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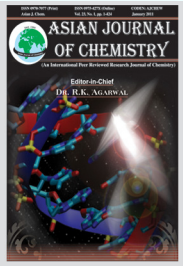

Microwave-Assisted Synthesis of 1,3,4-Oxadiazoles Containing Pyrazolones

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The key intermediate (Z)-2-(5-oxo-4-(2-phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro-1*H*-pyrazole-1-yl)acetohydrazide (**5**) cyclization with aryl substituted acids **6a-h** in presence of phosphorous oxy chloride ($POCl_3$) under microwave irradiation resulted in the formation of the corresponding (Z)-1-((5-phenyl-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-4-(2-substituted aryl hydrazono)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (**7a-h**) in quantitative yields. The results obtained indicate that, unlike classical heating, microwave irradiation results in higher yields, shorter reaction times (5-12 min) and cleaner reactions.

Key Words: Microwave irradiation, Pyrazolones derivatives, Heterocyclic synthesis.

INTRODUCTION

Over a last decade, microwave-assisted chemistry has matured into a highly useful technique and provides an interesting alternative for heating chemical reactions. Microwave techniques in synthetic chemistry often elicit a dramatic increase of the reaction rate, is suited to increased demands of industry. The combination of solvent-free conditions and microwave irradiation, leads to reductions in reaction times, enhancement in conversions and sometimes[1,2], in selectivity with several advantages of eco-friendly approach. A number of reviews[2-9] and monographs[10] have been published on the use of microwave technology in chemical synthesis.

Various substituted pyrazolines and their derivatives are important biological agents and a significant amount of research activity has been directed towards this class. In particular, they are used as antitumor[11], antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal agents[12-20]. Some of these compounds have also antiinflammatory, antidiabetic, anesthetic and analgesic properties[21-24]. Moreover, pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively as useful synthons in organic synthesis[25-29].

EXPERIMENTAL

All the chemicals were used as received without further purification. Melting points were determined in open capillary tubes in Buchi 530 circulating oil apparatus and are not corrected. Reactions were carried out using household micro oven (power consumption 1200 W, microwave frequency 2450 MHz) and monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}) visualizing with ultraviolet light or iodine spray. ^{1}H NMR spectra were determined either in DMSO-d_6 solution on 400 MHz AMX spectrometers.

General procedure: 4,4,4-Trichloro-3-oxo-2-(phenylhydrazono)-butyric acid ethyl ester **2** was prepared by diazotization of required primary amine is diazotized with sodium nitrite and HCl mixture at 0-5 ºC and it is coupled with ethyl 4,4,4-trichloro-3-oxobutanoate and afforded phenyl diazonium aceto acetic ester.

Condensation of 4,4,4-trichloro-3-oxo-2-(phenylhydrazono)-butyric acid ethyl ester (**2**) and hydrazine in presence of catalytic amount of dimethyl formamide under microwave irradiation afforded synthesis of 4-(substituted aryl hydrazono)-5-trichloromethyl-2,4-dihydro-pyrazol-3-one (**3**).

A mixture of 4-(substituted aryl hydrazono)-5-trichloromethyl-2,4-dihydro-pyrazol-3-one (**3**), anhydrous K_2CO_3, chloro ethyl acetate and DMF were stirred at room temperature for 10 h. The reaction mixture was diluted with ice-cold water. The separated solid was identified as (**4**) this was collected by filtration.

(Z)-2-(5-Oxo-4-(2-phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro-1*H*-pyrazole-1-yl) acetohydrazide (5): A solution of compound **4** (0.01 M) and hydrazine hydrate (0.015 M) in ethanol 20 mL was refluxed for 5 h. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford compound **5**. Yield 64 %, m.p. 132 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.21 (s, 1H, Ar-NH), 6.8-7.46 (m, 5H, Ar-H), 8.47 (s, 1H, NH),

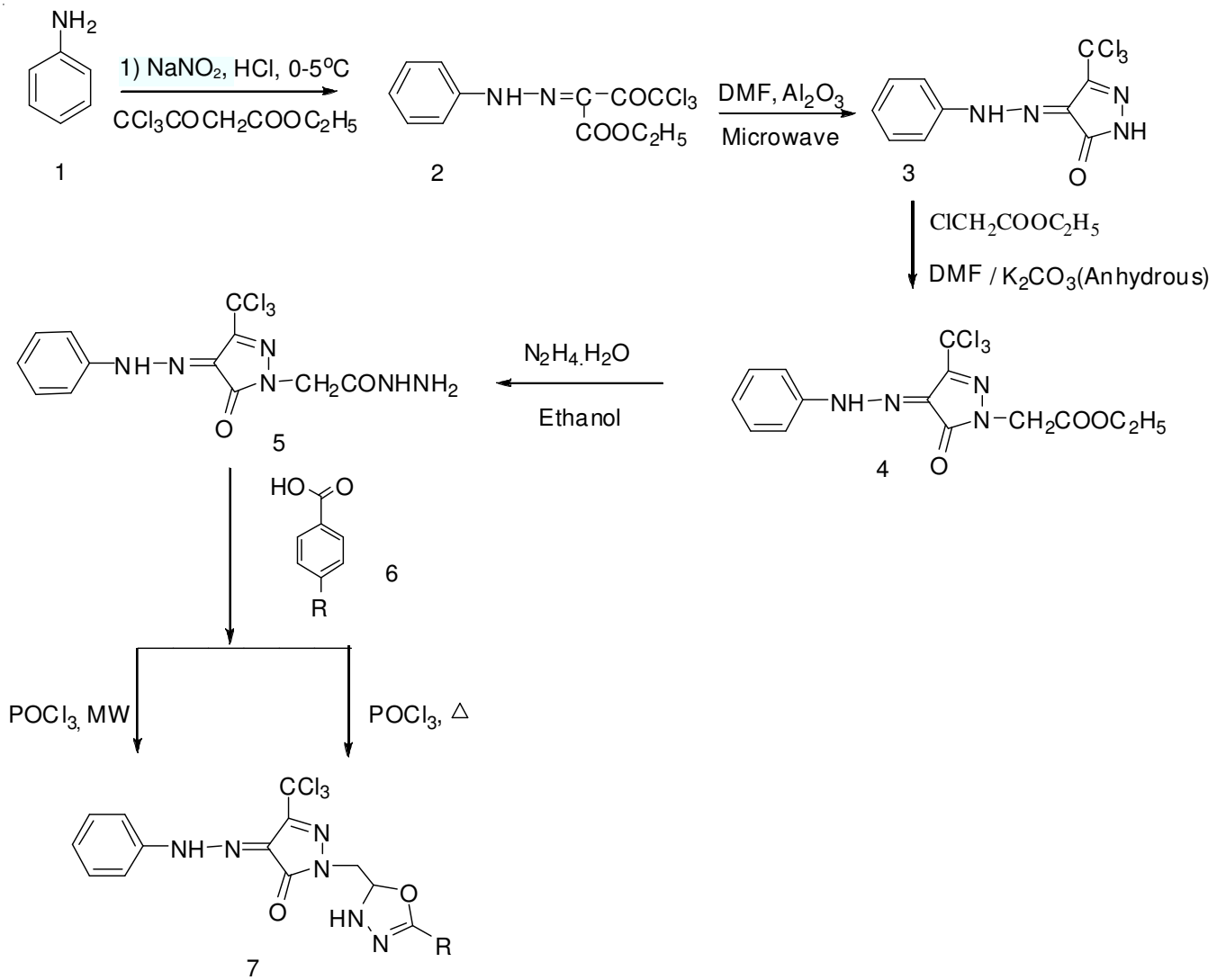
1.34 (S, 3H, CH_3), 4.21 (q, 2H, CH_2) 3.84 (S, 2H, N-CH_2); ^{13}C NMR (400 MHz, DMSO-d_6): δ 14.13 (CH_3), 60.5 (CH_2), 116-140 (Ar-C), 133 (NH-N=C), 154 (pyrazole C=O), 117 (CF_3), 121 (CF_3-C), 168.4 (ester C=O); IR (KBr, ν_{max}, cm^{-1}): 3445, 3425, (2 bands) 3305, 1620, 1665, 1460 and 1455 due to -NH_2, >NH exo >C=N, cyclic carbonyl and five membered heterocyclic ring. Anal. calcd. (%) for $C_{12}H_{11}N_6O_2Cl_3$ (376.61); C: 38.17, H: 2.94, N: 22.26 found (%); C: 38.23, H: 3.13, N: 22.31.

General procedure for microwave-assisted preparation of (Z)-1-((5-phenyl-2,3-dihydro-1,3,4 oxadiazole-2-yl)-methyl)-4-(2-phenyl hydrazono)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*) one (7a-h): A mixture of compound **5** (0.01 mol) and corresponding benzoic acid **6a-h** (0.01 mol) and 5 drops of phosphorous oxy chloride under microwave irradiation for few min at (160 W). After completion of the reaction as indicated by TLC, the reaction mixture was cooled and poured in to crushed ice. Finally, it was neutralized by 5 % $NaHCO_3$. After usual workup (Z)-1-((5-phenyl-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-4-(2-phenyl hydrazono)-3-(trichloro-methyl)-1*H*-pyrazole-5(4*H*) one (**7a**) (R = C_6H_5) was obtained in 60 % yield (**Scheme-I**).

(Z)-1-((5-Phenyl-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-4-(2-phenyl hydrazono)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (7a): Yield 60 %, m.p. 162 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.21 (s, 1H, Ar - NH), 6.8-7.46 (m, 10H, Ar -H), 8.47 (s, 1H, NH), 3.76 (S, 2H, N-CH_2), 4.21(m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6); δ 58.2,72.9, 89.2, 112.6, 119.6, 123.4, 126.5, 129.8, 139.2, 152, 161; IR (KBr, ν_{max}, cm^{-1}): 3116, 1670 and 1602. Anal. calcd. (%) for $C_{19}H_{15}N_6O_2Cl_3$ (465.72); C: 49.00, H: 3.25, N: 18.05 found (%); C: 49.20, H: 3.34, N: 18.21.

(Z)-1-((5-(4-Chloro phenyl)-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-4-(2-phenyl hydrazono)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (7b): Yield 62 %, m.p. 167 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.31 (s, 1H, Ar-NH), 6.8-7.76 (m, 10H, Ar-H), 8.47 (s, 1H, NH), 3.84 (S, 2H, N-CH_2) 4.21(m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 57.2, 72.9, 89.2, 112.6, 119.6, 123.4, 126.5, 129.8, 139.2, 152, 161; IR (KBr, ν_{max}, cm^{-1}): 3125, 1675 and 1605. Anal. calcd. (%) for $C_{19}H_{14}N_6O_2Cl_4$ (500.17); C: 45.63, H: 2.82, N: 16.80 found (%); C: 45.82, H: 3.14, N: 17.06.

(Z)-1-((5-(Furan-2-yl)-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-4-(2-phenyl hydrazono)-3-(trichloromethyl)-



R = Phenyl (**7a**); chloro phenyl (**7b**); 2-furyl (**7c**); *p*-tolyl (**7d**); *p*-anisyl (**7e**); *o*-tolyl (**7f**); *p*-nicotinyl (**7g**); nitro phenyl (**7h**)

Scheme-I

1*H*-pyrazole-5(4*H*)one (7c): Yield 67 %, m.p. 163 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H, Ar-NH), 6.8-7.75 (m, 8H, Ar-H), 8.47 (s, 1H, NH), 3.84 (S, 2H, N-CH_2), 4.21 (m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 57.5, 69.5, 87.6, 109.7, 113.6, 122.3, 127.5, 139.7, 142, 154, 161; IR (KBr, ν_{max}, cm^{-1}): 3241,1668 and 1600. Anal. calcd. (%) for $C_{23}H_{17}N_6O_3Cl_3$ (531.78); C: 51.95, H: 3.22, N: 15.80 found (%); C: 52.01, H: 3.31, N: 15.94.

(Z)-4-(2-Phenyl hydrazono)-1-((5-*para*-tolyl-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (7d): Yield 61 %, m.p. 165 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H, Ar-NH), 6.8-7.75 (m, 8H, Ar -H), 8.47 (s, 1H, NH), 2.23 (s, 3H, CH_3), 3.84 (S, 2H, N-CH_2), 4.21 (m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 57.5, 69.5, 87.6, 109.7, 113.6, 122.3, 127.5, 139.7, 142, 154, 161; IR (KBr, ν_{max}, cm^{-1}): 3110, 1650 and 1595. Anal. calcd. (%) for $C_{20}H_{17}N_6O_2Cl_3$ (479.75); C: 50.07, H: 3.57, N: 17.52 found (%); C: 50.12, H: 3.63, N: 17.86.

(Z)-1-((5-(4-Methoxy phenyl)-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-4-(2-phenyl hydrazono)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (7e): Yield 69 %, m.p. 163 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H, Ar-NH), 6.8-7.75 (m, 10H, Ar-H), 8.47 (s, 1H, NH), 3.83 (s, 3H, O-CH_3), 3.84 (S, 2H, N-CH_2), 4.21(m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 55.7, 58.2, 69.9, 87.6, 109.7, 113.6, 122.3, 127.5, 139.7, 142, 152, 161; IR (KBr, ν_{max}, cm^{-1}): 3120, 1690 and 1640. Anal. calcd. (%) for $C_{20}H_{17}N_6O_3Cl_3$ (495.75); C: 48.46, H: 3.46, N: 16.95 found (%); C: 48.58, H: 3.61, N: 17.05.

(Z)-4-(2-Phenyl hydrazono)-1-((5-*ortho*-tolyl-2,3-dihydro-1,3,4oxadiazole-2-yl)methyl)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (7f): Yield 65 %, m.p. 161 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H, Ar-NH), 6.8-7.75 (m, 8H, Ar-H), 8.47 (s, 1H, NH), 2.23 (s, 3H, CH_3), 3.84 (S, 2H, N-CH_2), 4.21 (m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 57.5, 69.5, 87.6, 109.7, 113.6, 122.3, 127.5, 139.7, 142, 154, 161; IR (KBr, ν_{max}, cm^{-1}): 3112, 1648 and 1595. Anal. calcd. (%) for $C_{20}H_{17}N_6O_2Cl_3$ (479.75); C: 50.07, H: 3.57, N: 17.52 found (%); C: 50.12, H: 3.63, N: 17.86.

(Z)-4-(2-Phenyl hydrazono)-1-((5-pyridin-3-ylmethyl)-2,3-dihydro-1,3,4-oxadiazole-2-yl)methyl)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (7g): Yield 65 %, m.p. 165 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H, Ar-NH), 6.8-8.5 (m, 9H, Ar-H), 8.47 (s, 1H, NH), 2.62 (S, 2H, CH_2) 3.84 (S, 2H, N-CH_2), 4.21(m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 36.7, 57.5, 69.5, 87.6, 109.7, 113.6, 122.3, 127.5, 139.7, 142, 146.2, 151, 161; IR (KBr, ν_{max}, cm^{-1}): 3225, 1672 and 1603. Anal. calcd. (%) for $C_{25}H_{20}N_7O_2Cl_3$ (556.83); C: 53.92, H: 3.62, N: 17.61 found (%); C: 54.01, H: 3.76, N: 17.72.

(Z)-1-((5-(4-Nitro phenyl)-2,3-dihydro-1,3,4 oxadiazole -2-yl)methyl)-4-(2-phenyl hydrazono)-3-(trichloromethyl)-1*H*-pyrazole-5(4*H*)one (7h): Yield 67 %, m.p. 164 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H, Ar-NH), 6.8-8.4 (m, 9H, Ar-H), 8.47 (s, 1H, NH), 3.84 (S, 2H, N-CH_2), 4.21 (m, 1H, CH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 57.5, 69.5, 87.6, 109.7, 113.6, 122.3,124.3, 127.5, 139.7, 142, 146.2, 149.2, 151, 161; IR (KBr, ν_{max}, cm^{-1}): 3210, 1675 and 1603. Anal. calcd. (%) for $C_{19}H_{14}N_7O_4Cl_3$ (510.72); C: 44.68, H: 2.76, N: 19.20 found (%); C: 44.75, H: 2.82, N: 19.63.

RESULTS AND DISCUSSION

As a result of present studies related to development of synthetic protocols using microwave irradiation, we now report a novel and easy procedure for 1,3,4-oxadiazoles contaiining pyrazolones. In this paper cyclization in presence of phosphorous oxy chloride (**5a**) under microwave irradiation at 160 W for about 5 min to yield 1,3,4-oxadiazole substituted pyrazolones quantitatively in 5-12 min. The heterocyclic product was characterized on the basis of their ^{1}H NMR, ^{13}C NMR, IR and MS spectral and elemental analysis.

Conclusion

In summary, this work demonstrates a rapid, efficient and environmentally friendly method of synthesis of 1,3,4-oxadiazole substituted pyrazolones under microwave heating and the results obtained confirm the superiority of the microwave irradiation method over the classical heating one.

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