Stereoselective Multicomponent Synthesis of [3-(5-Substituted 2-Methoxyphenyl)-5-aryl-2-phenyltetrahydro-4-isoxazolyl](2-thienyl)methanones *via* 1,3-Dipolar Cycloaddition

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Three-component stereoselective synthesis of a set of new tetra substituted isoxazolidines from 5-substituted 2-methoxybenzaldehydes, *N*-phenylhydroxylamine and 1-(2-thienyl)-3-arylprop-2-en-1-ones has been achieved. The effect of microwave irradiation on the reaction under solvent-free conditions has also been investigated. The stereochemistry of the final products has been confirmed by NMR and single crystal X-ray analysis.

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Introduction.

Multicomponent reactions (MCRs) are a promising, "hot" field of chemistry, since they allow complicated molecules to be created using one reaction in a fast, efficient and time efficient manner and they have found numerous applications in synthetic organic chemistry by accessing highly functionalized molecules in straightforward one step transformations [1]. MCRs leading to interesting heterocycles are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening, since the combination of three or more small molecular weight building blocks in a single operation leads to high combinatorial efficacy [2].

In recent years solvent-free organic synthesis attracted the attention of organic chemists for a number of reasons, the main one being the ability to synthesize large collections of compounds in few synthetic steps *via* the split and mix technique [3-6]. Parallel to the multicomponent syntheses, microwave assisted solvent free syntheses have also attracted attention [7-10].

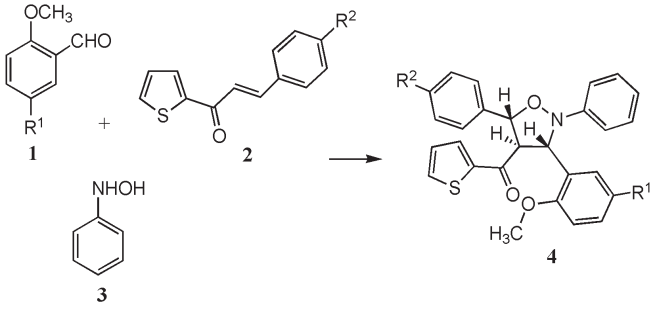
Isoxazolidines are biologically interesting molecules [11,12], which have been generally synthesized from the 1,3-dipolar cycloaddition of nitrones with activated olefins [13-16]. The organosulfur compounds assume importance because of their pharmaceutical and industrial applications [17-18]. The presence of both isoxazolidine and sulfur heterocycles in a molecule may lead to additional interesting biological activities. In the present investigation, it has been planned to synthesize several substituted isoxazolidines with a 2-thienylmethanone group at the 4-position by a multicomponent synthesis.

Results and Discussion.

We have recently reported the synthesis of a set of tetra substituted isoxazolidines from C-(5-substituted 2-methoxyphenyl)-N-phenyl nitrones with different activated olefins and their structural features have been analyzed by employing NMR and X-ray techniques [16]. In continuation of this work, we report the synthesis of a few isoxazolidines with a thienyl ring using the multicomponent tandem process. The 5-substituted 2-methoxybenzaldehydes (**1**) employed in this synthesis have been prepared from the corresponding 4-substituted phenols [4]. The activated olefins, 1-(2-thienyl)-3-arylprop-2-en-1-ones (**2a-c**) used for this work have been prepared from 2-acetylthiophene and arylaldehydes in an equimolar mixture with 10% sodium hydroxide solution at room temperature in good yields.

The synthesis of isoxazolidines has been carried out in toluene under reflux by mixing equimolar quantities of 5-substituted 2-methoxybenzaldehydes (**1**), 1-(2-thienyl)-3-arylprop-2-en-1-ones (**2**) and *N*-phenylhydroxylamine. The reaction time varies between 10 to 15 hours and the corresponding isoxazolidines (**4**) have been obtained in good yields (Scheme 1). It should be noted that the initial

Scheme 1



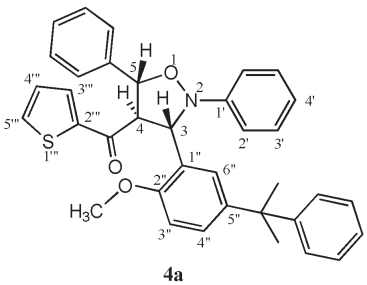
	R^1	R^2
4a	$C(CH_3)_2Ph$	H
4b	$C(CH_3)_2Ph$	Cl
4c	$C(CH_3)_2Ph$	OCH_3
4d	$C(CH_3)_2CH_2CH_3$	H
4e	$C(CH_3)_3$	Cl
4f	$C(CH_3)_3$	OCH_3
4g	$CH(CH_3)_2$	Cl

formation of nitrone followed by the reaction with chalcone should have occurred, in spite of the fact that the chalcones are very good Michael acceptors towards nucleophiles like *N*-phenylhydroxylamine. It is interesting that when the nitrones were treated with chalcones in toluene, the reaction is completed in the same time duration and with the same yield (70-80%) as in the case of the multicomponent reaction.

The use of microwave irradiation has also been explored with respect to the above synthesis. An equimolar mixture of aldehyde, *N*-phenylhydroxylamine and chalcones has been irradiated in a domestic microwave oven of power 1200 W in the absence of solvent resulting in reaction times within 10 minutes with no enhancement in yield. It is interesting to note that when the nitrones obtained from 5-substituted 2-methoxybenzaldehydes (**1**) and *N*-phenylhydroxylamine have been irradiated in a microwave oven with chalcone **2**, the formation of the products are relatively poor (~50%) compared to the multicomponent irradiation process. When the aldehyde, *N*-phenylhydroxylamine and the chalcone are mixed together under solvent-free condition, it becomes a viscous liquid, but when the nitrone and the chalcone are mixed together, the mixture remains as a solid. This may be the reason for higher yield of the multicomponent reaction during microwave irradiation. A mixture of the aldehyde, hydroxylamine and the chalcone left at room temperature in the absence of microwave irradiation does not form the isoxazolidine but leads to the nitrone.

In total, seven new isoxazolidines have been synthesized and were characterized by their NMR spectra. The yields, physical constants and reaction times are given in the experimental section. Compounds **4b**, **e** and **g** are formed at a relatively faster rate, while **4c** and **f** are formed slowly. The reaction is highly regio- and stereoselective yielding only one product in all the cases as observed in a related system [16].

For a representative case (**4a**), the salient features of the NMR and X-ray details are presented here. The 400 MHz ^{1}H NMR spectrum of **4a** (Figure 1) has two singlets at 1.72 and 1.73 ppm each accounting for three hydrogens due to



4a

Figure 1

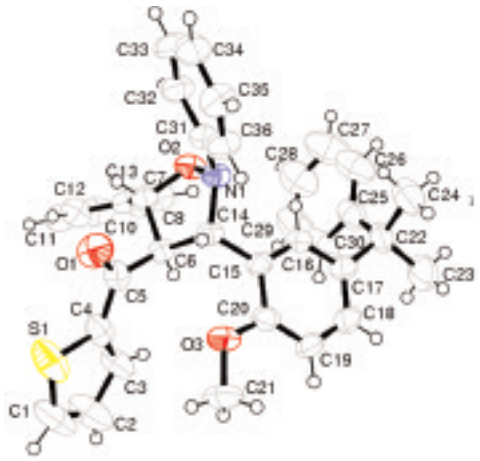


Figure 2. ORTEP diagram of [3-[2-methoxy-5-(1-methyl-1-phenylethyl)-phenyl]-2,5-diphenyltetrahydro-4-isoxazolyl](2-thienyl)methanone (**4a**).

the geminal dimethyl group of the cumyl group. Due to the diastereotopic nature of these two methyl groups, they appear at slightly different positions. The methoxy group of the 3-aryl ring appears at 3.36 ppm as a sharp singlet. The three one hydrogen signals at 5.63 (d, J = 5.2 Hz), 4.12 (dd, J = 9.2, 5.2 Hz) and 5.28 (d, J = 9.2 Hz) could be assigned to H-3, H-4 and H-5 of isoxazolidines moiety by analogy [16]. The coupling constants between H-4 and H-5 ($J_{4,5}$ = 9.2 Hz) and that between H-3 and H-4 ($J_{3,4}$ = 5.2 Hz) suggest that this pair of hydrogen atoms are *trans* to each other. This has been confirmed from the single crystal X-ray analysis (*vide infra*). The other aromatic hydrogen resonances appeared between 6.6 to 8.0 ppm. The one hydrogen doublet at 6.67 ppm (J = 8.4 Hz) is due to H-3" since it is *ortho* to the methoxy group. The hydrogen H-6" appears in the comparatively downfield region as a singlet at 7.90 ppm due to van der Waals deshielding effect of the adjacent cumyl and isoxazolidine moieties. The hydrogen atom *ortho* to sulphur atom, H-5''' appears as a doublet with coupling constant 4.8 Hz at 7.53 ppm. The other two hydrogen atoms, H-3''' and H-4''' of the thienyl ring, appear as a doublet at 6.89 ppm (J = 3.2 Hz) and doublet of doublets at 6.85 ppm (J = 4.8, 3.2 Hz) respectively. The upfield one hydrogen triplet at 6.96 ppm is due to H-4' since it is *para* to the nitrogen atom. The remaining 15 hydrogen atoms appear as a multiplet between 7.07 to 7.30 ppm. The ^{13}C NMR data are in accordance with the proposed structure.

To confirm the assigned regio- and stereochemistry, single crystal x-ray analysis has been carried out for **4a** [19] (Figure 2). The X-ray structure shows that the five membered isoxazolidine ring exists in an envelope form and the torsional angles between N-C_3 and C_4-C_5 (2.50°) and C_3-C_4 and C_5-O (24.76°) clearly show that the oxygen atom, rather than the nitrogen atom, is out of plane. The dihedral

angles between the H_3-C_3 and H_4-C_4 and H_4-C_4 and H_5-C_5 are in well agreement with the observed coupling constants between these pairs suggesting that the molecule has a similar stereochemistry in solution.

In conclusion, the multicomponent synthesis of isoxazolidines has been found to be effective in the sense that it decreases the overall reaction time and the number of steps involved. Microwave irradiation has been found to be more efficient. Regardless of the reaction conditions, the regiochemistry and stereochemistry of the products are unaltered.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument in $CDCl_3$ using TMS as internal standard. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. The single crystal X-ray data set was collected on a Nonius MACH3 Kappa diffractometer with Mo Kalpha radiation (λ = 0.71073 A). The structure was solved by direct methods using SHELXS-86 and refined by full matrix least squares on F^2 by SHELXL-93. The molecular views were realized by ZORTEP. IR Spectra were recorded on a Jasco FT-IR instrument as KBr pellets. Column chromatography was carried out in silica gel (60-120 mesh) using pet ether-ethyl acetate as eluent.

Preparation of (*E*)-1-(2-Thienyl)-3-arylprop-2-en-1-ones (**2**).

General Procedure.

A mixture of 3 g of sodium hydroxide in 30 mL of water and 0.05 mole of 2-acetylthiophene in 15 mL of ethanol was cooled in an ice bath. To this mixture, 0.05 mole of arylaldehyde was added with constant stirring and the temperature was maintained below 15 °C during the addition. This stirring was continued at 25 °C for 3 hours and the mixture was poured into crushed ice. The separated solid was collected by filtration, dried and recrystallised from ethanol.

Multicomponent Synthesis of Isoxazolidines (**4**).

General Procedure.

A mixture of 0.005 mole of 5-substituted 2-methoxybenzaldehydes (**1**), 0.005 mole of (*E*)-1-(2-thienyl)-3-arylprop-2-en-1-ones (**2**) and 0.005 mole of *N*-phenylhydroxylamine was refluxed in 50 mL of dry toluene for the time period specified below. The progress of the reaction was monitored by tlc. After completion of the reaction, the solvent was evaporated under reduced pressure and the product was separated by silica column using petroleum ether-ethyl acetate as eluent and recrystallised from petroleum ether-ethyl acetate mixture.

3-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-2,5-diphenyltetrahydro-4-isoxazolyl(2-thienyl)methanone (4a).

This compound was obtained as colorless crystals (petroleum ether-ethyl acetate mixture), reaction time 12 h, yield 2.10 g (75%), mp 112-113°; ir (potassium bromide): 3064, 2960, 1654, 1596, 1492, 1413, 1355, 1241, 1064, 1024, 815, 763, 698 cm^{-1}; ^{1}H nmr: δ 1.72 (s, 3H), 1.73 (s, 3H), 3.36 (s, 3H), 4.12 (dd, 1H, J = 9.2, 5.2 Hz), 5.28 (d, 1H, J = 9.2 Hz), 5.63 (d, 1H, J = 5.2 Hz), 6.67 (d, 1H, J = 8.4 Hz), 6.85 (dd, 1H, J = 4.8, 3.2 Hz), 6.89 (d, 1H, J = 3.2 Hz), 6.96 (t, 1H, J = 7.2 Hz), 7.07 – 7.29 (m, 15H), 7.53 (d, 1H, J = 4.8 Hz), 7.90 (s, 1H); ^{13}C nmr*: δ 30.84, 30.94, 42.54. 54.43, 70.61, 70.89, 85.04, 109.34, 173.96, 121.34, 125.03, 125.51, 126.70, 126.88, 126.95, 127.95, 128.63, 128.69, 128.99, 129.62, 132.45, 134.39, 136.70, 143.22, 144.44, 150.93, 151.57, 153.74, 189.81.

* One aromatic carbon has merged with others

Anal. Calcd. for $C_{36}H_{33}NO_3S$: C, 77.25; H, 5.94; N, 2.50. Found: C, 77.18; H, 5.99; N, 2.45.

5-(4-Chlorophenyl)-3-[2-methoxy-5-(1-methyl-1-phenylethyl)phenyl]-2-phenyltetrahydro-4-isoxazolyl(2-thienyl)methanone (4b).

This compound was obtained as colorless crystals (petroleum ether-ethyl acetate mixture), reaction time 11 h, yield 2.25 g (76%), mp 153-154°; ir (potassium bromide): 3089, 2960, 1650, 1596, 1490, 1411, 1355, 1241, 1081, 1022, 821, 767, 698 cm^{-1}; ^{1}H nmr: δ 1.71 (s, 3H), 1.72 (s, 3H), 3.35 (s, 3H), 4.05 (dd, 1H, J = 9.2, 4.8 Hz), 5.27 (d, 1H, J = 9.2 Hz), 5.59 (d, 1H, J = 4.8 Hz), 6.67 (d, 1H, J = 8.8 Hz), 6.89 (dd, 1H, J = 4.0, 4.8 Hz), 6.94 – 6.98 (m, 2H), 7.05 (d, 2H, J = 8.0 Hz), 7.11 (dd, 1H, J = 8.8, 2.0 Hz), 7.16 – 7.31 (m, 11H), 7.55 (d, 1H, J = 4.8 Hz), 7.83, d, 1H, J = 2.0 Hz); ^{13}C nmr: δ 30.83, 30.89, 42.53, 54.45, 70.46, 70.88, 84.15, 109.39, 114.02, 121.53, 125.12, 125.64, 126.69, 126.86, 127.96, 128.05, 128.22, 128.85, 129.01, 129.35, 132.44, 134.42, 134.61, 135.40, 143.28, 144.29, 150.89, 151.39, 153.73, 189.54.

Anal. Calcd. for $C_{36}H_{32}ClNO_3S$: C, 72.77; H, 5.43; N, 2.36. Found: C, 72.85; H, 5.49; N, 2.25.

[3-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-(4-methoxyphenyl)-2-phenyltetrahydro-4-isoxazolyl](2-thienyl)methanone (**4c**).

This compound was obtained as colorless crystals (petroleum ether-ethyl acetate mixture), reaction time 14 h, yield 2.30 g (78%), mp 158-159°; ir (potassium bromide): 3087, 2962, 1654, 1604, 1492, 1413, 1357, 1247, 1080, 1027, 825, 767, 700 cm^{-1}; ^{1}H nmr: δ 1.71 (s, 3H), 1.72 (s, 3H), 3.35 (s, 3H), 3.72 (s, 3H), 4.10 (dd, 1H, J = 9.2, 5.2 Hz), 5.20 (d, 1H, J = 9.2 Hz), 5.55 (d, 1H, J = 5.2 Hz), 6.65 (d, 1H, J = 8.4 Hz), 6.86 (dd, 1H, J = 4.8, 4.0 Hz), 6.90-7.11 (m, 5H), 7.18-7.32 (m, 11H), 7.56 (d, 1H, J = 4.8 Hz), 7.82 (d, 1H, J = 2.0 Hz).

Anal. Calcd. for $C_{37}H_{35}NO_4S$: C, 75.35; H, 5.98; N, 2.38. Found: C, 75.45; H, 6.10; N, 2.27.

3-[2-Methoxy-5-(*t*-pentyl)phenyl]-2,5-diphenyltetrahydro-4-isoxazolyl(2-thienyl)methanone (**4d**).

This compound was obtained as colorless crystals (petroleum ether-ethyl acetate mixture), reaction time 10 h, yield 1.92 g (75%), mp 128-129°; ir (potassium bromide): 3065, 2960, 1652, 1594, 1492, 1411, 1355, 1240, 1075, 1022, 813, 763, 696 cm^{-1}; ^{1}H nmr: δ 0.75 (t, 3H, J = 7.5 Hz), 1.33 (s, 6H), 1.72 (q, 2H, J = 7.5 Hz), 3.38 (s, 3H), 4.12 (dd, 1H, J = 9.2, 5.2 Hz), 5.25 (d, 1H, J = 9.2 Hz), 5.58 (d, 1H, J = 5.2 Hz), 6.65 (d, 1H, J = 8.4 Hz), 6.85 (dd, 1H, J = 4.8, 4.0 Hz), 6.88 (d, 1H, J = 4.0 Hz), 7.05-7.28 (m, 11H), 7.56 (d, 1H, J = 4.8 Hz), 7.85 (d, 1H, J = 2.0 Hz); ^{13}C nmr*: δ 9.20, 28.69, 36.96, 37.61, 54.40, 70.64, 71.08, 85.12, 109.35, 114.02, 121.34, 124.51, 125.66, 127.01, 127.94, 128.66, 129.03, 129.58, 132.37, 134.26, 136.87, 141.11, 144.62, 151.76, 153.65, 189.82.

* One aromatic carbon has merged with other

Anal. Calcd. for $C_{32}H_{33}NO_3S$: C, 75.11; H, 6.50; N, 2.74. Found: C, 75.22; H, 6.58; N, 2.67.

[3-[5-(*t*-Butyl)-2-methoxyphenyl]-5-(4-chlorophenyl)-2-phenyltetrahydro-4-isoxazolyl](2-thienyl)methanone (**4e**).

This compound was obtained as colorless crystals (petroleum ether-ethyl acetate mixture), reaction time 9 h, yield 2.21 g (83%), mp 173-174°; ir (potassium bromide): 3070, 2960, 1658, 1596, 1492, 1411, 1361, 1245, 1085, 1024, 825, 728, 694 cm^{-1}; ^1H nmr: δ 1.32 (s, 9H), 3.30 (s, 3H), 4.11 (dd, 1H, J = 9.2, 5.2 Hz), 5.22 (d, 1H, J = 9.2 Hz), 5.56 (d, 1H, J = 5.2 Hz), 6.66 (d, 1H, J = 8.4 Hz), 6.84 (dd, 1H, J = 4.8, 4.0 Hz), 6.89 (d, 1H, J = 4.0 Hz), 7.00-7.31 (m, 10H), 7.55 (d, 1H, J = 4.8 Hz), 7.83 (d, 1H, J = 2.0 Hz).

Anal. Calcd. for $C_{31}H_{30}ClNO_3S$: C, 69.97; H, 5.68; N, 2.63. Found: C, 70.05; H, 6.57; N, 2.70.

[3-[5-(*t*-Butyl)-2-methoxyphenyl]-5-(4-methoxyphenyl)-2-phenyltetrahydro-4-isoxazolyl](2-thienyl)methanone (**4f**).

This compound was obtained as colorless crystals (petroleum ether-ethyl acetate mixture), reaction time 15 h, yield 2.03 g (77%), mp 137-138°; ir (potassium bromide): 3064, 2958, 1656, 1602, 1490, 1413, 1359, 1247, 1074, 1027, 823, 765, 690 cm^{-1}; ^1H nmr: δ 1.33 (s, 9H), 3.28 (s, 3H), 3.72 (s, 3H), 4.12 (dd, 1H, J = 9.2, 5.2 Hz), 5.22 (d, 1H, J = 9.2 Hz), 5.53 (d, 1H, J = 5.2 Hz), 6.64 (d, 1H, J = 8.4 Hz), 6.86 (dd, 1H, J = 4.8, 4.0 Hz), 6.91-7.15 (m, 4H), 7.20-7.35 (m, 7H), 7.55 (d, 1H, J = 4.8 Hz), 7.81 (d, 1H, J = 2.0 Hz).

Anal. Calcd. for $C_{32}H_{33}NO_4S$: C, 72.84; H, 6.30; N, 2.65. Found: C, 72.90; H, 6.45; N, 2.72.

[5-(4-Chlorophenyl)-3-(5-isopropyl-2-methoxyphenyl)-2-phenyltetrahydro-4-isoxazolyl](2-thienyl)methanone (**4g**).

This compound was obtained as colorless crystals (petroleum ether-ethyl acetate mixture), reaction time 11 h, yield 2.05 g (79%), mp 125-126°; ir (potassium bromide): 3064, 2960, 1656, 1596, 1490, 1411, 1361, 1243, 1083, 1024, 825, 728 cm^{-1}; ^1H nmr: δ 1.27 (d, 6H, J = 6.8 Hz), 2.94 (sep, 1H, J = 6.8 Hz), 3.31 (s, 3H), 4.11 (dd, 1H, J = 9.2, 5.2 Hz), 5.27 (d, 1H, J = 9.2 Hz), 5.59 (d, 1H, J = 5.2 Hz), 6.71 (d, 1H, J = 8.4 Hz), 6.89 (dd, 1H, J = 4.4, 4.0 Hz), 6.95-6.99 (m, 2H), 7.08 (d, 2H, J = 8.0 Hz), 7.15 (dd, 1H, J = 8.4, 2.0 Hz), 7.24-7.32 (m, 6H), 7.56 (d, 1H, J = 4.8 Hz), 7.79 (d, 1H, J = 2.0 Hz); ^{13}C nmr*: δ 24.25, 24.28, 54.26, 70.23, 71.29, 84.50, 109.66, 113.77, 121.47, 124.71, 125.86, 128.08, 128.25, 128.84, 129.08, 129.61, 132.28, 134.51, 135.01, 141.46, 144.39, 151.58, 153.84, 189.40.

* One aromatic carbon has merged with other

Anal. Calcd. for $C_{30}H_{28}ClNO_3S$: C, 69.55; H, 5.45; N, 2.70. Found: C, 70.05; H, 5.51; N, 2.78.

Microwave-assisted Multicomponent Synthesis of Isoxazolidines (**4**).

General Procedure.

A mixture of 0.005 mole of 5-substituted 2-methoxybenzaldehyde (**1**), 0.005 mole of (*E*)-1-(2-thienyl)-3-arylprop-2-en-1-one (**2**) and 0.005 mole of *N*-phenylhydroxylamine was ground well and the pasty reaction mixture was placed in a domestic microwave oven of power 1200 W for 10 minutes. After completion of the reaction the mixture was recrystallised from petroleum ether-ethyl acetate mixture to give compounds **4** in the following yields: **4a**, 1.96 g (70%); **4b**, 2.22 g (75%); **4c**, 2.33 g (79%); **4d**, 2.00 g (78%); **4e**, 2.13 g (80%); **4f**, 1.98 g (75%); **4g**, 2.08 g (80%).

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