using a combination of a hydroxyproline and Bronsted acids (such as TFA and substituted benzoic acids). However, the reaction yields were poor (8-22%). Another publication of a similar nature[10] also mentions use of a few aromatic acids but with longer reaction period (72-98 hrs.).

Some preliminary experiments in our laboratories using benzoic acids as catalysts were successful which encouraged us to follow this with other aromatic and heteroaromatic acids. The results are being reported in the present communication.

MATERIAL AND METHODS

All the chemicals and reagents used in the present study were commercial products. These were purified by usual methods of distillation (for liquids) and crystallization from appropriate solvents (for solids). Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer spectrum BX-1 and NMR on a Brucker 400 MHz spectrometer using tetramethylsilane as an internal reference.

Synthesis of 4-aryl-6-methyl-2-oxo (or thio)-1,2,3,4-tetrahydropyrimidine-5-carboxylates and 5-acetyl-4-aryl-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-ones (or thiones) (I and II)

General method

A mixture of 40 mmole of an aldehyde, 40mmol β-diketo compound, 45 mmole urea or thiourea and catalytic amount of the acid (10 mg) in 10 mL of ethanol or methanol was heated under reflux for a 8-16 hours period. The reaction was monitored by TLC. After cooling the reaction mixture was diluted with water, kept for a few hours, the precipitates were filtered off, washed with water and dried. A portion was recrystallised from ethanol to give the expected dihydropyrimidinone (or thione) (**I** and **II**, **Scheme 1**). The results are presented in **Table 1**.

All the products of the reactions were compared with the authentic samples prepared by the literature methods and were found to be identical in all respects m.p., mixed m.p., FTIR or other spectra. IR and ^{1}HNMR spectra of some representative compounds are given below.

Ethyl 6-methyl-2-oxo-4- phenyl-1, 2, 3, 4- tetrahydropyrimidine -5-carboxylate (Ia)

FTIR (KBr) cm^{-1}: 3414(NH), 3230, 3109, 2936, 1735(C=O, ester), 1680(C=O, Pyrimidine), 1620, 1490(Aromatic).

^{1}H-NMR (DMSO-d_6): δ 9.17 (s, 1 H, NH), 7.72 (s, 1 H, NH), 7.21–7.32 (m, 5H, Ar-H), 5.5 (s, 1 H, CH), 3.98 (q, *J* = 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.24 (s, 3 H, Me), 1.08 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C$\underline{H}_3$).

^{13}C-NMR (DMSO-d_6): δ 165.4, 152.2, 148.4, 144.9, 128.4, 127.9, 127.8, 127.3, 126.3, 99.3, 59.2, 54.0, 17.8, 14.1.

Ethyl 4-(4'-hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (Ib)

FTIR (KBr) cm^{-1}: 3417(NH), 3241(OH), 3120, 2984, 1742(C=O, ester), 1687(C=O, Pyrimidine), 1612, 1485(Aromatic).

^{1}H NMR (DMSO-d_6): δ 9.32 (s, 1 H,NH), 7.67 (s, 1 H,NH), 6.69-7.02 (m, 4 H, Ar-H), 5.61 (s, 1H,OH), 5.04 (s, 1 H), 3.97 (q, *J* = 7.2 Hz, 2 H, OC$\underline{H}_2$CH$_3$), 2.23 (s, 3 H), 1.08 (t, *J* = 7.2 Hz,3 H, OCH$_2$C$\underline{H}_3$).

^{13}C NMR (DMSO-d_6): δ 165.4, 156.6, 152.2, 147.8, 135.5, 128.9, 128.4 127.4, 115.0, 99.8, 59.1, 53.5, 17.8, 14.1.

Ethyl 6-methyl-4- phenyl-2-thioxo-1, 2, 3, 4- tetrahydropyrimidine-5-carboxylate (IIa)

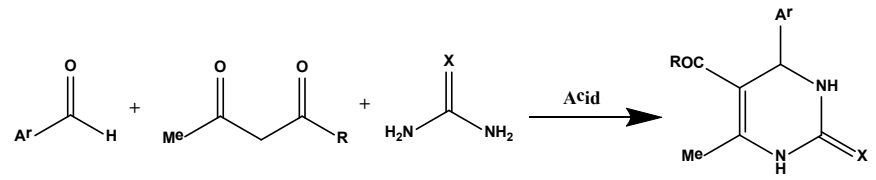
FTIR (KBr) cm^{-1}: 3327(NH), 3174, 3105, 2981, 1745(C=O, ester), 1622 ,1498(Aromatic), 1571 (C=C), 1465, 1326, 1197, 759.

^{1}H NMR (DMSO-d_6): δ 7.27-7.31 (m, 5H, Ph), 5.30 (s, 1H, CH, H- 4), 4.07 (q, 2H, OC$\underline{H}_2$CH$_3$, *J* = 7.32 Hz), 2.44 (s, 1H, NH), 2.34 (s, 3H, CH3), 2.15 (s, 1H, NH), 1.16 (t, 3H, OCH$_2$C$\underline{H}_3$, *J* = 7.23 Hz).

^{13}C NMR (DMSO-d_6): δ 176.0, 166.9, 145.6, 144.5, 129.5, 128.8, 127.6, 127.4, 126.2 102.8, 61.0, 56.1, 17.8, 14.5.

RESULTS AND DISCUSSION

A condensation reaction for the preparation of dihyropyrimidinones and thiones (DHPM, X=O or S) was carried out. In this preliminary reaction of benzaldehyde, ethyl acetoacetate and urea in ethanol solvent, benzoic acid was used as a catalyst. DHPM was isolated in 28% yield with urea **(Table 1)** while with thiourea the product was isolated in 17% yield **(Table 2)**. However, when the reaction with thiourea was carried out in methanol over a period of 16 hrs., the yield was somewhat improved (47%) **(Table 3)**. Encouraged by these results other aromatic acids and some derivatives of heteroaromatic acids were employed for these Biginelli reactions **(Table 1-3)**.It was observed that benzoic acids with electron withdrawing groups and the heteroaromatic acids gave better results. In the case of nicotinic and isonicotinic acids, the pyridine ring has a similar influence (heteroaromatic acids such as pyridine carboxylic acids are slightly stronger acids than benzoic acid[11]). It is interesting to note that in these Biginelli condensations commercial pharmaceutical products such as mefenamic acid and nalidixic acid can also be used as catalysts. Furthermore change of solvent, from ethanol to



Ia Ar = Ph R = OEt
Ib Ar = 4-HOC_6H_4 R = OEt
Ic Ar = 4-HOC_6H_4 R = Me
Id Ar = Ph R = Me
Ie Ar = 3,4-$O(CH_2)_2C_6H_3$ R = OEt

Ia-Ie X = O
IIa-IIb X = S

IIa Ar = Ph R = OEt
IIb Ar = 4- HOC_6H_4 R = Me

Scheme 1

methanol, also somewhat improved the yields. Various other aspects of this reaction are continuously under exploration in our laboratories.

Table 1: *Dihyropyrimidin-2-ones, aromatic and heteroaromatic acids catalysts in ethanol*

Catalyst	Solvent	Time (hr.)	Product	Yield	m.p.	Lit. m.p.
Benzoic acid	EtOH	8	**Ia**	28	200	202-204[12]
2-Chlorobenzoic acid	EtOH	8	**Ia**	30	200	202-204[12]
2-Chloro-4-nitrobenzoic acid	EtOH	8	**Ia**	39	200	202-204[12]
2-Chloro-4-nitrobenzoic acid	EtOH	8	**Ia**	47	200	202-204[12]
Phenylacetic acid	EtOH	8	**Ia**	50	200	202-204[12]
Mefenamic acid	EtOH	8	**Ia**	31	200	202-204[12]
Nicotinic acid	EtOH	8	**Ia**	79	200	202-204[12]
Isonicotinic acid	EtOH	8	**Ia**	73	200	202-204[12]
Nalidixic acid	EtOH	8	**Ia**	53	200	202-204[12]
Pyrazine-2-carboxylic acid	EtOH	8	**Ia**	36	200	202-204[12]
1,3-diphenylpyrazole-4-carboxylic acid	EtOH	8	**Ia**	59	200	202-204[12]
3,5-dimethyl-1-phenyl-pyrazole-4-carboxylic acid	EtOH	8	**Ia**	59	200	202-204[12]
3,5-dimethyl-1-(*p*-nitrophenyl-pyrazole-4-carboxylic acid	EtOH	8	**Ia**	51	200	202-204[12]
2-Furoic acid	EtOH	8	**Ia**	57	200	202-204[12]
Indole-2-carboxylic acid	EtOH EtOH	8 10	**Ib** **Ic**	75 72	202 183	196-198[14] 206-208[16]
Indole-3-acetic acid	EtOH EtOH	8 15	**Id** **Ie**	80 71	197 195	234-235[15] 186-189[17]

Table 2: *Dihyropyrimidin-2-thiones, aromatic and heteroaromatic acids catalysts in ethanol*

Catalyst	Solvent	Time (hr.)	Product	Yield	m.p.	Lit. m.p.
Benzoic acid	EtOH	12	**IIa**	17	202	209-211[13]
2-Chlorobenzoic acid	EtOH	10	**IIa**	21	204	209-211[13]
2-Chloro-4-nitrobenzoic acid	EtOH	10	**IIa**	23	203	209-211[13]
2-Chloro-4-nitrobenzoic acid	EtOH	12	**IIa**	25	203	209-211[13]

Phenylacetic acid	EtOH	10	**IIa**	16	204	209-211[13]
Nicotinic acid	EtOH	12	**IIa**	25	204	209-211[13]
3,5-dimethyl-1-phenyl-pyrazole-4-carboxylic acid	EtOH	12	**IIa**	21	203	209-211[13]
3,5-dimethyl-1-(p-nitrophenyl-pyrazole-4-carboxylic acid	EtOH	12	**IIa**	22	203	209-211[13]
Indole-2-carboxylic acid	EtOH	16	**IIb**	65	185	252-254[18]

Table 3: *Dihyropyrimidin-2-thiones, aromatic and heteroaromatic acids as catalysts in methanol*

Catalyst	Solvent	Time (hr.)	Product	**Yield**	**m.p.**	**Lit. m.p.**
Benzoic acid	MeOH	16	**IIa**	49	202	209-211[13]
2-Chlorobenzoic acid	MeOH	12	**IIa**	45	204	209-211[13]
2-Chloro-4-nitrobenzoic acid	MeOH	16	**IIa**	48	203	209-211[13]
2-Chloro-4-nitrobenzoic acid	MeOH	12	**IIa**	59	203	209-211[13]
Phenylacetic acid	MeOH	12	**IIa**	50	204	209-211[13]
Mefenamic acid	MeOH	16	**IIa**	63	204	209-211[13]
Nicotinic acid	MeOH	16	**IIa**	59	204	209-211[13]
Isonicotinic acid	MeOH	16	**IIa**	61	203	209-211[13]
Nalidixic acid	MeOH	16	**IIa**	66	204	209-211[13]
Pyrazine-2-carboxylic acid	MeOH	16	**IIa**	58	205	209-211[13]
1,3-diphenylpyrazole-4-carboxylic acid	MeOH	16	**IIa**	57	204	209-211[13]
3,5-dimethyl-1-phenyl-pyrazole-4-carboxylic acid	MeOH	16	**IIa**	51	203	209-211[13]
3,5-dimethyl-1-(*p*-nitrophenyl-pyrazole-4-carboxylic acid	MeOH	16	**IIa**	47	203	209-211[13]
2-Furoic acid	MeOH	12	**IIa**	44	202	209-211[13]

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