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KF/Al_2O_3 Catalyzed One-Pot Three-Component Process for the Synthesis of Some 2-Thioxoquinazolin-4(1*H*)-one Derivatives

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Three component one-pot reaction for synthesis of 2-thioxoquinazolin-4(1*H*)-ones are given by the condensation of isatoic anhydride, primary amine and phenyl isothiocyanate by using KF/Al_2O_3 as a environmentally friendly catalyst.

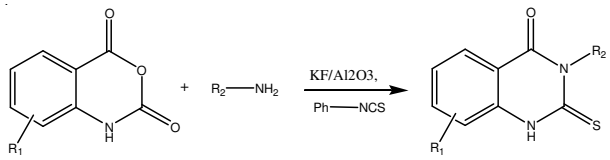
Key Words: 2-Thioxoquinazolin-4(1*H*)-one, One-pot, Three component, KF/Al_2O_3, Microwave.

INTRODUCTION

Today multicomponent reactions (MCRs) emphasizes the development of organic compounds as drug precursor on environmentally friendly when synthesized compounds without solvent and catalyst or water solvent and non-toxic catalyst. Multicomponent reactions aid to play a key role in the development of synthetic compounds because of their possible generation of an adduct in a single step from multi reactants usually used by bond-forming efficiency[1]. Application of multicomponent reaction is on the high chemoselectivity in the presence of all the reactants[2].

Quinazolinones are very important structure in the field of drug chemistry with wide range of biological and pharmacological activity[3]. The quinazolinones scaffold are important class of fused heterocycles with a show promise such as anti-inflammatory[4], antimalarial[5], anti HIV[6] and anti cancer[7] and dihydrofolate reductase inhibitors[8]. Moreover, few methods are reported for the synthesis of 2-thioxoquinazolin-4-ones, as most of the methods reported are for quinazolin-2,4(1*H*,3*H*)-diones[9,10].

Several methods have been proposed for quinazolinones over the years, provide a simple method with the environmentally friendly catalyst for synthesis of 2-thioxoquinazolinones. As part of our ongoing interest in developing new methods for the synthesis of various heterocyclic scaffolds[11-17], therefore in this study, we have synthesized derivatives of 2-thioxoquinazolin-4(1*H*)-one with the condensation of isatoic anhydride, primary amine and phenyl isothiocyanate by using KF/Al_2O_3 as a catalyst (**Scheme-I**).

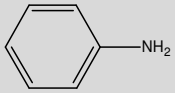
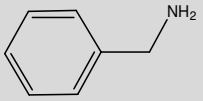
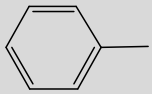
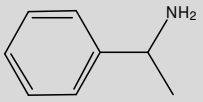
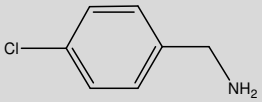


Scheme-I

IR spectral data of 3-benzyl-2,3-dihydro-2-thioxoquinazoline-4(1*H*)-one (**4b**) shows the characteristic single broad N-H peak in the range 3280 cm^{-1}, a sharp C=O peak at 1698 cm^{-1} and C=S peak at 1185 cm^{-1}. ^1H NMR shows characteristic broad singlet for N-H at δ 12.01 in addition to those due to aromatic protons at d 7.33-7.86 ppm[13]. In ^{13}C NMR C=S appears at δ 170 C=O appears at δ 161 ppm. Therefore in the present investigation we have used KF/Al_2O_3 is a widely used solid supported reagent which is cheap and easy for catalysis of a variety of reactions. Due to its strongly basic nature it has been used as a replacement for organic bases in a number of organic reactions[18]. Variously substituted isothiocyanates were condensed isatoic anhydride, primary amine and phenyl isothiocyanate in water by using KF/Al_2O_3 as a environmentally friendly catalyst to afford the desired 2-thioxoquinazolin-4(1*H*)-one derivatives in 60-79 % yields and was completed within 90-140 min (Table-1).

All chemicals were obtained from Merck or Fluka without further purification. Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 spectrophotometer. ^1H and ^{13}C NMR spectra were determined on Bruker 500 DRX AVANCE instrument at 500 and 125 MHz, respectively. The element analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer.

TABLE-1
SYNTHESIS OF VARIOUS 2-THIOXOQUINAZOLIN-4(1*H*)-ONES FROM DIFFERENT ISATOIC ANHYDRIDE, PRIMARY AMINE AND ISOTHIOCYANATE

Entry	R_1	R_2–NH_2	m.p. (ºC)	Yields (%)	Reaction time (min)
4a	H		307-309	76	100
4b	H		253-256	70	120
4c	*meta*-Cl		324-325	65	120
4d	H		264-266	60	140
4e	H		317-319	76	90

Typical synthesis of compounds (4a-e): A mixture of KF/Al_2O_3 (0.2 g), isatoic anhydride (1 mmol), primary amine (2 mmol) and phenyl isothiocyanate (1 mmol) was refluxed in ethanol (5 mL) for 90-140 min. The progress of reaction was monitored by TLC. The mixture was extracted with 3 cm × 30 cm CH_2Cl_2, filtered and dried with anh. Na_2SO_4 sulphate. The solution was dried under high vacuum and the resulting solid residue recrystallized from ethanol to give the pure crystalline solid (**4a-e**).

2,3-Dihydro-3-phenyl-2-thioxoquinazolin-4(1*H*)-one (4a): White powder, m.p. 307-309 ºC; IR (KBr, ν_{max}, cm^{-1}): 3239 (N-H), 3091 (C-H_{arom}), 1676 (C=O), 1189 (C=S); ^{1}H NMR (500 MHz, DMSO): δ = 7.29-7.96 (m, 9H , CH_{arom}), 12.03 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 118.6, 119.1, 121.3, 124.6, 125.0, 128.8, 129.9, 132.8, 137.1, 138.6, 158.8, 177.0 ppm. MS (m/z, %): 254 (M^+). Anal. calcd. (%) for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02. Found (%): C, 65.71; H, 3.81; N, 10.74.

3-Benzyl-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one (4b): White powder, m.p. 253-256 ºC; IR (KBr, ν_{max}, cm^{-1}): 3280 (N-H), 3080 (C-H_{arom}), 1698 (C=O), 1185 (C=S); ^{1}H NMR (500 MHz, DMSO): δ = 5.59 (s, 2H), 7.33-7.86 (m, 8H, CH_{arom}), 12.01 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 44.8, 111.5, 114.4, 122.8, 125.1, 126.7, 127.8, 128.9, 134.1, 135.7, 138.1, 161.0, 170.0 ppm. MS (m/z, %): 268 (M^+). Anal. calcd. (%) for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found (%): C, 66.89; H, 4.21; N, 10.26.

7-Chloro-2,3-dihydro-3-phenyl-2-thioxoquinazolin-4(1*H*)-one (4c): White powder, m.p. 324-326 ºC; IR (KBr, ν_{max}, cm^{-1}): 3188 (N-H), 3010 (C-H_{arom}), 1700 (C=O), 1200 (C=S); ^{1}H NMR (500 MHz, DMSO): δ = 7.30-7.92 (m, 8H, CH_{arom}), 12.06 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 20.1, 55.5, 113.1, 115.2, 123.9, 124.2, 125.7, 126.5, 129.2, 131.9, 135.6, 138.8, 153.7, 169.3 ppm. MS (m/z, %): 288 (M^+). Anal. calcd. (%) for $C_{14}H_9N_2OSCl$: C, 58.23; H, 3.14; N, 9.70. Found (%): C, 57.95; H, 2.85; N, 9.58.

2,3-Dihydro-3-(1-phenylethyl)-2-thioxoquinazolin-4(1*H*)-one (4d): White powder, m.p. 264-266 ºC; IR (KBr, ν_{max}, cm^{-1}): 3291 (N-H), 3036 (C-H_{arom}), 1677 (C=O), 1179 (C=S); ^{1}H NMR (500 MHz, DMSO): δ = 1.79 (d, *J* = 7.1 Hz, 3H), 2.02 (q, *J* = 7.1 Hz, H), 7.15-7.82 (m, 9H , CH_{arom}), 11.96 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 27.7, 46.5, 58.2, 113.8, 114.5, 115.8, 118.6, 121.9, 125.6, 128.5, 132.4, 134.9, 138.0, 145.4, 147.3, 160.1, 171.9, ppm. MS (m/z, %): 282 (M^+). Anal. calcd. (%) for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found (%): C, 67.81; H, 4.76; N, 9.71.

3-(4-Chlorobenzyl)-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one (4e): White powder, m.p. 317-319 ºC; IR (KBr, ν_{max}, cm^{-1}): 3122 (N-H), 3032 (C-H_{arom}), 1681 (C=O), 1209 (C=S); ^{1}H NMR (500 MHz, DMSO): δ = 5.16 (s, 2H), 7.16-7.79 (m, 8H , CH_{arom}), 12.02 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO): 46.4, 115.8, 122.4, 125.0, 126.7, 127.7, 130.6, 133.2, 134.5, 140.8, 145.8, 157.1, 172.3 ppm. MS (m/z, %): 302 (M^+). Anal. calcd. (%) for $C_{15}H_{11}N_2OSCl$: C, 59.50; H, 3.66; N, 9.25. Found (%): C, 59.33; H, 3.50; N, 9.18.

Conclusion

We have developed an efficient, one-pot synthesis of 2-thioxoquinazolin-4(1*H*)-ones by the condensation of isatoic anhydride, primary amine and phenyl isothiocyanate by using KF/Al_2O_3 in providing increased yields. KF/Al_2O_3 can act as heterogeneous catalyst which is low cost and environmentally friendly.

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