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POTASSIUM FLUORIDE ON ALUMINA: DRY CONDENSATION OF 3-PHENYLISOXAZOL-5-ONE WITH ALDEHYDES UNDER MICROWAVE IRRADIATION.

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Abstract: 3-Phenylisoxazol-5-one (**2**) and aromatic aldehydes were condensed to 3-phenyl-(4-arylmethylene) isoxazol-5-one (**3**) in the presence of Al_2O_3-KF without solvent under microwave irradiation.

Alkylideneisoxazol-5-ones are useful intermediates in synthesis [1] and some alkylideneisoxazol-5-ones present interesting properties as fungicide [2], drug [3] and dye [4].

4-Alkylideneisoxazol-5-ones can be obtained by reaction of Grignard reagent with 4-chloromethylisoxazol-5-one [5]. 3-Phenylisoxazol-5-one is a planar molecule with a methylene connected to an electron withdrawing group as Meldrum acid [6], tetronic acid [7], barbituric acid [8], which gave condensation product with aldehyde catalysed by clay. The pKa of the methylene group of 3-phenylisoxazol-5-one estimated [9] by CAMEO is about 10.

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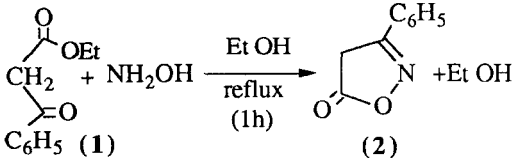
3-Phenylisoxazol-5-one (**2**) was obtained by condensation of ethylbenzoylacetate with hydroxylamine according to the scheme 1 :

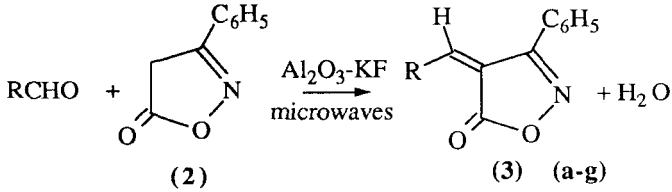
Scheme 1



According to these regards, we described herein the dry condensation of 3-phenylisoxazol-5-one (**2**) with aromatic aldehydes by adsorption on potassium fluoride on alumina under microwave irradiation [10]. Neutral alumina without solvent with or without microwave gave only partial condensation. This result was due to the insufficient basicity of alumina as catalyst.

The condensation of (**2**) with aldehydes under microwave irradiation gave the E isomer of 3-phenyl-4-arylmethylene isoxazol-5-one (**3**), according to the scheme 2:

Scheme 2



R= 4-MeOC$_6$H$_4$ (a); 3,4-(CH$_3$O)$_2$C$_6$H$_3$(b); 3,4-(CH$_3$O)$_2$C$_6$H$_3$(c); 4-ClC$_6$H$_4$ (d); 2,6-Cl$_2$C$_6$H$_3$ (e); 3-Thien (f); 2-Thien(g); 2-Fur (h); CH$_2$O$_2$C$_6$H$_3$ (i)

Works are in progress to extend these condensations to reactive ketones and other carbonyl compounds. The biological properties of 3-phenyl-4-arylmethylene isoxazol-5-ones are under investigation.

Experimental

Infrared spectra were recorded on Perkin Elmer 684 IR spectrophotometer in KBr with absorptions in cm^{-1}. Proton NMR spectra (PMR) and CMR recorded in

ppm downfield from internal Me_4Si were recorded on a Brucker AC 250 instrument from a solution in DMSO-d_6 or $CDCl_3$ of the product. Mass spectra were recorded on a Nermag R10.10H spectrometer. Melting point (Mp) in °C are uncorrected. Microwave irradiations were carried out with a commercial microwave oven Toshiba ER 7620 at 2450 MHz.

3-phenyl isoxazol-5-one (2)

A mixture of hydrochlorid hydroxylamine (0.1 mol) and pyridine (0.1 mol) in ethanol was stirred and heated at reflux. Ethylbenzoylacetate (0.1 mol) was added during 1h. After cooling, 3-phenyl isoxazol-5-one was obtained by filtration. The solid was washed with water and was recrystallized in ethanol.

Yield=76%; white solid; Mp=154°C (lit. Mp=150-152°C); $C_9H_7NO_2$; PMR ($CDCl_3$) δ: 3.8 (s, 2 H, CH_2) 7.4 to 7.6 (br, 3 H, H arom) 7.7 (d, 2H, H arom); CMR ($CDCl_3$) δ: 44.0 ($\underline{C}H_2$) 126.6 ($\underline{C}$ arom o) 127.6 ($\underline{C}$-C=N-) 129.2 ($\underline{C}$ arom m) 132.2 ($\underline{C}$ arom p) 163.1 ($\underline{C}$=N-) 174.7 ($\underline{C}$=O); MS m/z (%): 162 (11.8) 161 (83.1) 119 (9.2) 103 (100); IR (KBr): 1714 ($\nu_{C=O}$) 1596 ($\nu_{C=N}$).

General Procedure

Equimolar quantities of aldehyde and active methylene compound were stirred in CH_2Cl_2 in presence of Al_2O_3-KF (3 g). Solvent was evaporated in vacuum and the obtained solid was irradiated in an opened erlenmeyer flask (25 ml) under microwaves (time and power as indicated). Condensation product was extracted in acetonitrile, filtered and the solvent was evaporated in vacuum. The coloured solid was recrystallized in ethanol.

3-phenyl-4-[4-(methoxyphenyl)methylene] isoxazol-5-one (3a)

Irradiation 2 mn 45, 350W, yield=79%; orange solid; Mp=174°C; $C_{17}H_{13}NO_3$; PMR ($CDCl_3$) δ: 3.9 (s, 3H, CH_3O) 7.0 (d, 2H, H arom, J=9.04 Hz) 7.52 (s, 1H, HC=) 7.3 to 7.55 (br, 5H, H arom) 8.42 (d, 2H, H arom, J= 9.04 Hz); CMR ($CDCl_3$) δ: 55.7 ($\underline{C}H_3O$) 114.5 (CH_3O-C=$\underline{C}$) 115.4 (CH=$\underline{C}$) 125.9 ($\underline{C}$-CH=C)

127.8 (C-C=N) 128.8 (C arom o) 129.2 (C arom m) 130.8 (C arom p) 137.2 (=CH-C=C) 152 (-CH=C) 164.2 (C=N-) 164.8 (CH_3O-C) 168.9 (C=O); MS m/z (%): 279 ($M^{+\cdot}$, 50) 235 (10) 221 (24); IR (KBr): 1730 ($\nu_{C=O}$) 1610 ($\nu_{C=C}$) 1575 ($\nu_{C=N}$).

3-phenyl-4-[3,4-(dimethoxyphenyl)methylene] isoxazol-5-one (3b)

Irradiation 4 mn, 350W, yield=85%; yellow solid; Mp=185°C; $C_{18}H_{15}NO_4$; PMR (DMSO-d_6) δ: 3.84 (s, 3H, CH_3O) 3.92 (s, 3H, CH_3O) 7.17 (d, 1H, H arom, J_1=8.6 Hz) 7.6 to 7.74 (br, 6H, H arom) 8.04 (dd, 1H, H arom, J_1=8.6 Hz, J_2=1.9 Hz) 8.44 (d, 1H, HC=, J_3=1.6 Hz); CMR (DMSO-d_6) δ: 55.4 ($CH_3$0) 55.95 (CH_3O) 111.4 (C' arom o) 113.9 (C' arom m) 115.9 (CH=C) 125.7 (C'arom o) 127.2 (C-C=N) 128.8 (C arom o) 129.1 (C arom m) 130.7 (C-CH=C) 131.4 (C arom p) 148.2 (CH_3O-C) 153.3 (CH=C) 154.6 (CH_3O-C) 164.2 (C=N-) 168.8 (C=O); MS m/z (%): 309 ($M^{+\cdot}$,6) 293 (37) 233 (63); IR (KBr): 1727 ($\nu_{C=O}$) 1603 ($\nu_{C=C}$) 1579 ($\nu_{C=N}$).

3-phenyl-4-[2,4-(dimethoxyphenyl)methylene] isoxazol-5-one (3c)

Irradiation 5 mn, 350W, yield 82%; yellow solid; Mp=211°C; $C_{18}H_{15}NO_4$; PMR (DMSO-d_6) δ: 3.83 (s, 3H, CH_3O) 3.92 (s, 3H, CH_3O) 6.67 (d, 1H, H arom, J_1=2.33 Hz) 6.77 (dd, 1H, H arom, J_1=2.3 Hz, J_2=8.9 Hz) 7.61 to 7.65 (br, 5H, H arom) 8.05 (s, 1H, H arom) 9.06 (d, 1H, HC= J_2=8.9 Hz); CMR (DMSO-d_6) δ: 55.6 (CH_3O) 55.9 (CH_3O) 107.5 (C' arom o) 109.3 (C' arom m) 114.9 (CH=C) 127.2 (C-C=N) 127.8 (C' arom m) 128.9 (C arom o) 129.5 (C arom m) 130.5 (C-CH=C) 131.3 (C arom p) 146.1 (CH_3O-C) 151.6 (CH=C) 156.2 (CH_3O-C) 164.25 (C=N-) 173.4 (C=O); MS m/z (%): 309 ($M^{+\cdot}$,36) 308 (100) 277 (57) 160 (62); IR (KBr): 1738 ($\nu_{C=O}$) 1605 ($\nu_{C=C}$) 1575 ($\nu_{C=N}$).

3-phenyl-4-[1-(chlorophenyl)methylene] isoxazol-5-one (3d)

Irradiation 12 mn, 490W, yield=76%; orange solid; Mp=184°C; $C_{16}H_{10}ClNO_2$; PMR (DMSO-d6) δ: 7.1 to 7.7 (br, 9H, H arom and HC=) 7.9 (dd, 1H, H arom,

J_1= 7.7 Hz, J_2=1.5 Hz); CMR (DMSO-d6) δ: 112.2 (CH=C) 126.5 to 131.7 (C arom) 141 (CH=C) 162.9 (C=N-) 176.3 (C=O); MS m/z (%): 284 (6) 283 ($M^{+\cdot}$,1) 248 (100) 225 (11) 189 (13); IR (KBr): 1713 ($\nu_{C=O}$) 1651 ($\nu_{C=C}$) 1603 ($\nu_{C=N}$).

3-phenyl-4-[2,6-(dichlorophenyl)methylene] isoxazol-5-one (3e)

Irradiation 3 mn, 350W, yield=72%; orange solid; Mp=172°C; $C_{16}H_9Cl_2NO_2$; PMR (DMSO-d_6) δ: 7.0 to 7.9 (br, 8H, H arom and HC=) 8.2 (d, 1H, H arom, J=Hz); CMR (DMSO-d_6) δ: 115.6 (CH= C) 127.3 (C arom o) 127.8 (C-C=N) 128.1 (HC=C-Cl-) 128.3 (C-CH=C)129.4 (C arom m) 131.9 (CH-CH=C-Cl-) 132.8 (C arom p) 134.5 (C=C-Cl) 148.3 (CH=C) 163 (C=N-) 177.1 (C=O); MS m/z (%): 318 ($M^{+\cdot}$,8) 283 (24) 282 (100) 281 (77) 280 (100) 260 (33) 258 (51) 222 (34) 188 (100); IR (KBr): 1766 ($\nu_{C=O}$) 1642 ($\nu_{C=C}$) 1570 ($\nu_{C=N}$).

3-phenyl-4-[thien-3-yl methylene] isoxazol-5-one (3f)

Irradiation 15 mn, 350W, yield=92%; black solid; Mp=198°C; $C_{14}H_9NO_2S$; PMR (DMSO-d_6) δ: 6.83 (d, 1H, H arom, J_1=5 Hz) 7.2 to 7.7 (br, 7H, H arom and HC=) 7.9 (d, 1H, H arom, J_2= 4 Hz); CMR (DMSO-d_6) δ: 119.9 (CH=C) 127.4 (C-C=N-) 127.8 (C arom m) 128.5 (C arom o) 128.8 (CH=CH-S) 129.2 (CH=CH-S) 130.9 (C arom p) 131.1 (C=CH-S) 142 (C=CH-S) 145.3 (-CH=C) 162.9 (C=N-) 175.2 (C=O); MS m/z (%): 255 ($M^{+\cdot}$,10) 211(12.5) 197 (15.5) 143 (34); IR (KBr) : 1714 ($\nu_{C=O}$) 1644 ($\nu_{C=C}$) 1596 ($\nu_{C=N}$).

3-phenyl-4-[thien-2-yl methylene] isoxazol-5-one (3g)

Irradiation 13 mn, 350W, yield=77%; black solid; Mp=196°C; $C_{14}H_9NO_2S$; PMR (DMSO-d_6) δ: 7.2 (dd, 1H, H arom) 7.4 to 7.6 (br, 5H, H arom) 7.95 (s, 1H, HC=) 8.1 (d, 1H, H arom) 8.2 (d, 1H, H arom); CMR (DMSO-d_6) δ: 112.9 (CH=C) 127.2 (C-C=N) 128.7 (C arom o) 129.0 (CH=CH-S) 129.3 (C arom m) 130.9 (C arom p) 136.2 (CH-S) 142.4 (CH=C-S) 143.3 (C-CH=C) 144.8

(CH=C) 163.1 (C=N-) 175.3 (C=O); MS m/z (%): 255($M^{+\cdot}$, 55.4) 246 (13.3) 211 (18.5) 197 (31); IR (KBr): 1724 ($\nu_{C=O}$) 1644 ($\nu_{C=C}$) 1596 ($\nu_{C=N}$).

3-phenyl-4-[furan-2-yl methylene] isoxazol-5-one (3h)

Irradiation 3 mn 30, 350W, yield=71%; black solid; Mp=194°C; $C_{14}H_9NO_3$; PMR (DMSO-d_6) δ: 7.01 (dd, 1H, H arom, J_1= 3.6 Hz, J_2= 1.2 Hz) 7.57 to 7.75 (br, 5H, H arom and HC=) 8.35 (d, 1H, H arom, J_2= 1.2 Hz) 8.46 (d, 1H, H arom, J_1= 3.6 Hz); CMR (DMSO-d_6) δ: 111.5 (CH=CH-O) 115.7 (CH=C) 126.7 (CH=C-CH) 127.7 (C-C=N) 128.4 (C arom o) 129.2 (C arom m) 130.9 (C arom p) 134.5 (C-CH=C) 149.9 (CH-O) 151.9 (CH=C) 163.1 (C=N-) 168.1 (C=O); MS m/z (%): 239 ($M^{+\cdot}$,5O) 181 (22) 152 (21); IR (KBr): 1738 ($\nu_{C=O}$) 1610 ($\nu_{C=C}$) 1590 ($\nu_{C=N}$).

3-phenyl-4-[3,4-(methylenedioxyphenyl)methylene] isoxazol-5-one (3i)

Irradiation 4 mn 30, 350W, yield=84%; yellow solid; Mp=222°C; $C_{17}H_{11}NO_4$; PMR (DMSO-d_6) δ: 6.1 (s, 2H, CH_2) 6.9 to 8.15 (br, 8H, H arom) 8.4 (s, 1H, HC=); CMR (DMSO-d_6) δ: 102.6 (CH_2) 108.7 (C-CH=CH) 111.6 (C-CH=) 114.4 (CH=C) 127.0 (C-C=N) 127.1 (C-CH) 128.7 (C arom o) 129.1 (C arom m) 130.8 (C-CH=C) 133.9 (C arom p) 147.5 (CH_2-O-C=) 153 (CH=C) 153.05 (CH_2-O-C) 164 (C=N-) 175.2 (C=O); MS m/z (%): 293 ($M^{+\cdot}$, 15) 235 (5) 176 (15) 146 (13) 105 (100); IR (KBr): 1714 ($\nu_{C=O}$) 1637 ($\nu_{C=C}$) 1596 ($\nu_{C=N}$).

References:

1. Mustapha A., Asker W., Harhash A.H., Kassab N.A.L and Elnafdi M.H. *Tetrahedron* , **1964**, *20*, 1133; Ehnargdi H.J., Wentrup C., *J. Org. Chem.*, **1985**, *50*, 2041; Becalli E.M., Marchesini A., Pilati T, *Tetrahedron*, **1989**, *45*, 7485.

2. Imperial Chemical Industries Ltd., *Belg.Pat.* 617 389, **1962**; *Chem. Abst.*, **59**, 6413c.

3. Giichi G., Akinobu N., Takeda Chemical Industries, *Ltd. Jpn Kokai Tokyo Koho JP* 01 242 526, **1988**; *Chem. Abst* ., **112**, 178970k.

4. Stolle R., Guenther B., VEB Filmfabrik Wolfen, *Ger.* 133177 , **1978**; *Chem. Abst.*, **90**, P88757u.

5. Rao Y.S., Muzycko T.M., Oven and Filler R., *Chem. Ind.*, **1965**, 36.

6. Villemin D., *Chem. Ind. (London)*, **1983**, 478.

7. Villemin D. and Labiad B., *Synthetic Commun.*, **1990**, *20*, 3207.

8. Villemin D. and Labiad B., *Synthetic Commun.*, **1990**, *20*, 3333.

9. Average of pKa=3 units; T.D. Salatin and W.L. Jorgensen, *J.Org.Chem.*, 1990, *45* , 2043.

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