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KO^tBu-$BF_3.OEt_2$ mediated synthesis of quinazolin-4(*3H*)-ones from 2-substituted amides with nitriles and aldehydes

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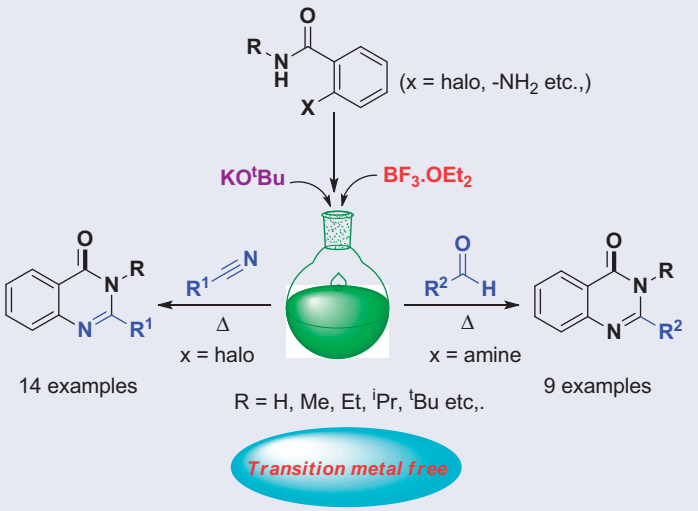
ABSTRACT

KO^tBu-$BF_3.OEt_2$ mediated synthesis of quinazolin-4(*3H*)-ones from 2-substituted amides with nitriles and aldehydes have been developed. In this protocol, a variety of nitriles as well as aldehydes react with 2-substituted benzamides to corresponding quinazolin-4(*3H*)-ones products in good to moderate yields, via the cleavage of C-X and C-N bonds and the formation of double C-N bonds simultaneously, in presence of potassium *tert*-butoxide.

GRAPHICAL ABSTRACT



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Nitriles; aldehydes; KOtBu; quinazolinones; metal-free conditions

Introduction

Nitrogen-containing heterocycles are back-bone of many bio-active natural products, agro-chemicals as well as pharmaceutical industry; these are much in demand due to their important physiological and biological activities (Figure 1).[1–2] In recent years various groups have explored the newer and efficient methodologies to synthesize

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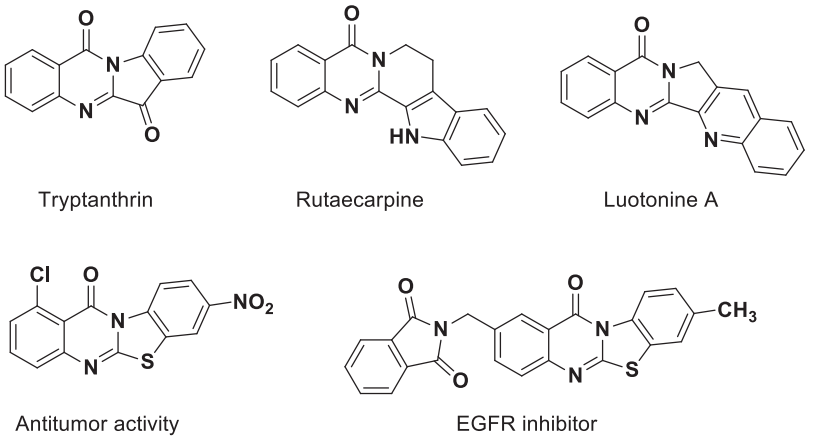


Figure 1. Selected quinazolinone containing natural products and drug candidates.

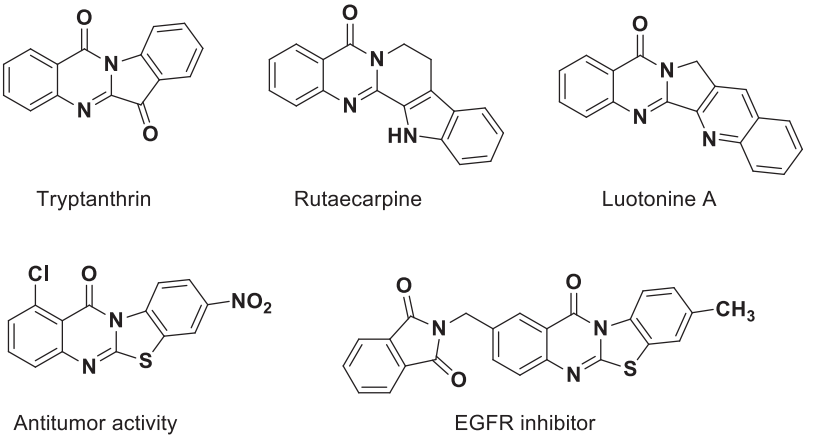


Figure 2. Our novel approach.

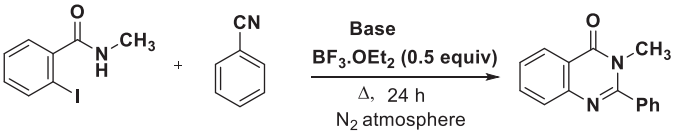
molecules containing nitrogen atoms. One such preferred scaffold is phenylquinazolin-4(*3H*)-one which has shown varying effects such as anti-cancer, anti-inflammatory, anti-microbial, anti-allergetic etc.[3–5] In addition, a latest report highlights the role of 4-methyl quinazoline derivatives in the treatment of one of the rare disease idiopathic pulmonary fibrosis through P13K inhibition.[6] During our efforts to develop new scaffolds for strengthening the drug discovery pipeline, we embarked on the synthesis of quinazolin-4(*3H*)-one derivatives using very mild reagents. The results of our studies are presented here.

Results and discussion

Synthesis of quinazolin-4(*3H*)-ones is traditionally being reported with the use of transition metal catalysts,[7–10] predominantly Cu(I) salts.[11–12] Our synthetic efforts are

focused on the complete elimination of the transition metal (Figure 2). Thus 2-iodo *N*-methyl benzamide **1a** and benzonitrile **2a** were reacted in presence of KO^{t}Bu, $BF_3.OEt_2$ in ^{t}BuOH at 130 °C where we observed the formation of 3-methyl-2-phenylquinazolin-4(3H)-one **3a** in 42% yield (Table 1, entry 1). This result enthused us to further explore the conditions to synthesize **3a** derivatives. In the first step we studied effect of solvents where DMF, DMSO, toluene, nitrobenzene, N-methyl-pyrrolidone and Dimethyl

Table 1. Optimization of reaction conditions.

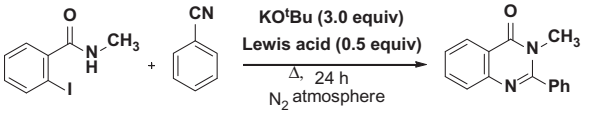


1a **2a** **3**

s.no.	base (equiv)	solvent	temp (°C)	yield[a]
1	KO^{t}Bu (3.0)	^{t}BuOH	130	42
2	KO^{t}Bu (3.0)	DMF	130	trace
3	KO^{t}Bu (3.0)	DMSO	130	trace
4	KO^{t}Bu (3.0)	Toluene	130	12
5	KO^{t}Bu (3.0)	Nitrobenzene	130	trace
6	KO^{t}Bu (3.0)	NMP	130	trace
7	KO^{t}Bu (3.0)	DMA	130	nd
8	KO^{t}Bu (3.0)	CH_3NO_2	130	nd
9	**KO^{t}Bu (3.0)**	**Dioxane**	**130**	**70**
10	KOH (3.0)	Dioxane	130	trace
11	K_2CO_3 (3.0)	Dioxane	130	nd
12	Cs_2CO_3 (3.0)	Dioxane	130	nd
13	NaO^{t}Bu (3.0)	Dioxane	130	trace
14	NaOH (3.0)	Dioxane	130	trace
15	KO^{t}Bu (3.0)	Dioxane	100	nd
16[b]	KO^{t}Bu (3.0)	Dioxane	130	nd
17	-- --	Dioxane	130	nd
18[c]	KO^{t}Bu (3.0)	Dioxane	130	30
19[d]	KO^{t}Bu (3.0)	Dioxane	130	37
20[e]	KO^{t}Bu (3.0)	Dioxane	130	40
21[f]	KO^{t}Bu (3.0)	Dioxane	130	58
22[g]	KO^{t}Bu (3.0)	Dioxane	130	26
23[h]	KO^{t}Bu (3.0)	Dioxane	130	55

Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), base (1.5 mmol, 3 equiv), $BF_3.OEt_2$ (0.5 equiv) in dioxane (3 mL) nd = not detected. [a] yields after column chromatography. [b] reaction performed in the presence of O_2 atm. [c] 0.1 equiv. of $BF_3.OEt_2$ was used. [d] 0.2 equiv. of $BF_3.OEt_2$ was used. [e] 0.3 equiv. of $BF_3.OEt_2$ was used. [f] 1.0 equiv. of $BF_3.OEt_2$ was used. [g] 1.5 equiv of benzonitrile was used. [h] 3.0 equiv of benzonitrile was used.

Table 2. Screening of different Lewis acids[a].



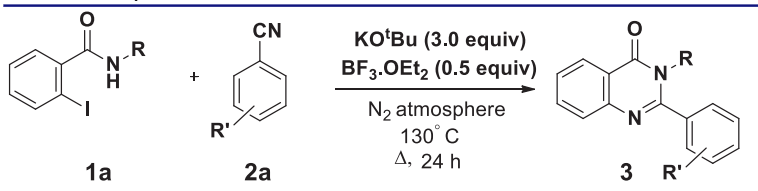
1a **2a** **3**

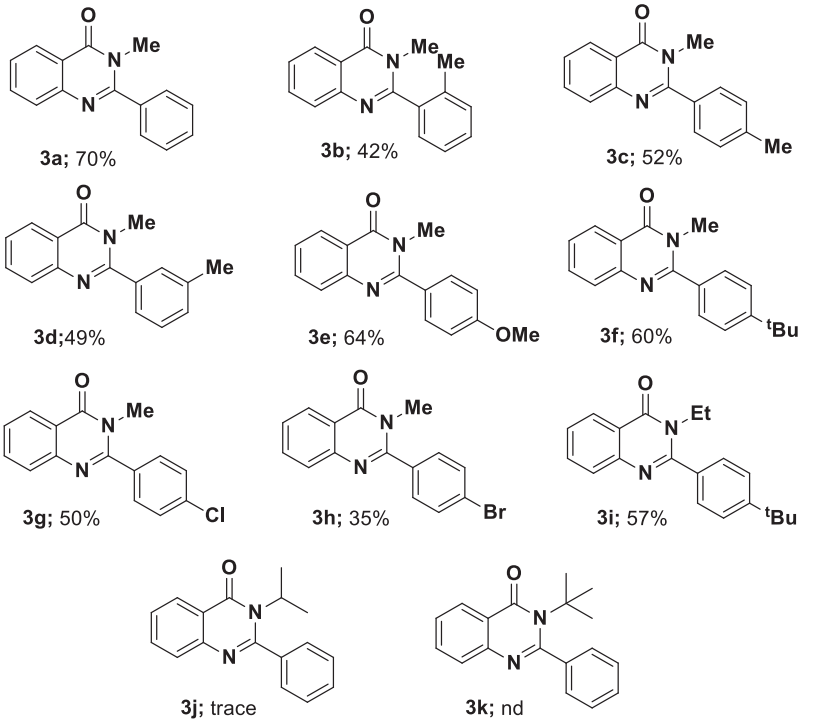
s.no.	lewis acid	solvent	product (3a)[b]
1	$InCl_3$	dioxane	35
2	$SnCl_2$	dioxane	nd
3	$SnBr_2$	dioxane	25
4	$Sc(OTf)_3$	dioxane	40
5	**$BF_3.OEt_2$**	**dioxane**	**70**
6	$TiCl_4$	dioxane	48
7	$AlCl_3$	dioxane	nd
8	$B(C_6F_5)_3$	dioxane	nd

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), base (1.5 mmol, 3 equiv), $BF_3.OEt_2$ (0.5 equiv) in dioxane (3 mL).[b] yields after column chromatography.

acetamide were explored, unfortunately none of these solvents could aid in increasing the yield (Table 1, entries 2–8). The solvent of choice was 1,4-dioxane which resulted in the increased yield of **3a** (Table 1, entry 9). We then studied bases such as KOH, K_2CO_3, Cs_2CO_3, ^{t}BuONa and NaOH which resulted in poor yields or non-formation of the products (Table 1, entries 10–14). The effect of temperature was also studied and it was found that, the reaction could not take place at 100 °C, under similar reaction conditions (Table 1, entry 15). Further, the role of inert atmosphere was determined when a reaction in optimized conditions open to air did not result in any product formation (Table 1, entry 16), clearly indicating that inert atmosphere is essential for this reaction. When the reaction was employed in the absence of the base no product formation was observed (Table 1, entry 17). On varying the concentration of $BF_3.OEt_2$ from 0.1 equiv to 1.0 equiv the yield ranged from 30% to 58% (Table 1, entries 18–21). And also we checked the requirement of benzonitrile equivalents; when we used 1.5 equiv and 3.0 equiv of benzonitrile, the resulting yields were lower (Table 1, entries 22–23). Based on the above observations, next we examined the reactivity of other Lewis acids like $InCl_3$, $SnCl_2$, $SnBr_2$, $Sc(OTf)_3$, $AlCl_3$ and $B(C_6F_5)_3$ under the same optimal reaction conditions (Table 2), lower yields of the final product **3a** were observed compared to entry 5 (Table 2). It indicates that $BF_3.OEt_2$ may easily activate nitrile (**2a**) than the other Lewis acids (Table 2). After establishment of the optimal reaction conditions, we then explored the substrate scope (Table 3). Thus, **1a** was treated with substituted benzonitriles **2a–2h** under the optimized reaction conditions. The yields of **3a–3h** were achieved in the range of 35–70%. When *N*-Methyl group of **1a** was substituted with *N*-ethyl, 57% of the product formation (**3i**) was observed. Although, *N*-isopropyl and *N*-tert-butyl substituents also tested, the reaction of *N*-isopropyl substituent, trace amount of product (**3j**) was observed. Similarly, no product formation was observed in the case of *N*-tert-butyl substituent (**3k**), due to steric hinderance.

Table 3. Scope of 2-halo amide with various nitriles[a].

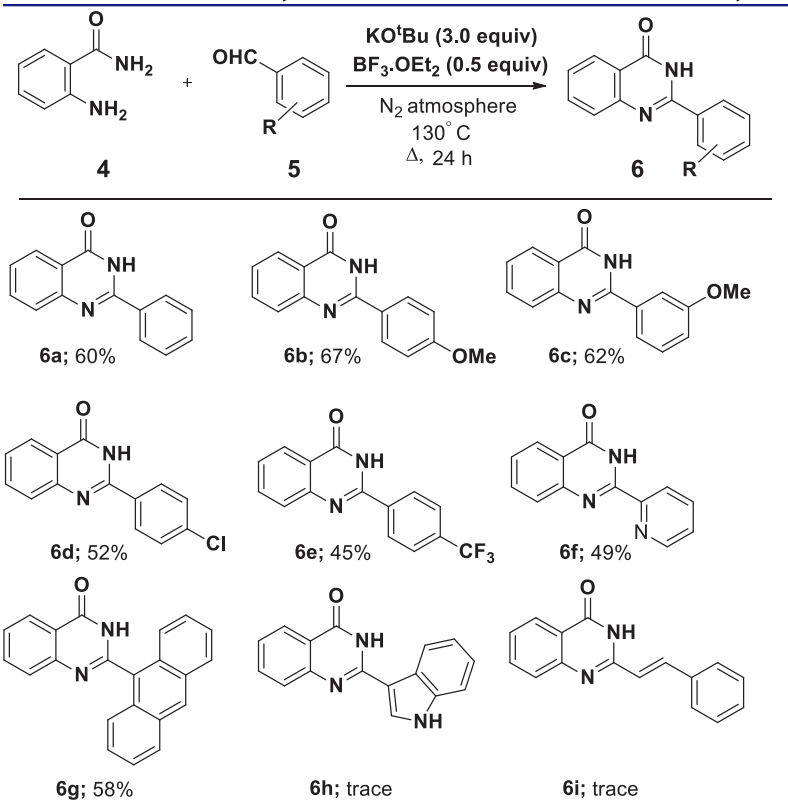




[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), KO^{t}Bu (1.5 mmol, 3 equiv), $BF_3.OEt_2$ (0.5 equiv) in dioxane (3 mL), nd = not detected.

We then varied the primary substrates, thus 2-halo benzamide **1** and benzonitrile **2** were replaced with 2-amino benzamide **4** and benzaldehyde **5**. In recent years, various groups have been developed elegant methods for synthesis of quinazolin-4(*3H*)-ones using 2-amino benzamide with aldehyde under metal and metal free conditions.[13–14] To our pleasure the same reaction conditions were applicable, 2-amino benzamide **4a** upon reaction with benzaldehyde **5a** gave quinazoline-4(*3H*)-ones **6a** in 60% yield. The substituted aldehydes **5a–5i** was reacted with **4a** and respective quinazoline-4(*3H*)-ones (**6a–6i**) were obtained in 45–67% yields (Table 4). We also explored the reaction of 2-bromo, 2-chloro, and 2-hydroxy-4-methoxy-*N*-methylbenzamides and found the products 55% and no product formation in the case of 2-chloro benzamide and 2-hydroxy-4-methoxy-*N*-methylbenzamide (Table 5, **3a** & **3l**). We tested the reaction of 2-(bromo-methyl) benzonitrile **2b** under optimal reaction conditions, where only a trace amount of respective product was formed (Table 5, **3l**) and no cyclized product was observed (Table 5, **3m**).

Table 4. Functional diversity of 2-amino benzamide with different aldehydes[a].



[a]Reaction conditions: **4** (0.5 mmol), **5** (1.0 mmol), KO^{t}Bu (1.5 mmol, 3 equiv), $BF_3.OEt_2$ (0.5 equiv) in dioxane (3 mL), 130 °C, 24 h.

Based on the previous literature reports,[15] we proposed a plausible reaction mechanism. Initially, nitrile **2**, with $BF_3.OEt_2$ may form intermediate (**I**). Further the reaction of **1** to the intermediate (**I**) may generate another intermediate (**II**) under basic conditions, which upon elimination of halogen from intermediate (**II**), it forms the cyclized product (**III**). Next, the subsequent oxidation of the intermediate (**III**) will give the desired product (Table 6, **3**).

Conclusion

In conclusion, we have developed an efficient method for the synthesis of quinazolin-4(*3H*)-ones from easily available starting materials. This present methodology exhibits good functional group tolerance with a variety of nitriles as well as aldehydes on the aryl group into the corresponding quinazolin-4(*3H*)-ones in moderate to good yields.

Experimental

Unless otherwise noted, all reagents were used as received from commercial suppliers. All non-aqueous reactions were performed under an atmosphere of nitrogen using oven-dried

Table 5. Reactivity of the various benzonitriles and 2-halobenzamides.

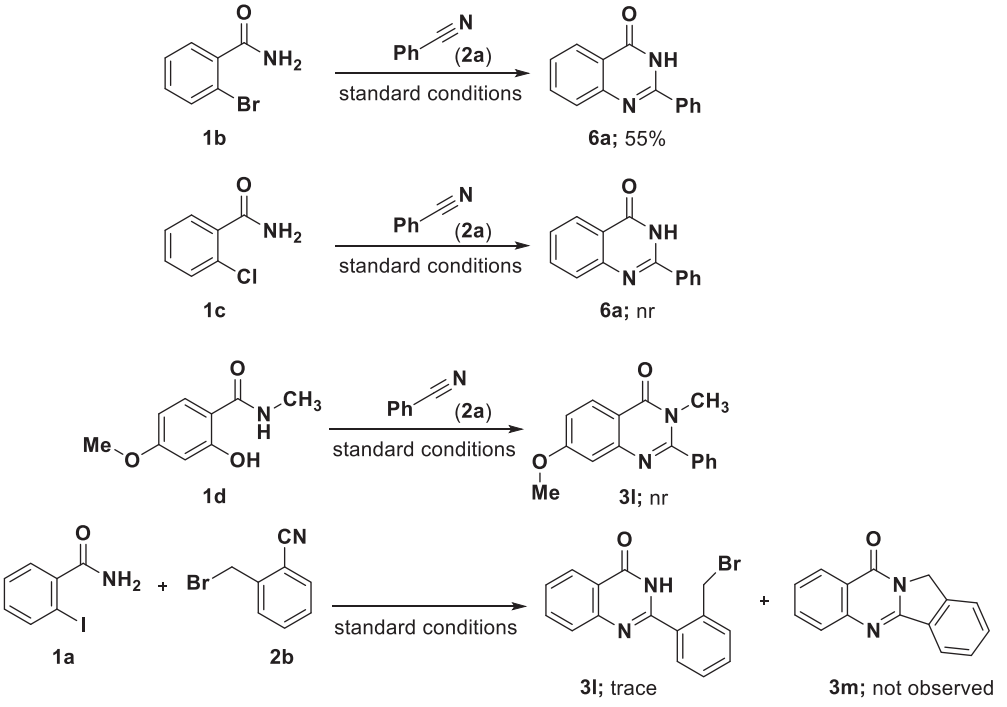
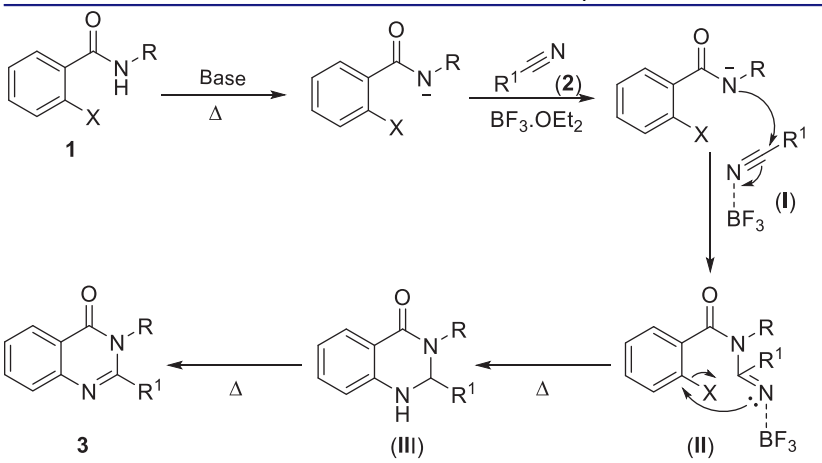


Table 6. Plausible reaction mechanism for formation of quinazolin-4(*3H*)-ones.[15]

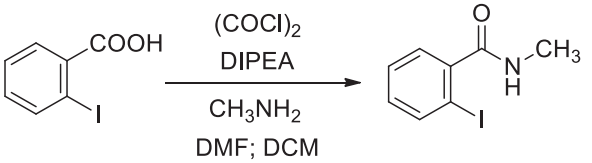


glassware. All solvents were dried before use, following the standard procedures. Reactions were monitored using thin-layer chromatography (SiO_2). TLC plates were visualized with UV light (254 nm), Column chromatography was carried out using silica gel (100–200 mesh) packed in glass columns. NMR spectra were recorded at 300, 400, 500 MHz (H) and

at 75, 101, 126 MHz (C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in CDCl3 (H: $\delta = 7.26$ and C: $\delta = 77.16$ ppm) as internal standard, and coupling constants (J) are given in Hz. High-resolution mass spectrometry (HRMS) was recorded using electro spray ionization (ESI)−Time-off light techniques.

General procedure for the preparation of starting materials[1]

DMF (0.2 mL) was added to oxalyl chloride (1.5 mL, 17.74 mmol), and 2- iodobenzoic acid (4.0 g, 16.12 mmol) in DCM (30 mL). The resulting mixture was stirred for 2 h. The mixture was concentrated in vacuo and cooled to 0 °C, the crude was directly used in the next step; this was taken up in DCM (30 mL). To acid chloride, were added amine 2M methylamine in THF (60 mL, 120 mmol) and N, N'-di-isopropylethylamine (3.09 mL, 17.74 mmol) added. This was stirred for 30 minutes, and a precipitate was formed. The reaction was left standing overnight. The mixture was filtered; the filtrate was washed with water. The crude reaction mixture was extracted with CH_2Cl_2, the organic solvent was removed in vacuo and the residue purified by recrystallization (PE: EA = 5:1) 2-iodo-*N*-methylbenzamide (3.40 g, 81%) as a white solid.



General procedure for the synthesis of 3-Methyl-2-phenylquinazolin-4(3*H*)-one (3a)

To a 25 mL round-bottom flask were added 2-iodo-*N*-methylbenzamide **1a** (130.5 mg, 0.5 mmol), Benzonitrile (206 mg, 2.0 mmol), KO^{t}Bu (168 mg, 1.5 mmol) and $BF_3.OEt_2$ (35.2 mg, 0.25 mmol) in 3.0 mL of 1, 4-dioxane. The reaction mixture was heated in an oil bath at 130 °C for 24 hrs. After completion of the reaction; it was allowed to attain room temperature. The reaction mixture was quenched by saturated $NaHCO_3$ (20 ml, $P^H = 10.3$) solution and extracted by ethyl acetate (15 mL × 3) dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure the residue was purified by column chromatography using silica gel (30% EtOAc/hexane) to afford **3a** (83.1 mg; 70% yield).

Full experimental detail, ^{1}H and ^{13}C NMR spectra can be found via the "Supplementary Content" section of this article's webpage.

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