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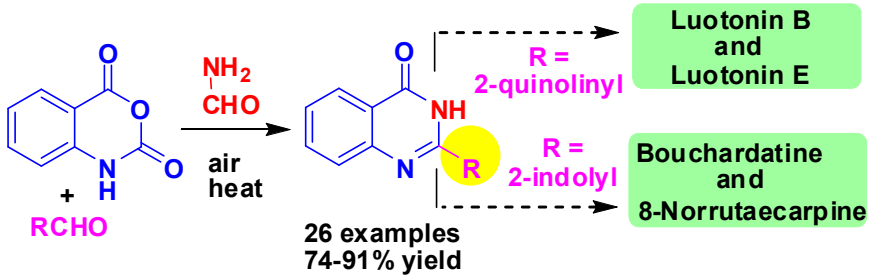

Formamide has been identified as an ammonia surrogate in the construction of quinazolin-4(3*H*)-one ring leading to several alkaloids.

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COMMUNICATION

A catalyst-free rapid, practical and general synthesis of 2-substituted quinazolin-4(3*H*)-ones leading to Luotonin B and E, Bouchardatine and 8-Norrutaecarpine

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A remarkably rapid but microwave / ultrasound / catalyst-free method has been developed for the construction of quinazolin-4(3*H*)-one ring using formamide as an efficient ammonia precursor and PEG-400 as an effective solvent. The methodology afforded various 2-substituted quinazolin-4(3*H*)-one derivatives in good yield via a three-component reaction of isatoic anhydride, aldehydes and formamide under open air. This single methodology was extended successfully to the synthesis of several alkaloids e.g. Leutonin B and E, Bouchardatine and 8-Norrutaecarpine.

Synthetic methodologies that allow a quicker and economical access to known and bioactive natural products are of great demand in modern organic synthesis as they can facilitate the research in medicinal/pharmaceutical and natural products chemistry.

The pyrrolo-quinazolinoquinoline alkaloids such as Luotonin B, and E[1] (**A** and **B**, Fig. 1) isolated from the aerial parts of a Chinese medicinal plant (i.e. *Peganum nigellastrum* Bunge) are used for the cure of several disease conditions like rheumatism, inflammation, abscesses, hepatitis etc. The quinazoline type alkaloid Bouchardatine[2,3] (**C**, Fig. 1) is from the rutaecarpine family whereas 8-Norrutaecarpine[3] (**D**, Fig. 1), a hybrid of rutaecarpine and luotonin A, contains the indolo-pyrroloquinazolinone ring. These quinazolin-4(3*H*)-one based alkaloids attracted our attention not only due to their promising pharmacological properties but also their intriguing chemical structures. Moreover, as part of our ongoing medicinal chemistry related programs we required a robust and continuous supply of these alkaloids and their analogues for the in-house pharmacological screening.

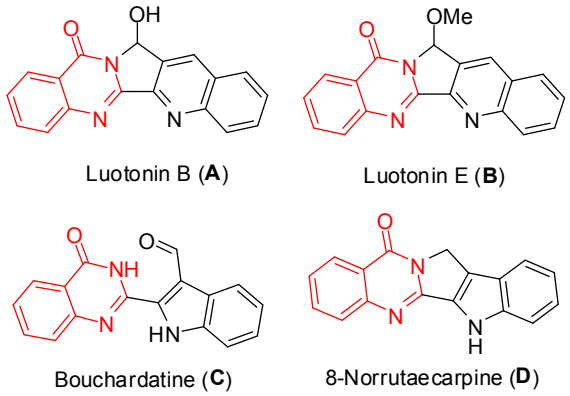

Fig. 1. Quinazolin-4(3*H*)-one based alkaloids.

In spite of their remarkable pharmacological properties not many methods have been reported for the synthesis of Leutonin B[1] and E,[1d-g] Bouchardatine[2,3] and 8-Norrutaecarpine.[3] While efforts have been devoted to establish various synthetic routes towards Leutonin B and E, only few are known for the remaining two alkaloids. Moreover, though several of these methods are elegant and interesting some of them are either not convenient or suitable for the quicker access to **A-D** (Fig. 1) due to the involvement of relatively longer synthetic routes and low overall yields. Notably, *o*-amino benzamide has been used as a key starting material in some of these syntheses that afforded the appropriate quinazolin-4(3*H*)-one intermediate for further reactions.[1d,e,g,3] This prompted us to design and explore a common and shorter route to **A-D** (Fig. 1) *via* constructing the required quinazolin-4(3*H*)-one ring in a straightforward manner followed by subsequent cyclization / other reactions (Scheme 1). Accordingly, we now report shorter syntheses of **A-D** *via* a new strategy involving the direct construction of quinazolin-4(3*H*)-one ring using isatoic anhydride (**1**), appropriate aldehydes (**2**) and formamide as an ammonia surrogate. While the use of a general strategy like this towards the synthesis of all these alkaloids has not been reported earlier, the strategy of constructing quinazolin-4(3*H*)-one ring using formamide as an ammonia surrogate is also not common in the literature.

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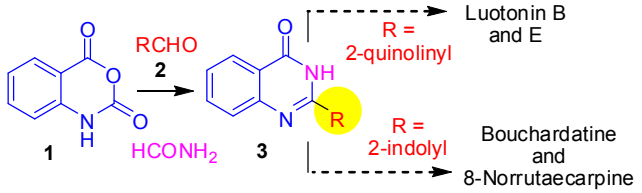
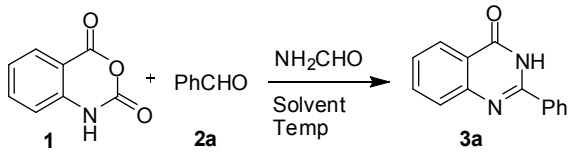


Scheme 1. Anticipated route to alkaloids **A-D** *via* construction of quinazolin-4(3*H*)-one ring

Various approaches have been reported for the synthesis of quinazolin-4(3*H*)-ones over the past few years,[4-8] the popular one being the reaction of anthranilamides with an aldehyde or orthoester in the presence of various promoting agents, such as $NaHSO_3$,[9] *p*-toluene-sulfonic acids / DDQ,[10] I_2,[11] $CuCl_2$ (3.0 equiv),[12] $FeCl_3$ (2.0 equiv),[13] and $Yb(OTf)_3$.[14] On other hand, one-pot three-component reactions of isatoic anhydride / anthranilic acid, orthoesters / aldehydes and amines / ammonium acetates in the presence of various catalysts leading to quinazolin-4(3*H*)-ones have been reported.[15-20] These catalysts include Nafion-H,[15] (α-Fe_2O_3)-MCM-41-l-prolinium nitrate,[16] I_2,[17] gallium trifluoro-methane-sulfonate,[18] ceric ammonium nitrate,[19] 100 U laccase from *trametes versicolor*,[20a] ultrasound based copper oxide[20b] etc. However, the use of expensive or complex metal or non-metal catalysts and longer reaction times are the major drawbacks of many of these methods. Moreover, some of the catalysts used are not easily accessible. Thus, development of an operationally simple, straightforward, and catalyst-free method was expected to be highly advantageous. Recently, we have demonstrated[21a] a catalyst-free synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones[21b,c] and quinazolin-4(3*H*)-ones *via* the reaction of isatoic anhydride, aldehyde, and urea as a ammonia surrogate in EtOH under open air conditions.[22] However, the method lacked in selectivity of product formation. We therefore decided to explore formamide as an ammonia surrogate in the selective synthesis of quinazolin-4(3*H*)-ones. Indeed, the earlier reports disclosing formamide as a source of ammonia in the synthesis of primary amides[23] prompted us to perform our study.

Several reactions were performed using isatoic anhydride (**1**), benzaldehyde (**2a**) and formamide as model substrates under various conditions to establish the optimal reaction conditions (Table 1). Initially, the reaction was performed in MeOH at 65 °C when trace of desired product **3a** was formed (entry 1, Table 1). Change of solvent to higher boiling EtOH or *n*-BuOH improved the product yield (entries 2 and 3, Table 1). Though the reaction did not proceed in chloroform (entry 4, Table 1), **3a** was isolated in 53 and 65% yield when toluene (entry 5, Table 1) and 1,4 dioxane (entry 6, Table1) was used. The use of other relatively low boiling solvents such as 2-propanol and 2-Me-THF afforded **3a** in poor yield (entries 7 and 8, Table 1). Notably, the duration of reaction was 8-50 h in all these cases. We then examined the use of a further high boiling solvent such as PEG-400 and to our surprise the reaction reached to completion within 35 min affording the high yield of **3a** (entry 9, Table 1). This observation clearly indicated that not only a polar protic solvent but elevated reaction temperature was necessary for the present reaction to proceed successfully in the forward direction (entries 1-3 vs 9, Table 1). We were delighted with this catalyst-free rapid synthesis of **3a** without using any microwave or ultrasound irradiation. To reduce the reaction time further the reaction was performed in neat under microwave irradiation (entry 10, Table 1). However the yield of **3a** was decreased (entry 9 vs 10, Table 1) due to the formation of an unknown side product. Since (i) the reaction rate was enhanced significantly in PEG and (ii) being an inexpensive, nontoxic and high boiling solvent, PEG has several advantages over other commonly used organic solvents, hence the reaction condition of entry 9 of Table 1 was used for further studies.

Table 1. Effect of conditions on the reaction of **1, 2a** and formamide.[a]



Entry	Solvent	Temp (ºC)	Time (h)	Yield[b] (%)
1	MeOH	65	48-50	Trace
2	EtOH	80	48-50	22[c]
3	n-BuOH	115	8-10	56
4	$CHCl_3$	60	48-50	--
5	Toluene	110	20-22	53[c]
6	1,4-Dioxane	105	20-24	65[c]
7	2- Propanol	85	20-24	32[c]
8	2-Me-THF	85	20-22	25[c]
9	PEG-400	120-125	35 min	91
10	Neat[d]	120	15-20 min	68

[a]Reaction was performed by using a mixture of **1** (1.0 equiv), **2a** (1.0 equiv) and formamide (1.0 equiv) in a solvent (4 mL) under open air. [b]Isolated yield. [c]No complete conversion of starting material observed. [d]The reaction was performed under microwave (300 W).

To check the generality of the present catalyst-free environmental friendly reaction a range of aliphatic, aryl and heteroaryl aldehydes were reacted with **1** under the optimized conditions (Table 2). The aliphatic aldehydes may contain groups like alkyl, cycloalkyl, alkylaryl etc (entries 7, 16, 17, 21 and 23, Table 2) whereas the aromatic aldehydes may contain various substituents like hydroxy, alkoxy, amine, halogens, phenyl, cyano, benzyloxy, etc on the aromatic ring (entries 2-6, 8, 9, 11-13, 15 and 18, Table 2). The aromatic aldehyde may be a simple benzaldehyde or α-naphthyl aldehyde (entry 1 and 14, Table 2). The heteroaryl ring of heteroaryl aldehydes may be furan, pyrrole, pyridine, thiophene, quinoline and indole (entries 10, 19, 20, 22, 24 and 25, Table 1). The reaction proceeded well in all these cases affording the desired quinazolin-4(3*H*)-ones (**3**) in good to excellent yields within short reaction time. Notably, the reaction afforded quinazolin-4(3*H*)-one (**3z**) when performed in the absence of an aldehyde for 90 min (entry 26, Table 2). All these observations clearly highlight the utility and robustness of formamide as an ammonia surrogate in the present catalyst-free and efficient synthesis of quinazolin-4(3*H*)-ones.

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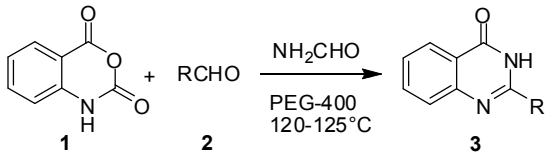
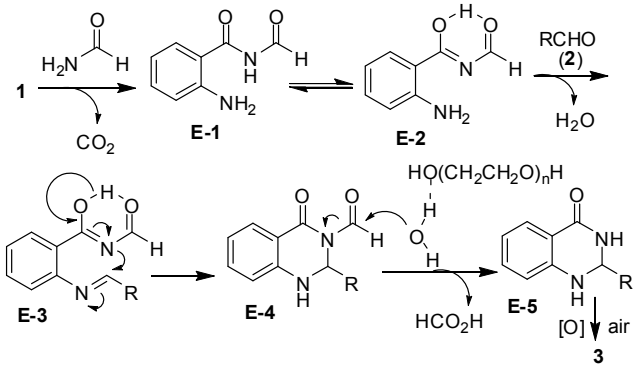
Table 2. Catalyst-free rapid synthesis of 2-substituted quinazolin-4(3*H*)-one derivatives (**3**).[a]



Entry	Aldehyde (**2**); R =	Time (min)	Product (**3**)	Yield[b] (%)
1	**2a**; Ph	35	**3a**	91
2	**2b**; C_6H_4OH-*p*	43	**3b**	84
3	**2c**; C_6H_4OMe-*p*	30	**3c**	87
4	**2d**; $C_6H_4NMe_2$-*p*	42	**3d**	85
5	**2e**; C_6H_4F-*p*	45	**3e**	92
6	**2f**; C_6H_4Ph-*p*	56	**3f**	81
7	**2g**; *n*-Pentyl	18	**3g**	88
8	**2h**; C_6H_4Cl-*p*	40	**3h**	83
9	**2i**; $C_6H_3Me_2$-*o*,*p*	42	**3i**	89
10	**2j**; Furyl	55	**3j**	74
11	**2k**; $C_6H_4Bu^t$-*p*	27	**3k**	84
12	**2l**; C_6H_4CN-*p*	50	**3l**	81
13	**2m**; C_6H_4OBn-*m*	47	**3m**	87
14	**2n**; α-Napthyl	32	**3n**	88
15	**2o**; $C_6H_2(OMe)_2$*m*,OMe-*p*	40	**3o**	79
16	**2p**; Ethyl	15	**3p**	93
17	**2q**; Cyclohexyl	20	**3q**	92
18	**2r**; C_6H_4Me-*m*	32	**3r**	85
19	**2s**; 2-Pyrrolyl	60	**3s**	76
20	**2t**; 4-Pyridinyl	55	**3t**	85
21	**2u**; *i*-Butyl	20	**3u**	91
22	**2v**; 2-Thienyl	46	**3v**	78
23	**2w**; $PhCH_2CH_2$	55	**3w**	76
24	**2x**; 2-Quinolinyl	45	**3x**	74
25	**2y**; 2-Indolyl	32	**3y**	80
26	No aldehyde	90	**3z** (R = H)	81

[a]Reaction was performed by using **1** (1.0 equiv), **2** (1.0 equiv) and formamide (1.0 equiv) in PEG-400 (4 mL) under open air. [b]Isolated yield.



Scheme 2. The proposed reaction mechanism for the formation of **3**.

The Scheme 2 represents a plausible mechanism for the present 3-component reaction leading to the compound **3**. The generation of intermediate **E-1** appeared to be the initial step of this reaction.[24a] Subsequent tautomerization of **E-1** to the enol **E-2** was facilitated by the intramolecular H-bonding in a six membered cyclic form. The amino group of **E-2** then reacts with the aldehyde[24b] **2** to give the imine **E-3** which on intramolecular cyclization afforded the intermediate **E-4**. The cleavage of –N-C(=O)- bond aided by H_2O (formed during the conversion of **E-2** to **E-3**) at elevated temperature afforded **E-5**. The ability of PEG to form H-bond with water is known in the literature and that its H-bond acceptor ability is similar to MeOH (though its H-bond donor ability is less than MeOH).[24c] Thus, the nucleophilicity of water molecule was greatly enhanced by the presence of PEG-400 via formation of H-bond between the oxygen atom of PEG and hydrogen atom of H_2O. Next, the oxidation of **E-5** in the presence of air afforded **3**. To gain further evidence on the intermediacy of **E-5** the MCR (multicomponent reaction) of **1**, **2a** and formamide was performed under inert atmosphere (in the absence of air) in PEG-400 at 120-125 ºC for 10 min (*cf* entry 9, Table 1). The isolation of 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**4a**), in addition to **3a** as a major product (**4a** : **3a** ~ 7:3) clearly indicated the intermediacy of **E-5** in the present reaction. Moreover, **4a** was converted to **3a** when the reaction was allowed to proceed for additional 25 min. This also suggested that formation of **E-5** is relatively a faster process whereas its oxidation to **3** is a slower one. Notably, the oxidative aromatization of 2,3-dihydroquinazolin-4(3*H*)-ones to the corresponding quinazolin-4(3*H*)-one analogues is a known process[9,12,25] and PEG-400 has been used as an effective solvent in several aerobic oxidation reactions.[24c] Overall, the role of PEG in the (i) deformylation step of **E-4** and (ii) aerobic oxidation of **E-5** at an elevated reaction temperature was the possible reason for the observed remarkable rate enhancement of the present catalyst free MCR in PEG-400.[24d,26]

Having developed a catalyst free rapid synthesis of quinazolin-4(3*H*)-ones we then applied this methodology for the synthesis of our target natural products i.e. Luotonin B and E (Scheme 3), and then Bouchardatine and 8-Norrutaecarpine (Scheme 4). Thus, the compound **3x** obtained via the reaction of isatoic anhydride (**1**), quinoline-2-carbaldehyde (**2x**) and formamide in PEG-400 at 120-125 °C for 45 min under open air (entry 24, Table 2) was treated with mesityllithium at -80 to -78 °C followed by DMF at -30 °C to afford the Luotonin B (**A**) in 71% yield.[1d] Luotonin E (**B**) was then prepared by treating Luotonin B with *p*-TSA in methanol at refluxing temperature for 3 h.[1d] Notably, the alkaloid **A** can also be transformed into Luotonin A via mesylation of the hydroxyl group of **A** followed by removal ot the resulting –OMs group in the presence of Pd/C.[27]

Similarly, the compound **3y** prepared via the reaction of isatoic anhydride (**1**) with 1*H*-indole-2-carbaldehyde (**2y**) and formamide in PEG-400 at 120-125 °C (entry 24, Table 2) was allowed to undergo Vilsmeier-Haak reaction[3] to provide Bouchardatine in 84% yield. Reduction of Bouchardatine with $NaBH_4$ followed by acid mediated dehydration produced 8-

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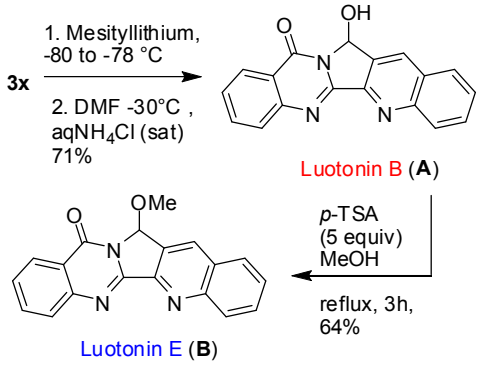
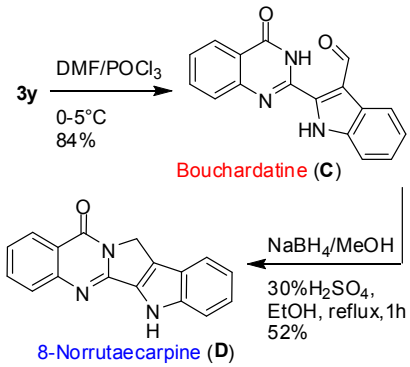


Scheme 3. Synthesis of Luotonin B (**A**) and Luotonin E (**B**) from quinazolin-4(3*H*)-one **3x**.



Scheme 4. Synthesis of Bouchardatine (**C**) and 8-Norrutaecarpine (**D**) from **3y**.

Norrutaecarpine in 52% yield.[3]

All the natural products synthesized e.g. alkaloids **A-D** were characterized by spectral data and compared with that reported earlier (see Table S-2 in the ESI). The selected ^{1}H and ^{13}C NMR signals of synthesized alkaloids **A-D** are shown in Fig.2. Thus, the ^{1}H and ^{13}C NMR signal appeared at δ 6.97 and 80.4 ppm in the respective spectra of **A** due to the –CH(OH)- moiety was correlated to that reported (i.e. δ 6.98 and 80.5 ppm) for Luotonin B.[1f] Similarly, **B** showed ^{1}H signals at δ 6.95 (CH) and 3.61 (OMe) due to the -CH(OMe)-group and ^{13}C signals at δ 87.0 (CH) and 56.3 (OMe) ppm for the same group that were correlated with the reported values i.e. δ 6.9 (CH) and 3.6 (OMe) in ^{1}H and δ 87.0 (CH) and 56.3 (OMe) ppm in ^{13}C NMR of Luotonin B.[1f] The aldehyde (-CHO) group of **C** appeared at δ 10.48 and 187.5 ppm in ^{1}H and ^{13}C NMR respectively that were compared with the corresponding NMR values (i.e. δ 10.48 and 187.5 ppm) reported for Bouchardatine.[3] The CH_2 moiety of **D** appeared at δ 5.03 and 57.0 ppm in ^{1}H and ^{13}C NMR respectively were compared with corresponding NMR values (i.e. δ 5.12 and 47.5 ppm) reported for 8-Norrutaecarpine.[3]

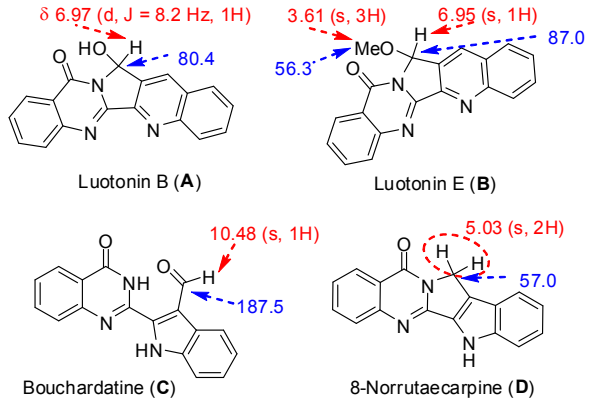


Fig. 2. Selected ^{1}H and ^{13}C NMR signals of synthesized alkaloids **A-D**

In conclusion, we have identified formamide as an efficient ammonia surrogate and PEG-400 as an effective solvent in the rapid construction of quinazolin-4(3*H*)-one ring for the first time. This strategy accomplished a practical and catalyst-free synthesis of various 2-substituted quinazolin-4(3*H*)-one derivatives via a three-component reaction of isatoic anhydride, aldehydes and formamide under open air. The notable advantages of this protocol include (i) simple operational procedure, (ii) shorter reaction time (iii) free from the use of microwave or ultrasound irradiation and (iv) good yields of products. This single methodology was extended successfully to the synthesis of several alkaloids e.g. Leutonin B and E, Bouchardatine and 8-Norrutaecarpine highlighting its immense utility in organic synthesis. Overall, this methodology is amenable not only for the generation of library of small molecules based on quinazolin-4(3*H*)-one framework but also for the synthesis of bioactive alkaloid natural products and their analogues.

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