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Hamid Reza Shaterian [a], Ali Reza Oveisi [a] & Moones Honarmand [a]

[a] Department of Chemistry, Faculty of Sciences, University of Sistan and Baluchestan, Zahedan, Iran

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SYNTHESIS OF 2,3-DIHYDROQUINAZOLINE-4(1*H*)-ONES

Hamid Reza Shaterian, Ali Reza Oveisi, and Moones Honarmand

Department of Chemistry, Faculty of Sciences, University of Sistan and Baluchestan, Zahedan, Iran

An efficient, inexpensive, and heterogeneous catalyst, [$Al(H_2PO_4)_3$], was applied in a three-component, one-pot cyclocondensation reaction of isatoic anhydride with primary amines (or ammonium salts) and aldehydes to afford the corresponding quinazolinone derivatives in excellent yields. Reactions occurred under thermal solvent-free conditions. It was found that this solid acidic catalyst could be easily recovered and reused for at least three cycles without any loss of activity.

Keywords: $[Al(H_2PO_4)_3]$; 3-(2′benzothiazolo)-2,3-dihydroqunazoline-4(1*H*)-ones; isatoic anhydride; solvent-free

INTRODUCTION

Quinazolin-4(1*H*)-ones constitute an important class of heterocycles with a wide range of pharmacological, physiological, and biological activities, such as anticancer, antidituric, anticonvulsant, antifertility, antibacterial, antifungal, and mono-amine oxidase inhibition and are also used as 5-hydroxytryptamine (5-HT) receptor ligands.[1] Recently, Lindsley and coworkers observed the metabotropic glutamate receptor (mGluR) properties of this class of compounds (Fig. 1).[2]

A literature survey showed that several methods for synthesis of quinazolinone compounds were reported such as cyclization of *o*-acylaminobenzamides,[3] amidation of 2-aminobenzonitrile followed by oxidative ring closure,[4] solid-phase synthesis of 2-arylamino-substituted quinazolinones,[5] reduction of the azide functionality,[6] preparation from isatoic anhydrides and Schiff bases,[7] conversion of 2-nitro-N-arylbenzamides to 2,3-dihydroquinazolin-4(1*H*)-ones using $SnCl_2$, and Pd-catalyzed heterocyclization of nitroenes.[8] All these procedures have certain limitations such as tedious process, long reaction times, harsh reaction conditions, and poor yields. It was reported that the synthesis of quinazolinones can be

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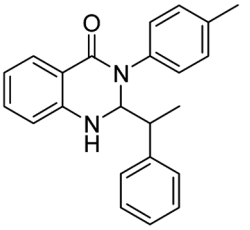
This article is dedicated to Professor Ahmad Akbari, Chancellor of Sistan and Baluchestan University, who dedicates himself to the progress of science.

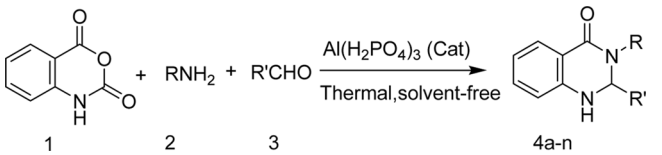
Address correspondence to Hamid Reza Shaterian, Department of Chemistry, Faculty of Sciences, University of Sistan and Baluchestan, P.O. Box 98135-674, Zahedan, Iran. E-mail: hrshaterian@hamoon.usb.ac.ir



2-(1-phenylethyl)-3-*p*-tolyl-2,3-dihydroquinazolin-4(1*H*)-one

Figure 1. Chemical structure of a mGluRs of quinazolin-4(1*H*)-ones.

catalyzed by *p*-toluenesulfonic acids,[9] silica sulfuric acid,[10] $KAl(SO_4)_2 \cdot 12H_2O$ (alum),[11] montmorillonite K-10,[12] zinc(II) perfluorooctanoate,[13] gallium(III) triflate,[14] Amberlyst-15,[15] and 1-butyl-3-methylimidazolium bromide [bmim]Br or [bmim]PF_6 as ionic liquids.[16] In addition, quinazolin-4(1*H*)-ones can easily be oxidized to their quinazolin-4(3*H*)-one analogs, which also show important pharmacologically active compounds.[1c] Thus, developing versatile approaches to synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones still remains a highly desired goal in organic synthesis. The development of efficient and environmentally benign chemical processes or methodologies for widely used heterogeneous recyclable catalysts under solvent-free conditions is one of the major challenges for chemists in organic synthesis. Meanwhile, the use of solvent-free methods gains importance from the viewpoint of green chemistry. In continuation of our research on the solid heterogeneous acidic catalysts,[17] we herein report a practical method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones employing three-component reactions of isatoic anhydride with a primary amines (or ammonium salts) and aldehydes under thermal solvent-free conditions in the presence of aluminium tris(dihydrogen phosphate) as a low-cost, nontoxic, environmentally compatible, reusable, more economical, and easy-to-handle catalyst (Scheme 1).



Scheme 1. Preparation of disubstituted-2,3-dihydroquinazolin-4(1*H*)-ones.

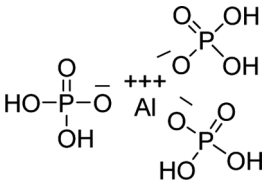


Figure 2. Molecular structure of $Al(H_2PO_4)_3$.

Aluminium tris(dihydrogen phosphate) (Fig. 2) is prepared by taking alumina (neutral) and concentrated phosphoric acid in the molar ratio of $Al:H_3PO_4$ as 1:3 under thermal conditions.[18]

RESULTS AND DISCUSSION

At the outset, to optimize the reaction conditions, we carried out the reaction of isatoic anhydride (1 mmol) with aniline (1.1 mmol) and benzaldehyde (1 mmol) as a model reaction in the presence of different amounts of the catalyst at different temperature under thermal solvent-free conditions. The results of this study are summarized in Table 1. As shown from Table 1, the best results used 0.05 g (16 mol%) of the catalyst at 100 °C.

Next, we applied the optimal protocol to a diverse range of primary amines and aldehydes with isatoic anhydride and studied the scope of this reaction for preparation of varieties of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (Scheme 1, Table 2). As shown in Table 2, the direct three-component reactions worked well with a variety of aryl aldehydes including those bearing electron-withdrawing and electron-donating groups such as OMe, Cl, Br, and NO_2, and the desired compounds were obtained in good to excellent yields (Table 2, entries 1–8).

Under the same conditions, this reaction did not proceed when aliphatic aldehydes were used as the starting material.

We also have introduced an efficient and environmental friendly approach for the synthesis of heterocyclic 3-(2′-benzothiazolo)-2,3-dihydroquinazolin-4(1*H*)-ones via the three-component condensation reaction of 2-aminobenzothiazole, isatoic anhydride, and aryl aldehydes under thermal solvent-free conditions in good yields (Table 2, entries 9–14).

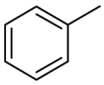
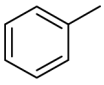
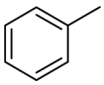
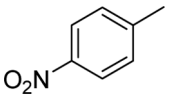
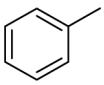
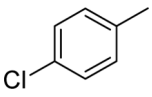
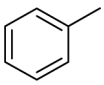
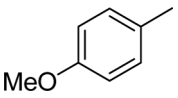
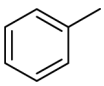
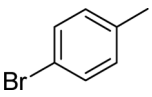
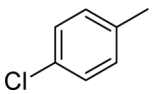
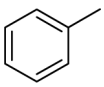
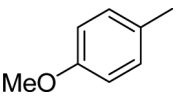
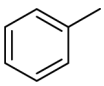
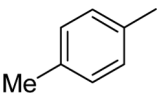
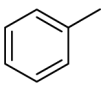
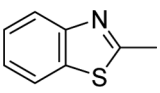
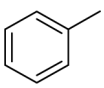
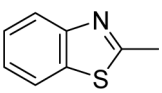
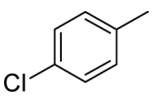
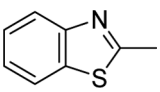
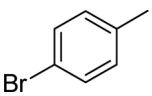
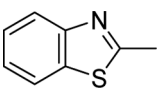
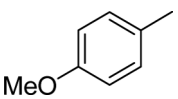
The suggested mechanism of the $Al(H_2PO_4)_3$-catalyzed preparation of quinazolinone is shown in Scheme 2. $Al(H_2PO_4)_3$ can act as Brønsted acid and also Lewis acid, using the empty aluminium p-orbital (Fig. 2). According to observation of evolution in the reaction conditions and other reported mechanisms in the literature,[13,14] we have suggested that an acid–base interaction in $Al(H_2PO_4)_3$ as

Table 1. Effects of different amounts of catalyst on the reaction rates at different temperatures in the reaction of isatoic anhydride (1 mmol) with aniline (1.1 mmol) and benzaldehyde (1 mmol) under solvent-free conditions

Entry	Amount of the catalyst (g)	Temperature (°C)	Time (min)	Yield (%)[a]
1	0.05	100	35	80
2	0.025	100	41	75
3	0.0125	100	46	74
4	0.006	100	3h	45
5	0.003	100	3.5h	40
6	0.05	120	17	76
7	0.05	80	3h	74
8	0.05	50	7h	50
9	0.05	Room temperature	24h	—

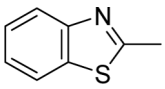
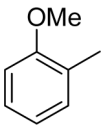
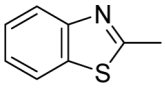
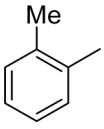
[a]Yield refer to the isolated pure product.

Table 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives via Scheme 1

Entry	R	R′	Time (min)	Yield (%)[a]	Product	Melting points (°C) Found	Melting points (°C) Lit.[Ref]
1			35	80	4a	213–214	214–215[14]
2			10 h	75	4b	193–196	194–196[13]
3			8.5 h	70	4c	212–215	214–217[11]
4			25	80	4d	213–214	204–205[13]
5			10 h	76	4e	218–220	222–225[13]
6			9 h	70	4f	219–220	216–217[10b]
7			32	85	4g	215–216	209–211[13]
8			55	80	4h	209–212	196–199[13]
9			20	85	4i	231–234	233–236[16b]
10			20	80	4j	198–200	190–193[16b]
11			18	79	4k	228–230	231–234[16b]
12			20	86	4l	179–183	184–186[16b]

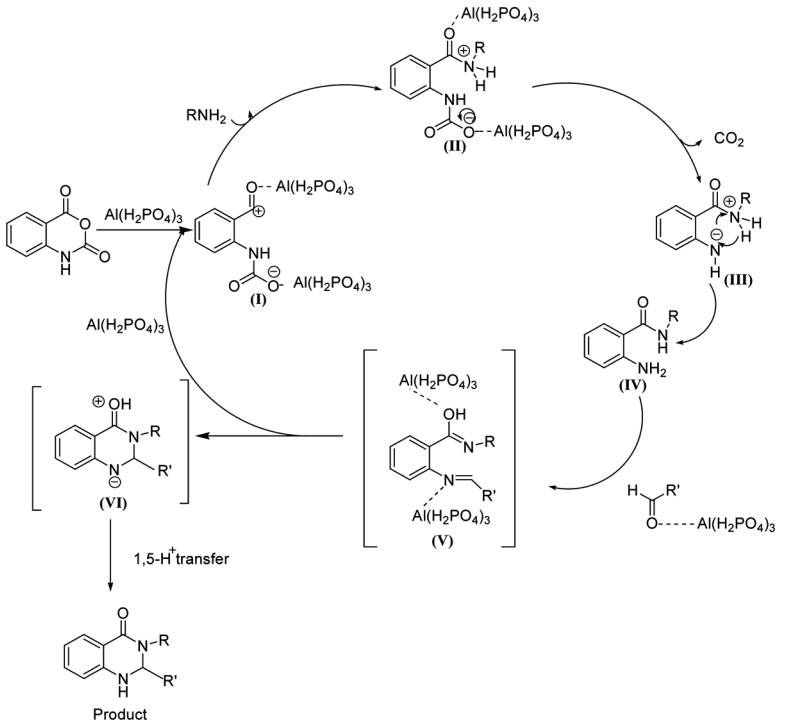
(*Continued*)

Table 2. Continued

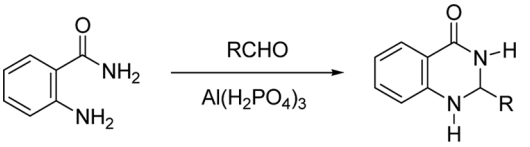
Entry	R	R′	Time (min)	Yield (%)[a]	Product	Melting points (°C) Found	Lit.[Ref]
13			13	80	4m	229–233	225–230[16b]
14			15	85	4n	198–201	198–200[16b]

[a]The reaction was conducted in an oil bath at 100 °C; the molar ratio of isatoic anhydride, primary amines, benzaldehydes, and $Al(H_2PO_4)_3$ as catalyst was chosen 1:1.1:1:0.16.

the catalyst and isatoic anhydride produces a reactive intermediate (I). The N-nucleophilic primary amine attack on the carbonyl unite of (I) produces a reactive intermediate (II), which in turn affords (III) through decarboxylation reaction. The proton transfer of (III) affords 2-amino-N-substituted-amide (IV).



Scheme 2. Suggested mechanism for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.



Scheme 3. The condensation of anthranilamide and aldehydes in the presence of $Al(H_2PO_4)_3$ as catalyst.

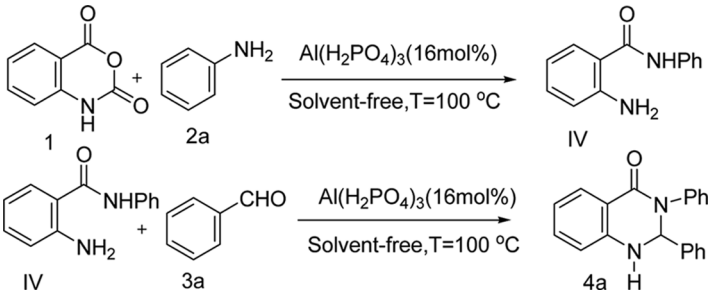
Subsequently, the reaction of activated aldehyde with (IV) proceeds to prepare the imine intermediate (V). The part of amide functional group in intermediate (IV) could be formed using tautomerism in the presence of the catalyst. Thus, intermediate (VI) could be prepared by intermolecular nucleophilic attack of the amide nitrogen on activated imine carbon, followed by a 1,5-proton transfer to yield the final 2,3-dihydroquinazoline-4-(1*H*)-ones as products.

Clarification of the reaction mechanism in detail is the next subject of investigation, in which the condensation of anthranilamide (IV) with aldehydes using $Al(H_2PO_4)_3$ as a catalyst is reported (Scheme 3).

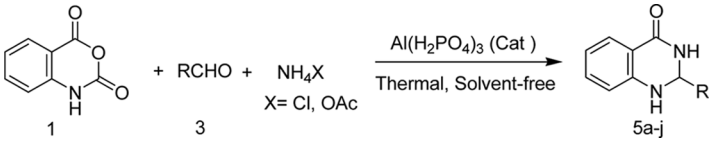
To confirm this suggested mechanism, 2-amino-N-phenylbenzamide (IV) was prepared from the reaction of isatoic anhydride (**1**) with aniline (**2a**) in the presence of $Al(H_2PO_4)_3$ (16 mol%) under solvent-free conditions. Next, this product (similar to intermediate IV in Scheme 2) reacted with benzaldehyde (**3a**) to give the corresponding product 2,3-dihydroquinazoline-4(1*H*)-one (Scheme 4).

Encouraged by the success of these results, the ammonium salts such as ammonium chloride and ammonium acetate were employed as the source of ammonia instead of primary amines in the reaction (Scheme 1). They were mixed with isatoic anhydride and benzaldehydes in the presence of $Al(H_2PO_4)_3$ under thermal solvent-free conditions (Scheme 5). The desired 2-aryl-2,3-dihydroquinazoline-4(1*H*)-one derivatives were obtained in good yields using ammonium acetate and ammonium chloride in the reaction conditions (Table 3).

We also investigated the recycling of the catalyst under solvent-free conditions using a model reaction of isatoic anhydride, benzaldehyde, and ammonium acetate. After completion of the reaction, the reaction was cooled to room temperature, and the crude solid product was dissolved in hot ethanol. The hot ethanolic solution was filtered for separation of the catalyst. The catalyst was washed twice (2×10 mL) using hot ethanol. Then it was dried at 100 °C for



Scheme 4. Confirmation mechanism using 2-amino-N-phenylbenzamide.

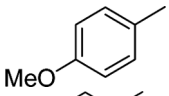
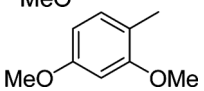
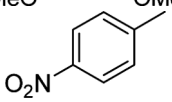
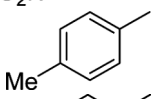
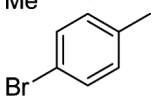
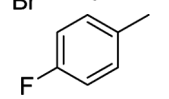
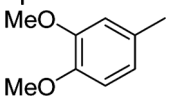
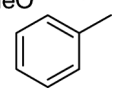
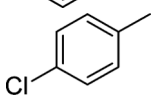
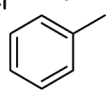


Scheme 5. Synthesis of 2-aryl-2,3-dihydroquinazoline-4(1*H*)-ones.

1 h. The recovered catalyst was reused three times without any loss of its activities (Table 4).

To show the merit of the present work in comparison with reported results in the literature, we compared results of $Al(H_2PO_4)_3$ with montmorillonite K-10,[12]

Table 3. Synthesis of 2-aryl substituted 2,3-dihydroquinazoline-4(1*H*)-one derivatives

Entry	R	NH_4X (X = OAc, Cl)	Time (min)	Yield (%)[a]	Product	Melting points (°C) Found	Lit.[Ref]
1		NH_4OAc	42	85	5a	202–203	192–193[10a]
2		NH_4OAc	4	90	5b	187–188	186–187[14]
3		NH_4OAc	2 h	70	5c	217–219	213–214[14]
4		NH_4OAc	10	82	5d	239–241	233–234[10b]
5		NH_4OAc	13	85	5e	200–202	205–206[16]
6		NH_4OAc	18	81	5f	205–206	199–200[14]
7		NH_4OAc	12	80	5g	222–225	210–213[12]
8		NH_4OAc	8	90	5h	227–230	221–223[13]
9		NH_4OAc	14	90	5i	205–206	205–206[14]
10		NH_4Cl	3 h	90	5j	227–230	221–223[13]

[a]The reaction was conducted in an oil bath at 100 °C; the molar ratio of isatoic anhydride, ammonium salts, benzaldehydes, and $Al(H_2PO_4)_3$ as catalyst was 1:1.2:1:0.16.

Table 4. Reusability of $Al(H_2PO_4)_3$ in the reaction of isatoic anhydride, ammonium acetate, and benzaldehyde

Run	Yield (%)[a]	Time (min)
1	90	8
2	90	8
3	89	8

[a]The molar ratio of isatoic anhydride, benzaldehyde, ammonium acetate, and $Al(H_2PO_4)_3$ was 1:1:1.2:0.16.

Table 5. Comparison of results of $Al(H_2PO_4)_3$ with montmorillonite K-10,[12] silica sulfuric acid,[10] $KAl(SO_4)_2 \cdot 12H_2O$(alum),[11] $[Zn(PFO)_2]$,[13] $Ga(OTf)_3$,[14] Amberlyst-15,[15] and *p*-TSA[9] as catalysts in the reaction of isatoic anhydride, aniline, and benzaldehyde

Entry	Catalyst	Conditions	Time (h)	Yield (%)
1	Montmorillonite K-10 (0.3 g)	EtOH, reflux	6.5	80
2	Silica sulfuric acid, 15 mol% (0.06 g equal to 0.15 mmol of H^+)	H_2O, 80 °C	4.5	85
3	Silica sulfuric acid, 20 mol% (0.06 g equal to 0.15 mmol of H^+)	Solvent-free,80 °C	5	80
4	$KAl(SO_4)_2 \cdot 12.H_2O$ (alum), (0.2 g)	EtOH, reflux	4	78
5	$[Zn(PFO)_2]$ (0.027 g, 0.03 mmol)	H_2O/EtOH (1/3), reflux	6	82
6	$Ga(OTf)_3$ (1 mol%)	EtOH, reflux	60 min	79
7	$Al(H_2PO_4)_3$ (0.05 g, 16 mol%)	Solvent-free, 100 °C	35 min	80 (present work)
8	Amberlyst-15 (80 mg)	Microwave	3 min	81
9	$KAl(SO_4)_2$-$12H_2O$(alum) (0.2 g)	H_2O, reflux	1	65
10	Silica sulfuric acid (0.3 mmol, 0.11 g)	EtOH, reflux	6.5	80
11	*p*-TSA (0.5 mmol)	H_2O	2.5	79

silica sulfuric acid,[10] $KAl(SO_4)_2 \cdot 12H_2O$(alum),[11] $[Zn(PFO)_2]$,[13] $Ga(OTf)_3$,[14] Amberlyst-15,[15] and *p*-TSA[9] as catalysts in the reaction of isatoic anhydride, aniline, and benzaldehyde in the synthesis of 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one. As shown in Table 5, $Al(H_2PO_4)_3$ can act as an effective catalyst with respect to reaction times and yields of the obtained products. Thus, the present protocol with $Al(H_2PO_4)_3$ as a catalyst is convincingly superior to the recently reported catalytic methods.

In conclusion, a three-component reaction of isatoic anhydride with primary amines (or ammonium salts) and aldehydes in the presence of an efficient, inexpensive, and heterogeneous catalyst, $[Al(H_2PO_4)_3]$, was applied to afford the corresponding quinazolinone derivatives in excellent yields under thermal solvent-free conditions. This catalyst could be easily recovered and reused for at least three cycles without any loss of activity.

EXPERIMENTAL

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. $Al(H_2PO_4)_3$ was prepared according to the reported procedure.[18]

All yields refer to isolated products after purification. Products were characterized by comparison of physical data with authentic samples and spectroscopic data (infrared, IR, and NMR). The NMR spectra were recorded on a Bruker Avance DPX 500-MHz instrument. The spectra were measured in dimethylsulfoxide (DMSO) relative to tetramethylsilane (TMS) (0.00 ppm). IR spectra were recorded on a Jasco Fourier transform (FT)–IR 460 plus spectrophotometer. Mass spectra were recorded on an Agilent Technologies 5973 network mass selective detector (MSD) operating at an ionization potential of 70 eV. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica-gel polygram SIL G/UV 254 plates.

General Procedure for the Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-one Derivatives

A stirred mixture of isatoic anhydride (1 mmol), primary amine (1.1 mmol) or ammonium salts (1.2 mmol), aldehydes (1 mmol), and $Al(H_2PO_4)_3$ (0.05 g, 16 mol%) was reacted in an oil bath at 100 °C for the appropriate times. Completion of the reaction was indicated by TLC. After completion of the reaction, it was cooled to room temperature, and the crude solid product was dissolved in hot ethanol and filtered for separation of the catalyst. The filtrate, ethanol solution, was concentrated. The solid product was purified by recrystallization procedure in aqueous EtOH (70%).

All the products were characterized by comparison of their spectroscopic and physical data with those of authentic samples.[10–16] The spectral data of some products are given next.

3-(2′-Benzothiazolyl)-2,3-dihydro-2-(2-methoxyphenyl)-quinazolin-4(1*H*)-one (Product 4m, Table 2, Entry 13)

Colorless crystals; mp 229–233 °C; IR (KBr): $\upsilon = 3346, 1647, 1614, 1511, 1460, 1440\,cm^{-1}$; ^1H NMR (500 MHz, DMSO-d_6): δ_H 8.01 (d, 1H, $J = 7.77$ Hz), 7.87 (d,1H, $J = 7.77$ Hz), 7.77 (d, 1H, $J = 3.48$ Hz), 7.73 (d,1H, $J = 7.86$ Hz), 7.67 (d, 1H, $J = 3.45$ Hz), 7.19–7.43 (m, 4H), 7.07 (d, 1H, $J = 8.13$ Hz), 6.71–6.89 (m, 4H), 3.94 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 162.65, 157.56, 157.08, 148.01, 147.15, 135.85, 133.04, 130.29, 128.68, 127.15, 126.68, 125.50, 124.54, 122.11, 121.46, 120.35, 118.49, 116.01, 113.05, 112.14, 65.71, 56.25 ppm; MS (EI, 70 eV), m/z (%): 388 (60), 253 (100), 238 (50), 167 (20), 132 (25), 77 (20).

2-Amino-N-phenylbenzamide (IV)

White solid; mp 130–132 °C; IR (KBr): $\upsilon = 3418, 3330, 3290, 1643, 1511, 1438, 1260,747\,cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.75 (s, 1H), 7.57 (d, 2H, $J = 7.6$ Hz), 7.47 (d, 1H, $J = 6.9$ Hz), 7.34–7.41 (m, 2H), 7.23–7.28 (m, 1H), 7.12–7.18 (m, 1H), 6.69–6.74 (m, 2H), 5.5 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 118.1, 118.8, 119.2, 122.5, 126.7, 129.3, 131.8, 134.8, 139.5, 151.8, 169.2 ppm; MS (EI, 70 eV), m/z (%): 212 (M^+, 100), 213 (13.35).

2,3-Dihydro-2-(4-methylphenyl)-quinazolin-4(*1H*)-one (Product 5d, Table 3, Entry 4)

White solid; mp 239–241 °C; IR (KBr): $\upsilon = 3313$, 3196, 1657, 1610, 1509, 1485 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ_H 8.26 (s, 1H), 7.62 (d, 1H, $J = 7.6$ Hz), 7.38 (d, 2H, $J = 8.0$ Hz), 7.17–7.25 (m, 3H), 7.07 (s, 1H), 6.75 (d, 1H, $J = 8.0$ Hz), 6.66 (t, 1H, $J = 7.6$ Hz), 5.72 (s, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 163.7, 148.0, 138.7, 137.8, 133.3, 128.9, 127.4, 126.9, 117.1, 115.0, 114.5, 66.5, 20.8 ppm; MS (EI, 70 eV) m/z (%): 238 (47), 237 (92), 147 (100), 120 (48).

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