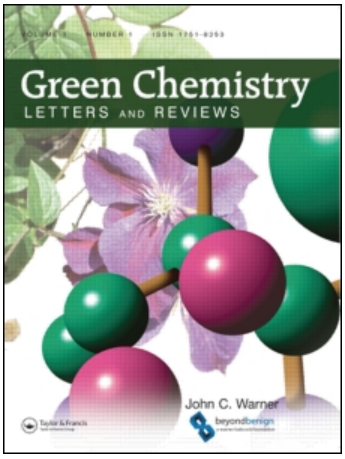

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RESEARCH ARTICLE

Vulnerability of substituted aromatic hydroxy aldehydes to undergo Biginelli reaction in water

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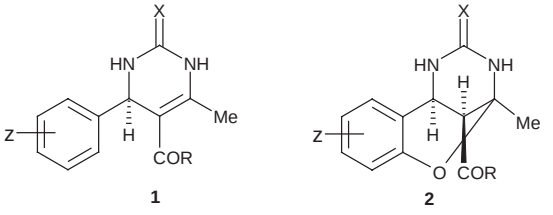
Aromatic aldehydes having hydroxyl substituent(s) react with urea (or thiourea), and ethyl acetoacetate (or acetylacetone) in the presence of *p*-toluenesulfonic acid as catalyst and water as solvent to give substituted dihydropyrimidinones (Biginelli compounds) in good to excellent yields.

Keywords: substituted aromatic hydroxy aldehydes; Biginelli reaction in water; dihydropyrimidinones

Introduction

The acid catalyzed one-pot cyclocondensation reaction between an aldehyde–urea (or thiourea) and a β-ketoester to produce substituted dihydropyrimidinones **1**, known as Biginelli (*1,2*) compounds, have received significant attention because of their diverse range of biological properties. In addition to their antihypertensive and vasodilator properties (*1–9*), dihydropyrimidinones are integral parts of biologically active compounds such as antiviral (*10,11*), antibacterial (*12*), antiinflammatory (*13,14*), and antitumor (*15–18*) agents. Due to their structure relationship to the clinically important nifidepine (*20,21*) (a dihydropyridine) they have emerged as integral backbones of several calcium channel blockers.



X = O, S; R = Me, OEt; Z = substituent(s)

Some of the interest in this heterocyclic system is the challenge of redesigning and improving its old preparative synthetic method. One of the factors which have direct influence on the product yield and found considerable attention is the type of the solvent media used. The reaction is usually carried out in an alcoholic solution catalyzed by a few drops of concentrated HCl or sulfuric acid as reported early by Biginelli (*1,2*). Other systems such as tetrahydrofuran (THF)/HCl, acetic acid (*22*), acetic acid/HCl (*22*), dioxin/HCl (*22*), tartaric acid/methanol (*23*), and acetonitrile with a substantial amount of iodine have been also employed (*24*). Several solvent-free methods have been recently reported using different Lewis acids such as LiBr (*25*), $ZnCl_2$ (*26*), benzyltriethylammonium chloride (*18,19*), chlorosulfonic acid (*27*) and many other methods including microwave irradiations (*28*).

Moreover, the grinding of Biginelli components was recently reported by Bose (*19*) who observed the presence of an exothermic reaction upon mixing the three components, this has developed the idea of using water to remove thermal energy from the reaction mixture and in turn as a solvent media. In a number of publications, Shutalev (*29–31*) has reported a two steps method involving the use of water as a solvent and α-tosyl substituted ureas (or thioureas) with enolates of β-oxoesters or 1,3-dicarbonyl compounds.

In the present work, we report our interesting observation about the vulnerability of various substituted aromatic hydroxy aldehydes to undergo Biginelli reaction in water under conditions similar to that reported by Shutalev, but by applying a one-pot reaction method in the presence of water as solvent and *p*-toluenesulfonic acid as catalyst. *p*-Toluenesulfonic acid may acts as a barrier for the hydroxyl group thus facilitating the reaction to occur in water.

Results and discussion

The Shutalev procedure was based on the reaction between N-tosylurea or N-tosyl-thiourea (obtained via reaction of *p*-toluenesulfinic acid and urea or thiourea) and the condensation product of aldehyde-β-ketoester. On this basis we believe that either the formation of N-tosylurea (or thiourea) or the

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presence of a hydroxyl substituent may present a media suitable for the reaction to take place in a hydrous solvent such as water. The aldehydes used in this investigation include salicylaldehyde and some of its derivatives, dihydroxy benzaldehydes, and other hydroxy aromatic aldehydes. The reaction was carried out simply by mixing the aldehyde, a slight excess of ethyl acetoacetate (or acetylacetone), two equivalents of urea (or thiourea) and *p*-toluenesulfonic acid using water as the solvent media. Some reactions occurred at room temperature and others required heating at the reflux temperature. The products were obtained in 75–95% yields in high purity. The products from salicylaldehyde derivatives depend on the type of the substituent group located at the ortho-position to the hydroxyl group as was reported and discussed in two of our previous publications (*32,33*). For example, salicylaldehyde gave the oxygen bridged oxacyclic product (2), while 3-nitrosalicylaldehyde gave the classical Biginelli product (1). This was tentatively explained by the creation of a hydrogen bond between the oxygen–nitro group and the hydroxyl-proton which prevents cyclization to occur. Condition of the reaction, yields and melting points of the prepared compounds are presented in Tables 1 and 2.

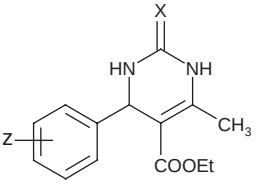
Experimental

Melting points were taken on a capillary melting point apparatus and are uncorrected. The IR spectra were recorded with a Philips Infracord Spectrophotometer Model PU9712 in KBr discs. ^{1}HNMR spectra were measured in $CDCl_3$ or DMSO-d_6 on JEOL-270 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained with a Schimadzu GCS-QP 1000 EX spectrometer at 70eV. Elemental analysis was performed at the Microanalytical Laboratory of the National Research Centre, Dokki, Giza, Egypt. Physical data of some of the prepared compounds are matched with those previously reported. The results of elemental analysis of the new compounds are in the acceptable range.

General procedure for preparation of 4-(substitutedphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (3a–h & 4a–g) and substituted-11-oxo-(thioxo)-8-oxa-10,12-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5a–c & 6a–f)

A mixture consisting of the aldehyde derivative (10 mmol), urea or thiourea (20 mmol), ethylacetoacetate or acetylacetone (25 mmol), *p*-toluenesulfonic

Table 1. Physical data of dihydropyrimidinones (thiones) under water-solvent condition.



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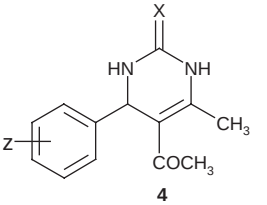

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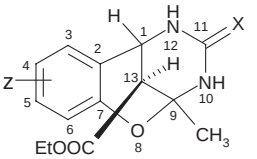
No.	X	Z	R.t./Refl.	Yield (%)	M.p.°C
3a	O	(4–OH) (3–OCH_3)	R.t.	88	231–233 (*34*)
3b	S	(4–OH) (3–OCH_3)	R.t.	95	267–269
3c	O	(3–OH)(4–OCH_3)	R.t.	85	202–204
3d	O	(2–OH)(3–OCH_3)	R.t.	80	185–187 (*33*)
3e	O	(2–OH)(3–NO_2)	Refl.	90	134–137 (*33*)
3f	O	(4–OH)	R.t.	93	228–230 (*26,27*)
3g	S	(4–OH)	R.t.	95	195–197 (*26*)
3h	O	3,5–$(OH)_2$	R.t.	92	230–234
4a	O	(3–OCH_3)(4–OH)	R.t.	90	235–236
4b	S	(3–OCH_3)(4–OH)	R.t.	86	232–234
4c	O	(3–OH)(4–OCH_3)	R.t.	83	202–204
4d	O	(2–OH)(3–NO_2)	Refl.	87	181–183 (*32*)
4e	O	(4–OH)	R.t.	90	230–233 (*24*)
4f	S	(4–OH)	R.t.	92	196–198
4g	O	3,5–$(OH)_2$	R.t.	89	230–232



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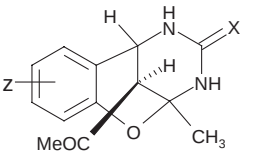

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Table 2. Physical data of diazatricyclotridecatrienes under water-solvent condition.

No.	X	Z	R.t./Refl.	Yield (%)	M.p.°C
5a	O	H	R.t.	83	200–203 (*24,26,32*)
5b	S	H	R.t.	87	204–206 (*32*)
5c	O	5–OH	R.t.	79	179–181 (*33*)
6a	O	H	R.t.	88	215–218 (*32*)
6b	S	H	R.t.	89	257 (decd.) (*32*)
6c	O	5–OH	R.t.	84	200–202
6d	S	5–OH	R.t.	89	146–148
6e	O	6–OCH_3	Refl.	86	245–247 (*32*)
6f	S	6–OCH_3	Refl.	89	240–243 (*32*)

acid (20 mmol) and water (50 mL) was stirred at room temperature (24–36 h, monitored by TLC). The compounds **3e**, **4d**, **6e**, and **6f** required heating under reflux for 8 h. The reaction mixture appeared clear during the course of the reaction and then the product starts to separate out. The solid obtained after completion of the reaction was filtered, washed with water, dried and crystallized from the proper solvent. Physical data of some prepared compounds are matched with those previously reported.

3b ^{1}H-NMR ($CDCl_3$): δ = 9.55 (s, 1H, OH), 8.20 (s, 1H, NH), 7.82 (s, 1H, NH), 6.80–6.7 (m, 3H, Ar–Hs), 5.35 (*d*, *J* = 3.2 Hz, 1H), 4.12 (*q*, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.78 (s, 3H, OCH_3), 2.31 (s, 3H, CH_3), 1.24 (*t*, *J* = 7.2 Hz, 3H, OCH_2CH_3). Anal. Calcd. for $C_{15}H_{18}N_2O_4S$ (322.39), C, 55.89; H, 5.63; N, 8.69; S, 9.95%; Found: C, 55.75; H, 5.80; N, 8.60; S, 9.85%.

3c ^{1}H-NMR (DMSO-d_6): δ = 9.44 (s, 1H, OH), 8.90 (s, 1H, NH), 7.65 (s, 1H, NH), 6.80–6.65 (m, 3H, Ar–Hs), 5.25 (*d*, *J* = 3.2 Hz, 1H, C4–H), 4.10 (*q*, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.72 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 1.11 (*t*, *J* = 7.2 Hz, 3H, OCH_2CH_3). Anal. Calcd. for $C_{15}H_{18}N_2O_5$ (306.32) C, 58.82; H, 5.92; N, 9.15; Found: C, 58.70; H, 6.15; N, 9.10.

3h ^{1}H-NMR (DMSO-d_6): δ = 9.2 (s, 1H, NH), 8.50 (s, 2H, 2OH), 7.05 (bs, 1H, NH), 6.88 (*d*, *J* = 1.2Hz, 2H, C2′,C6′–H), 6.67, (s, 1H, C4′–H), 5.0 (*d*, *J* = 2 Hz, 1H, C4–H), 4.05 (*q*, 2H, OCH_2CH_3), 2.30 (s, 3H, CH_3), 1.06 (t, 3H, OCH_2CH_3). Anal. Calcd. for $C_{14}H_{16}N_2O_5$ (292.29), C, 57.53; H, 5.52; N, 9.58%; Found: C, 57.50; H, 5.60; N, 9.50%.

4a ^{1}H-NMR (DMSO-d_6): δ = 9.10 (s, 1H, NH), 8.84 (s, 1H, OH), 7.62 (s, 1H, NH), 6.82 (d, *J* = 3 Hz, 1H, C2′–H), 6.7 (*d*, *J* = 12 Hz, 1H, C5′–H), 6.6 (dd, *J* = 12 Hz, 1H, C6′–H), 5,18 (*d*, *J* = 5 Hz, 1H, C4–H), 3.75 (s, 3H, OCH_3), 2.25 (s, 3H, $COCH_3$), and 2.15 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{16}N_2O_4$ (276.29) C, 60.86; H, 5.84; N, 10.14%; Found: C, 60.80; H, 5.95; N, 10.0%.

4b ^{1}H-NMR (DMSO-d_6): ^{1}H-NMR (DMSO-d_6): δ = 9.12 (s, 1H, OH), 8.80 (s, 1H, NH), 7.25 (s, 1H, NH), 6.72 (*d*, *J* = 2Hz, 1H, C2′–H), 6.7 (*d*, *J* = 10Hz, 1H, C5′–H), 6.6 (*dd*, *J* = 10Hz, 1H, C6′–H), 5.24 (*d*, *J* = 5Hz, 1H, C4–H), 3.75 (s, 3H, OCH_3), 2.22 (s, 3H, $COCH_3$), and 2.10 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{16}N_2O_3S$ (292.36) $C_{14}H_{16}N_2O_3S$ C, 57.52; H, 5.52; N, 9.58; S, 10.97%; Found: C, 57.25; H, 5.80; N, 9.40.

4c ^{1}H-NMR (DMSO-d_6): δ = 9.60 (s, 1H, OH), 8.17 (s, 1H, NH), 7.81 (s, 1H, NH), 6.72 (*d*, *J* = 3 Hz, 1H, C2′–H), 6.62 (*d*, *J* = 10 Hz, 1H, C5′–H), 6.56 (*d*, *J* = 10 Hz, 1H, C6′–H), 5.10 (*d*, *J* = 3 Hz, 1H, C4–H), 3.85 (s, 3H, OCH_3), 2.35 (s, 3H, $COCH_3$), and 2.15 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{16}N_2O_4$ (276.29) C, 60.86; H, 5.84; N, 10.14%; Found: C, 60.65; H, 5.90; N, 10.10%.

4d ^{1}H-NMR (DMSO-d_6): δ = 11.46 (s, 1H, OH), 9.24 (s, 1H, NH), 8.05 (*d*, 1H, C4′–H), 7.84 (*d*, *J* = 2 Hz, 1H, C6′–H), 7.50 (s, 1H, NH), 7.01 (*t*, 1H, C5′–H), 5.55 (*d*, *J* = 2 Hz, 1H, C4–H), 2.24 (s, 3H, $COCH_3$), and 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{13}N_3O_5$ (291.27) C, 53.61; H, 4.50; N, 14.43%; Found: C, 53.55; H, 4.60; N, 14.40%.

4g ^{1}H-NMR (DMSO-d_6): δ = 9.52 (s, 1H, OH), 8.50 (s, 1H, OH), 7.45 (s, 1H, NH), 7.05 (d, 1H, ArC4′–H), 6.97 (s, 2H, ArC2′C6′-Hs), 6.13 (s, 1H, NH), 4.52 (*d*, *J* = 2 Hz, 1H, C4–H), 2.24 (s, 3H, $COCH_3$), and 1.39 (s, 3H, CH_3).

6c ^{1}H-NMR (DMSO-d_6): δ = 8.25 (s, 1H, OH) 7.45 (s, 1H, NH), 7.04 (*d*, *J* = 6Hz, 1H, ArC3′–H), 6.97 (*d*, *J* = 6Hz, 1H, ArC4′–H), 6.31 (s, 1H, ArC6′–H), 6.10 (s, 1H, NH), 5.12 (*d*, *J* = 2 Hz, 1H, C1–H), 3.28 (s,

1H, C13–H), 2.22 (s, 3H, $COCH_3$), and 1.50 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{14}N_2O_4$ (262.27) Calcd. C, 59.54; H, 5.38; N, 10.68%; Found: C, 59.50; H, 5.35; N, 10.55%.

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