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Amberlyst Supported, Microwave Assisted Synthesis of Methyl Isoxazole Derivatives of Chalcones

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Abstract:
A simple and efficient condition for Claisen condensation for the synthesis of chalcones involving conventional, microwave irradiation and solvent free conditions in the presence of Amberlyst A26OH has been described. A faster reaction and higher yields are the advantages of present protocol. The structural assignment for these compounds was made by their IR, NMR and MASS spectral and elemental analysis.

Keywords: Chalcones, conventional, Amberlyst A26OH, microwave assisted organic synthesis, methyl isoxazoles.

INTRODUCTION:

Microwave-assisted organic synthesis represents a major and revolutionized breakthrough in organic synthesis. Small molecules can be built in a fraction of the time required by classical thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes.[1] The microwave region of electromagnetic spectrum lies between infrared and radio frequency region, corresponding to wavelength of 1cm to 1m (frequencies 30 MHz to 300 GHz respectively). Domestic and industrial microwave ovens operate at 12.2 cm (2450 MHz) or 33.3 cm (900 MHz) so that there is no interference. Virtually all commercially available microwave reactors operate at 2450 MHz (2.45 GHz) for chemical use. [2]

The chalcones are open chain flavonoids in which two aromatic rings are joined by a three carbon □,β-unsaturated carbonyl system. Fundamentally they are considered to be the derivative of phenyl styryl ketone. Besides their biosynthetic importance, the chalcones play an important role in nature in relation to plant colours. The term chalcones was coined by Kostanecki [3] who did pioneering work in the synthesis of naturally occurring compounds. Chemically these compounds may be termed as benzalacetophenone, β-phenylacrylophenone, □-phenyl-β-benzoyl ethyenes or 1,3-diphenyl-2-propen-1-ones also.

The chalcones have two aromatic rings A and B, joined together through a three carbon □,β-unsaturated carbonyl system. Ring A carbon atoms are identified with prime numbers and the ring B carbon atoms by unprimed numbers. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[4],anti-inflammatory[5], analgesic [6], antiplatelet[7], antiulcerative[8], antimalarial [9], anticancer[10], antiviral[11], antileishmanial [12], antioxidant[13],

antitubercular [14], antihyper-glycemic [15], immune-modulatory[16], inhibition of chemical mediators release, inhibition of leukotriene B4[17], inhibition of tyrosinase[18] and inhibition of aldose reductase activities. The presence of a reactive ,β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity[19-20].

The title compounds were synthesized in this study using commonly available reagents under dry media microwave irradiation to overcome the mentioned drawbacks. Microwave assisted organic synthesis proceeds with facile reactions to provide high yield within a very short reaction time period. This methodology also avoids the use of excess solvents and harmful acids or bases, which are generally used for the catalysis of the reactions.

EXPERIMENTAL SECTION:

All the chemicals of Aldrich and Merck were used without further purification. The solvents used were of S. D. fine and purified by standard procedures before use. Thin layer chromatography was carried out on Merck pre-coated silica gel 60 F254 plates (thickness 0.25 mm). Spots were visualized with UV light at 254 nm for fluorescence quenching spots and at 366 nm for fluorescent spots with Iodine vapors. Column chromatography was carried out using silica gel (60-120 mesh).

1H-NMR and C-13 NMR analysis were carried out on a Bruker AM-400 spectrometer. Chemical shift values are reported as δ values (in ppm) relative to tetramethylsilane (TMS) as internal standard. IR spectra were recorded on Perkin-Elmer IR spectrophotometer using KBr pellets. Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected Mass spectra were recorded on Agilent 6520 Q-Tof Mass spectrophotometer. Microwave reactions were carried out in digital Videocon microwave. Elemental analysis was carried out on Carlo-Ebra-1108 instrument or Elementar's Vario EL III microanalyser. C, H and N values calculated as per atomic weight of C = 12.001, H = 1.008, Br = 79.904, Cl = 35.453, F = 18.998, N = 14.007, O = 15.999, S = 32.065. The values obtained for each element was expressed as percentage of total molecular weight of compound.

RESULTS & DISCUSSION:

In the first step initially N-(4-acetylphenyl)-5-methylisoxazole-4-carboxamide was synthesized. To a stirred solution of the mixture of 5-methyl isoxazoles-4-carboxylic acid in MDC at 0-5^{o}C , slowly thionyl chloride 1(mol) was added and allowed to stir for 15 minutes, then refluxed for 4 hours under nitrogen atmosphere, progress of reaction was checked by TLC. After completion of the reaction MDC was evaporated (to remove the excess thionyl chloride). Oily viscous mass was obtained (N-(4-acetylphenyl)-5-methylisoxazole-4-carboxamide)) which was kept under nitrogen atmosphere for further use. In other assembly, a mixture of 4-amino acetophenone in MDC and few drops of triethylamine were added and cool to 0-5^{o}C under nitrogen atmosphere, then above synthesized oily mass of 5-methyl isoxazoles-4-carbonyl chloride was dissolved in MDC and slowly added in the above solution. The reaction mixture was allowed to stir for 2-hours at 0-5^{o}C. Reaction progress was checked by TLC (ethyl acetate: hexane, 4:6, v/v). Solid obtained was filtered and purified in MDC to afford pure.

In the second step reaction of N-(4-acetylphenyl)-5- methylisoxazole-4-carboxamide (0.01 mol) with aromatic aldehyde (2) were carried out in presence of basic alumina without solvent under microwave irradiation. The result shows the synthesis of chalcones (C1-10) in 90-95% in yield within 3-5 min.

The characterization of chalcones has also been made by their IR spectra. Characteristic absorption is in the region 3500-3200 cm-1 for intermolecular hydrogen bonding is also observed. In the IR frequency of

carbonyl group which shift the carbonyl band to lower frequency region 1640-1630 cm-1. Characteristic aromatic C-H stretching band in the 3100-3000 cm-1 region is also observed. Two absorption peaks of medium to strong intensity occur in the region 1000-950 cm-1 these may be attributed to-CH=CH- out of plane deformation vibrations. The ^{1}H NMR spectra exhibited protons as two doublets around δ 7.83-7.85 due to α-proton and δ 7.87-7.95 due to β proton of α,β-unsaturated system. Mass spectral studies of chalcones (3a-f) revealed the presence of strong ions for $[M]^+$, $[M-H]^+$ and $[M-CO]^+$.

GENERAL PROCEDURE FOR SYNTHESIS OF CHALCONES:

Conventional method: A mixture of N-(4-acetylphenyl)-5-methylisoxazole-4-carboxamide (I) (0.01 mol) and aryl aldehydes (II) (0.01 mol) was stirred in ethanol (30 ml) , To this 100 mg of Amberlyst A26OH was added with constant stirring adsorbed material was mixed properly, then reaction mixture was refluxed under stirring for 24 hours. Progress of the reaction was monitored by TLC (ethyl acetate: hexane, 3:7, v/v) and then it was poured in to crushed ice and acidified with HCl. Solid was extracted in dichloro methane and filtered then was evaporated. Compound was recrystallized from ethanol to afford pure compound.

Solid phase Microwave Method: An equimolar mixture of N-(4-acetylphenyl)-5-methylisoxazole-4-carboxamide (I) (0.01 mol) and aryl aldehydes(II) (0.01 mol) dissolved in minimum amount of ethanol and catalytic amount 100mg of Amberlyst A26OH were mixed and placed in a conical flask. The conical flask was covered with a funnel and then the flask was place in a microwave oven. The reaction mixture was irradiated under 140-280 watt microwave irradiation for 2-3 min. The progress of the reaction was monitored by TLC (n-hexane: ethyl acetate, 7:3) after every 30 sec. then it was poured in to crushed ice and acidified with HCl. Solid was extracted in dichloro methane and filtered then was evaporated. Compound was recrystallized from ethanol to afford pure compound.

The characterization data of some synthesized compound chalcones are given below,

C-01; 5-Methyl-N-{4-[(2E)-3-phenylprop-2-enoyl]phenyl}-1,2-oxazole-4-carboxamide, yellow crystals, M.P: 191-193°C, Mol. wt. 332.5, MF: $C_{2o}H_{16}N_2O_3$, IR absorption (KBr) at 3053,3089, 1671, 1659, 1533, 1491,conforms the presence of –C=O, Ar-H, C=C, and at 983, 830, 860, clearly indicate the presence of CH=CH trans, and substituted ring in the molecule. 1HNMR (400 MHz, CDCl3-d6) spectrum shows signals at H 2.43 (s, 3H, H), 7.41 and 7.56 (d, 2H, trans -H), 7.86-8.11(m, 10H,-Ar-H), 15.8(s, H, -NH). C-13 NMR spectrum shows signals at, 11.81, 100.55, 122.22, 127.61, 128.53, 128.61, 131.4, 133.5, 135.24, 143.34, 145.11, 160.83, 164.76, 172.7, 206.22 ppm. ESI-MS: shows base peak at 355[M+], Molecular ion peak is at 333[M+1], shows fragments at 325.1[M+,–NO].

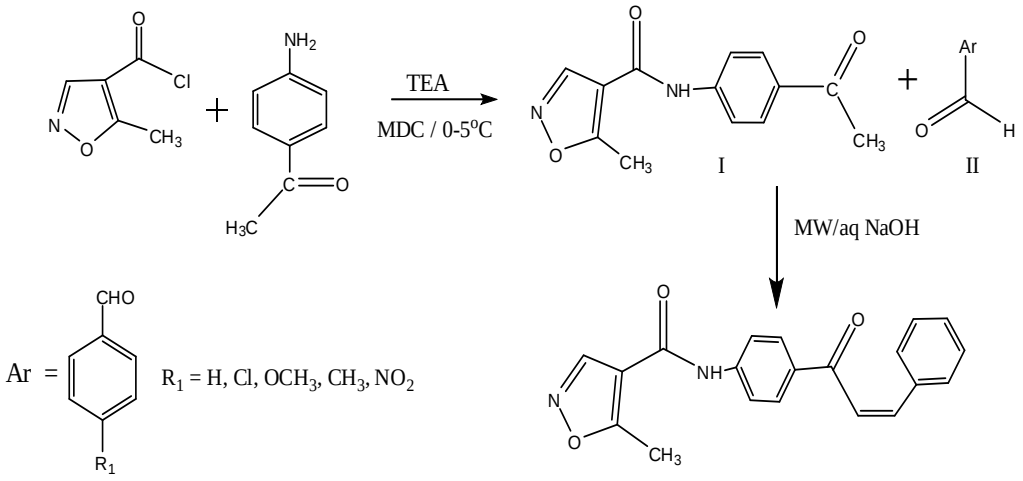
C-03;(E)-N-(4-(3-(3,5-dimethoxyphenyl) acryloyl) phenyl)-5-methyl-isoxazole-4-carboxa-mide, yellow crystals, M.P: 151-153°C, Mol. wt. 392.40, MF: $C_{22}H_{20}N_2O_5$, IR absorption (KBr) at 3056,2967, 1670, 1661, 1557, 1533, 1480cm-1 conforms the presence of –C=O aromatic ring, 1236 and 1056 cm^{-1} shows the methoxy moieties and at 971, 867, 818 cm-1 clearly indicate the presence of CH=CH trans, and substituted ring in the molecule. ^{1}HNMR (300 MHz, Acetone-d6) spectrum shows signals at H 2.55 (s, 6H, H), 7.04 and 8.04 (d, 2H, tans-H), 7.34-8.98 (m, 10H,-Ar-H), 9.27 (s, H, -NH). C-13 NMR spectrum shows signals at, 22.81, 56.23, 56.34, 81.64, 111.81, 112.56, 116.07, 120.37, 122.21, 124.45, 129.01, 130.03, 130.21, 134.87, 135.99, 142.0, 145.22, 150.73, 152.93, 169.34, 188.60, 190.26, 196.88, 206.30 ppm established the structure. ESI-MS: Spectrum shows peak at 393.26[M+1], and the fragments at 365[M+-NO breaking of iso-oxazole ring], 363.13[M+-OCH3], 332 M+, 2 × -OCH3], 282[M+-C5H5NO2].

C-04; (E)-N-(4-(3-(2-butyl-4-chloro-4H-imidazol-5-yl)acryloyl)phenyl)-5- methyl isoxazole-4-carboxamide, dark yellow crystals, M.P: 181-183°C, Mol. wt. 412.87, and MF: $C_{21}H_{21}ClN_4O_3$, IR absorptions (KBr) at 3053, 3089, 1670, 1660, 1530, 1490 cm^{-1} conforms the presence of –C=O, -CONH, C=C and aromatic ring, and at 983, 830, 860, clearly indicates the presence of CH=CH trans, and substituted ring in the molecule. 1HNMR (300 MHz, Acetone-d6) spectrum showed signals at H 0.94 (t, 3H,H), 1.18-1.62 (sextet, 2H, H), 1.78-1.83 (t, 2H, H), 1.91-1.98, 2.52 (s, 3H,H), 6.44 and 6.98 (d, 2H, tans-H), 7.52-8.13(m, 10H, -Ar-H), 9.35(s, H, -NH). C-13 NMR spectrum shows signals at, 13.40, 13.45, 19.58, 21.25, 22.25, 26.62, 81.58, 116.23, 122.21, 130.05, 130.21, 134.85, 142.11, 169.40, 190.32, 196.87, 206.30 ppm established the structure. ESI-MS: Supports the structure by showing peak at 413.38[M+1], and the fragments at 385.43[M+-NO], 330.40[M+-isoxazole ring], 303.46[M+,-$C_6H_7NO_2$ (Isoxazole ring with -CO)], 378.47[M+-Cl], 356.71[M+- C_5H_{12}].

C-08: (E)-N-(4-(3-(4-(dimethylamino) phenyl) acryloyl) phenyl)-5-ethylisoxazole-4-carboxamide, dark yellow crystals, IR absorptions (KBr) shows N,N-dimethyl moieties in the molecule which was confirmed by ^{1}HNMR δ3.09(s, 6H, -N(CH3)2. C-13 NMR, and ESI-MS at 375.19 and fragments at 360.44[M+-CH3], 346.17[M+-NO], 331.56[M+-2×CH3], established the structure as (E)-N-(4-(3-(4-(dimethyl amino)phenyl)acryloyl) phenyl)-5-methylisoxazole-4-carboxamide.

Thus by changing the aldehydes as shown we have prepared different substituted chalcones as given. All the synthesized compounds were well characterized using IR, 1HNMR, 13C-NMR and ESI-MS and M.P. The spectral characteristics were almost similar and have shown expected shielding, deshielding and shift in the position of bands.

In order to optimise the reaction conditions, the synthesis of Chalcone **C-01** and **C-06** was used as a model reaction. The structures of the synthesized compounds have been established by spectroscopic techniques like ^{1}HNMR, 13C-NMR, ESI-MASS, and IR.



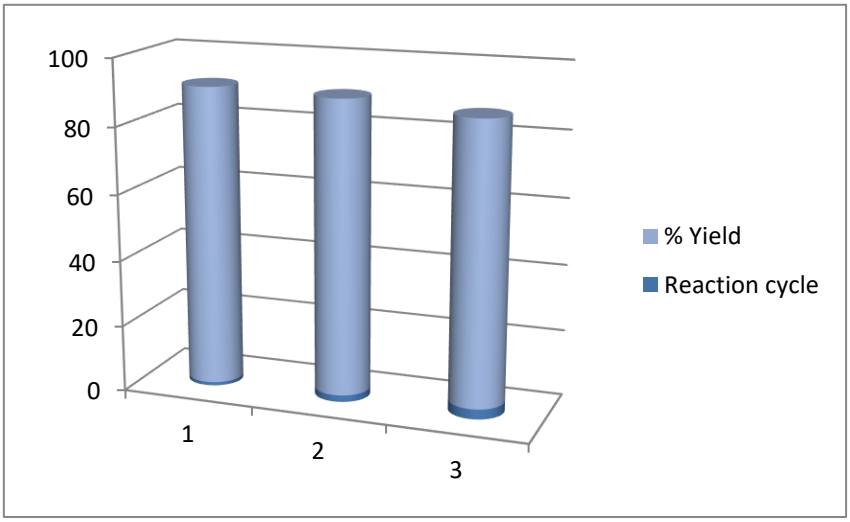
SCHEME-I

C-1: R_1 = H; **C-2**: R_1 =OH; **C-3**:R_1 = OCH_3×2; **C-4**: R_1 = imidazol ring; **C-5**: R_1= furan ring; **C-6**:R_1= OCH_3; **C-7**: R_1**=** methyl thiofuran; **C-8**:R_1= N,N-dimethyl benzaldehyde; **C-9**:R_1= methyl furan; **C-10**:R= Cl-Ar**.**

RECYCLING AND REUSING OF THE CATALYST:

Reusability of the catalyst was also investigated. For this purpose, the model reaction for the synthesis of compound 4e was studied under optimized reaction conditions. After the completion of the reaction, the catalyst was separated by simple filtration, washed with Dichloromethane (2x10ml), EtOH (2x10 ml) and dried at 100°C under vacuum for 1 h, and reused for a similar reaction. As shown in Fig 1. catalyst could be reused at least three times without significant loss of activity.

Fig 1: Reusability of catalyst Amberlyst A26OH for model reaction.



CONCLUSION:

All the transformation were carried out using conventional and microwave irradiation method which lead to considerable time saving, better yields and environmentally profitable procedure. The less solvent condition diminishes the problem of waste disposal and is eco friendly. In investigations, our group has made contributions to green methodologies by providing greener approaches to several heteroaromatic compounds.

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