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Synthesis of 2-hydroxy-3-alkyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one *via* molybdenum hexacarbonyl mediated CO gas- and ligand free carbonylative reactions†

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Carbon monoxide gas and ligand-free conditions were developed for the synthesis of 2-hydroxy-3-alkyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one *via* catalytic carbonylation with molybdenum hexacarbonyl as an efficient carbonylating agent for the three-component reaction of isatoic anhydride, amine, iodobenzene. $Mo(CO)_6$ is a solid carbon monoxide source. The quinazolinone synthesis proceeds *via* a sequential series of reactions such as nucleophilic attack of the amine group on the carbonyl group of isatoic anhydride followed by ring opening, subsequent decarboxylation, carbonylation and heterocyclization.

The development of novel and efficient synthetic methods towards the building of a nitrogen containing heterocyclic ring is an important area of synthetic and medicinal chemistry as many drugs or bioactive agents belong to this class of heterocycles.[1] 2-Arylquinazolin-4(3*H*)-ones are a highly important class of heteroaromatic compounds that are widely found in pharmaceuticals, and bioactive molecules. The quinazoline core unit is found in many natural products, including alkaloids like bouchardatine **1**,[2] batracylin **2**,[3] ophiuroidine **3**,[4] (−)-benzomalvin A **4**,[5] luotonon A **5**,[6] luotonon B **6**, luotonon E **7** and asperlicin D **8** (Fig. 1).[7] Some quinazolinone based natural products *e.g.* febrifugine and isofebrifugine have been identified as potential antimalarial agents.[8]

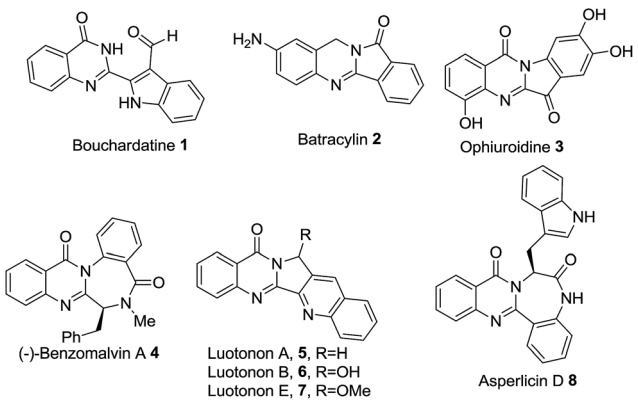

Fig. 1 Selected examples of bioactive natural products which contain quinazolin-4(3*H*)-ones skeleton.

Scheme 1 Retrosynthesis of **12**.

Table 1 Screening of various CO sources, solvents and bases[a]

Entry	CO source (eq.)	Solvent	Base	Isolated yield (%)
1	$Mo(CO)_6$ (0.2)	DMF	Bu_3N	23
2	$Cr(CO)_6$ (0.2)	DMF	Bu_3N	8
3	$W(CO)_6$ (0.2)	DMF	Bu_3N	11
4	$Mo(CO)_6$ (0.5)	DMF	Bu_3N	45
5	$Mo(CO)_6$ (1.0)	DMF	Bu_3N	72
6	$Mo(CO)_6$ (1.0)	1,4-Dioxane	Bu_3N	31
7	$Mo(CO)_6$ (1.0)	DMSO	Bu_3N	42
8	$Mo(CO)_6$ (1.0)	Diglyme	Bu_3N	36
9	$Mo(CO)_6$ (1.0)	DMF	TEA	10
10	$Mo(CO)_6$ (1.0)	DMF	K_2CO_3	0
11	$Mo(CO)_6$ (1.0)	DMF	Cs_2CO_3	0
12	Without CO source	DMF	Cs_2CO_3	0

[a] *Reaction and conditions*: isatoic anhydride (1.0 eq.), *n*-butyl amine (1.0 eq.), 4-iodo-1,1′-biphenyl (1.0 eq.), $Mo(CO)_6$ (1.0 eq.) and Bu_3N (1.2 eq.), TBAB (0.2 eq.), in DMF at 150 °C.

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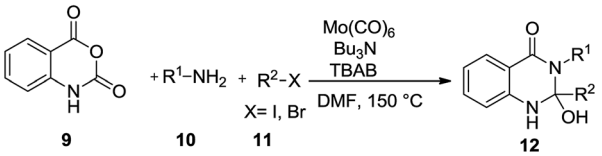
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, copies of spectra. See DOI: 10.1039/c6ra12510g

Table 2 Synthesis of various isoindoloquinazolinones derivatives



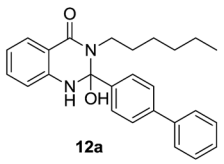
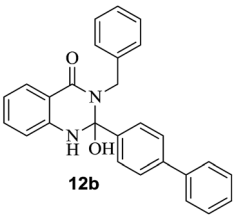
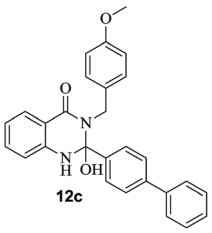
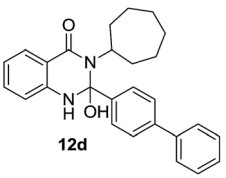
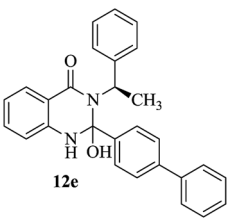
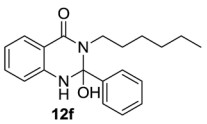
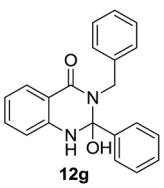
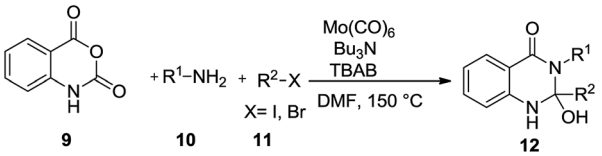
Entry	Amine **1**; R^1=	Aryl **2**; R^2=	Product **3**	Yield[a] (%)
1	**10a**; *n*-hexyl	**11a**; 4-biphenyl	 **12a**	78
2	**10b**; $-CH_2Ph$	**11a**	 **12b**	72
3	**10c**; $-CH_2C_6H_4OMe$-*p*	**11a**	 **12c**	62
4	**10d**; –cycloheptyl	**11a**	 **12d**	75
5	**10e**; –(*S*)-1-phenylethyl	**11a**	 **12e**	67
6	**10a**	**11b**; bromobenzene	 **12f**	71
7	**10b**	**11b**	 **12g**	72

Table 2 (*Contd.*)



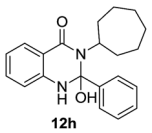
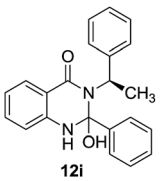
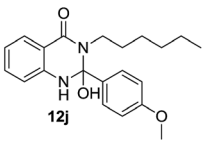
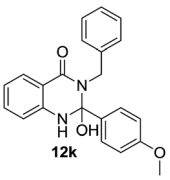
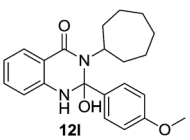
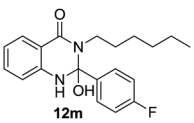
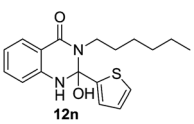
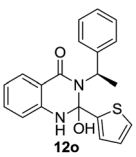
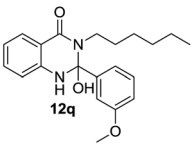
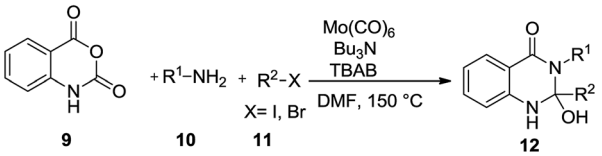
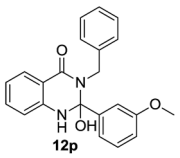
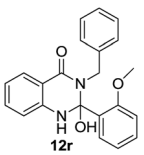
Entry	Amine **1**; R^1=	Aryl **2**; R^2=	Product **3**	Yield[a] (%)
8	**10d**	**11b**	 **12h**	70
9	**10e**	**11b**	 **12i**	63
10	**10a**	**11c**; BrC_6H_4OMe-*p*	 **12j**	58
11	**10b**	**11c**	 **12k**	56
12	**10d**;	**11c**	 **12l**	57
13	**10a**	**11d**; BrC_6H_4F-*p*	 **12m**	36
14	**10a**	**11e**; 2-iodothiophene	 **12n**	85
15	**10e**	**11e**	 **12o**	82
16	**10a**	**11f**; 1-bromo-3-methoxybenzene	 **12q**	62

Table 2 (*Contd.*)



Entry	Amine **1**; R^1=	Aryl **2**; R^2=	Product **3**	Yield[a] (%)
17	**10b**	**11f**	 **12p**	55
18	**10b**	**11g**; 1-bromo-2-methoxybenzene	 **12r**	45

[a] Isolated yields.

Medicinal chemists have synthesized a variety of arylquinazolin-4(3*H*)-ones compounds with different biological activities by installing various active groups. Because of varied biological properties of quinazolinone derivatives, a number of methodologies have been developed for their synthesis towards quinazolin-4(3*H*)-ones derivatives. Rao *et al.* reported a versatile method for the solid-phase synthesis of differentially substituted quinazolin-4(3*H*)-ones.[9] Recently, Besson *et al.* reported a ligand-free palladium catalyzed and copper-assisted intermolecular C-2–*H* arylations with (hetero)aryl iodides.[10]

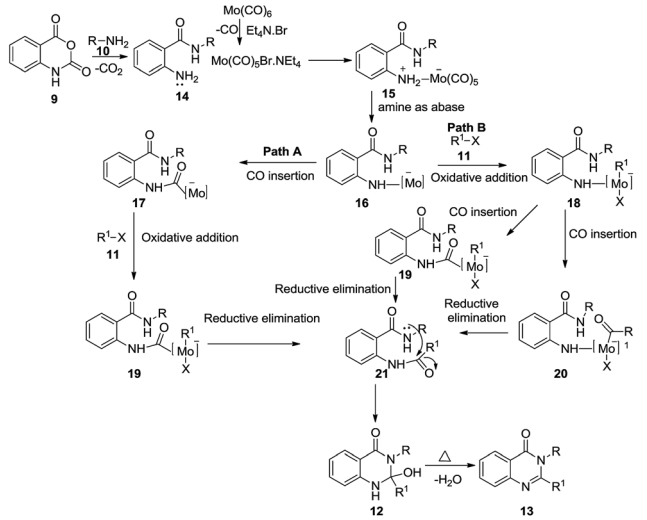
Following our efforts on the functionalization of quinazolin-4(3*H*)-one derivatives, Robert *et al.* also reported the molybdenum-mediated synthesis of quinazolin-4(3*H*)-ones *via* cyclocarbonylation using microwave irradiation.[11] In the context of our ongoing research work, recently our research group has demonstrated that substituted quinazolin-4(3*H*)-ones based biologically active natural products and their derivatives.[12]

Carbonylation is a classical synthetic methodology in organic chemistry for introducing carbon monoxide to C–C and C–N bond formation.[13] Organometallic methodologies have been also examined as a substitute for phosgene chemistry. A variety of metal centres can be used as catalysts in the presence of CO_2 or CO. However, not all transition-metal catalysts are useful in the oxidative carbonylation. Oxidative carbonylation of primary amines to substituted urea's has been reported for transition-metal catalysts involving Ni, Co, Mn, Ru and most commonly Pd.[14]

Bhanage reported palladium-catalyzed synthesis of primary amides by aminocarbonylation of aryl and heteroaryl iodides.[15] Yamane reported a similar molybdenum-mediated carbamoylation of aryl halides under thermal conditions with molybdenum carbonyl complexes.[16] Roberts and team also reported molybdenum-mediated carbonylation of aryl halides with nucleophiles to give carbonyl products under microwave irradiation.[17] We have explored the possibility of an operatively simple and novel synthesis of 2-hydroxy-3-alkyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one derivatives **12** with isatoic anhydride **9**,[18] amine **10** and iodobenzene **11** with molybdenum hexacarbonyl mediated CO gas-free cyclocarbonylation[19] *via* multi-component reaction strategy.

The retro synthetic strategy employed for the synthesis of 2-hydroxy-3-alkyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one derivatives is depicted in Scheme 1. The phenylquinazolin-4(3*H*)-one derivative **13** could be obtained *via* dehydration of **12** under heating. Initially when isatoic anhydride **9**, amine **10a** and iodobenzene **11a** were treated under the conditions applied for construction of dihydroquinazolin-4(1*H*)-one in DMF using 0.2 eq. of $Mo(CO)_6$ gives 23% of the desired product **12a**.

In an effort to develop optimal conditions, various reaction parameters like different catalysts, bases and solvents were studied for the preparation of **12**. The CO sources, namely $Mo(CO)_6$, $Cr(CO)_6$ and $W(CO)_6$ were screened (Table 1, entries 1–5). The best result was obtained when the reaction was performed in the presence of 1.0 eq. of $Mo(CO)_6$. Further various solvents like DMF, 1,4-dioxane, DMSO, and diglyme were screened (Table 1, entries 5–8) finally it was found that DMF was the suitable solvent for the carbonylation reaction. Once we established the suitable CO source and solvent for the synthesis of 2-hydroxy-3-alkyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-ones, further we screened various bases like triethylamine, tributylamine, potassium carbonate and cesium carbonate in DMF (Table 1, entries 9–12). The best result was obtained when the reaction was performed with tributylamine as a base.



Scheme 2 The proposed reaction mechanism for the formation of **12**.

However, the reaction did not give the corresponding carbonylation product when the reaction was conducted with potassium carbonate as well as with cesium carbonate, we screened various temperatures at lower temperature (below 100 °C) product formation was not observed only isatoic anhydride open product **14** was observed. Further we screened TBAB and TBAI both are working well and we observed 3% less yield with TBAI.

With these conditions in hand, the scope of this transformation was tested using several substituted aliphatic and aromatic amine and various aryl halides (Table 2). When the reaction was conducted with aryl iodide high yields were obtained when compared with aryl bromide.

Less yield was observed when the reaction was conducted with 4-fluro bromo benzene (entry 13). Placing electron withdrawing groups in the *para* position seems to be less reactivity. During the reaction around 5% aromatized product **13** formation was observed, when we maintained reaction for 48 h at 150 °C product **12** was completely undergoing for the de hydration leading to the formation of **13** with 75% of isolated yield.

The Scheme 2 represents a plausible mechanism for the three component reaction leading to the compound **12**. The nucleophilic attack of primary amine on carbonyl group of isatoic anhydride followed by ring opening and subsequent decarboxylation provided the compound **14**·Et_4NBr readily displaces a CO ligand from $Mo(CO)_6$ to give $Mo(CO)_5Br{\cdot}NEt_4$ and this complex reacts readily with nitrogen nucleophile of **14** will yield the **15**, which on deprotonation provides **16**. This could then undergo oxidative-addition or CO insertion to give **18** or **17**. Intermediate **17** undergo oxidative-addition with aryl halide to give **19**. Alternatively intermediate **18** undergo CO insertion to give **19** and **20**. Reductive elimination of **19** and **20** would give the diamide **21** and subsequent cyclization of **21** would give the product **12**, which undergo the de hydration leading to the formation of **13**.

In conclusion, we have developed a short and efficient novel methodology for the synthesis of 2-hydroxy-3-alkyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one derivative *via* multi-component reaction strategy in good yields from isatoic anhydride, amine and iodobenzene in a one pot process. Carbon monoxide gas and ligand free condition was developed for the synthesis of 2-hydroxy-3-alkyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one *via* catalytic carbonylation with molybdenum hexacarbonyl as an efficient carbonylating agent for three-component reaction of isatoic anhydride, amine, iodobenzene and $Mo(CO)_6$ as a solid carbon monoxide source. The quinazolinone synthesis proceeds *via* a sequential series of reactions such as nucleophilic attack of amine group on carbonyl group of isatoic anhydride followed ring opening and subsequent decarboxylation, carbonylation and heterocyclization.

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