Asian Journal of Chemistry; Vol. 35, No. 1 (2023), 224-232

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.26932

Synthesis of Multi-Substituted 4,5-Dihydrofurans: Microwave Assisted Reaction of β-Ketonitriles, Aldehydes and Pyridinium Phenacyl Salts *via* [1+1+3] Knoevenagel-Michael-Oxa-Michael Cyclization Triple Cascade Sequence

VENKATESWARLU CHIMALADENNE[1,2], SRI RAMA KRISHNA SURAPUREDDI[1], KRISHNA REDDY VALLURU[2], ANIL KAMPLI[2], PRADEEP KUMAR BRAHMAN[1], VEERA BABU GUDISE[2] and SOMARAPU VIJAYA LAXMI[1,3,*]

[1]Department of Chemistry, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Tadepalli, Guntur-522502, India
[2]Chemistry Services, Aragen Life Sciences, Survey Nos: 125 (part) & 126, IDA Mallapur, Hyderabad-500076, India
[3]Department of Chemistry, Palamuru University, Mahabubnagar-509001, India

*Corresponding author: E-mail: vijaya1214@gmail.com

Received: 13 November 2022; *Accepted*: 22 December 2022; *Published online*: 27 December 2022; AJC-21102

A microwave assisted protocol for the development of fully substituted dihydrofurans has been explained as a three component triple cascade reaction between pyridinium ylide, phenacyl nitriles and aldehydes. This [1+1+3] annulation protocol produced the dihydrofurans having two stereocentres. A total of 14 molecules have been synthesized with high chemical yields.

Keywords: Microwave irradiation, Three-component reaction, Pyridinium salts, [1+1+3] Annulation, Triple cascade, 4,5-Dihydrofuran.

INTRODUCTION

Cascade/Tandem/Domino reaction is an organosynthetic conversion in which two or more successive transformations (bond breaking/making) involved under the same reaction conditions [1]. Several research groups excessively demonstrated the cascade reactions [2-10]. After the first triple cascade reaction reported in 2006 [11], these reactions have been evolved into quadruple [12-14] and quintuple [15-18] cascade reactions. Similarly, microwave irradiation mediated synthesis has become one of most interesting areas in organic chemistry and other areas like inorganic, nanochemistry, *etc.* It has been considered as the green protocol due to the several advantages like solvent free/less solvent, lower reaction timings, less energy consumption, higher yields, *etc.* Due to all these facts, cascade reactions using microwave irradiation are the primary choice for synthetic chemists.

Multi-substituted furans/dihydrofurans are the core skeleton in a variety of natural and biologically active molecules (Fig. 1) [19-23]. Several strategies have been developed for the construction of dihydrofurans *via* various cascade strategies including the utilization of compounds with active methylene group [24-27], pyridinium ylides [28,29]. But the reports on synthesizing dihydrofurans under microwave irradiation in a cascade manner were scarce. Herein, a microwave assisted, three-component triple cascade protocol for the development of fully substituted dihydrofurans is proposed.

Sathiyamoorthi *et al.* [30] successfully demonstrated the utility of imidazolium ylides for developing substituted dihydrofurans (eqn. a, **Scheme-I**). In contemporary, similar molecules were synthesized by Osyanin *et al.* [31] but in this case, pyridinium ylides were used for the synthesis of dihydrofurans (eqn. b, **Scheme-I**). The utilization of aromatic and aliphatic aldehydes was well explored earlier, however its utility of various heterocyclic aldehydes was limited. Herein, a three component triple cascade protocol is reported for for synthesizing fully substituted dihydrofurans using pyridinium ylide, phenacyl nitrile and aldehydes under microwave irradiation (eqn. c, **Scheme-I**).

EXPERIMENTAL

All the reagents and chemicals were procured from reputed commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was perfomed with Merck silica gel 60-F_{254} (0.5 mm) precoated glass plates. Spots were visualized by UV light. Column chromatography was performed using 100-200 mesh silica gel. ^{1}H & ^{13}C NMR spectra were recorded with 400, 500, 100.6 and 125 MHz (a Bruker) NMR instruments in DMSO and deuterated chloroform with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and coupling constants (*J*) are reported in

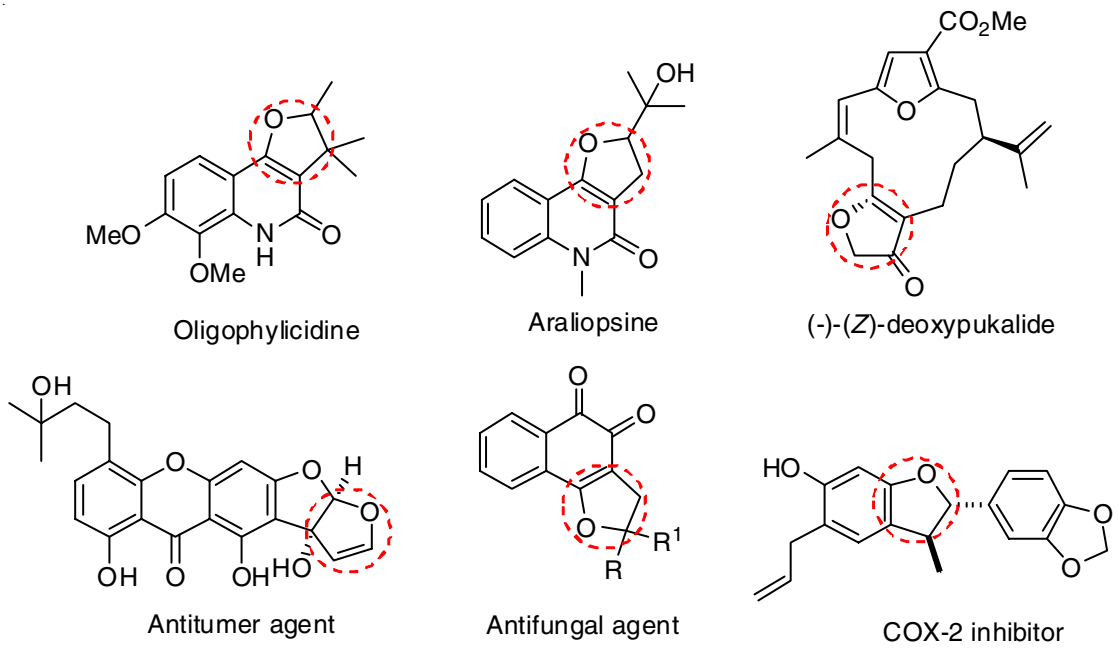
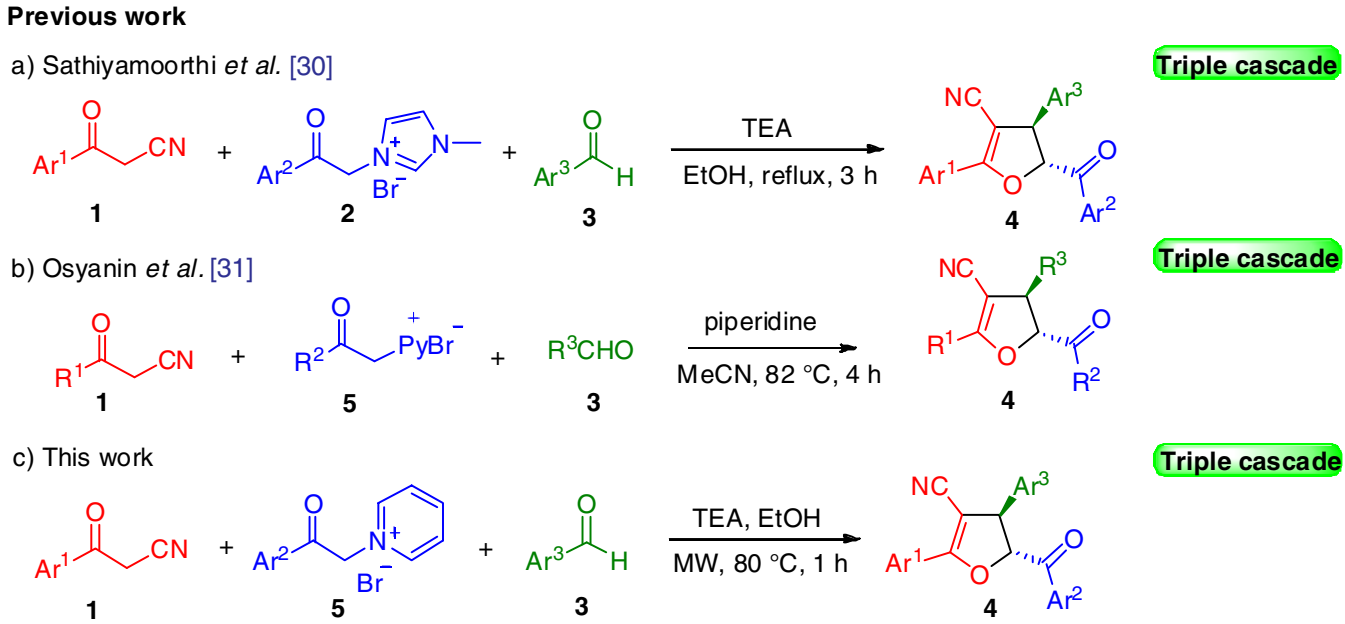


Fig. 1. Natural and medicinally active molecules having dihydrofuran core



Scheme-I: Triple cascade synthesis strategies for constructing dihydrofurans

parts per million (ppm) and Hertz (Hz) respectively. IR (KBr) spectra were recorded on Perkin-Elmer FT/IR-4000 using ATR (ν_{max}, cm^{-1}) in the frequency range of 4000-600 cm^{-1}. Melting points were determined in a capillary tube using an electro-thermal apparatus (Model IA9200) and were uncorrected. High-resolution mass spectra (HRMS) were recorded on Thermo Q Exactive orbitrap mass spectrometer.

Microwave irradiation experiment: Experiments with microwave irradiation were carried out using a Discover® SP Monowave 300 single-mode microwave cavity reactor (USA). An external infrared (IR) sensor embedded in the microwave cavity's side walls measures the reaction vessel's surface temperature to monitor the reaction's temperature. Not the whole time under the radiation source, but the time required to maintain the target temperature is meant by reaction time. The instrument's hydraulic pressure sensor was housed in the rotating top. Specially made caps protected the reusable 10 mL and 35 mL Pyrex vial. After the heating time, compressed air was used to perform automated reaction cooling. Hydraulic sealing of the vials with the initial force of 6-8 bar to resist 30 bar and to ensure smooth release of any leftover pressure before opening the cover.

General procedure (A) for the synthesis of substituted pyridinium salt of phenacyl bromide (5a-d) from the reactions of substituted phenacyl bromide with pyridine: Under a nitrogen environment, a solution of pyridine (1.1 mmol) and

phenacyl bromide (1 mmol) in ethyl acetate (20 mL) was agitated at room temperature for 12 h. The resultant product was filtered and washed with 5 mL of ethyl acetate to yield substituted pyridinium salt of phenacyl bromide derivatives.

1-(2-(4-Methoxyphenyl)-2-oxoethyl)pyridin-1-ium bromide (5a): Compound **5a** was synthesized according to the general procedure **A** by taking 2-bromo-4′-methoxyacetophenone (2 g, 1.0 mmol, 1.0 equiv.), pyridine (765 mg, 1.1 mmol, 1.1 equiv.) in ethyl acetate (20 mL) and the resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. Yield: 2.56 g (95%), off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.00 (d, *J* = 5.20 Hz, 2H), 8.73 (t, *J* = 7.60 Hz, 1H), 8.27 (t, *J* = 7.20 Hz, 2H), 8.04 (d, *J* = 8.80 Hz, 2H), 7.19 (d, *J* = 8.80 Hz, 2H), 6.44 (s, 2H), 3.90 (s, 3H).

1-(2-Oxo-2-(4-(trifluoromethyl)phenyl)ethyl)pyridin-1-ium bromide (5b): Compound **5b** was synthesized according to the general procedure **A** by taking 4-trifluoromethylphenacyl bromide (2 g, 1.0 mmol, 1.0 equiv.), pyridine (650 mg, 1.1 mmol, 1.1 equiv.) in ethyl acetate (20 mL) and the resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. Yield: 2.34 g (90%), off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.02 (d, *J* = 6.00 Hz, 1H), 8.76 (t, *J* = 7.60 Hz, 2H), 8.26-8.32 (m, 2H), 8.07 (d, *J* = 8.40 Hz, 2H), 6.56 (s, 1H).

1-(2-Oxo-2-phenylethyl)pyridin-1-ium bromide (5c): Compound **5c** was synthesized according to the general procedure **A** by taking 2-bromoacetophenone (2 g, 1.0 mmol, 1.0 equiv.), pyridine (873 mg, 1.1 mmol, 1.1 equiv.) in ethyl acetate (20 mL) and the resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. Yield: 2.64 g (95%), off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.05 (dd, *J* = 6.7, 1.3 Hz, 1H), 8.75 (tt, *J* = 7.9, 1.3 Hz, 1H), 8.29 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.11-8.05 (m, 1H), 7.83-7.78 (m, 1H), 7.70-7.65 (m, 1H), 6.55 (s, 1H).

1-(2-Oxo-2-(*p*-tolyl)ethyl)pyridin-1-ium bromide (5d): Compound **5d** was synthesized according to the general procedure **A** by treating 2-bromo-4′-methylacetophenone (2 g, 1.0 mmol, 1.0 equiv.), pyridine (815 mg, 1.1 mmol, 1.1 equiv.) in ethyl acetate (20 mL) and the resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. Yield: 2.67 g (98%), off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.00 (d, *J* = 5.60 Hz, 2H), 8.74 (t, *J* = 7.60 Hz, 1H), 8.74 (t, *J* = 7.60 Hz, 1H), 8.26-8.29 (m, 2H), 7.97 (d, *J* = 8.40 Hz, 2H), 7.97 (d, *J* = 8.40 Hz, 2H), 7.48 (d, *J* = 7.60 Hz, 2H), 6.46 (s, 2H), 2.45 (s, 3H).

General procedure (B) for the synthesis of dihydrofurans: Into a monowave vial G10 (30 mL) with a Teflon covered stir bar, a solution of aroyl acetonitrile **1** (1.0 mmol), aromatic aldehyde **3** (1.1 mmol), pyridinium salt of phenacyl bromide **5** (1.1 mmol) and triethylamine (TEA, 3.0 mmol) was dissolved in the minimum amount of ethanol (10 mL). The reaction mixture was then placed in the microwave-ready vessel and microwaved for 60 min at 80 ºC. The progress of the reaction was monitored by TLC. The reaction mixture was cooled for 1 h and then the precipitate was filtered, washed with cold ethanol and dried under vacuum to yield pure dihydrofurans derivatives **4**.

(4*R*,5*R*)-2-(4-Fluorophenyl)-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-4,5-dihydrofuran-3-carbonitrile (4a): Compound **4a** was synthesized according to the general procedure **B** by taking aroyl acetonitrile **1** (500 mg, 3.0 mmol, 1.0 equiv.), *p*-methoxy benzaldehyde (**3a**) (458 mg, 3.37 mmol, 1.1 equiv.), 1-(2-(4-methoxyphenyl)-2-oxoethyl)pyridin-1-ium bromide (**5a**) (1.03 g, 3.37 mmol, 1.1 equiv.), triethylamine (TEA) (1.29 mL, 9.20 mmol, 3.0 equiv.) in ethanol (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1.1 g (84%), pale yellow solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 3:7), m.p.: 146-149 ºC; IR (KBr, ν_{max}, cm^{-1}): 2929, 2837, 1687, 1598, 1506, 1415, 1365, 1251, 1172, 1111, 1016, 943, 835, 775, 648, 601, 553; ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 7.96-8.03 (m, 1H), 7.83-7.90 (m, 1H), 7.42-7.50 (m, 1H), 7.27-7.32 (m, 1H), 7.07-7.11 (m, 1H), 6.98-7.03 (m, 1H), 6.37 (d, *J* = 5.50 Hz, 1H), 4.64 (d, *J* = 5.50 Hz, 1H), 3.86 (s, 1H), 3.79 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 190.83, 165.79, 165.13, 164.41, 163.27, 159.66, 131.44, 131.18, 129.83, 129.74, 128.77, 126.21, 123.63,123.60, 116.45, 116.10, 115.88, 114.76, 114.19, 89.40, 85.10, 55.56, 55.32, 52.26. HRMS (ESI) calcd. for $C_{26}H_{20}FNO_4$ ([M+H]$^+$): 430.1376, found: 430.1434.

(4*R*,5*R*)-2-(4-Fluorophenyl)-4-(4-methoxyphenyl)-5-(4-(trifluoromethyl)benzoyl)-4,5-dihydrofuran-3-carbonitrile (4b): Compound **4b** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3a** (458 mg, 3.37 mmol, 1.1 equiv.), **5b** (1.16 g, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in ethanol (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1.1 g (71%), off-white solid, R_f = 0.70 (ethyl acetate/*n*-hexane, 3:7), m.p.: 101-104 ºC. IR (KBr, ν_{max}, cm^{-1}): 3398, 3074, 2893, 2214, 1705, 1612, 1510, 1371, 1325, 1242, 1174, 1126, 1062, 939, 839, 653, 557. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 8.08 (d, *J* = 8.25 Hz, 1H), 7.93-8.02 (m, 2H), 7.47 (t, *J* = 9.01 Hz, 1H), 7.29 (d, *J* = 8.75 Hz, 1H), 7.01 (d, *J* = 8.50 Hz, 1H), 6.47 (d, *J* = 5.25 Hz, 1H), 4.75 (d, *J* = 5.25 Hz, 1H), 3.78 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 191.70, 165.96, 164.85, 163.43, 159.91, 157.65, 136.16, 136.01, 135.68, 135.36, 135.03, 132.27, 132.18, 131.05, 130.68, 130.00, 129.95, 129.85, 129.76, 129.53, 128.78, 128.11, 127.42, 126.10, 126.06, 126.03, 125.99, 125.61, 125.57, 124.70, 123.37, 123.34, 121.99, 120.18, 89.67, 87.04, 85.33, 85.32, 55.40, 55.18, 53.21, 51.88. HRMS (ESI) calcd. for $C_{26}H_{17}FNO_3$ ([M-H]$^+$): 466.1145, found: 466.1042.

(4*R*,5*R*)-5-Benzoyl-2-(4-fluorophenyl)-4-(4-methoxyphenyl)-4,5-dihydrofuran-3-carbonitrile (4c): Compound **4c** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3a** (458 mg, 3.37 mmol, 1.1 equiv.), **5c** (934 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in ethanol (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1 g (82%), off-white solid, R_f = 0.60 (ethyl acetate/*n*-hexane, 3:7), m.p.: 163-166 ºC; IR (KBr, ν_{max}, cm^{-1}): 2989, 2206, 1687, 1635, 1595, 1454, 1402, 1357, 1298, 1244, 1165, 1107, 1091, 1033, 1018, 941, 883, 835, 800, 758, 690, 651, 553. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 7.99-8.30 (m, 1H), 7.86-7.89 (m, 1H), 7.69-7.74 (m, 1H), 7.53-7.60 (m, 1H), 7.45-

7.51 (m, 1H), 7.27-7.31 (m, 1H), 6.99-7.03 (m, 1H), 6.43 (d, *J* = 5.25 Hz, 1H), 4.67 (d, *J* = 5.25 Hz, 1H), 3.79 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 192.39, 165.84, 165.12, 163.31, 159.73, 134.32, 133.29, 131.02, 129.86, 129.77, 129.07, 128.96, 128.74, 123.55, 123.52, 116.34, 116.14, 115.92, 114.81, 89.53, 85.13, 85.12, 55.34, 52.14; HRMS (ESI) calcd. for $C_{25}H_{18}FNO_3$ ([M+H]$^+$): 400.1271, found: 400.1323.

(4*R*,5*R*)-5-Benzoyl-2,4-*bis*(4-fluorophenyl)-4,5-dihydrofuran-3-carbonitrile (4d): Compound **4d** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3b** (418 mg, 3.37 mmol, 1.1 equiv.), **5c** (934 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 950 mg (80%), off-white solid, R_f = 0.80 (ethyl acetate/*n*-hexane, 3:7), m.p.: 136-139 ºC; IR (KBr, ν_{max}, cm^{-1}): 3074, 2927, 2206, 1689, 1629, 1593, 1502, 1452, 1411, 1361, 1232, 1157, 1107, 1091, 1041, 941, 835, 794, 779, 682, 653, 549. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 8.02-8.10 (m, 1H), 7.90-7.96 (m, 1H), 7.63-7.69 (m, 1H), 7.49-7.56 (m, 1H), 7.29-7.35 (m, 1H), 7.09-7.21 (m, 2H), 5.86 (d, *J* = 5.75 Hz, 1H), 4.75 (d, *J* = 5.50 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 192.17, 165.99, 165.42, 164.00, 163.46, 161.54, 134.92, 134.89, 134.49, 133.37, 129.94, 129.85, 129.44, 129.36, 129.16, 129.06, 123.38, 123.35, 116.59, 116.38, 116.27, 116.18, 116.05, 89.45, 84.79, 51.82; HRMS (ESI) calcd. for $C_{24}H_{15}F_2NO_2$ ([M-H]$^+$): 386.1071, found: 386.0979.

(4*R*,5*R*)-2-(4-Fluorophenyl)-4-(4-methoxybenzyl)-5-(4-methylbenzoyl)-4,5-dihydrofuran-3-carbonitrile (4e): Compound **4e** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3c** (506 mg, 3.37 mmol, 1.1 equiv.), **5d** (981 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1.1 g (84%), off-white solid, R_f = 0.60 (ethyl acetate/*n*-hexane, 3:7), m.p.: 101-104 ºC; IR (KBr, ν_{max}, cm^{-1}): 2738, 2200, 2160, 1924, 1693, 1600, 1500, 1440, 1371, 1300, 1256, 1232, 1151, 1107, 1091, 1039, 947, 846, 727, 688, 561. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.97-8.03 (m, 1H), 7.27-7.37 (m, 2H), 7.14 (t, *J* = 8.76 Hz, 1H), 7.09 (d, *J* = 8.00 Hz, 1H), 6.87-6.91 (m, 1H), 6.77-6.81 (m, 1H), 5.73 (d, *J* = 3.50 Hz, 1H), 3.77 (s, 1H), 3.70-3.75 (m, 1H), 3.27 (dd, *J* = 13.76, 4.50 Hz 1H), 2.83-2.89 (m, 1H), 2.38 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 192.56, 166.22, 165.81, 163.28, 160.20, 144.96, 138.39, 130.39, 130.17, 129.88, 129.79, 129.47, 128.84, 123.75, 121.88, 116.70, 116.10, 115.88, 114.85, 112.97, 84.88, 83.73, 55.18, 49.17, 39.52, 21.72; HRMS (ESI) calcd. for $C_{27}H_{22}FNO_3$ ([M+H]$^+$): 428.1584, found: 428.1660.

(4*R*,5*R*)-5-Benzoyl-4-cyclobutyl-2-(4-fluorophenyl)-4,5-dihydrofuran-3-carbonitrile (4f): Compound **4f** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3d** (283 mg, 3.37 mmol, 1.1 equiv.), **5c** (934 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 800 mg (80%), yellow solid, R_f = 0.80 (ethyl acetate/*n*-hexane, 3:7), m.p.: 110-113 ºC; IR (KBr, ν_{max}, cm^{-1}): 3664, 2974, 2202, 1820, 1695, 1624, 1595, 1504, 1438, 1371, 1325, 1232, 1163, 1105, 1001, 943, 846, 698, 545. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.93-8.03 (m, 1H), 7.62-7.68 (m, 1H), 7.50-7.57 (m, 1H), 7.06-7.14 (m, 1H), 5.57 (d, *J* = 5.00 Hz, 1H), 3.66 (dd, *J* = 8.38, 4.88 Hz, 1H), 2.69-2.80 (m, 1H), 2.20-2.30 (m, 1H), 2.10-2.17 (m, 1H), 1.87-2.05 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 193.69, 165.70, 165.34, 163.18, 134.15, 133.89, 129.76, 129.67, 129.07, 128.96, 123.81, 123.78, 117.20, 116.07, 115.85, 85.79, 82.85, 51.45, 39.69, 25.92, 25.91, 18.40; HRMS (ESI) calcd. for $C_{22}H_{18}FNO_2$ ([M+H]$^+$): 348.1322, found: 348.1392.

(4*S*,5*R*)-5-Benzoyl-2-(4-fluorophenyl)-4-(1*H*-pyrrol-2-yl)-4,5-dihydrofuran-3-carbonitrile (4g): Compound **4g** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3e** (320 mg, 3.37 mmol, 1.1 equiv.), **5c** (934 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 900 mg (82.5%) , pale yellow solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 3:7), m.p.: 176-179 ºC; IR (KBr, ν_{max}, cm^{-1}): 3107, 3061, 2926, 2206, 1691, 1627, 1597, 1506, 1442, 1363, 1228, 1166, 1109, 999, 954, 879, 852, 746, 688, 644, 597, 547, 501. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 11.05 (br s, 1H), 7.95-8.00 (m, 2H), 7.91 (dd, *J* = 8.25, 1.25 Hz, 2H), 7.68-7.74 (m, 1H), 7.45-7.61 (m, 2H), 7.41-7.49 (m, 2H), 6.79-6.82 (m, 1H), 6.34 (d, *J* = 5.75 Hz, 1H), 6.03-6.08 (m, 2H), 4.77 (d, *J* = 5.50 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 192.80, 192.34, 165.93, 165.23, 163.40, 162.87, 144.62, 136.81, 133.42, 133.04, 131.52, 131.43, 130.71, 130.12, 129.88, 129.80, 129.26, 129.04, 128.60, 128.40, 127.18, 125.72, 124.24, 119.00, 116.51, 116.36, 116.23, 116.02, 109.40, 107.14, 88.59, 83.23, 45.83; HRMS (ESI) calcd. for $C_{22}H_{15}FN_2O_2$ ([M-H]$^+$): 357.1118, found: 357.1028.

(4*R*,5*R*)-2-(4-Fluorophenyl)-5-(4-methoxybenzoyl)-4-(1*H*-pyrazol-4-yl)-4,5-dihydrofuran-3-carbonitrile (4h): Compound **4h** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3f** (323 mg, 3.37 mmol, 1.1 equiv.), **5a** (1 g, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 920 mg (77%), off-white solid, R_f = 0.10 (ethyl acetate/*n*-hexane, 3:7), m.p.: 169-171 ºC; IR (KBr, ν_{max}, cm^{-1}): 3581, 3358, 2960, 2843, 2206, 1905, 1687, 1508, 1417, 1242, 1170, 1018, 941, 840, 671, 501. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 8.00-8.06 (m, 1H), 7.96 (d, *J* = 9.01 Hz, 1H), 7.65 (s, 1H), 7.26 (s, 1H), 7.12-7.20 (m, 1H), 6.95-7.02 (m, 1H), 5.80 (d, *J* = 6.00 Hz, 1H), 4.86 (d, *J* = 6.25 Hz, 1H), 3.91 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 190.73, 165.82, 164.99, 164.52, 163.30, 132.51, 131.50, 130.23, 129.92, 129.83, 129.79, 129.70, 127.89, 126.34, 123.50, 123.47, 119.63, 116.47, 116.18, 116.14, 115.96, 115.92, 114.27, 114.13, 89.12, 86.06, 84.42, 84.41, 55.59, 44.24, 42.96; HRMS (ESI) calcd. for $C_{22}H_{16}FN_3O_3$ ([M+H]$^+$): 390.1176, found: 390.1261.

(4*R*,5*R*)-2-(4-Fluorophenyl)-5-(4-methoxybenzoyl)-4-(thiazol-2-yl)-4,5-dihydrofuran-3-carbonitrile (4i): Compound **4i** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3g** (377 mg, 3.37

mmol, 1.1 equiv.), **5a** (1 g, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1 g (80%), off-white solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 3:7), m.p.: 142-145 ºC; IR (KBr, ν_{max}, cm^{-1}): 3739, 3352, 3103, 3003, 2970, 2841, 2586, 2233, 2056, 1683, 1608, 1506, 1413, 1361, 1321, 1261, 1244, 1174, 1103, 1039, 1018, 945, 884, 833, 744, 648. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 8.91 (d, *J* = 2.00 Hz, 1H), 8.00-8.08 (m, 4H), 7.38 (d, *J* = 2.00 Hz, 1H), 7.14 (t, *J* = 8.76 Hz, 2H), 6.97-7.01(m, 2H), 6.32 (d, *J* = 5.50 Hz, 1H), 5.08 (d, *J* = 5.50 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 190.72, 166.10, 165.91, 164.50, 163.38, 154.49, 154.30, 131.75, 130.01, 129.92, 126.41, 123.56, 116.55, 116.52, 116.11, 115.90, 114.25, 87.09, 83.09, 83.07, 55.62, 48.20; HRMS (ESI) calcd. for $C_{22}H_{16}FN_2O_3$ ($[M+H]^+$): 407.0866, found: 407.0841.

(4*R*,5*R*)-2-(4-Fluorophenyl)-5-(4-methylbenzoyl)-4-(pyridin-4-yl)-4,5-dihydrofuran-3-carbonitrile (4j): Compound **4j** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3h** (361 mg, 3.37 mmol, 1.1 equiv.), **5a** (981 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 900 mg (77%), off-white solid, R_f = 0.20 (ethyl acetate/*n*-hexane, 3:7), m.p.: 144-146 ºC; IR (KBr, ν_{max}, cm^{-1}): 3739, 3066, 3035, 1691, 1604, 1570, 1506, 1398, 1354, 1342, 1240, 1037, 887, 823, 769, 678, 563. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 8.65 (d, *J* = 6.00, 1H), 7.98-8.02 (m, 1H), 7.83 (d, *J* = 8.00 Hz, 1H), 7.36-7.52 (m, 3H), 6.53 (d, *J* = 5.25 Hz, 1H), 4.83 (d, *J* = 5.25 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 191.20, 166.18, 166.10, 163.57, 150.71, 148.13, 145.94, 130.75, 130.75, 130.01, 129.92, 12.84, 129.65, 129.34, 129.10, 127.91, 123.10, 123.07, 122.73, 116.34, 116.12, 115.84, 88.62, 83.35, 83.34, 51.26, 21.86; HRMS (ESI) calcd. for $C_{24}H_{17}FN_2O_2$ ($[M+H]^+$): 385.1274, found: 385.1241.

(4*R*,5*R*)-4-(5-Bromopyridin-3-yl)-2-(4-fluorophenyl)-5-(4-methoxybenzoyl)-4,5-dihydrofuran-3-carbonitrile (4k): Compound **4k** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3i** (624 mg, 3.37 mmol, 1.1 equiv.), **5a** (1 g, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1.3 g (87%), pale yellow solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 3:7), m.p.: 144-147 ºC; IR (KBr, ν_{max}, cm^{-1}): 3034, 2893, 2202, 1693, 1591, 1504, 1419, 1348, 1307, 1255, 1165, 1087, 1016, 945, 902, 835, 690, 644, 638, 567. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 8.71 (d, *J* = 2.25 Hz, 1H), 8.54 (d, *J* = 2.00 Hz, 1H), 8.01-8.09 (m, 2H), 7.93-7.99 (m, 2H), 7.84 (t, *J* = 2.00 Hz, 1H), 7.18 (t, *J* = 8.76 Hz, 2H), 6.96-7.05 (m, 2H), 5.78 (d, *J* = 6.00 Hz, 1H), 4.94 (d, *J* = 5.75 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 189.73, 166.14, 166.07, 164.77, 163.60, 151.18, 147.40, 138.63, 137.82, 136.69, 132.55, 131.70, 130.03, 129.94, 126.17, 123.03, 123.00, 121.60, 116.37, 116.15, 115.76, 114.44, 114.38, 88.86, 86.12, 83.42, 83.41, 60.64, 58.41, 55.71, 50.78, 49.11, 45.98; HRMS (ESI) calcd. for $C_{24}H_{13}BrF_4N_2O_2$ ($[M+H]^+$): 479.0328, found: 479.0433.

(4*R*,5*R*)-2-(4-Fluorophenyl)-5-(4-methoxybenzoyl)-4-(quinolin-3-yl)-4,5-dihydrofuran-3-carbonitrile (4l): Compound **4l** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3j** (529 mg, 3.37 mmol, 1.1 equiv.), **5a** (1 g, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1.2 g (87%), off-white solid, R_f = 0.30 (ethyl acetate/*n*-hexane, 3:7), m.p.: 132-135 ºC; IR (KBr, ν_{max}, cm^{-1}): 2582, 2239, 1689, 1604, 1502, 1419, 1335, 1255, 1170, 1095, 1039, 956, 914, 846, 788, 756, 648, 555. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 8.90 (d, *J* = 2.25, 1H), 8.43 (d, *J* = 1.75 Hz, 1H), 8.02-8.10 (m, 4H), 7.94 (d, *J* = 8.76 Hz, 2H), 7.82 (td, *J* = 7.69, 1.13 Hz, 1H), 7.64-7.70 (m, 1H), 7.50 (t, *J* = 8.88 Hz, 2H), 7.10 (d, *J* = 9.01 Hz, 2H), 6.66 (d, *J* = 5.50 Hz 1H), 5.08 (d, *J* = 5.25 Hz 1H), 3.86 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ, ppm: 191.69, 165.95, 165.35, 163.42, 153.49, 145.75, 142.70, 133.82, 131.00, 129.91, 129.82, 129.66, 129.58, 128.82, 128.61, 127.66, 123.20, 121.88, 116.27, 116.05, 88.63, 83.64, 21.81; HRMS (ESI) calcd. for $C_{28}H_{19}FN_2O_3$ ($[M+H]^+$): 451.1380, found: 451.1446.

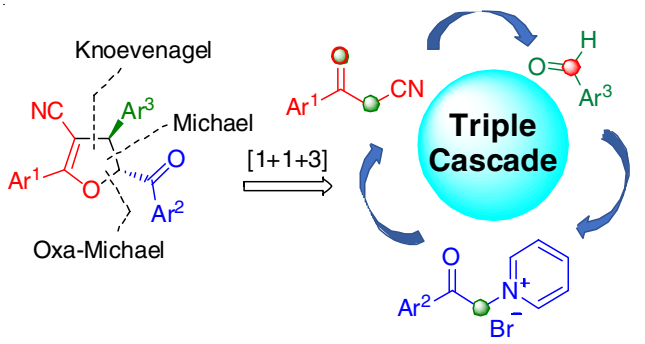
(4*R*,5*R*)-2-(4-Fluorophenyl)-4-(isoquinolin-4-yl)-5-(4-methylbenzoyl)-4,5-dihydrofuran-3-carbonitrile (4m): Compound **4m** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3k** (529 mg, 3.37 mmol, 1.1 equiv.), **5d** (981 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 1.1 g (83%), off-white solid, R_f = 0.30 (ethyl acetate/*n*-hexane, 1:1), m.p.: 139-141 °C; IR (KBr, ν_{max}, cm^{-1}): 3753, 3439, 3047, 2922, 2204, 1689, 1612, 1504, 1406, 1354, 1294, 1234, 1159, 1103, 1008, 844, 748, 650, 534. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 9.38 (s, 1H), 8.59 (s, 1H), 8.23-8.26 (m, 1H), 7.98-8.07 (m, 3H), 7.75-7.84 (m, 4H), 7.46-7.51 (m, 2H), 7.30 (d, *J* = 8.00 Hz, 2H), 6.66 (d, *J* = 5.25 Hz, 1H), 5.66-5.68 (m, 1H), 2.37 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ ppm 190.18, 166.08, 166.00, 164.69, 163.55, 149.89, 148.13, 134.92, 131.99, 131.61, 130.17, 130.04, 129.95, 129.42, 127.89, 127.49, 126.21, 123.27, 116.34, 116.12, 114.43, 89.04, 84.00, 55.67, 50.17; HRMS (ESI) calcd. for $C_{28}H_{19}FN_2O_2$ ($[M+H]^+$): 435.1431, found: 435.1502.

(4*S*,5*R*)-2-(4-Fluorophenyl)-4-(1*H*-indol-2-yl)-5-(4-methylbenzoyl)-4,5-dihydrofuran-3-carbonitrile (4n): Compound **4n** was synthesized according to the general procedure **B** by taking **1** (500 mg, 3.0 mmol, 1.0 equiv.), **3l** (489 mg, 3.37 mmol, 1.1 equiv.), **5d** (981 mg, 3.37 mmol, 1.1 equiv.), TEA (1.29 mL, 9.20 mmol, 3.0 equiv.) in EtOH (10 mL) and the resulting reaction mixture was microwave irradiated for 60 min at 80 ºC. Yield: 950 mg (73%), off-white solid, R_f = 0.60 (ethyl acetate/*n*-hexane, 3:7), m.p.: 178-181 ºC; IR (KBr, ν_{max}, cm^{-1}): 3298, 3057, 2854, 1685, 1602, 1504, 1421, 1298, 1234, 1111, 1060, 1008, 952, 844, 786, 744, 686, 636, 597, 542. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 11.35 (s, 1H), 8.00-8.04 (m, 2H), 7.86 (d, *J* = 8.25 Hz, 3H), 7.45-7.55 (m, 4H), 7.36-7.42 (m, 4H), 7.09-7.15 (m, 1H), 6.96-7.06 (m, 1H), 6.51 (d, *J* = 5.25 Hz, 1H), 6.46 (d, *J* = 1.50 Hz, 1H), 4.97 (d, *J* = 5.25 Hz, 1H) 2.40 (s, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$)

δ, ppm: 192.24, 166.03, 165.83, 163.50, 145.92, 136.69, 135.33, 130.80, 129.99, 129.91, 129.82, 129.43, 128.31, 123.36, 123.32, 122.68, 120.79, 120.40, 116.28, 116.23, 116.06, 111.15, 101.61, 88.27, 82.60, 46.26, 21.88; HRMS (ESI) calcd. for $C_{27}H_{19}FN_2O_2$ ([M-H]$^+$): 421.1435, found: 421.1354.

RESULTS AND DISCUSSION

Microwave assisted synthesis of dihydrofurans as a three component triple cascade reaction progressed *via* Knoevenagel-Michael-oxa-Michael sequence in a unique [1+1+3] annulation (**Scheme-II**) was carried out in this work. In order to carry out the initial investigation of our hypothesis, phenacyl nitrile (**1a**), pyridinium ylide (**5a**) and *p*-methoxy benzaldehyde (**3a**) were chosen as precursors under microwave irradiation. The optimization studies were started with inorganic bases. The use of K_2CO_3 as a base in water at 30 ºC gave 40% of the desired product (entry 1, Table-1). The yield was decreased when acetonitrile was used as solvent (entry 2, Table-1). It was observed that there is an improvement in the yield *i.e.* 52% when the temperature was increased to 80 ºC from 30 ºC (entry 3, Table-1). The usage of EtOH in the reaction lowers the formation of the desired product (entry 4, Table-1). Other inorganic bases like Cs_2CO_3, NaOAc weren't improved the yield as expected (entries 5-7, Table-1). Later, the attention was shifted towards the organic bases, where DMAP in EtOH gave a good yield of 56% (entry 8, Table-1). There is no improvement in the yield with the use of pyrrolidine/piperidine (entry 9-10, Table-1). Implementation of TEA gave

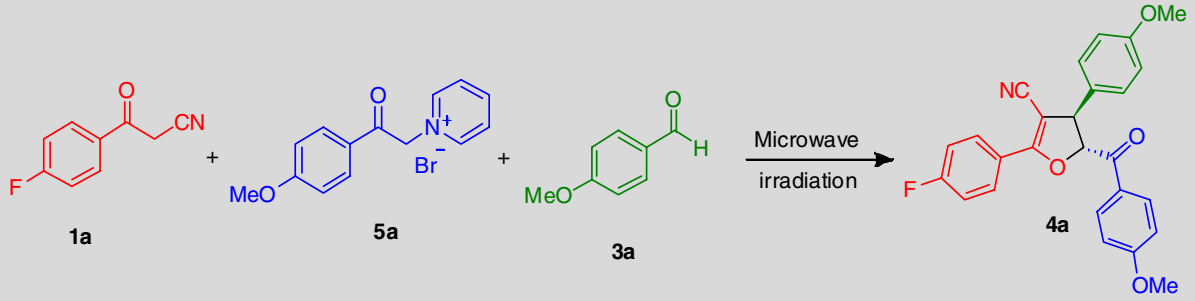


Scheme-II: Three component triple cascade sequence for the synthesis of dihydrofurans

a maximum yield of 85% for the desired product (entry 11, Table-1). In order to get the improvement in the yield, TEA in different solvents was screened in order to produce the required compound to the maximum yield of 70% (entries 12-17). Thus, the execution of TEA in EtOH at 80 ºC for 1 h under microwave irradiation gave the maximum yield.

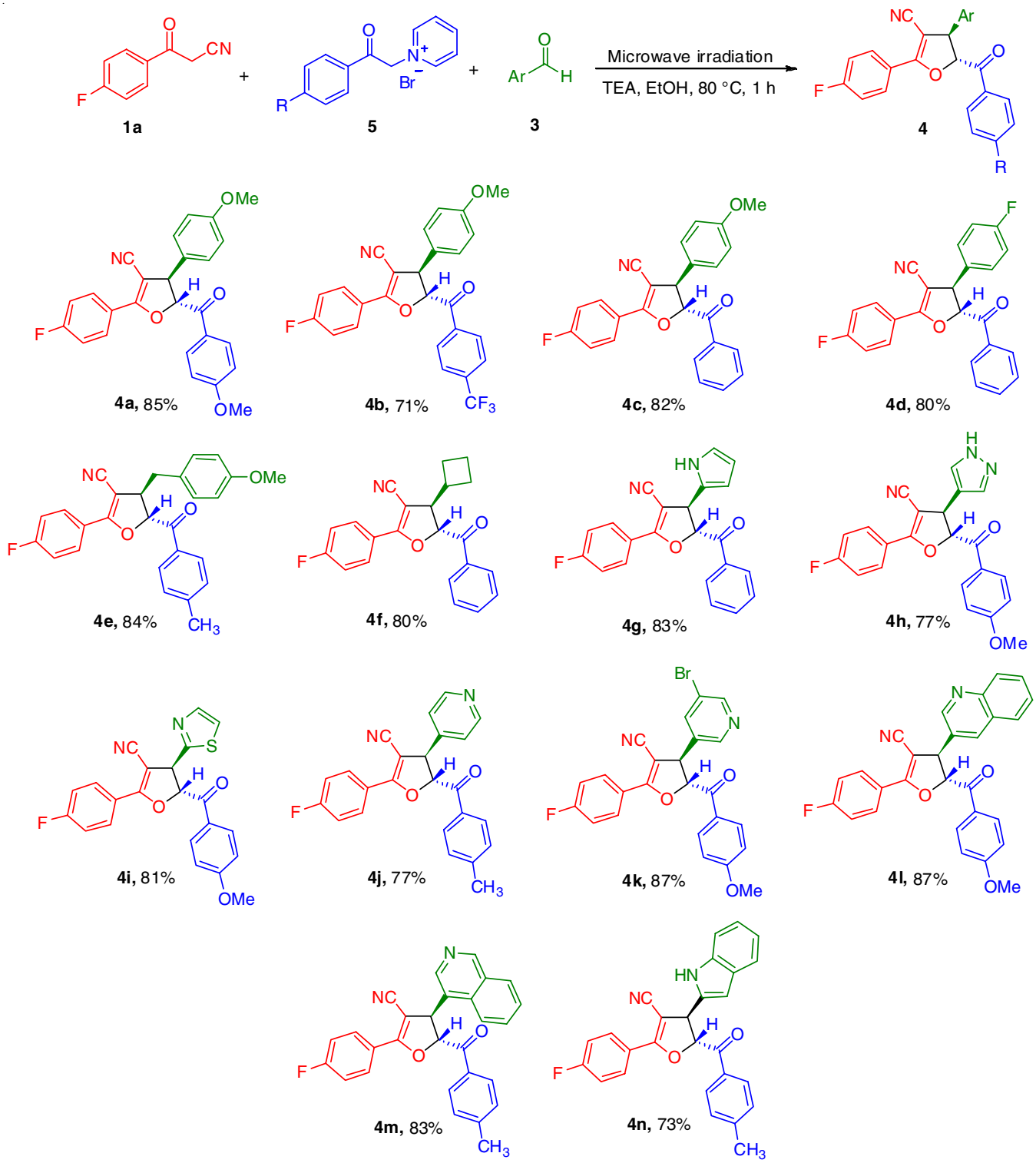
Following the optimized conditions, the substrate scope was further explored for this triple cascade reaction (**Scheme-III**). *p*-Fluoro phenacyl nitrile was treated with various pyridinium ylides as well as aldehydes. *p*-Methoxy benzaldehyde with pyridinium ylide with *p*-methoxy phenyl ring gave compound **4a** in 85% of yield. Whereas pyridinium salt containing *p*-CF_3 phenyl ring was able to produce compound **4b** in 71% only. The unsubstituted phenyl ring in pyridinium salt afforded

TABLE-1
OPTIMIZATION STUDIES TOWARDS THE TRIPLE CASCADE REACTION FOR THE SYNTHESIS OF DIHYDROFURANS[a]



S. No.	Base	Solvent	Temp. (°C)	Time (h)	Isolated yield (%)
1	K_2CO_3	H_2O	30	4	40
2	K_2CO_3	ACN	30	5	30
3	K_2CO_3	ACN	80	4	52
4	K_2CO_3	EtOH	80	2	20
5	Cs_2CO_3	ACN	80	4	34
6	NaOAc	ACN	30	8	25
7	NaOAc	EtOH	80	1	41
8	DMAP	EtOH	80	4	56
9	pyrrolidine	EtOH	80	1	32
10	piperidine	EtOH	80	1	36
11	TEA	EtOH	80	1	85
12	TEA	MeOH	80	1	70
13	TEA	H_2O	80	1	40
14	TEA	DMF	80	1	75
15	TEA	ACN	80	1	64
16	TEA	THF	80	1	43
17	TEA	1,4-Dioxane	80	1	50

[a]All the reactions were performed under microwave irradiation by using **1a** (0.15 mmol), **5a** (0.165 mmol), **3a** (0.165 mmol) and base (0.45 mmol) in 2 mL of solvent.



Scheme-III: Substrate scope studies for the triple cascade reaction [all the reactions were performed under microwave irradiation by using **1a** (3 mmol), **5** (3.3 mmol) **3** (3.3 mmol) and TEA (9 mmol) in 5 mL of solvent (see SI), isolated yield]

compound **4c** in better yield *i.e.,* 82%. *p*-Fluoro benzaldehyde on treatment with *p*-fluoro phenacyl nitrile and phenyl ring containing pyridinium salt yielded compound **4d** in a good yield of 80%. The yield was slightly higher when *p*-methoxy benzylaldehyde was used for the triple cascade reaction and able to get **4e** in 84% yield. This protocol is well suited with aliphatic cyclic aldehydes also, for example, dihydrofuran **4f** in 80% of yield was achieved from cyclobutanal.

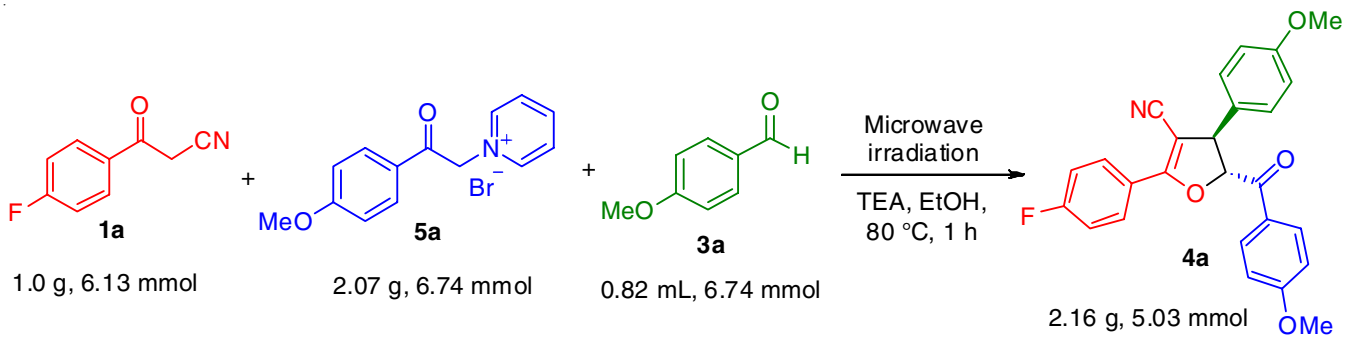
Further on, attention again shifted to various heterocyclic aldehydes, which are less explored. Dihydrofuran **4g** was obtained in 83% yield when prrole-2-carbaldehyde was involved in this three component protocol. It was observed that there is

slight decrease in the yield for compound **4h** when pyrazole-4-aldehyde was used and gave 77% of yield. Thioimidazole-2-carbaldehyde on reaction with *p*-fluoro phenacyl nitrile and *p*-methoxy phenyl ring containing pyridinium salt produced **4i** in a good yield of 81%. A decrement in the yield was found when pyridine-4-carbaldehyde was included in this three component triple cascade protocol. It was able to get **4j** in 77% yield. Whereas 3-bromo pyridine 4-carbaldehyde afforded the required dihydrofuran **4k** in a yield 87%. This protocol was well studied with the quinoline aldehyde as well as isoquinoline aldehyde and produced the corresponding dihydrofurans **4l**, **4m** in 87 and 83% yields, respectively. Indole-2-carbaldehyde on triple cascade reaction with *p*-fluorophenacyl nitrile and *p*-tolyl ring containing pyridinium salt get dihydrofuran **4n** in 73% yield. In order to investigate the scalability of [1+1+3] triple cascade protocol, the reaction in a gram scale (**Scheme-IV**) was also carried out, where the desired dihydrofuran **4a** was obtained in a yield of 82%.

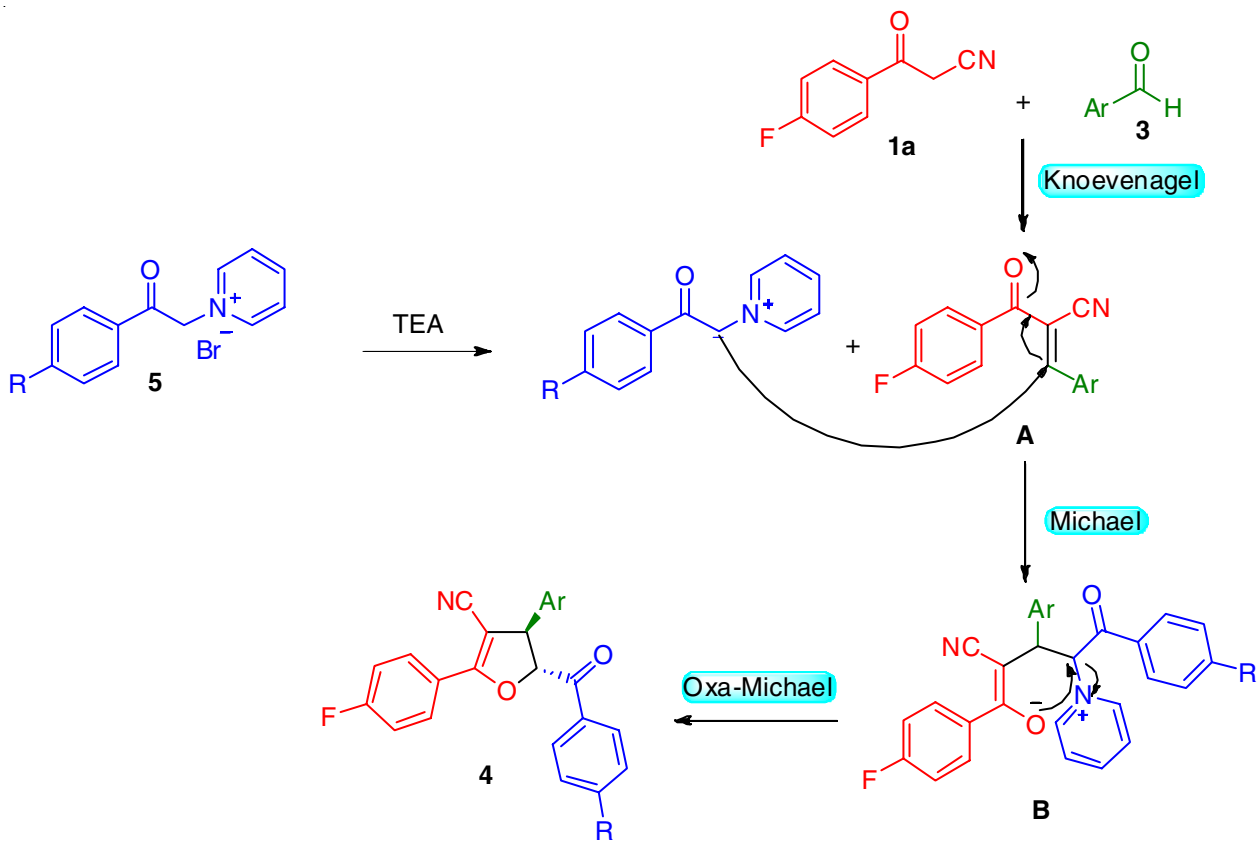
A plausible mechanism is also proposed for the three component triple cascade reaction. Pyridinium ylide in the presence of a base generates the activated anion. This anion undergoes Michael addition with intermediate **A** which is formed by the Knoevenagel condensation between **1a** and **3**. This Michael addition lead to the formation of intermediate **B**. This intermediate **B** undergoes intramolecular cyclization *via* oxa-Michael reaction get compound **4** (**Scheme-V**).

Conclusion

In conclusion, a three component cascade reaction protocol was demonstrated for the synthesis of fully substituted dihydrofurans. This entire protocol was carried out under microwave irradiation and the reaction was progressed *via* Knoevenagel-



Scheme-IV: Gram scale synthesis of dihydrofuran **4a**



Scheme-V: Plausible reaction mechanism of the triple cascade reaction

Michael-oxa-Michael triple cascade sequence as [1+1+3] annulation manner. The proposed strategy was well explored and accepted with various aromatic, aliphatic and heterocyclic precursors and delivered the products in high yields.

ACKNOWLEDGEMENTS

The authors grateful to acknowledge Aragen Life Sciences for providing research facility and high-resolution analytical facilities. We specially thank to Dr. Sudhir Kumar Singh and Dr. Somesh Sharma and for their valuable suggestions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. L.F. Tietze, *Chem. Rev.*, **96**, 115 (1996); https://doi.org/10.1021/cr950027e
2. N. Halland, P.S. Aburel and K.A. Jorgensen, *Angew. Chem. Int. Ed.*, **43**, 1272 (2004); https://doi.org/10.1002/anie.200353364
3. V.B. Gudise, P.C. Settipalli, Y.P. Reddy and S. Anwar, *ChemistrySelect*, **6**, 13589 (2021); https://doi.org/10.1002/slct.202103885
4. P.C. Settipalli, Y.P. Reddy, V.B. Gudise and S. Anwar, *ChemistrySelect*, **6**, 47 (2021); https://doi.org/10.1002/slct.202004619
5. S. Anwar, L.-T. Lin, V. Srinivasadesikan, V.B. Gudise and K. Chen, *RSC Adv.*, **11**, 38648 (2021); https://doi.org/10.1039/D1RA07165C
6. V.B. Gudise, P.C. Settipalli, E. Reddy and S. Anwar, *Eur. J. Org. Chem.*, **2019**, 2234 (2019); https://doi.org/10.1002/ejoc.201801709
7. S.F. Basha, T.N. Prasad, V.B. Gudise, V.S. Kumar, N. Mulakayala and S. Anwar, *Synth. Commun.*, **49**, 3181 (2019); https://doi.org/10.1080/00397911.2019.1659973
8. P. Saha, A. Biswas, N. Molleti and V.K. Singh, *J. Org. Chem.*, **80**, 11115 (2015); https://doi.org/10.1021/acs.joc.5b01751
9. R. Karmakar, A. Suneja and V.K. Singh, *Org. Lett.*, **18**, 2636 (2016); https://doi.org/10.1021/acs.orglett.6b01057
10. V.S. Kumar, V.B. Gudise, P.C. Settipalli, E.K. Reddy, S.F. Basha, Y.P. Reddy, V. Srinivasadesikan, S.-L. Lee and S. Anwar, *ChemistrySelect*, **5**, 3080 (2020); https://doi.org/10.1002/slct.201904618
11. D. Enders, M.R.M. Hüttl, C. Grondal and G. Raabe, *Nature*, **441**, 861 (2006); https://doi.org/10.1038/nature04820
12. S.M. Yang, Y.L. Tsai, G.M. Reddy, L. Mohlmann and W. Lin, *J. Org. Chem.*, **82**, 9182 (2017); https://doi.org/10.1021/acs.joc.7b01415
13. S. Mukherjee, A. Ghosh, U.K. Marelli and A.T. Biju, *Org. Lett.*, **20**, 2952 (2018); https://doi.org/10.1021/acs.orglett.8b00998
14. M. Bakthadoss, D. Kannan and R. Selvakumar, *Chem. Commun.*, **49**, 10947 (2013); https://doi.org/10.1039/c3cc45502e
15. P. Kotame, B.-C. Hong, J.-H. Liao, J.-H., *Tetrahedron Lett.,* **50**, 704 (2020); https://doi.org/10.1016/j.tetlet.2008.11.106
16. D. Enders, R. Krull and W. Bettray, *Synthesis,* 567 (2010); https://doi.org/10.1055/s-0029-1217146
17. N. Sundaravelu, S. Guha and G. Sekar, *J. Org. Chem.,* **85**, 5895 (2020); https://doi.org/10.1021/acs.joc.0c00183
18. S.K. Bankar, J. Mathew and S.S.V. Ramasastry, *Chem. Commun.*, **52**, 5569 (2016); https://doi.org/10.1039/C6CC01016D
19. Y. Tangella, K.L. Manasa, V. Laxma Nayak, M. Sathish, B. Sridhar, A. Alarifi, N. Nagesh and A. Kamal, *Org. Biomol. Chem.*, **15**, 6837 (2017); https://doi.org/10.1039/C7OB01456B
20. A.E. Wright, N.S. Burres and G.K. Schulte, *Tetrahedron Lett.*, **30**, 3491 (1989); https://doi.org/10.1016/S0040-4039(00)99421-8
21. K.M. Marks, E.S. Park, A. Arefolov, K. Russo, K. Ishihara, J.E. Ring, J. Clardy, A.S. Clarke and H.E. Pelish, *J. Nat. Prod.*, **74**, 567 (2011); https://doi.org/10.1021/np100429s
22. C.P.V. Freire, S.B. Ferreira, N.S.M. de Oliveira, A.B.J. Matsuura, I.L. Gama, F.C. da Silva, M.C.B.V. de Souza, E.S. Lima and V.F. Ferreira, *MedChemComm*, **1**, 229 (2010); https://doi.org/10.1039/c0md00074d
23. E.D. Coy, L.E. Cuca and M. Sefkow, *Bioorg. Med. Chem. Lett.*, **19**, 6922 (2009); https://doi.org/10.1016/j.bmcl.2009.10.069
24. L. Dutta, M. Sharma and PJ. Bhuyan, *Tetrahedron,* **72**, 6654 (2016); https://doi.org/10.1016/j.tet.2016.08.084
25. C.-P. Chuang and K.-P. Chen, *Tetrahedron*, **68**, 1401 (2012); https://doi.org/10.1016/j.tet.2011.12.035
26. A.T. Khan, M. Lal and R.S. Basha, *Synthesis*, **45**, 406 (2013); https://doi.org/10.1055/s-0032-1316837
27. P. Gunasekaran, K. Balamurugan, S. Sivakumar, S. Perumal, J.C. Menéndez and A.I. Almansour, *Green Chem.*, **14**, 750 (2012); https://doi.org/10.1039/C2GC16517A
28. S. Ahadi, T. Kamranifard, M. Armaghan, H.R. Khavasi and A. Bazgir, *RSC Adv.*, **4**, 7296 (2014); https://doi.org/10.1039/c3ra45795h
29. J.-R. Ma, W.-M. Shu, K.-L. Zheng, F. Ni, G.-D. Yin and A.-X. Wu, *Org. Biomol. Chem.*, **13**, 4976 (2015); https://doi.org/10.1039/C5OB00163C
30. S. Sathiyamoorthi, A.I. Almansour, S.K. Raju, A. Natarajan and R.R. Kumar, *Synth. Commun.*, **51**, 234 (2021); https://doi.org/10.1080/00397911.2020.1821226
31. M.R. Demidov, V.A. Osyanin, D.V. Osipov and Y.N. Klimochkin, *J. Org. Chem.*, **86**, 7460 (2021); https://doi.org/10.1021/acs.joc.1c00423