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A microwave-mediated catalyst- and solvent-free regioselective Biginelli reaction in the synthesis of highly functionalized novel tetrahydropyrimidines

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ABSTRACT

A series of novel ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates has been synthesized regioselectively by the Biginelli reaction of ethyl 3-oxo-4-(arylsulfonyl)butanoate, aromatic aldehyde and urea/thiourea under microwave irradiation and solvent- and catalyst-free conditions.

Dihydropyrimidinones (DHPMs) have received great attention from synthetic and medicinal chemists due to their interesting biological applications.[1] They exhibit a wide range of medicinal applications such as antiviral,[2] antibacterial and antifungal,[3] anticancer[4] and calcium channel modulation.[1a] Monastrol (**I**), (Fig. 1) with the pyrimidine-2-thione motif, specifically inhibits the motility of the mitotic kinesin Eg5,[5] while SQ 32926 (**II**)[6] and Mon-97 (**III**)[1a] display antihypertensive and anticancer activities. In the present work, we proposed to synthesize pyrimidines bearing the arylsulfonylmethyl group, as several arylsulfone derivatives are known to display antiviral[7] and antitumour[8] properties and act as Bradykinin B1 receptor antagonists[9] for treatment of chronic pain. Arylsulfone moiety is also prevalent in several biologically interesting compounds that display antifungal, antibacterial or antitumour activities[10] and inhibit several enzymes, viz. cyclooxygenase-2 (COX-2)[11] and HIV-1 reverse transcriptase.[12]

The three-component Biginelli reaction is a preferred methodology for the construction of structurally diverse DHPMs from simple starting materials, viz. aromatic aldehyde, diamide and keto esters.[13] In recent years, multicomponent reactions (MCRs)[14] have emerged as a versatile synthetic tool for the construction of biologically important new chemical entities with pot, atom and step economies (PASE) in view of their green credentials such as convergence, minimum waste generation and hence have carved a niche in synthetic and medicinal chemistry arenas.[15]

The diversity of available methodologies for the Biginelli reaction in the literature employs catalysts such as Fe_3O_4@ mesoporous SBA-15(mesoporous nanocatalyst),[16] [Gmim]Cl-Cu(II) complex in neat condition,[17] Mg–Al–CO_3 and Ca–Al–CO_3 hydrotalcite,[18] SPINOL–phosphoric acid,[19] poly(1-vinyl-3-(3-sulfopropyl) imidazolium hydrogen sulfate) (poly(SIL)),[20] chiral organocatalyst,[21] 1-methylimidazolium hydrogen sulfate in the presence of catalytic amount of chlorotrimethylsilane ([Hmim]HSO_4/TMSCl),[22] 5% perchloric acid doped silica ($HClO_4/SiO_2$),[23] bioglycerol-based sulfonic acid functionalized carbon catalyst[24] and *t*-BuOK.[25] These methods suffer from one or more disadvantages such as use of corrosive/expensive catalysts, inconsistent/moderate yields and organic solvents. With this background in mind, we set out to establish a protocol for the efficient eco-friendly synthesis of novel medicinally relevant tetrahydropyrimidines with arylsulfonylmethyl moiety at the 6th position via three-component reaction employing solvent- and catalyst-free reaction conditions. It is pertinent to note that studies on the Biginelli reaction employing a solvent- and catalyst-free green approach are meagre.[26] The present study stems as a part of our ongoing research programme on the exploration of green transformations and domino/sequential multicomponent reactions for the assembly of novel heterocycles of biological importance.[27]

In the present investigation, a series of hitherto unreported novel ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **4** has been synthesized by the Biginelli reaction of ethyl 3-oxo-4-(arylsulfonyl)butanoate **1**, aromatic aldehyde **2** and diamide (urea/thiourea) **3** under microwave

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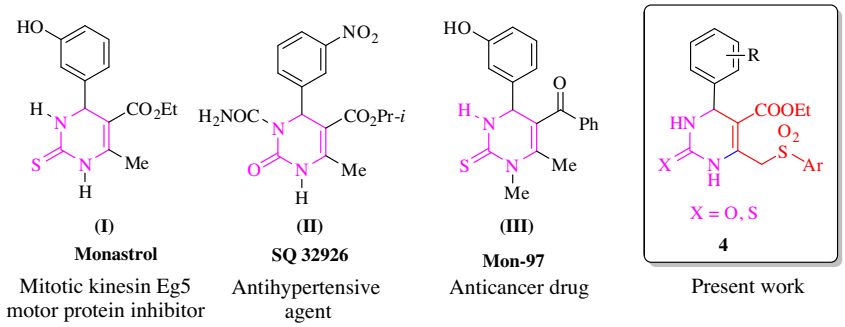
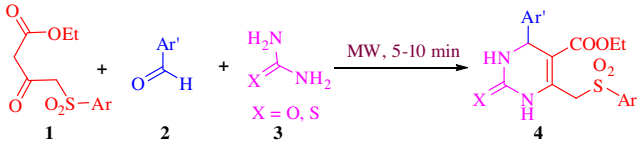


Figure 1. Biologically important DHPMs.



Scheme 1. Synthesis of ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **4**.

Table 1
Solvent-, catalyst- and temperature optimization for the synthesis of **4a** under microwave irradiation

Entry	Catalyst[a]	Solvent[b]	Time (min)	Temp (°C)	Yield of **4a** (%)
1	—	—	10	100	65
2	—	—	10	110	68
3	—	—	10	120	72
4	—	—	10	130	75
5	—	—	10	140	83
6	—	—	10	150	88
7	—	—	10	180	86
8	—	EtOH	15	150	60
9	—	MeOH	15	150	58
10	—	DMF	20	150	40
11	—	CH_3CN	15	150	62
12	CH_3COOH	—	10	150	78
13	$AlCl_3$	—	10	150	72
14	$SnCl_2$	—	10	150	75
15	$CeCl_3{\cdot}7H_2O$	—	10	150	68
16	$FeCl_3$	—	10	150	75
17	$Cu(OAc)_2$	—	10	150	70

[a,b] No solvent or catalyst employed unless specified.

irradiation and solvent- and catalyst-free conditions (Scheme 1). The efficiency of this method has also been compared with reactions carried out in the presence of acid catalysts, viz. acetic acid, aluminium chloride, stannous chloride, cerium(III) chloride·$7H_2O$, ferric chloride and cupric acetate (Scheme 1) and solvents viz. ethanol, methanol, dimethyl formamide and acetonitrile taking the model reaction of ethyl 3-oxo-4-(*p*-chlorophenylsulfonyl)butanoate, 4-methoxybenzaldehyde and urea leading to **4a** (Table 1). The results disclose that a maximum yield of **4a** was obtained when the reaction was performed in the absence of any catalyst and solvent.

The reaction under microwave irradiation affording **4a** was also examined at temperatures ranging from 100 to 150 °C with an increment of 10 °C. The results show that the yield of **4a** reaches a maximum at 150 °C and that the reaction is completed in 10 min. Performing the reaction at 180 °C did not significantly alter the yield. Consequently, all subsequent reactions under microwave-irradiation were performed under solvent- and catalyst-free conditions at 150 °C (Table 2).[28,29]

In addition, the reactions for synthesizing **4** were also performed under the classical thermal method in ethanol at reflux. The results reveal that the yield of the reaction under microwave irradiation (74–93%) is significantly more than that realized under conventional heating conditions, 45–58% (Table 2). The reaction under microwave irradiation could also be completed more rapidly in minutes than under traditional heating conditions, *albeit* different temperatures employed render the two protocols incomparable with respect to the reaction time.

Table 2
Synthesis of tetrahydropyrimidines **4** under thermal and microwave irradiation

Compd	Ar	Ar′	X	Reaction time		Yield (%)		Mp (°C)
				Reflux[a] (h) (80 °C)	MW[b] (min) (150 °C)	Reflux[c]	MW	
4a	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	O	8	10	45	88	222–223
4b	*p*-ClC_6H_4	*p*-MeC_6H_4	O	8	10	52	86	218–219
4c	*p*-ClC_6H_4	*p*-ClC_6H_4	O	8	10	48	90	215–216
4d	*p*-ClC_6H_4	*p*-FC_6H_4	O	8	10	55	80	209–210
4e	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	O	8	10	45	93	226–227
4f	*p*-MeC_6H_4	*p*-MeC_6H_4	O	8	10	50	89	220–221
4g	*p*-MeC_6H_4	*p*-ClC_6H_4	O	8	10	58	78	217–218
4h	*p*-MeC_6H_4	*p*-FC_6H_4	O	8	10	52	91	207–208
4i	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	S	8	10	44	78	211–212
4j	*p*-ClC_6H_4	*p*-MeC_6H_4	S	8	10	56	92	212–213
4k	*p*-ClC_6H_4	*p*-Cl-C_6H_4	S	8	10	48	75	201–202
4l	*p*-ClC_6H_4	*p*-F-C_6H_4	S	8	10	48	93	198–199
4m	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	S	8	10	56	86	219–220
4n	*p*-MeC_6H_4	*p*-MeC_6H_4	S	8	10	52	74	229–230
4o	*p*-MeC_6H_4	*p*-Cl-C_6H_4	S	8	10	56	85	224–225
4p	*p*-MeC_6H_4	*p*-F-C_6H_4	S	8	10	45	92	204–205

[a] Refluxed in ethanol.
[b] Irradiation was programmed at 150 °C, 53 W and 2 bar pressure with high absorption level.
[c] Isolated yield after purification.

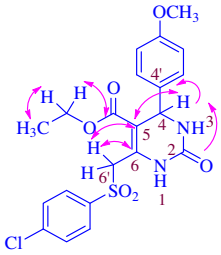


Figure 2. Selected HMBCs of **4a**.

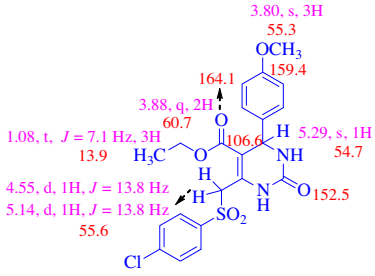
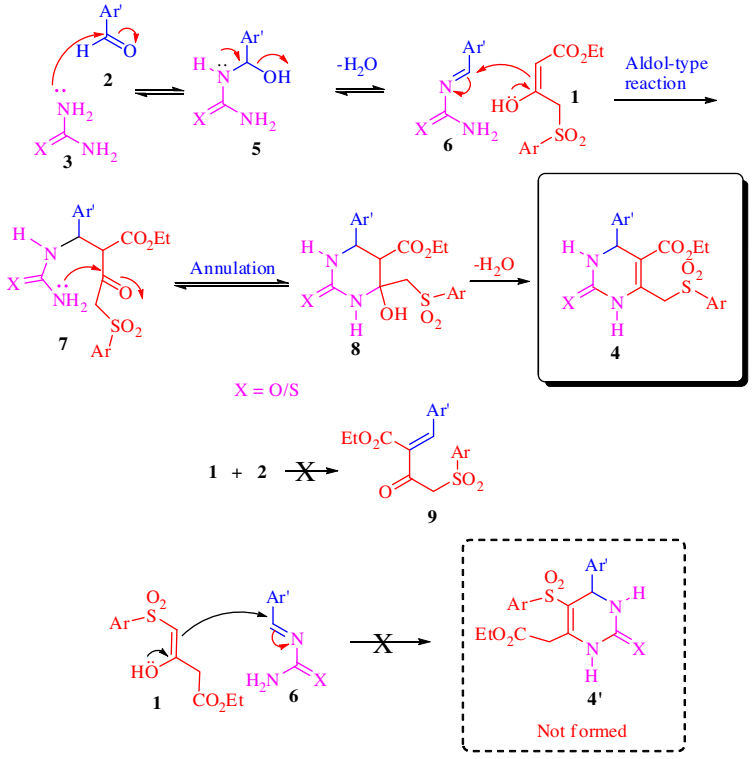


Figure 3. Selected NMR data of **4a**.

The structure of these ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **4** is in accord with elemental analyses and ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example **4a**. In the ^{1}H NMR spectrum of **4a**, H-4 appears as a singlet at 5.29 ppm, which shows HMBCs with C-5 at 106.6 ppm and C-4′ at 127.7.3 ppm (Figs. 2 and 3). The methylenic hydrogens at the 6th position appear as doublets at 4.55 and 5.14 ppm (J = 13.8 Hz), which show HMBCs with C-6 at 114.0 and C-5 at 106.6 ppm. The ethyl hydrogens of the ester function appear as a quartet and triplet at 3.88 and 1.08 ppm (J = 7.1 Hz) respectively, the former shows HMBC with ester carbonyl at 164.1 ppm and CH_3 carbon at 13.9 ppm. The carbonyl carbon C-2 appearing at 152.5 ppm shows HMBC with H-4 at 5.29 ppm, while the methoxy hydrogens occur as a singlet at 3.80 ppm.

A plurality of mechanisms[28,29] proceeding via intermediates such as Knovenagel condensation product, enamine, iminium ion etc for the Biginelli reaction in presence of catalysts has been postulated. Since the present transformation has been effected in the absence of any catalyst and solvent, the mechanistic investigation of this Biginelli transformation is worthy of investigation. That this transformation does not occur through the intermediacy of α,β-unsaturated ketosulfonyl ester **9** is evident from the fact that it is not formed in the reaction of **1** with 4-methoxybenzaldehyde under microwave irradiation. The reaction of **1** with urea/thiourea required microwave irradiation for a much longer time than that needed for the completion of the overall three-component reaction of **1** with aldehyde and amide affording **4**, as evident from the fact that even after microwave irradiation of a mixture of **1** and diamide for 15 min, the reaction was not complete. Thus, the transformation via enamine intermediate is also unlikely under the reaction conditions.

Consequently, the formation of ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **4** is visualized to involve the formation of (i) *N*-arylideneurea intermediate **6** generated by the dehydration of intermediate **5**, which, in turn, is formed from the reaction of aldehyde **2** and urea/thiourea **3** (Scheme 2). Presumably, subsequent reaction of *N*-arylideneurea **6** with the enol form of ethyl 3-oxo-4-(arylsulfonyl)butanoate **1** produces an open-chain ureide **7**, which undergoes condensative annulation to afford **4**. This mechanism is further supported by the fact that the reaction of 4-methoxybenzaldehyde with urea/thiourea conducted separately under microwave irradiation for 5 min afforded the corresponding imine, which upon further



Scheme 2. Plausible mechanistic pathway for the formation of **4**.

reaction with **1** under microwave irradiation for 5 min furnished product **4**. These reactions together require 10 min microwave irradiation for completion similar to the three-component overall reaction leading to **4** which was also completed in 10 min.

This reaction proceeds regioselectively as the product is formed by the reaction of the methylene group flanked by the keto and ester functions of **1** resulting in the exclusive formation of regioisomer **4**, while the other regioisomer **4′**, formed by the involvement of the methylene adjacent to the arylsulfonyl group is not detected even in traces. The absence of formation of regioisomer **4′** is presumably ascribable to the steric interaction between the arylsulfonyl group in the enol of **1** and the aryl ring of the imine **5** impeding the formation of **4′** (Scheme 2).

In conclusion, an expedient and environment-friendly procedure for the synthesis of ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates **4** in high yields in the absence of catalyst under solvent-free microwave irradiation is described in this Letter.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.034.

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28. *General Procedure Conventional method:* A mixture of ethyl 3-oxo-4-(arylsulfonyl)butanoate **1** (1 mmol), (4-methoxybenzaldehyde) **2** (1 mmol) and diamide **3** (1 mol) was heated to reflux in ethanol for the time given in Table 2. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated and poured into ice water with stirring. The product was filtered, washed with water (2 × 10 ml), dried and purified by passing through a short column of silica gel employing ethyl acetate/petroleum ether (1:4 v/v) as eluent to obtain pure product **4a**.
Under microwave irradiation: A mixture of ethyl 3-oxo-4-(arylsulfonyl)butanoate **1** (1 mmol), (4-methoxybenzaldehyde) **2** (1 mmol) and diamide **3** (1 mol) was taken in a 10 ml quartz vial, sealed and placed in a Biotage microwave oven. The vial was subjected to microwave irradiation, programmed at 150 °C, 53 W, 2 bar pressure and very high absorption level for the time given in Table 2. After a period of 1–2 min, the temperature reached a plateau, 150 °C, and remained constant. After gas jet cooling to room temperature (3 min), the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), dried over $MgSO_4$ and concentrated in vacuo to obtain the crude product which was purified as done for the thermal reaction. The yield, analytical and spectroscopic data for a representative compound are given below:
*Ethyl 6-((4-chlorophenylsulfonyl)methyl)-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetra hydropyrimidine-5-carboxylate (**4a**)*
Pale yellow solid; yield 88%; mp 222–223 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.08 (t, 3H, J = 7.2 Hz, CH_3), 3.79 (s, 3H, $-OCH_3$), 3.90 (q, 2H, J = 7.2 Hz, $-CH_2$), 4.54 (d, 1H, J = 13.8 Hz), 5.13 (d, 1H, J = 13.8 Hz), 5.28 (s, 1H), 5.99 (s. 1H, –NH), 6.81 (d, 2H, J = 8.7 Hz, Ar-H), 7.07 (d, 2H, J = 8.7 Hz, Ar-H), 7.33 (d, 2H, J = 8.7 Hz, Ar-H), 7.75 (d, 2H, J = 8.7 Hz, Ar-H), 8.24 (s, 1H, –NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 13.9, 54.8, 55.3, 55.7, 60.7, 106.7, 114.0, 127.7, 129.1, 130.3, 134.7, 135.8, 136.2, 140.8, 152.5, 159.4, 164.1. Anal. Calcd for $C_{21}H_{21}ClN_2O_6S$: C, 54.25; H, 4.55; N, 6.03. Found C, 54.32; H, 4.47; N, 6.13.
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