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Synthesis of Some Hexahydroquinazolinones Using $K_3AlF_6(Al_2O_3/KF)$ as an Efficient Catalyst in Some Hexahydroquinazolinone Derivatives

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Abstract

A protocol for the synthesis of some 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (HHQs) was developed by means of a three-component condensation reaction of an aromatic aldehyde, 1,3-cylohexadione and urea in the presence of K_3AlF_6 (Al_2O_3/KF) as catalyst. This reaction is carried out under different conditions including 1) solvent free; 2) reflux in acetonitrile; 3) reflux in ethanol; 4) reflux in chloroform; and 5) reflux in water. In all conditions, the desired products are obtained in high yields after relatively short reaction times. Nevertheless, the reactions proceed faster and in higher yields when they were carried out in acetonitrile. This adopted protocol for some Biginelli-type products has offered the advantages of reusability of the catalyst, high yields and ease of separation of pure products. Furthermore, the catalyst is easily prepared, stabilized and efficiently used under reaction conditions.

Keywords

4-Aryl-1,3,4,6,7,8-Hexahydroquinazolin-2,5(1*H*,6*H*)-Diones (HHQs), $K_3AlF_6(Al_2O_3/KF)$, 1,3-Cylohexadione, Acetonitrile

1. Introduction

Six membered heterocyclic compounds, as important constituents exist in biologically active natural products [1] [2]. Among them, 3,4-dihydropyrimidinones (3,4-DHPMs) have exhibited important therapeutic and pharmacological properties [3] [4] [5]. Some of 3,4-DHPMs derivatives are also used as calcium

channel blockers [6]. However, some of the cores of 3,4-DHPMs have an antiviral, antibacterial, antihypertensive and antitumor activities [7] [8]. Also, among them, 3,4-DHPMs derivatives, which are found as core units in many marine alkaloids, have been found to be potent HIV gp-120CD4 inhibitors [9] [10] [11] [12]. In 1893, Petero Biginelli, for the first time reported the synthesis of some 3,4-dihydropyrimidinones compounds (3,4-DHPMs) [12]. Octahydroquinazolinone derivatives are a class of 3,4-DHPMs. These compounds, due to their molecular structure, have an important biological activity. However, these derivatives have been suggested to be a useful antibacterial activity and calcium antagonist activity [13] [14] [15] [16] [17].

Fluoride ion is useful as a weak basic and non-nucleophilic catalyst in many organic chemical processes [18] [19]. Effectiveness of various inorganic solids as a support for potassium fluoride for promoting synthesis of organic compounds has been studied. Many supported fluoride systems, such as KF-SiO_2, KF-molecular sieves have been found to be considerably and surprisingly more reactive than non-supported KF [20] [21] [22] [23]. Among them, the supported fluoride systems, potassium fluoride (KF) on activated alumina have been found to be surprisingly more reactive. Therefore, in 1979, Junko Yamawaki and a coworker investigated a support of potassium fluoride on Alumina compound [24]. As well as, Weinstock *et al.* have examined the characterization of the actual catalytic agent in potassium fluoride on active alumina system. They have argued that K_3AlF_6 derives its basicity from the formation of KOH in the initial preparation of the solid supported material by the reaction of KF with the alumina support [25].

$$12KF(s) + Al_2O_3 + 3H_2O_2 \xrightarrow{(65^\circ C-75^\circ C)/1h} K_3AlF_6(s) + 6KOH$$

Many derivatives fluorides complexes with the general $A_2BB'X_6$ composition are known to crystallize in the elpasolite (K_2NaAlF_6) (or ordered double perovskite) structure. The analysis of the data reported in literature shows that the information is available on $K_3AlF_6(Al_2O_3/KF)$ being compared with its closest analogues cryolite Na_3AlF_6 and elpasolite K_2NaAlF_6. It has been reported that the room temperature of $K_3AlF_6(Al_2O_3/KF)$ has a tetragonally distorted elpasolite-type structure, which transforms into the high symmetric cubic phase above 300˚C - 310˚C [26] [27].

By having these facts in minds, we reported here for the first time, the synthesis, characterization, and experimental assays of a some series of some 4-Aryl-1, 3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (HHQs) derivatives using $K_3AlF_6(Al_2O_3/KF)$ as catalyst.

2. Experimental

The FT-IR spectra were recorded on a FT-IR spectroscopy Perkinelemer BX-II. UV spectra (in EtOH) were recorded on a CINTRAL 101 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 500 MHz spectro-

meter in DMSO-d6 with TMS as an internal standard. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV.

2.1. Preparation of $K_3AlF_6(Al_2O_3/KF)$

At first, the $K_3AlF_6(Al_2O_3/KF)$ catalytic system was produced according to the literature [28] [29]. In this method, $KF{\cdot}2H_2O$ (20 g) was dissolved in water (80 ml), and then basic Al_2O_3 (30 g) was added. The resulting mixture was stirred at 65˚C - 75˚C for 1 h. The water was removed under reduced pressure, and the resulting powder was dried at 120˚C for 4 h to give active $K_3AlF_6(Al_2O_3/KF)$.

2.2. General Procedure for the Synthesis of Hexahydroquinazolinone Derivatives Catalyzed by $K_3AlF_6(Al_2O_3/KF)$

A suspension of aromatic aldehydes (10 mmol), 1,3-cyclohexadione (10 mmol), urea (12 mmol) and K_3AlF_6 (Al_2O_3/KF) (0.05g) and acetonitrile (10 ml) were heated under reflux conditions for appropriate time. The progress of the reaction was monitored by TLC (eluent:n-hexane/ethyl acetate (5:1)). After completion of the reaction, the catalyst was separated by simple filtration. The crude product was produced by solvent evaporation under reduced pressure. The product was crystallized in ethanol.

4-phenyl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**a**):

M.P. = (227˚C - 229˚C, lit. [30] 226 - 228).

FT-IR (KBr): 3380.25, 2920.93, 1725.05, 1710.01, 1610.17 cm^{-1}.

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 265.66 nm (5.50).

4-(4-methylphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**b**):

FT-IR (KBr): 3336.85, 2941.02, 1722.08, 1602.37 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.90 (m, J = 7 Hz, 2H, H-8), 2.01 (m, J = 7.05 Hz, 2H, H-7), 2.19 (m, J = 6.9 Hz, 2H, H-9), 2.36 (m, J = 7.35 Hz, 3H, CH_3), 2.94 (d, J = 10.7 Hz, 1H, H-4), 3.90 (d, J = 9.6 Hz, 1H, NH), 6.83 (s, 1H, NH), 6.94 (m, J = 7.55 Hz, 2H, Ar-H), 7.08 ppm (m, J = 7.85 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.02, 29.05, 35.41, 37.24, 60.54, 101.41, 116.39, 128.72, 128.96, 134.02, 134.41, 141.68, 142.60, 195.83, 205.25 ppm.

MS (EI, 70 eV): *m/z* (%): 255.1 (M^+, $C_{15}H_{15}N_2O_2$), 253.2 (M^+-2H), 240.1 (M^+-$C_{15}H_{14}NO_2$), 227.2 (M^+-$C_{15}H_{15}O_2$), 164.1 (M^+-C_7H_7), 148.1 (M^+-C_7H_7-CH-NH-CO-NH), 131.1 (M^+-C_7H_7-CH-CH=CH_2), 119.1 (M^+-C_7H_7-CH-NH), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 257.98 nm (5.49).

4-(3-methylphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**c**):

FT-IR (KBr): 3359.99, 2975.01, 1720.79, 1609.14 cm^{-1}.

^{1}HNMR (500 MHz, DMSO-*d*6): δ = 1.89 (m, J = 7.3 Hz, 2H, H-8), 2.10 (m, J = 7.4 Hz, 2H, H-7), 2.16 (m, J = 6.9 Hz, 2H, H-9), 2.38 (m, J = 6.7 Hz, 3H, CH_3), 2.99 (d, J = 10.65 Hz, 1H, H-4), 3.90 (d, J = 9.6 Hz, 1H, NH), 6.78 (s, 1H, NH), 6.84 (m, J = 6.35 Hz, 1H, Ar-H), 6.91 (m, J = 7.4 Hz, 1H, Ar-H), 7.00 (m, J = 6.65

Hz, 1H, Ar-H), 7.04 (m, J = 7.45 Hz, 1H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.63, 29.09, 33.44, 37.14, 37.24, 100.44, 101.39, 127.58, 128.79, 129.43, 136.45, 144.74, 145.63, 196.27, 206.67 ppm.

MS (EI, 70 eV): *m/z* (%): 255.2 (M^+; $C_{15}H_{15}N_2O_2$), 253.2 (M^+-2H), 240.1 (M^+-$C_{15}H_{14}NO_2$), 227.2 (M^+-$C_{15}H_{15}O_2$), 164.1 (M^+-C_7H_7), 148.1 (M^+-C_7H_7-CH-NH-CO-NH), 131.1 (M^+-C_7H_7-CH-CH=CH_2), 119.1 (M^+-C_7H_7-CH-NH), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): λ_{max}(logε) = 268.22 nm (5.50).

4-(2-methylphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**d**):

FT-IR (KBr): 3314.86, 2936.99, 1712.01, 1617.22 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.84 (m, J = 8.85 Hz, 2H, H-8), 2.08 (m, J = 8.3 Hz, 2H, H-7), 2.20 (m, J = 8.65 Hz, 2H, H-9), 2.36 (m, J = 5.65 Hz, 3H, CH_3), 3.15 (d, J = 10.9 Hz, 1H, H-4), 4.01 (d, J = 10.65 Hz, 1H, NH), 6.90 (s, 1H, NH), 6.93 (m, J = 5 Hz, 1H, Ar-H), 6.97 (m, J = 5 Hz, 1H, Ar-H), 7.02 (m, J = 5 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.35, 28.95, 35.98, 37.82, 61.81, 101.07, 101.89, 125.72, 126.18, 130.13, 135.49, 139.36, 144.54, 196.42, 206.32 ppm.

MS (EI, 70 eV): *m/z* (%): 255.1 (M^+; $C_{15}H_{15}N_2O_2$), 253.2 (M^+-2H), 240.1 (M^+-$C_{15}H_{14}NO_2$), 227.2 (M^+-$C_{15}H_{15}O_2$), 164.1 (M^+-C_7H_7), 148.1 (M^+-C_7H_7-CH-NH-CO-NH), 131.1 (M^+-C_7H_7-CH-CH=CH_2), 119.1 (M^+-C_7H_7-CH-NH), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): λ_{max}(logε) = 258.40 nm (5.49).

4-(4-methoxyphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**e**):

FT-IR (KBr): 3389.23, 2959.93, 1722.04, 1601.58, 1375.17 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.86 (m, J = 5.7 Hz, 2H, H-8), 2.15 (m, J = 5.8 Hz, 2H, H-7), 2.39 (m, J = 5.75 Hz, 2H, H-9), 3.68 (m, J = 6.8 Hz, 3H, OCH_3), 2.96 (d, J = 10.7 Hz, 1H, H-4), 3.88 (d, J = 10.75 Hz, 1H, NH), 6.84 (s, 1H, NH), 6.75 (m, J = 6.95 Hz, 2H, Ar-H), 7.10 (m, J = 6.45 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 20.99, 29.07, 32.18, 55.38, 60.58, 100.50, 101.44, 113.71, 116.25, 116.47, 129.70, 137.51, 157.26, 195.87, 205.37 ppm.

MS (EI, 70 eV): *m/z* (%): 271.1 (M^+, $C_{15}H_{15}N_2O_3$), 269.2 (M^+-2H), 256.1 (M^+-$C_{15}H_{14}NO_3$), 255.1 (M^+-CH_3), 243.1 (M^+-$C_{15}H_{15}O_3$), 164.1 (M^+-C_7H_7O-CH-NH-CO-NH), 147.1 (M^+-C_7H_7O-CH-CH=CH_2), 135.1 (M^+-C_7H_7O-CH-NH), 107.1 (M^+-C_7H_7O), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): λ_{max}(logε) = 265.66 nm (5.50).

4-(3-methoxyphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**f**):

FT-IR (KBr): 3374.80, 2941.18, 1719.71, 1614.34, 1374.19 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.89 (m, J = 5.45 Hz, 2H, H-8), 2.16 (m, J = 5.6 Hz, 2H, H-7) 2.39 (m, J = 5.65 Hz, 2H, H-9), 3.69 (s, 3H, OCH_3), 2.98 (d, J

= 10.7 Hz, 1H, H-4), 3.91 (d, *J* = 10.6 Hz, 1H, NH), 6.85 (s, 1H, NH), 6.62 (m, *J* = 6.8 Hz, 1H, Ar-H), 6.79 (d, *J* = 6.55 Hz, 1H, Ar-H), 7.07 (t, *J* = 6.85 Hz, 1H, Ar-H), 6.73 (s, 1H, Ar-H).

^{13}CNMR (500 MHz, DMSO-*d*6): δ = 21.09, 29.12, 32.67, 55.22, 59.66, 100.48, 101.24, 120.72, 121.33, 128.64, 128.79, 146.48, 147.31, 196.31, 206.66 ppm.

MS (EI, 70 eV): *m/z* (%): 271.1 (M^+, $C_{15}H_{15}N_2O_3$), 269.2 (M^+-2H), 256.1 (M^+-$C_{15}H_{14}NO_3$), 255.1 (M^+-CH_3), 243.2 (M^+-$C_{15}H_{15}O_3$), 164.1 (M^+-C_7H_7O-CH-NH-CO-NH), 147.1 (M^+-C_7H_7O-CH-CH=CH_2), 135.1 (M^+-C_7H_7O-CH-NH), 107.1 (M^+-C_7H_7O), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 275.12 nm (5.49).

4-(2-methoxyphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**g**):

FT-IR (KBr): 3260.57, 2955.07, 1710.75, 1611.88, 1383.05 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.87 (m, *J* = 4.65 Hz, 2H, H-8), 2.36 (m, *J* = 4.95 Hz, 2H, H-7), 2.38 (m, *J* = 5.35 Hz, 2H, H-9), 3.72 (s, 3H, OCH_3), 2.90 (s, 1H, H-4), 4.55 (s, 1H, NH), 6.81 (s, 1H, NH), 7.05 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.74 (t, *J* = 8.3 Hz, 1H, Ar-H), 6.88 (m, *J* = 7.55 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 20.50, 20.98, 28.99, 37.26, 55.61, 101.60, 110.41, 111.47, 119.83, 126.55, 129.20, 131.69, 156.54, 196.07, 206.42 ppm.

MS (EI, 70 eV): *m/z* (%): 271.1 (M^+; $C_{15}H_{15}N_2O_3$), 269.2 (M^+-2H), 256.1 (M^+-$C_{15}H_{14}NO_3$), 256.1 (M^+-CH_3), 243.2 (M^+-$C_{15}H_{15}O_3$), 164.1 (M^+-C_7H_7O-CH-NH-CO-NH), 147.1 (M^+-C_7H_7O-CH-CH=CH_2), 135.1 (M^+-C_7H_7O-CH-NH), 107.1 (M^+-C_7H_7O), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 267.79 nm (5.50).

4-(4-Chlorophenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**h**):

FT-IR (KBr): 3321.06, 2938.79, 1716.15, 1614.90, 773.18 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.86 (m, *J* = 4.65 Hz, 2H, H-8), 2.04 (m, *J* = 6.65 Hz, 2H, H-7), 2.29 (m, *J* = 6.3 Hz, 2H, H-9), 3.06 (s, 1H, H-4), 4.64 (s, 1H, NH), 6.93 (s, 1H, NH), 7.12 (d, *J* = 7.85 Hz, 2H, Ar-H), 7.30 (d, *J* = 7.55 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 20.53, 21.01, 28.93, 37.16, 101.55, 110.92, 126.23, 127.34, 128.93, 131.53, 132.50, 141.28, 196.22, 205.65 ppm.

MS (EI, 70 eV): *m/z* (%): 277.1 (M^+, $C_{14}H_{13}N_2ClO_2$), 274.1 (M^+-2H), 262.1 (M^+-$C_{14}H_{12}NClO_2$), 249.1 (M^+-$C_{14}H_{13}ClO_2$), 247.1 (M^+-$C_{14}H_{11}ClO_2$), 182.1 (M^+-C_6H_4Cl-CH-NH-CO-NH), 151.1 (M^+-C_6H_4Cl-CH-CH=CH_2), 139.1 (M^+-C_6H_4 Cl-CH-NH), 111 (M^+-C_6H_4 Cl), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 262.24 nm (5.49).

4-(3-Chlorophenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**i**):

FT-IR (KBr): 3074.81, 2984.07, 1718.42, 1603.53, 782.22 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.89 (m, *J* = 4.45 Hz, 2H, H-8), 2.18 (m, *J* = 4.8 Hz, 2H, H-7), 2.41 (m, *J* = 8.05 Hz, 2H, H-9), 3.04 (d, *J* = 10.85 Hz, 1H, H-4), 3.94 (d, *J* = 10.8 Hz, 1H, NH), 6.94 (s, 1H, NH), 7.21 (d, *J* = 7.45 Hz, 1H, Ar-H), 7.18 (m, *J* = 7.65 Hz, 1H, Ar-H), 7.16 (m, *J* = 7.45 Hz, 1H, Ar-H), 7.14 (m, *J* = 7.35 Hz, 1H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 20.87, 29.07, 32.95, 59.76, 100.48, 101.46, 125.71, 128.18, 129.50, 132.33, 132.40, 148.20, 195.95, 205.40 ppm.

MS (EI, 70 eV): *m/z* (%): 277.1 (M^+, $C_{14}H_{13}N_2ClO_2$), 274.1 (M^+-2H), 262.1 (M^+-$C_{14}H_{12}NClO_2$), 249.1 (M^+-$C_{14}H_{13}ClO_2$), 247.1 (M^+-$C_{14}H_{11}ClO_2$), 182.1 (M^+-C_6H_4Cl-CH-NH-CO-NH), 151.1 (M^+-C_6H_4Cl-CH-CH=CH_2), 139.1 (M^+-C_6H_4Cl-CH-NH), 111.1 (M^+-C_6H_4 Cl), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): λ_{max}(logε) = 262.24 nm (5.49).

4-(2-Chlorophenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**j**):

FT-IR (KBr): 3084.82, 2944.99, 1719.08, 1603.92, 796.06 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.89 (m, *J* = 5.95 Hz, 2H, H-8), 2.17 (m, *J* = 5.95 Hz, 2H, H-7), 2.39 (m, *J* = 6.95 Hz, 2H, H-9), 3.01 (d, *J* = 10.85 Hz, 1H, H-4), 3.88 (d, *J* = 9.65 Hz, 1H, NH), 6.87 (s, 1H, NH), 7.21 (m, *J* = 8.4 Hz, 1H, Ar-H), 7.19 (m, *J* = 8.05 Hz, 2H, Ar-H), 7.07 (d, *J* = 8.4 Hz, 1H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 20.87, 31.93, 32.55, 59.92, 100.45, 101.44, 127.71, 130.09, 130.15, 130.77, 143.91, 144.63, 196.37, 205.33 ppm.

MS (EI, 70 eV): *m/z* (%): 277.1 (M^+; $C_{14}H_{13}N_2ClO_2$), 274.1 (M^+-2H), 262.1 (M^+-$C_{14}H_{12}NClO_2$), 249.1 (M^+-$C_{14}H_{13}ClO_2$), 247.1(M^+-$C_{14}H_{11}ClO_2$), 182.1 (M^+-C_6H_4Cl-CH-NH-CO-NH), 151.1 (M^+-C_6H_4 Cl-CH-CH=CH_2), 139.1 (M^+-C_6H_4 Cl-CH-NH), 111.1 (M^+-C_6H_4Cl), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): λ_{max}(logε) = 258.83 nm (5.49).

4-(4-Boromophenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**k**):

FT-IR (KBr): 3174.20, 2945.97, 1720.89, 1603.05 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.89 (m, *J* = 8.95 Hz, 2H, H-8), 2.15 (m, *J* = 6.47 Hz, 2H, H-7), 2.40 (m, *J* = 4.19 Hz, 2H, H-9), 3.00 (d, *J* = 10.87 Hz, 1H, H-4), 3.88 (d, *J* = 10.85 Hz, 1H, NH), 6.91 (s, 1H, NH), 7.16 (d, *J* = 8.43 Hz, 2H, Ar-H), 7.30 (d, *J* = 8.43 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.06, 28.95, 36.71, 56.71, 101.33, 101.44, 111.22, 127.74, 131.90, 132.24, 142.73, 150.16, 196.24, 205.46 ppm.

MS (EI, 70 eV): *m/z* (%): 321 (M^+, $C_{14}H_{13}N_2BrO_2$), 318 (M^+-2H), 306 (M^+-$C_{14}H_{12}NBrO_2$), 293 (M^+-$C_{14}H_{13}BrO_2$), 241 (M^+-$C_{14}H_{13}N_2O_2$), 213.1 (M^+-C_6H_4Br-CH-NH-CO-NH), 197 (M^+-C_6H_4Br-CH-CH=CH_2), 185 (M^+-C_6H_4 Br-CH-NH), 157 (M^+-C_6H_4Br), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.8 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): λ_{max}(logε) = 255.42 nm (5.48).

4-(3-Boromo phenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**l**):

FT-IR (KBr): 3100.14, 2939.21, 1718.91, 1598.64 cm^{-1}.

^1H NMR (500 MHz, DMSO-*d*6): δ = 1.83 (m, *J* = 7.25 Hz, 2H, H-8), 2.13 (m, *J* = 6.35 Hz, 2H, H-7), 2.36 (m, *J* = 6.7 Hz, 2H, H-9), 3.03 (d, *J* = 10.85 Hz, 1H, H-4), 3.88 (d, *J* = 9.6 Hz, 1H, NH), 6.93 (s, 1H, NH), 7.31 (s, 1H, Ar-H), 7.22 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.18 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.11 (t, *J* = 7.7 Hz, 1H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.91, 36.71, 37.21, 57.71, 101.07, 110.27, 123.64, 126.75, 127.74, 130.28, 132.24, 145.78, 196.51, 206.52 ppm.

MS (EI, 70 eV): *m/z* (%): 321.1 (M^+; $C_{14}H_{13}N_2BrO_2$), 318.1 (M^+-2H), 306.1 (M^+-$C_{14}H_{12}NBrO_2$), 293.1 (M^+-$C_{14}H_{13}BrO_2$), 241.1 (M^+-$C_{14}H_{13}N_2O_2$), 213.1 (M^+-C_6H_4Br-CH-NH-CO-NH), 197.1 (M^+-C_6H_4 Br-CH-CH=CH_2), 185 (M^+-C_6H_4Br-CH-NH), 157 (M^+-C_6H_4Br), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.8 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 260.54 nm (5.49).

4-(2-Boromophenyl) -1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**m**):

FT-IR (KBr): 3328.76, 2935.95, 1713.36, 1615.06 cm^{-1}.

^1H NMR (500 MHz, DMSO-*d*6): δ = 1.86 (m, *J* = 6.1 Hz, 2H, H-8), 2.16 (m, *J* = 6.9 Hz, 2H, H-7), 2.37 (m, *J* = 5.4 Hz, 2H, H-9), 3.06 (s, 1H, H-4), 4.51 (s, 1H, NH), 7.03 (s, 1H, NH), 7.45 (d, *J* = 7.65 Hz, 1H, Ar-H), 7.12 (d, *J* = 3.85 Hz, 2H, Ar-H), 7.04 (d, *J* = 4.2 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.06, 32.43, 37.21, 56.71, 101.63, 111.22, 123.64, 126.75, 127.74, 131.90, 132.24, 142.73, 196.24, 205.46 ppm.

MS (EI, 70 eV): *m/z* (%): 321.1 (M^+; $C_{14}H_{13}N_2BrO_2$), 318.1 (M^+-2H), 306.1 (M^+-$C_{14}H_{12}NBrO_2$), 293.1 (M^+-$C_{14}H_{13}BrO_2$), 241.1 (M^+-$C_{14}H_{13}N_2O_2$), 213.2 (M^+-C_6H_4Br-CH-NH-CO-NH), 197.1 (M^+-C_6H_4Br-CH-CH=CH_2), 185.1 (M^+-C_6H_4 Br-CH-NH), 157.1 (M^+-C_6H_4 Br), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.8 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 260.54 nm (5.49).

4-(4-Nitrophenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**n**):

FT-IR (KBr): 3123.71, 2950.15, 1719.29, 1600.86, 1515.07, 1343.04 cm^{-1}.

^1H NMR (500 MHz, DMSO-*d*6): δ = 1.90 (m, *J* = 6.2 Hz, 2H, H-8), 2.19 (m, *J* = 6.95 Hz, 2H, H-7), 2.39 (m, *J* = 6.75 Hz, 2H, H-9), 3.08 (d, *J* = 10.95 Hz, 1H, H-4), 4.01 (d, *J* = 9.95 Hz, 1H, NH), 7.10 (s, 1H, NH), 7.49 (d, *J* = 8.55 Hz, 2H, Ar-H), 8.02 (d, *J* = 8.55 Hz, 2H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.03, 28.88, 32.33, 59.39, 100.45, 101.50, 123.00, 130.28, 145.60, 145.78, 153.76, 154.17, 196.51, 205.88 ppm.

MS (EI, 70 eV): *m/z* (%): 287.1 (M^+; $C_{14}H_{13}N_3O_4$), 285.1 (M^+-2H), 272.1 (M^+-$C_{14}H_{12}N_2O_4$), 259.1 (M^+-$C_{14}H_{13}NO_4$), 258.1 (M^+-$C_{14}H_{13}N_2O_3$), 241.1 (M^+-

$C_{14}H_{13}N_2O_2$), 193.1 (M^+-C_6H_4 NO_2-CH-NH-CO-NH), 165.1 (M^+-$C_6H_4NO_2$), 162.1 (M^+-C_6H_4 NO_2-CH-CH=CH_2), 150.1 (M^+-C_6H_4 NO_2-CH-NH), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.8 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 262.67 nm (5.50).

4-(3-Nitrophenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**o**):

FT-IR (KBr): 3119.91, 2953.97, 1719.17, 1601.62, 1524.68, 1351.53 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.96 (m, *J* = 4.65 Hz, 2H, H-8), 2.12 (m, *J* = 6.15 Hz, 2H, H-7), 2.38 (m, *J* = 6.65 Hz, 2H, H-9), 3.17 (d, *J* = 10.95 Hz, 1H, H-4), 4.01 (d, *J* = 10.05 Hz, 1H, NH), 7.04 (s, 1H, NH), 8.01 (s, 1H, Ar-H), 7.95 (d, *J* = 9.4 Hz, 1H, Ar-H), 7.48 (m, *J* = 8.05 Hz, 1H, Ar-H), 7.67 (m, *J* = 8.95 Hz, 1H, Ar-H).

^{13}C NMR (500 MHz, DMSO-*d*6): δ = 20.78, 26.95, 31.87, 59.29, 114.93, 115.15, 120.95, 123.23, 129.23, 130.08, 147.65, 147.93, 196.04, 205.57 ppm.

MS (EI, 70 eV): *m/z* (%): 287.1 (M^+, $C_{14}H_{13}N_3O_4$), 285.2 (M^+-2H), 272.1 (M^+-$C_{14}H_{12}N_2O_4$), 259.1 (M^+-$C_{14}H_{13}NO_4$), 258.1 (M^+-$C_{14}H_{13}N_2O_3$), 241.1 (M^+-$C_{14}H_{13}N_2O_2$), 193.1 (M^+-$C_6H_4NO_2$-CH-NH-CO-NH), 165.1 (M^+-$C_6H_4NO_2$), 162.1 (M^+-C_6H_4 NO_2-CH-CH=CH_2), 150.1 (M^+-$C_6H_4NO_2$-CH-NH), 71.1 (M^+-NH-CH=CH-COH), 70.1 (M^+-CH_3-CO-CH=CH_2), 57.8 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 263.52 nm (5.50).

4-(2,6-dichlorophenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2**p**):

FT-IR (KBr): 3321.96, 3164.29, 2948.40, 1715.82, 1636.05, 775.76, 753.90 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*6): δ = 1.90 (m, *J* = 5.95 Hz, 2H, H-8), 2.13 (m, *J* = 5.8 Hz, 2H, H-7), 2.38 (m, *J* = 5.25 Hz, 2H, H-9), 5.66 (s, 1H, H-4), 6.08 (s, 1H, NH), 7.59 (s, 1H, NH), 7.38 (m, *J* = 7.6 Hz, 2H, Ar-H), 7.24 (t, *J* = 7.95 Hz, 1H, Ar-H).

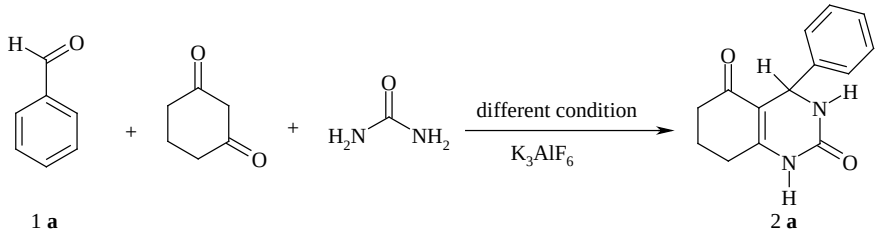
^{13}C NMR (500 MHz, DMSO-*d*6): δ = 21.27, 26.43, 33.50, 51.41, 101.05, 104.85, 115.53, 127.56, 127.71, 129.58, 137.34, 150.97, 195.34, 205.34 ppm.

MS (EI, 70 eV): *m/z* (%): 310.1 (M^+, $C_{14}H_{12}N_2Cl_2O_2$), 309.1 (M^+-2H), 295 (M^+-$C_{14}H_{11}NCl_2O_2$), 282.1 (M^+-$C_{14}H_{12}Cl_2O_2$), 275.1 (M^+-Cl), 240.1 (M^+-2Cl), 216.1 (M^+-C_6H_3 Cl_2-CH-NH-CO-NH), 185.1 (M^+-C_6H_3 Cl_2-CH-CH=CH_2), 173 (M^+-$C_6H_3Cl_2$-CH-NH), 145 (M^+-C_6H_3 Cl_2), 70.2 (M^+-CH_3-CO-CH=CH_2), 57.1 (M^+-NH-CO-NH), 51.1 (M^+-CH_2=CH-COH), 42.1 (M^+-CH_2-CH_2-CH_2).

UV/Vis (EtOH): $\lambda_{max}(\log\varepsilon)$ = 271.63 nm (5.51).

3. Result and Discussion

Initially, we studied the Biginelli-type condensation reaction of benzaldehyde (1**a**), 1,3-cyclohexadione (CY), urea catalyzed by K_3AlF_6(Al_2O_3/KF) in different solvents under different conditions. (Scheme 1, Table 1). The effects of different factors were examined, including solvents, the reaction temperature, an amount of catalyst and the reaction time. The results have been summarized in Table 1.



1 **a** 2 **a**

Scheme 1. $K_3AlF_6(Al_2O_3/KF)$ catalyzed synthesis of the 4-phenyl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (2a).

Table 1. K_3AlF_6 catalyzed synthesis of 4-phenyl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones product (2**a**) under different conditions.

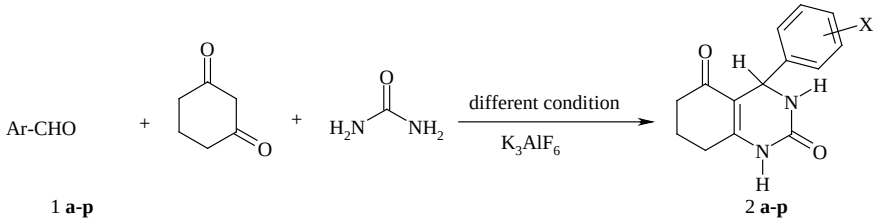
Comp.	Amount of catalyst (g)	T (˚C)	Solvent (mL)	Yield (%)[a]	Time (h)[b]
2a	0.1	r.t.	Solvent free	24	4.15
2a	0.1	100	Solvent free	24	3
2a	0.1	Reflux	H_2O (10)	30	3.5
2a	0.1	Reflux	EtOH (10)	35	3
2a	0.1	Reflux	CH_3CN (10)	45	2
2a	0.05	Reflux	CH_3CN (10)	53	2
2a	0.025	Reflux	CH_3CN (10)	43	3.5
2a	With Al_2O_3 (0.05 g)	Reflux	CH_3CN (10)	51	3
2a	With KF (0.05 g)	Reflux	CH_3CN (10)	55	3.5
2a	With mixture of Al_2O_3-KF (0.05 g)	Reflux	CH_3CN (10)	53	2

[a]Isolated yield; [b]Times are given after maximum progression of the reaction.

Different solvents, such as H_2O, EtOH, $CHCl_3$ and CH_3CN were used in this reaction. As well as, it was studied under solvent-free condition. The results show that the reaction was sluggish and the lower yield was observed under solvent free conditions.

According to the data presented in Table 1, the best conditions were achieved as a mixture of the following materials as aldehyde (10 mmol), 1,3-cyclohexadione (10 mmol), urea (12 mmol) and $K_3AlF_6(Al_2O_3/KF)$ (0.05 g) in acetonitrile (10 mL) as solvent under reflux condition (Scheme 2). The progress of reaction was followed by TLC using *n*-hexane/ethyl acetate (5:1) as eluents until the total disappearance of the 1,3-cyclohexadione was carried out. Then the product was washed with water, followed by crystallization from ethanol. The catalyst was separated by simple filtration and reused several times (Table 2). All the products are characterized by mp, Uv-vis, IR and ^{1}H-NMR, ^{13}C-NMR, Ms spectra. The results are reported in Table 3.

In summary, we have described an alternative and general method for the multicomponent synthesis of functionalized of some 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones using $K_3AlF_6(Al_2O_3/KF)$ as a basic catalyst.



1 **a-p** 2 **a-p**

Scheme 2. $K_3AlF_6(Al_2O_3/KF)$ catalyzed synthesis of some 4-aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones.

Table 2. Recyclability of K_3AlF_6 for synthesis of 4-phenyl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones product (**2a**).

Entry	Amount of catalyst (g)	T (˚C)	Solvent (mL)	Yield (%)[a]	Time (h)[b]
1	0.05	Reflux	CH_3CN (10)	80	2
2	0.05	Reflux	CH_3CN (10)	80	2.5
3	0.05	Reflux	CH_3CN (10)	75	3
4	0.05	Reflux	CH_3CN (10)	75	3

[a]Isolated yield; [b]Times are given after maximum progression of the reaction.

Table 3. $K_3AlF_6(Al_2O_3/KF)$ catalyzed synthesis of 4-aryl-3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones **2a-p**.

Comp.	Ar	Amount of products (g)	Time (h)	Yield %	m.p (˚C)
2a	C_6H_5-	0.808	2	80	227 - 229
2b	4-CH_3-C_6H_4-	0.959	2.5	82	190 - 193
2c	3-CH_3-C_6H_4-	0.994	3	85	210 - 212
2d	2-CH_3-C_6H_4-	0.971	2	83	218 - 220
2e	4-CH_3O-C_6H_4-	1.028	3	85	198 - 202
2f	3-CH_3O-C_6H_4-	0.907	2.5	75	198 - 202
2g	2-CH_3O-C_6H_4-	0.907	2.5	75	208 - 209
2h	4-Cl-C_6H_4-	0.918	2	82	231 - 234
2i	3-Cl-C_6H_4-	0.896	2.15	80	218 - 219
2j	2-Cl-C_6H_4-	0.952	2	85	221 - 223
2k	4-Br-C_6H_4-	1.309	2	77	215 - 216
2l	3-Br-C_6H_4-	1.479	2.5	87	214 - 215
2m	2-Br-C_6H_4-	1.428	2.5	84	218 - 220
2n	4-NO_2-C_6H_4-	1.283	2	85	224 - 226
2o	3-NO_2-C_6H_4-	1.208	2.5	80	215 - 217
2p	2,6-Cl_2-C_6H_3-	1.312	2	75	248 - 250

The prospect of the reusability of this catalyst has also been demonstrated without compromising on the yield of the product. On the whole, the protocol presented here is an excellent alternative to many of the reported procedures by the use of K_3AlF_6(Al_2O_3/KF) as an environmentally benign and recyclable catalyst.

Consequently, the possibility to recycle catalyst was examined. As shown in Table 2, K_3AlF_6 could be reused without significant loss of activity.

Furthermore, we use the other 1,-3-dicarbonyl compounds for synthesis of the others 3,4-dihydropyrimidinoes. These data are reported in Scheme 3 and Table 4.

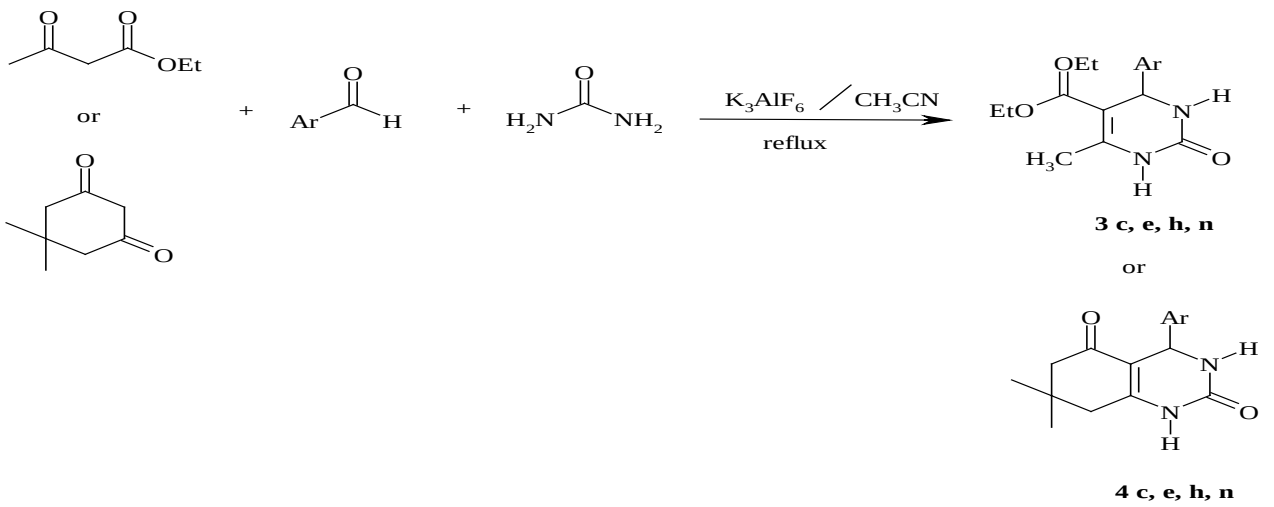
According to these data, we proposed the following mechanism (Scheme 4) for this method.

4. Conclusion

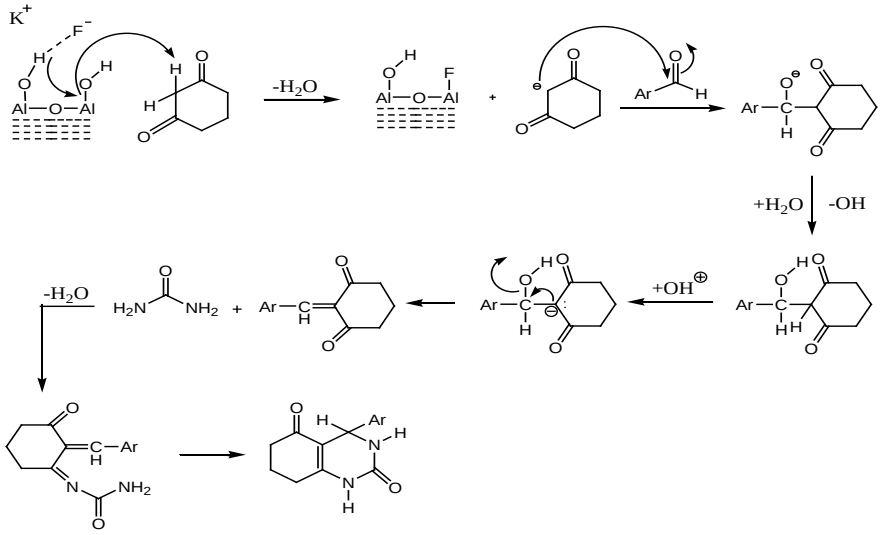
In summary, we have described an alternative and general method for the multicomponent synthesis functionalized of 4-Aryl-1,3,4,6,7,8-hexahydroquinazo-

Table 4. Synthesis of the others 3,4-dihydropyrimidiones using ethyl acetoacetate and dimedone as 1,3-carbonyl compound. (3 **c, e, h, n**) and (4 **c, e, h, n**).

Comp.	Ar	Amount of products (g)	Yield (%)	Time (h)
3c	3-CH_3-C_6H_4-	0.936	80	3
3e	4-CH_3O-C_6H_4-	0.847	70	1.45
3n	4-NO_2-C_6H_4-	1.238	82	1.5
3h	4-Cl-C_6H_4-	0.896	80	2
4c	3-CH_3-C_6H_4-	0.819	70	4
4e	4-CH_3O-C_6H_4-	0.907	75	3.5
4h	4-Cl-C_6H_4-	0.952	85	3
4n	4-NO_2-C_6H_4-	1.208	80	2.5



Scheme 3. Synthesis the others 3,4-dihydropyrimidinones.



Scheme 4. Proposed the mechanism for this method.

lin-2,5-diones using Al_2O_3/KF as a basic catalyst. The prospect of the reusability of Al_2O_3/KF has also been demonstrated without compromising on the yield of the product. On the whole, the protocol presented here is an excellent alternative to many of the reported procedures by the use of Al_2O_3/KF as an environmentally benign and recyclable catalyst. Furthermore, these data show that the reactivity of K_3AlF_6 is more than KF and miture of Al_2O_3-KF. In this work, we observed the substituent effect in the synthesis of some hexahydroquinazolinones compounds.

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