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# Microwave irradiated high-speed and classical synthesis of benzylidene acetyl pyrroles

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## ABSTRACT

*A microwave irradiated high-speed and classical synthesis of benzylidene acetyl pyrroles involving Claisen-Schimidt condensation reaction using solid basic alumina under microwave irradiation (MWI) is described. All compounds show antibacterial and antifungal activities when compared with standard drug Norfloxacin and Griseofulvine against Bacterial cultures such as E. coli, Pseudomonus aeruginosa, S. aureus, Proteus vulgaris and fungal cultures Aspergillus niger and Candida albicans. The synthesized compounds are characterized by FTIR, $^{1}$H NMR elemental and chemical properties.*

**Key words**: Pyrrole, azo compounds, 4-hydroxy benzaldehyde.

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## INTRODUCTION

The chemistry of benzylideneacetophenones and their heterocyclic analogues has been an interesting field of study for long time. The benzylideneacetophenones are used as building blocks for many heterocyclic rings[1]. Benzylideneacetophenones are found to inhibit the growth of several pathogenic microorganisms and fungi where as some of the benzylideneacetophenones are reported to possess important therapeutic properties such as hypertensive, antipeptic-ulcer activity etc. Heterocyclic analogues of benzylideneacetophenones are reported to possess bactericidal bacteriostatic, chloerostatic activities[2-4].

Benzylideneacetophenones play an ecological role in nature , in relation to plant colour. These brightly yellow coloured compounds are found in many plant organs, but most conspicuously in flowers. Benzylideneacetophenones contain reactive keto ethylenic (enone) group. The presence of enone function in the benzylideneacetophenone molecule confers antibiotic activity[5-8].

Microwave-induced Organic Reaction Enhancement(MORE) is used for carrying out chemical transformations e.g. organic reactions and their uses in ecofriendly manners[9-11]. The microwave assisted organic reactions occur more safely and in an environmentally friendly manner with enhanced product purity and chemical yields[12]. Shorter reaction time periods, simple reaction conditions and higher yields render the microwave method superior[13].

## MATERIALS AND METHODS

### Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. IR spectra were run in KBr pellets on a Perkin-Elmer 157 spectrometer. H NMR spectra were recorded in $CDCl_3$ on a Bruker-Variah 300MHz FT NMR spectrometer using TMS as internal standard. Purity of the compounds was checked by TLC on silica gel G plates and the spots were located by exposure to iodine vapours. The characterization data of the compounds is given in **Table –II.**

**Table – II Characterization data of compounds 3a – m**

| Comp. | R★ | Mol. Formula | M. Pt (°C) | RF Value Eluent* | | Analysis Found (Calcd)% | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| 3a | H | $C_{13}H_{11}ON$ | 122° | 0.93 | 61 | 79.1 (79.3) | 5.5 (5.4) | 7.1 (7.0) |
| 3b | 2-OH | $C_{13}H_{11}O_2N$ | 132° | 0.71 | 55 | 67.5 (67.4) | 4.7 (4.6) | 6.0 (6.1) |
| 3c | 3-OH | $C_{13}H_{11}O_2N$ | 137° | 0.75 | 57 | 67.5 (67.4) | 4.7 (4.6) | 6.0 (6.1) |
| 3d | 4-OH | $C_{13}H_{11}O_2N$ | 153° | 0.82 | 62 | 67.5 (67.4) | 4.7 (4.6) | 6.0 (6.1) |
| 3e | 2-$NO_2$ | $C_{13}H_{10}O_3N_2$ | 142° | 0.77 | 57 | 64.4 (64.1) | 4.1 (4.0) | 11.5 (11.4) |
| 3f | 3-$NO_2$ | $C_{13}H_{10}O_3N_2$ | 136° | 0.54 | 62 | 64.4 (64.1) | 4.1 (4.0) | 11.5 (11.4) |
| 3g | 4-$NO_2$ | $C_{13}H_{10}O_3N_2$ | 129° | 0.86 | 52 | 64.4 (64.1) | 4.1 (4.0) | 11.5 (11.4) |
| 3h | 2-Cl | $C_{13}H_{10}ONCl$ | 143° | 0.75 | 64 | 67.4 (67.3) | 4.3 (4.2) | 6.9 (6.2) |
| 3i | 4-Cl | $C_{13}H_{10}ONCl$ | 157° | 0.78 | 59 | 67.4 (67.3) | 4.3 (4.2) | 6.9 (6.2) |
| 3j | 3-$OCH_3$ | $C_{14}H_{13}O_2N$ | 173° | 0.50 | 52 | 74.0 (74.2) | 5.7 (5.6) | 6.1 (6.0) |
| 3k | 4-$OCH_3$ | $C_{14}H_{13}O_2N$ | 213° | 0.60 | 54 | 74.0 (74.2) | 5.7 (5.6) | 6.1 (6.0) |
| 3l | 3,4,5-$(OCH_3)_3$ | $C_{16}H_{17}O_4N$ | 171° | 0.82 | 61 | 66.8 (66.4) | 5.9 (5.7) | 4.8 (4.3) |
| 3m | 4-$N(CH_3)_2$ | $C_{15}H_{16}ON_2$ | 191° | 0.70 | 68 | 75.0 (75.1) | 6.6 (6.4) | 11.6 (11.4) |

* *Eluents for TLC: Benzene – acetone (6 : 4) for 3a-m*

★ *Solvent for crystallization ; aq. ethanol for 3a-m.*

The reaction mixture was thoroughly mixed and adsorbed material was dried in air and irradiated inside a microwave oven for 2-3 min. at medium power level(600W). After the completion of reaction (TLC) the reaction mixture was cooled at room temp. and the product was extracted with ethanol (3x10ml). Removal of the solvent and subsequent recrystallization using ethanol resulted analytical pure samples of (3a-m) **(Table-II).**

**B) Solution phase MWI** –Equimolar quantities of 2-acetyl pyrrople and substituted aromatic aldehyde in ethanol (30ml) and NaOH (2ml, 40%) were taken in a 100 ml borosil flask fitted with a funnel as a loose top. The reaction mixture was irradiated in a microwave oven for 2-3 min. at 20% power level (300W) with short interruption of 20 sec, to avoid the excessive evaporation of the solvent. This protocol was repeated in overall heating time. On completion of the reaction (TLC) the reaction mixture was cooled to room temp.acidified with dil HCl. The product separated was filtered, washed with cold water, dried and recrystallized from ethanol.

**Table-III- Comparative study data of compounds 3a-m**

| Compd | M.P. | Reaction time | | | Yield (%) | | |
|---|---|---|---|---|---|---|---|
| | ($^0$C) | Microwave | | Classical (hr) | Microwave | | |
| | | Solid phase (min) | Solvent phase (min) | | Solid phase | Sovent phase | Classical |
| 3a | $122^0$ | 2 | 2 | 8 | 77 | 72 | 61 |
| 3b | $132^0$ | 3 | 3 | 8 | 82 | 80 | 55 |
| 3c | $137^0$ | 2.5 | 5 | 7 | 78 | 73 | 57 |
| 3d | $153^0$ | 3 | 4 | 8 | 85 | 83 | 62 |
| 3e | $142^0$ | 1 | 3 | 7 | 76 | 73 | 57 |
| 3f | $136^0$ | 2 | 3 | 8 | 80 | 78 | 62 |
| 3g | $129^0$ | 3 | 2 | 7 | 85 | 76 | 52 |
| 3h | $143^0$ | 2.5 | 4 | 8 | 76 | 71 | 64 |
| 3i | $157^0$ | 3 | 4 | 7 | 68 | 62 | 59 |
| 3j | $173^0$ | 2 | 4 | 7 | 69 | 64 | 52 |
| 3k | $213^0$ | 3 | 5 | 8 | 71 | 68 | 54 |
| 3l | $171^0$ | 2 | 4 | 8 | 78 | 76 | 61 |
| 3m | $191^0$ | 3 | 5 | 8 | 82 | 80 | 68 |

**Classical method (3a-m)**- 2-acetyl pyrrole (0.01mol) and substituted benzaldehyde (0.01mol) was dissolved in 100ml ethanol. To this solution, NaOH (40%, 10ml) was added dropwise with constant stirring at room temp. The pale to dark yellow solid was obtained.The reaction mixture was kept 7-8 hr and acidified with dil HCl. The solid obtained was washed with cold water. It was filteredand dried.It was crystallized from ethanol.

**3a: Benzylidene acetyl pyrrole**

Yield 61, M.P. 122°C: IR(KBr); 3504(NH-pyrrole),3120(C-H-pyrrole, stretching), 1644 (C=O),1601 (C=C), 1630(ArH) ;$^1$HNMR (300MHz DMSO) δ 8.21(1H,s,NH), 7.02 (3H, m, pyrrole-C-H), 7.8(5H,m,ArH), 6.8 (2H,in ethylenic CH=CH ).

**3b: 2-Hydroxybenzylidene acetyl pyrrole**

Yield 55% , M.P.132°C: IR(KBr); 3622 (OH), 3524(NH-pyrrole), 3135(C-H-pyrrole, stretching)1640 (C=O),1610 (C=C), 1632(ArH), ;$^1$HNMR (300MHz DMSO) δ 8.9 (1H, s, OH), 8.3(1H,s,NH), 7.0 (3H, m, pyrrole-C-H), 7.9(5H,m,ArH). 6.2 (2H,in ethylenic CH=CH ) .

**3c: 3-Hydroxybenzylidene acetyl pyrrole**

Yield 57% , M.P.137°C: IR(KBr); 3626 (OH), 3527(NH-pyrrole), 3126(C-H-pyrrole, stretching)1648 (C=O),1619 (C=C), 1612(ArH) ;$^1$HNMR (300MHz DMSO) δ 8.2 (1H, s, OH), 7.3(1H,s,NH), 7.02 (3H, m, pyrrole-C-H), 6.2 (2H,in ethylenic CH=CH ), 7.7(5H,m,ArH).

**3d: 4-Hydroxybenzylidene acetyl pyrrole**

Yield 62%, M.P.153°C: IR(KBr); 3626 (OH), 3527(NH-pyrrole), 3151(C-H-pyrrole, stretching)1648 (C=O),1619 (C=C), 1612(ArH) ;$^1$HNMR (300MHz DMSO) δ 8.2 (1H, s, OH), 7.3(1H,s,NH), 7.02 (3H, m, pyrrole-C-H), 6.2 (2H,in ethylenic CH=CH ), 7.7(5H,m,ArH).

**3e: 2-Nitrobenzylidene acetyl pyrrole**

Yield 57%, M.P142°C: IR(KBr); 3537(NH-pyrrole), 3125(C-H-pyrrole, stretching)1658 (C=O),1629 (C=C), 1622(ArH), 1540 ($NO_2$) ;$^1$HNMR (300MHz DMSO) δ 7.3(1H,s,NH), 7.03 (3H, m, pyrrole-C-H), 6.2 (2H,in ethylenic CH=CH ), 7.7(5H,m,ArH).

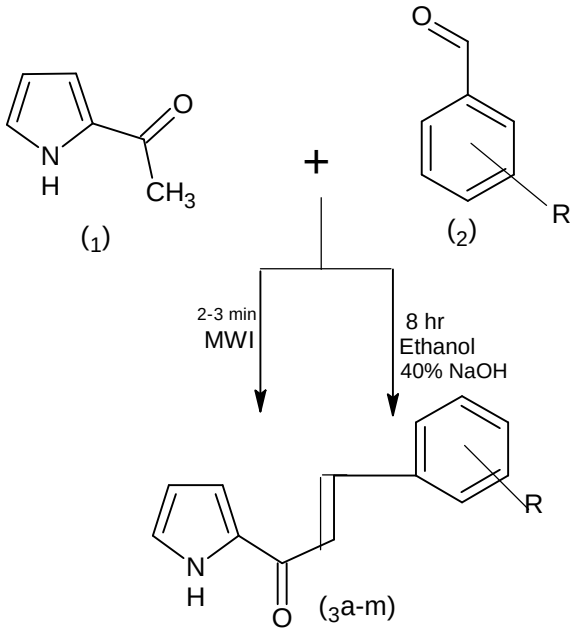
**.3f: 3-Nitrobenzylidene acetyl pyrrole**
Yield 62%, M.P. 136°C: IR(KBr); 3547(NH-pyrrole), 3140(C-H-pyrrole, stretching), 1628 (C=O),1629 (C=C), 1622(ArH), 1545 ($NO_2$) ;$^1$HNMR (300MHz DMSO) δ 8.3(1H,s,NH), 7.7(5H,m,ArH) 7.1 (3H, m, pyrrole-C-H), 6.2 (2H,in ethylenic CH=CH).

**3g: 4-Nitrobenzylidene acetyl pyrrole**
Yield 52%, M.P. 129°C: IR(KBr); 3557(NH-pyrrole), 3123(C-H-pyrrole, stretching)1678 (C=O),1629 (C=C), 1622(ArH), 1542 ($NO_2$) ;$^1$HNMR (300MHz DMSO) δ 7.3(1H,s,NH), 7.02 (3H, m, pyrrole-C-H), 6.2 (2H,in ethylenic CH=CH ), 7.7(5H,m,ArH).

**3h: 2-Chlorobenzylidene acetyl pyrrole**
Yield 64%, M.P. 143°C: IR(KBr); 3546(NH-pyrrole), 3124(C-H-pyrrole, stretching), 1620 (C=O),1626 (C=C), 1622(ArH), 768 (Cl) ;$^1$HNMR (300MHz DMSO) δ 8.3(1H,s,NH), 7.04 (3H, m, pyrrole-C-H), 7.7(5H,m,ArH), 6.2 (2H,in ethylenic CH=CH ).

## RESULTS AND DISCUSSION

The condensation of substituted aromatic-aldehyde with 2-acetyl pyrrole has been carried out by both classical and microwave methods to give compounds **(3a-m)**. In classical method reaction is carried out in ethanol and it takes about 7-8 hr, while under microwave irradiation it takes only 2-3 min.In classical method the yield is lower as compared to microwave irradiation. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur. A comparative study in terms of yield and reaction period is shown in **Table-III**




Scheme-I

**Biological Studies**
Comparative study of 2-acetyl pyrrole(1) and 2-substituted benzylidene acetyl pyrrople **(3a-j)** have been observed by using Norfloxacine and Griseofulvine as standards. The enhancement in biological activity of compound (1) as compared with the newly synthesized **(3a-j)** has been observed. The synthesized compounds were tested at 100µg/ml concentration against

Escherichia *coli*, Staphylococcus *aureus*, Ps. *acruginosa*, P.*vulgaris*, A. *niger* and C. *albicans* for its antibacterial and antifungal screening as shown in **Table-I.**

**Table I-Antibacterial and antifungal activities of compounds 3 a-j**

| | Antibacterial activity | | | Antifungal activity | |
|---|---|---|---|---|---|
| Compd | *S .aureus* | *B. substillis* | *E. coli* | *C. albicans* | *A. niger* |
| 3 a | ++ | ++ | + | ++ | ++ |
| 3b | + | +++ | +++ | +++ | +++ |
| 3c | - | ++ | +++ | +++ | ++ |
| 3d | +++ | + + | ++ | ++ | ++ |
| 3e | + | ++ + | +++ | ++ | + |
| 3f | ++ | +++ | ++ | +++ | ++ |
| 3 g | +++ | ++ | - | ++ | ++ |
| 3 h | ++ | - | + | - | +++ |
| 3 i | +++ | ++ | +++ | +++ | - |
| 3 j | ++ | + | ++ | + | +++ |
| SM | +++ | +++ | ++++ | | |
| GF | | | | ++++ | +++ |

*SM (Streptomycin) and GF (Griesofulvin). The inhibition diameter in Mm: (-)<6, (+)7-9, (++)10-15,(+++)16-22, (++++)23-28.*

## CONCLUSION

Researchers across the globe have developed green resolution to design synthesis in the organic chemistry. The microwave assisted greener chemical transformation affords excellent product yield, reduced reaction time and minimization or elimination of by product. The result obtained confirms superiority of microwave irradiation over classical heating method **(Table-III).**

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