Green chemistry approach to synthesis of some new trifluoromethyl containing tetrahydropyrimidines under solvent free conditions

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Abstract

A simple, efficient and modified Biginelli procedure was carried out for the synthesis of tetrahydropyrimidines **4a-o** by a solvent-free and catalyst-free condition, by the condensation of 1,3-dicarbonyl compound **1**, arylaldehydes **2** and urea/thiourea **3**. Neat reactants subjected to microwave irradiation gave the required products more quickly and in better yield in comparison to traditional methodologies. The observed yields and improvement in reaction rates are due to the solvent free conditions coupled with the use of microwave radiation.

Keywords: Tetrahydropyrimidines, microwave irradiation synthesis, solvent-free and catalyst-free

Introduction

Environmental concerns in research and industry are increasing[1] with the increasing pressure to reduce the amount of pollutants produced, including organic solvents whose recovery is mandated by ever more strict laws. Hence the challenge for a sustainable environment calls for the use of clean procedures to avoid the use of harmful solvents. The emergence of microwave assisted solid phase synthesis[2] is a step forward in this direction. In this expeditious and solvent-free approach[3] the adsorbed reactants over solid supports are exposed to microwave irradiation. The salient features of these high yield protocols with enhanced reaction rates are greater selectivity and experimental ease of manipulation,[4] but this technique does not exactly meet the definition of 'no solvent'.[5] The usage of solvent is only eliminated at the primary reaction stage whereas an appreciable amount of solvent is still required for the adsorption of reactants and elution of the product at the pre- and post- reaction stages, respectively. A "neat reaction" is an alternative solvent-free approach that eliminates the use of a solid support as well as solvent from the reaction. There has not been much advancement in this area as direct heating of the reactants in the absence of solvent with a solid support often leads to charring. But these

reactions can prove to be advantageous for environmental reasons and can also offer the benefits of shorter reaction times especially, when coupled with microwave radiation[6] due to their uniform heating effect.

Dihydropyrimidines and their derivatives[7] are medicinally important[8] as calcium channel blockers, antihypertensive and anti-inflammatory agents and α_{1a}-antagonists. The first one-pot synthesis of 3,4-dihydropyrimidine was reported by Biginelli[9] in 1893. A serious drawback of the original procedure was low yield with substituted aliphatic and aromatic aldehydes.[10] Several improved procedures have been reported using Lewis acids catalysts such as BF_3,[11a] $FeCl_3$, [11b] $InCl_3$, [11c] $BiCl_3$, [11d] $LaCl_3$,[11e] $LiClO_4$,[11f] Mn-$(OAc)_3$,[11g] CAN,[11h] in a solvent such as CH_3CN, CH_2Cl_2, or THF. Recently, a number of procedures under solvent-free conditions using $Y(NO_3)_3.6H_2O$,[11i] silica triflate[11j] lanthanide triflate[11k], samarium diiodide[11l] and ionic liquid[11m] as catalysts have also been reported. Obviously, many of these catalysts and solvents are not at all acceptable in the context of green synthesis.

Thus, in the present paper we look forward to green synthesis of the Biginelli reaction (Scheme 1) under solvent free condition. The equimolar amount of neat 1,3-dicarbonyl compound **1**, different aromatic aldehydes **2** and urea/thiourea **3** on the exposure to microwave irradiation, which gave the required products **4a-o** without using solid support, solvent or acid.[12,13] The product was isolated by triturating with distilled water.

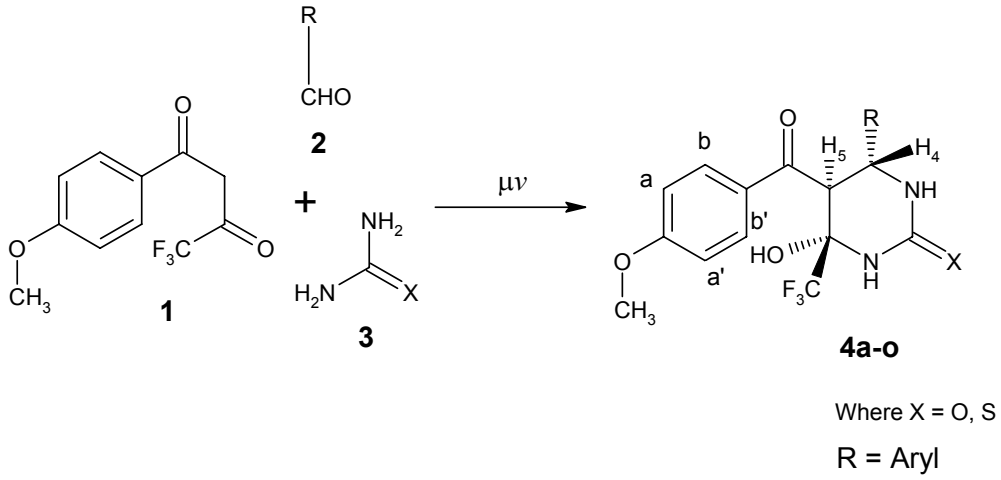
In general, the reactions are very clean, without any side product in every run. In fact, the crude products obtained are of high purity (>90% by ^{1}H NMR) with remarkable yields and do not require any chromatographic separation. Recrystallization from hot ethanol provides analytically pure sample. Most significantly, the whole operation involves no organic solvent at any stage.

Results and Discussions

The present procedure for the synthesis of tetrahydropyrimidines by a solvent-free and catalyst-free condensation of 1,3-dicarbonyl compound, aldehyde, and urea/thiourea provides a simple, efficient, cost-effective with 100% green modification of the Biginelli's reaction. Most significantly, this solvent-free and catalyst-free process of three-component condensation throws a challenge to the existing procedures,[11,14] which use volatile and hazardous solvents and toxic catalysts, and in general lead to a new direction in organic synthesis.

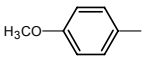
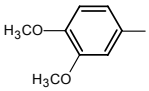
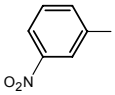
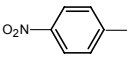
The 1,3-dicarbonyl i.e. 4,4,4-trifluoro-1-(4-methoxypheny)butane-1,3-dione **1** was cyclized with arylaldehydes **2** and urea/thiourea **3** to give the tetrahydropyrimidines[15] **4a-o** (Scheme 1), which was considered to be a final product in Biginelli reaction. The structure of the final products was confirmed by the earlier report by Saloutin, V. I *et al.,*[16] Kappe *et al.*[17] and D. Subhas Bose *et al.*[18] In the ^{1}H NMR spectrum of **4b,** the most characteristic signals are two doublets at 4.14-4.16 and 4.96-4.99 δppm which are corresponding to the *trans*-axial methane protons. The observed coupling constant J = 10.96 Hz and 11.0 Hz assigned to the H_4 and H_5

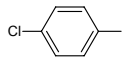
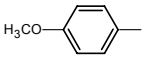
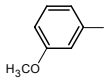
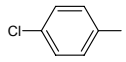
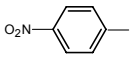
protons respectively, agree very well with the values found in the references.[16,18] It is therefore reasonable to assume that the same relative stereochemistry appears in **4a-o**. It may be presumed that the -OH group at C-6 may be cis to H_5, thereby the elimination of water requires drastic conditions. In MS the molecular ion peak appears at 424 m/z which was further supports that the elimination of water does not take place.



Scheme 1

Table 1. Synthesis of 1,4-dihydropyrimidine without any solvent and catalyst

Compd.	R	X	Yield (%)$_a$	mp °C	Time/min
4a		O	85	180-182	1.5
4b		O	82	205-206	2.0
4c		O	79	212-214	1.5
4d		O	83	198-200	4.5
4e		O	82	160-162	6.5
4f		O	84	220-222	3.0
4g		O	78	234-236	3.5

4h		O	80	221-223	5.0
4i		O	82	214-216	4.0
4j		S	83	220-222	2.5
4k		S	81	193-195	2.0
4l		S	82	245-247	5.5
4m		S	84	185-187	3.5
4n		S	79	204-206	4.5
4o		S	80	209-211	3.0

a Yields refer to those of recrystallized pure products characterized by mp and spectral data (IR, ^{1}H NMR and mass spectra).

Experimental Section

General Procedures. Melting points were measured in open capillaries and are uncorrected. The syntheses were carried out in a Questron Technologies Corp. QPro-M microwave synthesizer. Elemental analyses were performed on a Carlo Erba EA 1108 elemental analyzer at SAIF, CDRI Lucknow. IR spectra were recorded on KBr discs, using FTIR-8400 spectrophotometer. ^{1}H-NMR spectra were taken on a Bruker AVANCE II 400 (^{1}H: 400 Mz, [d_6] DMSO) spectrometer. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer. Analytical thin layer chromatography (TLC) was performed on Silica Gel 60 F254 precoated plates.

General procedure for the preparation of tetrahydropyrimidines

A mixture of 4,4,4-trifluoro-1-(4-methoxypheny)butane-1,3-dione **1** (5 mmol), different aromatic aldehydes **2** (5 mmol) and thio/urea **3** (5 mmol) was placed in a flask and irradiated under microwave at the power of 600W and 110-120 ^{o}C for different time which is described in Table 1. After cooling, the resulting solid was crushed, washed with cold water, filtered and dried under vacuum to give the crude product which is reasonably pure (>90%, purity by ^{1}H NMR). However, recrystallization from hot ethanol provides the analytically pure product.

4-Hydroxy-5-(4-methoxybenzoyl)-6-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4a). White powder in 85% yield. mp 180-182 ^{o}C. IR (KBr): ν 3447 (-NH), 3209 (-OH), 3109 (ArH), 1691 and 1676 (C=O) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.17 (d, 1H, J = 11.0Hz), 5.03 (d, 1H, J = 11.0Hz), 6.49 (s, 1H, NH), 6.64 (s, 1H, NH), 6.72-7.54 (m, 9H, Ar-H). MS *m/z*: 394 (M^+). Anal. Calcd. for $C_{19}H_{17}F_3N_2O_4$: C, 57.87; H, 4.35, N, 7.10%. Found: C, 57.75; H, 4.12, N, 6.93%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4b).White solid in 82% yield. mp 205-206 ^{o}C. IR (KBr): ν 3443 (-NH), 3217 (-OH), 3070 (ArH), 1676 and 1668 (C=O) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 3.67 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.16 (d, 1H, J = 11.0Hz), 4.99 (d, 1H, J = 10.9Hz), 6.13 (s, 1H, NH), 6.49 (s, 1H, NH), 6.67-6.70 (dd, 2H, Ar-H, J = 6.9Hz), 6.75-6.77 (dd, 2H, Ar-H, J = 7.0Hz), 7.20-7.22 (dd, 2H, Ar-Ha-a' J = 6.8Hz), 7.56-7.58 (dd, 2H, Ar-Hb-b' J = 7.0Hz). MS *m/z*: 424 (M^+). Anal. Calcd. for $C_{20}H_{19}F_3N_2O_5$: C, 56.60; H, 4.51, N, 6.60%. Found: C, 56.48; H, 4.29, N, 6.25%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(2-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4c). White powder in 79% yield. mp 212-214 ^{o}C. IR (KBr): ν 3429 (-NH), 3205 (-OH), 3101 (ArH), 1687 and 1676 (C=O) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 3.67 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.43 (d, 1H, J = 11.0Hz), 5.31 (d, 1H, J = 10.8Hz), 5.93 (s, 1H, NH), 6.43 (s, 1H, NH), 6.56-7.54 (m, 8H, Ar-H). MS *m/z*: 424 (M^+). Anal. Calcd. for $C_{20}H_{19}F_3N_2O_5$: C, 56.60; H, 4.51, N, 6.60%. Found: C, 56.47; H, 4.31, N, 6.27%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3,4-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4d). White crystal in 83% yield. mp 198-200 ^{o}C. IR (KBr): ν 3599 (-NH), 3215 (-OH), 3076 (ArH), 1691 and 1670 (C=O) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.24 (d, 1H, J = 10.9Hz), 4.96 (d, 1H, J = 10.9Hz), 6.64-7.73 (m, 9H, Ar-H). MS *m/z*: 454 (M^+). Anal. Calcd. for $C_{21}H_{21}F_3N_2O_6$: C, 55.51; H, 4.66, N, 6.16%. Found: C, 55.36; H, 4.37, N, 6.03%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(2,5-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4e). White crystal in 82% yield. mp 160-162 ^{o}C. IR (KBr): ν 3365 (-NH), 3205 (-OH), 3085 (ArH), 1680 and 1599 (C=O) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 3.61 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.24 (d, 1H, J = 11.0Hz), 5.27 (d, 1H, J = 10.7Hz), 6.34 (s, 1H, NH), 6.91 (s, 1H, NH), 6.51-7.61 (m, 7H, Ar-H). MS *m/z*: 454 (M^+). Anal. Calcd. for $C_{21}H_{21}F_3N_2O_6$: C, 55.51; H, 4.66, N, 6.16%. Found: C, 55.33; H, 4.44, N, 6.00%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-nitroyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4f). Pale white powder in 84% yield. mp 220-222 ^{o}C. IR (KBr): ν 3463 (-NH), 3196 (-OH), 3046 (ArH), 1691 and 1676 (C=O) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.27 (d, 1H, J = 11.0Hz), 5.19 (d, 1H, J = 11.0Hz), 6.94 (s, 1H, NH), 7.17 (s, 1H, NH), 6.74-8.24 (m, 8H, Ar-H). MS *m/z*: 439 (M^+). Anal. Calcd. for $C_{19}H_{16}F_3N_3O_6$: C, 51.94; H, 3.67, N, 9.56%. Found: C, 51.83; H, 3.58, N, 9.33%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-nitrophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4g). White powder in 78% yield. mp 234-236 °C. IR (KBr): ν 3429 (-NH), 3234 (-OH), 3107 (ArH), 1710 and 1689 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.24 (d, 1H, J = 11.0Hz), 5.20 (d, 1H, J = 11.0Hz), 7.07 (s, 1H, NH), 7.20 (s, 1H, NH), 6.76-8.03 (m, 8H, Ar-H). MS *m/z*: 439 (M^+). Anal. Calcd. for $C_{19}H_{16}F_3N_3O_6$: C, 51.94; H, 3.67, N, 9.56%. Found: C, 51.85; H, 3.55, N, 9.36%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-chlorophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4h). Solid white in 80% yield. mp 221-223 °C. IR (KBr): ν 3456 (-NH), 3212 (-OH), 3117 (ArH), 1685 and 1672 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 4.13 (d, 1H, J = 10.9Hz), 5.02 (d, 1H, J = 10.9Hz), 5.65 (s, 1H, NH), 6.06 (s, 1H, NH), 6.75-7.55 (m, 8H, Ar-H). MS *m/z*: 428 (M^+). Anal. Calcd. for $C_{19}H_{16}ClF_3N_2O_4$: C, 53.22; H, 3.76, N, 6.53%. Found: C, 53.06; H, 3.58, N, 6.31%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-hydroxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (4i). Solid white in 82% yield. mp 214-216 °C. IR (KBr): ν 3445 (-NH), 3218 (-OH), 3087 (ArH), 1710 and 1682 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.76 (s, 3H, OCH_3), 4.09 (d, 1H, J = 10.7Hz), 4.88 (d, 1H, J = 11.0Hz), 6.20 (s, 1H, NH), 6.44 (s, 1H, NH), 6.69-7.53 (m, 8H, Ar-H), 7.71 (s, 1H, OH), MS *m/z*: 410 (M^+). Anal. Calcd. for $C_{19}H_{17}F_3N_2O_5$: C, 55.61; H, 4.18, N, 6.83%. Found: C, 55.47; H, 4.06, N, 6.68%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-thione (4j). Solid white in 83% yield. mp 220-222 °C. IR (KBr): ν 3445 (-NH), 3234 (-OH), 3132 (ArH), 1674 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.22 (d, 1H, J = 11.0Hz), 5.05 (d, 1H, J = 11.3Hz), 6.74-7.56 (m, 9H, Ar-H), 7.76 (s, 1H, NH), 8.46 (s, 1H, NH). MS *m/z*: 410 (M^+). Anal. Calcd. for $C_{19}H_{17}F_3N_2O_3S$: C, 55.60; H, 4.18, N, 6.83%. Found: C, 55.60; H, 4.06, N, 6.62%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-thione (4k). White solid in 81% yield. mp 193-195 °C. IR (KBr): ν 3465 (-NH), 3186 (-OH), 2953 (ArH), 1674 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.68 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.22 (d, 1H, J = 11.3Hz), 5.01 (d, 1H, J = 11.3Hz), 6.70-6.72 (dd, 2H, Ar-H, J = 6.9Hz), 6.76-6.78 (dd, 2H, Ar-H, J = 7.0Hz), 7.21-7.23 (dd, 2H, Ar-Ha-a' J = 6.7Hz), 7.58-7.60 (dd, 2H, Ar-Hb-b' J = 7.0Hz), 6.94 (s, 1H OH) 7.70 (s, 1H, NH), 8.14 (s, 1H, NH). MS *m/z*: 440 (M^+). Anal. Calcd. for $C_{20}H_{19}F_3N_2O_4S$: C, 54.54; H, 4.35, N, 6.36%. Found: C, 54.45; H, 4.26, N, 6.19%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-thione (4l). White powder in 82% yield. mp 245-247 °C. IR (KBr): ν 3417 (-NH), 3180 (-OH), 2958 (ArH), 1668 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.68 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.19 (d, 1H, J = 10.9Hz), 4.96 (d, 1H, J = 11.0Hz), 6.38 (s, 1H, NH), 7.06 (s, 1H, NH), 6.70-7.59 (m, 8H, Ar-H). MS *m/z*: 440 (M^+). Anal. Calcd. for $C_{20}H_{19}F_3N_2O_4S$: C, 54.54; H, 4.35, N, 6.36%. Found: C, 54.44; H, 4.27, N, 6.21%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(2-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-thione (4m). Solid white in 84% yield. mp 185-187 °C. IR (KBr): ν 3448

(- NH), 3192 (-OH), 3232 (ArH), 1670 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.56 (d, 1H, J = 11.0Hz), 5.26 (d, Ha, J = 11.1Hz), 6.64-7.59 (m, 10H, Ar-H). MS *m/z*: 440 (M^+). Anal. Calcd. for $C_{20}H_{19}F_3N_2O_4S$: C, 54.54; H, 4.35, N, 6.36%. Found: C, 54.49; H, 4.22, N, 6.17%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-chlorophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-thione (4n). Solid white in 79% yield. mp 204-206 °C. IR (KBr): ν 3483 (-NH), 3178 (-OH), 2918 (ArH), 1666 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.23 (d, 1H, J = 11.0Hz), 5.19 (d, 1H, J = 11.0Hz), 6.61 (s, 1H, NH), 6.90 (s, 1H, NH), 6.73-8.25 (m, 8H, Ar-H). MS *m/z*: 444 (M^+). Anal. Calcd. for $C_{19}H_{16}ClF_3N_2O_3S$: C, 51.30; H, 3.63, N, 6.30%. Found: C, 51.18; H, 3.55, N, 6.17%.

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-nitrophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-thione (4o). Pale yellow powder in 80% yield. mp 209-211 °C. IR (KBr): ν 3420 (-NH), 3196 (-OH), 3229, (ArH), 1676 (C=O) cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 4.15 (d, 1H, J = 11.0Hz), 5.00-5.03 (d, 1H, J = 11.0Hz), 6.84 (s, 1H, NH), 6.93 (s, 1H, NH), 6.75.7.58 (m, 8H, Ar-H). MS *m/z*: 455 (M^+). Anal. Calcd. for $C_{19}H_{16}F_3N_3O_5S$: C, 50.11; H, 3.54, N, 9.23%. Found: C, 49.98; H, 3.49, N, 9.12%.

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