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An efficient one pot synthesis of 2-amino quinazolin-4(3*H*)-one derivative via MCR strategy

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ABSTRACT

A novel multi-component reaction strategy was developed for the construction of important building blocks, 2-amino 3-substituted quinazolinone derivatives from isatoic anhydride and amine with electrophilic cyanating compound, *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide (NCTS). 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 ring opening and subsequent decarboxylation, nucleophilic attack of amine to nitrile, followed by heterocyclization.

Quinazolinone and their derivatives exhibit a wide range of biological and pharmacological properties some of these activities include anti-cancer,[1] anti-inflammatory,[2] anti-fungal,[3] anti-microbial and anti-malarial properties.[4] Furthermore, the heterocyclic core constitutes more than 40 alkaloids and various natural products like luotonon A **1**, B **2**, and E **3**,[5] rutaecarpine **4**,[6] tryptanthrin **5**,[7] macckinazolinone **6**,[8] vasicinone **7**,[9] deoxy vasicinone **8**, and evodiamine **9**,[10] (Fig. 1).

Because of varied biological properties of quinazolinone derivatives, a number of methodologies have been developed for their synthesis. However a limited number of synthetic strategies were reported in the literature for the synthesis of 2-amino 3-substituted quinazolinone with the free amino group at 2nd position.[11] Zeghida and co-workers reported a novel synthetic method involving the Friedel-craft type substitution from aniline.[12] Kundu et al. reported the synthesis of 2-amino quinazolinone via polymer-linked anthranilamide with isothiocyanates followed by coupling with secondary amines in the presence of DIC.[13] Yang and Kaplan reported solid-phase syntheses of quinazolin-4(3*H*)-ones via cyclocondensation of anthranilic acid with amino acids and aldehydes or by aza-wittig mediated annulation involving *o*-azidobenzoic acid.[14] Other methods reported recently involve cyclocondensation of 2-nitrobenzyl chloride with aryl amines and thioureas with isatoic anhydride.[15]

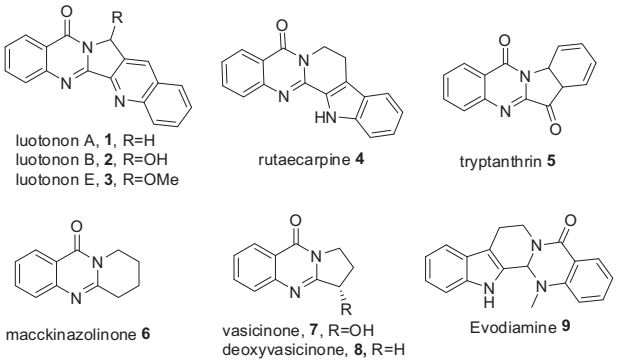
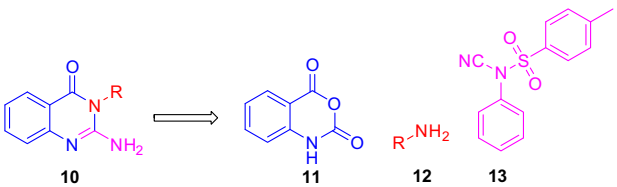


Figure 1. Examples of natural products which contain the quinazolinone skeleton.



Scheme 1. Retrosynthesis of **10**.

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0040-4039/

Table 1
Screening of solvents

Entry	Solvents	Isolated yield (%)
1	DMSO	45
2	DMF	48
3	1,4-Dioxane	70
4	Ethanol	0
5	Acetonitrile	48
6	THF	55
7	Toluene	40

Reaction and conditions: isatoic anhydride (1.0 equiv), NCTS (1.0 equiv), benzylamine (1.0 equiv) and LiHMDS (3.0 equiv) at reflux.

Table 2
Screening of bases

Entry	Base	Isolated yield (%)
1	K_2CO_3	45
2	DBU	38
3	DABCO	35
4	TEA	0
5	CS_2CO_3	52
6	LiHMDS (3.0 equiv)	72
7	LiHMDS (2.0 equiv)	68
8	LiHMDS (1.0 equiv)	62

Reaction and conditions: isatoic anhydride (1.0 equiv), NCTS (1.0 equiv), and benzylamine (1.0 equiv) at 100 °C.

The development of a simple methodology for the synthesis of 2-amino 3-substituted quinazolinone derivatives is always in demand due to its extensive biological activity. Multi-component reactions (MCRs) are highly desirable in any process as the target products are directly yielded by cascade or domino reaction sequences offer considerable advantages over conventional linear-step synthesis. Herein we wish to report a straight forward novel multi-component reaction for the synthesis of 2-amino 3-substituted quinazolinone derivatives.

The retro synthetic strategy employed for the synthesis of 2-amino 3-substituted quinazolinone is depicted in Scheme 1. The 2-amino quinazolinone could be easily obtained by a reaction of isatoic anhydride **11** with amine **12** and NCTS (*N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide) **13**. NCTS could be synthesised using the reported methodology by Kurzer.[16] NCTS are quite stable, non toxic, crystalline solids, which is used as a potential electrophilic cyanating agent on indoles and pyrroles.[17]

In an effort to develop optimal conditions, various reaction parameters were studied for the preparation of **10** via condensation of isotoic anhydride **11** (1.0 mmol) with *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide **13** (1.0 mmol) and benzylamine (1.0 mmol). The base and solvent had a pronounced effect on these reactions with respect to yield.

Table 3
Synthesis of various 2-amino 3-substituted quinazolinone derivatives

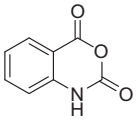
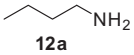
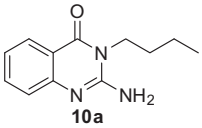
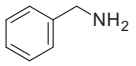
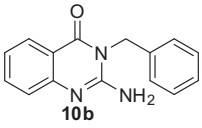
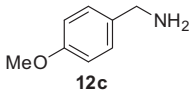
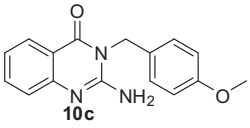
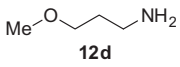
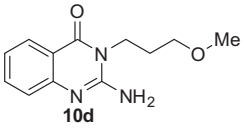
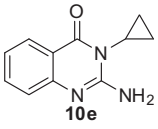
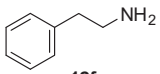
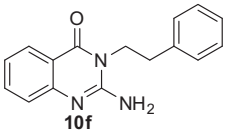
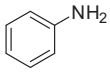
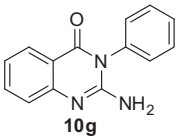
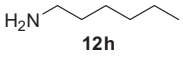
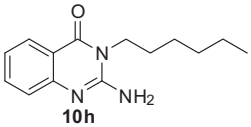
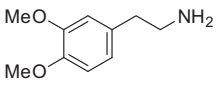
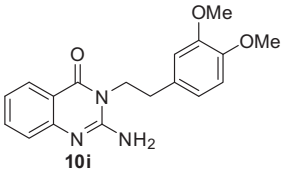
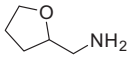
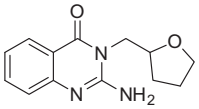
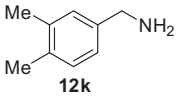
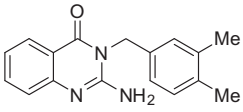
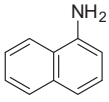
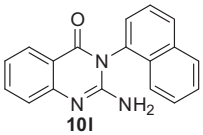
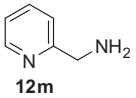
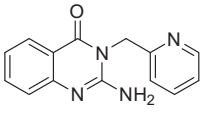
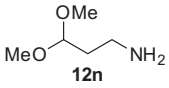
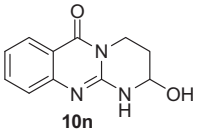
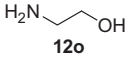
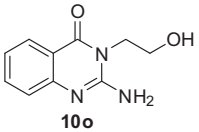
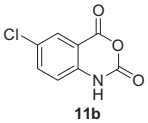
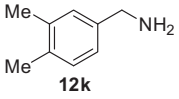
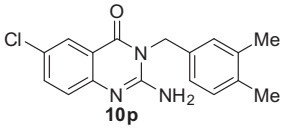
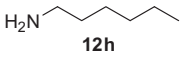
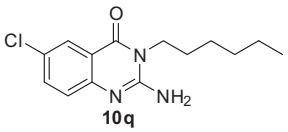
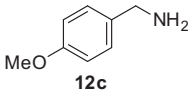
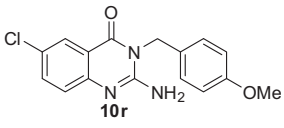
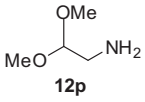
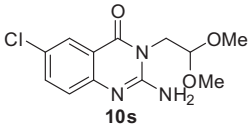
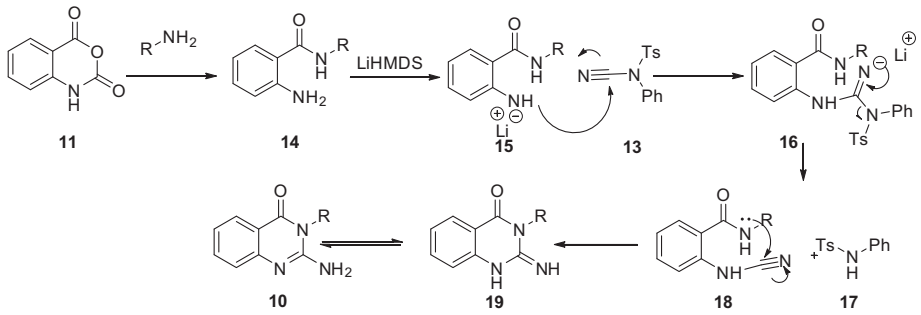
Entry	Isatoic anhydride	Amine	Product	Isolated yield (%)
1	 **11a**	 **12a**	 **10a**	71
2	**11a**	 **12b**	 **10b**	72
3	**11a**	 **12c**	 **10c**	67
4	**11a**	 **12d**	 **10d**	78
5	**11a**	 **12e**	 **10e**	77
6	**11a**	 **12f**	 **10f**	52
7	**11a**	 **12g**	 **10g**	47

Table 3 (*continued*)

Entry	Isatoic anhydride	Amine	Product	Isolated yield (%)
8	**11a**	 **12h**	 **10h**	70
9	**11a**	 **12i**	 **10i**	72
10	**11a**	 **12j**	 **10j**	60
11	**11a**	 **12k**	 **10k**	57
12	**11a**	 **12l**	 **10l**	36
13	**11a**	 **12m**	 **10m**	52
14	**11a**	 **12n**	 **10n**	68
15	**11a**	 **12o**	 **10o**	50
16	 **11b**	 **12k**	 **10p**	56
17	**11b**	 **12h**	 **10q**	59
18	**11b**	 **12c**	 **10r**	62
19	**11b**	 **12p**	 **10s**	69



Scheme 2. The proposed reaction mechanism for the formation of **10**.

The bases, namely K_2CO_3, DBU, DABCO, TEA, CS_2CO_3, and LiHMDS were screened. The best result was obtained when the reaction was performed in the presence of LiHMDS in 1,4 dioxane solvent (Table 2, entries 1–8), solvents like DMSO, DMF, THF, acetonitrile, toluene, and 1,4-dioxane were screened in the presence of LiHMDS. 1,4-Dioxane had proven to be the best solvent for this MCR (Table 1, entries 1–7).

We chose a variety of structurally diverse amines possessing a wide range of functional groups for our study to understand the scope and the generality of this MCR and the results are summarized in Table 3. The amines chosen for the study include aliphatic, aromatic, and hetero aromatic amines

When the reaction was conducted with 3,3-dimethoxypropan-1-amine **12n** the cyclized product 2-hydroxy-3,4-dihydro-1*H*-pyrimido[2,1-b]quinazolin-6(2*H*)-one **10n** was obtained via the formation of the 2-amino 3-substituted quinazolinone followed by intramolecular cyclization. The reaction when was conducted with Aromatic amines afforded lower yields compared to aliphatic amines.

The Scheme 2 represents a plausible mechanism for the three component reaction leading to the compound **10**. The nucleophilic attack of primary amine on the carbonyl group of isatoic anhydride followed by ring opening and subsequent decarboxylation will yield compound **14**. Deprotonation of aromatic amine **15** in the presence of a base followed by the nucleophilic attack to the nitrile group, **13** will yield imine **16**; subsequent cyclization followed by elimination of the *N*-phenyl tosyl group will yield intermediate **17**. Cyclization of compound **18** will yield compound **19**. The intermediate **19** will undergo tautomerization leading to the formation of **10**.

Conclusion

In conclusion, we have developed a novel multi-component reaction strategy for the synthesis of 2-amino 3-substituted quinazolinone in good yields from isatoic anhydride, amine, and electrophilic cyanating agent, *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide in a one pot process. The synthesis of 2-amino 3-substituted quinazolinone proceeded via a series of reactions such as ring opening, decarboxylation, dehydration, elimination, and heterocycloannulation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.040.

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