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Glyoxylic acid in the reaction of isatoic anhydride with amines: a rapid synthesis of 3-(un)substituted quinazolin-4(3*H*)-ones leading to rutaecarpine and evodiamine

K. Raghavendra Rao [a], Akula Raghunadh [a], Ramamohan Mekala [a], Suresh Babu Meruva [a], T. V. Pratap [a], T. Krishna [a], Dipak Kalita [a], Eppakayala Laxminarayana [b], Bagineni Prasad [c], Manojit Pal [c,*]

[a] *Custom Pharmaceutical Services, Dr. Reddy's Laboratories Limited, Bollaram Road Miyapur, Hyderabad 500 049, India*
[b] *Sreenidhi Institute of Science and Technology (Autonomous), Yamnampet, Ghatkesar, Hyderabad 501 301, India*
[c] *Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India*

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ABSTRACT

A dual reactant/catalyst role of glyoxylic acid in the reaction of isatoic anhydride with various amines afforded a novel, robust and rapid synthesis of 3-(un)substituted quinazolin-4(3*H*)-ones. This metal catalyst-free reaction proceeds via an unusual and unexpected cleavage of C–C bond. A shorter and common route to two alkaloids, that is, rutaecarpine and evodiamine is also accomplished.

Development of shorter routes to the known and bioactive natural products via newly established methodologies is of high demand in modern organic synthesis. Indeed, these strategies allow quicker and economical access to these compounds for medicinal and other uses.

Rutaecarpine[1a] (**A**, Fig. 1), an indolopyridoquinazolinone alkaloid isolated from *Evodia rutaecarpa* and related herbs has shown a range of pharmacological properties including anti-thrombotic, anticancer, anti-inflammatory and anti-obesity activities.[1b,c] Evodiamine (**B**, Fig. 1) on the other hand belongs to quinazolin-carboline alkaloid isolated from the fruit of *Evodia rutaecarpa* and possesses diverse pharmacological properties such as resisting tumour, antinociception, weight losing, protecting heart and reducing blood pressure etc.[2] Both these alkaloids attracted our attention due to their promising anti-cancer properties. Indeed, evodiamine has shown strong cytotoxic effects against human cancer cells in addition to apoptosis induction, suppression of invasion and metastasis. In continuation of our efforts on identification of novel inducers of apoptosis[3] we required robust and continuous supply of these two alkaloids for our in-house pharmacological screen.

Since the isolation of these alkaloids, a number of methods have been reported for the synthesis of rutaecarpine[1b,4] and evodiamine.[5] While many of these methods are elegant and interesting several of them however, are either not convenient or not suitable for scale-up preparation due to the involvement of relatively longer synthetic routes and low overall yields. Notably, tryptamine has been used as a key starting material in some of these syntheses. Accordingly, we wondered if a new, shorter and common route to both **A** and **B** starting from common reactants, that is, isatoic anhydride (**1**) and tryptamine (**2a**) can be developed (Scheme 1). Indeed, the synthesis of **A** and **B** via a common intermediate is not known in the literature.

Our proposed strategy was mainly based on the elegant construction of 3-substituted quinazolin-4(3*H*)-one ring as a key step

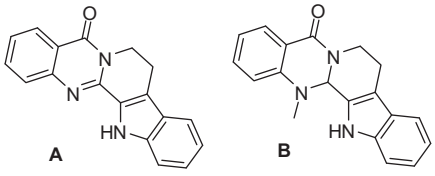

Figure 1. Rutaecarpine (**A**) and (±)-evodiamine (**B**).

* Corresponding author. Tel.: +91 40 6657 1500; fax: +91 40 6657 1581.
E-mail address: manojitpal@rediffmail.com (M. Pal).

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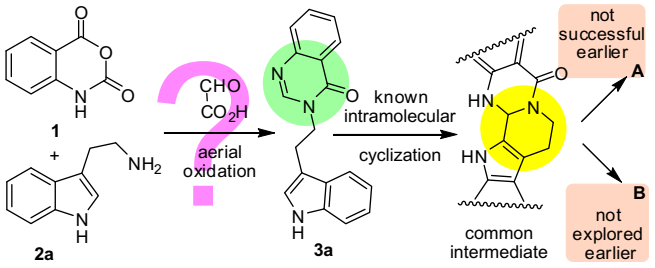
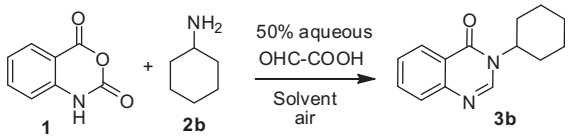


Scheme 1. Proposed synthesis of rutaecarpine (**A**) and evodiamine (**B**).

followed by a subsequent cyclization leading to the common precursor for **A** and **B**. A literature search revealed that the proposed strategy of constructing quinazolin-4(3*H*)-one ring using glyoxylic acid was not only an unknown fact but also unusual and unexpected as it involved the cleavage of a C–C bond. We therefore decided to expand the scope and generality of this novel methodology further. Herein we report our preliminary results on the rapid synthesis of 3-(un)substituted quinazolin-4(3*H*)-ones leading to rutaecarpine and evodiamine.

The 3-substituted quinazolin-4(3*H*)-ones are generally synthesized via a 3-component reaction of anthranilic acid, amines and ortho esters. The reaction proceeds in the presence of a range of catalysts such as $NaHSO_4$ or Amberlyst-15,[6] Yb(III)-resin,[7] $Yb(OTf)_3$,[8] $Bi(TFA)_3$-[nbp]$FeCl_4$ ionic liquid,[9] $La(NO_3)_3{\cdot}6H_2O$ or *p*-toluenesulfonic acid,[10] Keggin-type heteropoly acid under microwave irradiation,[11] $SnCl_4{\cdot}4H_2O$,[12] SiO_2–$FeCl_3$[13] and $Al(NO_3)_3{\cdot}6H_2O$.[14] However, the use of expensive metal or non-metal catalysts and longer reaction times are the main drawbacks of many of these methods. A catalyst-free synthesis of 3-aryl quinazolin-4(3*H*)-ones via the reaction of isatoic anhydride, formic acid and anilines under solvent-free conditions has been reported.[15] However, the method involved microwave heating and yields of products were not particularly high. We anticipated that the commercially available 50% aqueous glyoxylic acid could be a cheaper alternative to the formic acid (neat) used earlier. Moreover, like formic acid the glyoxylic acid also could play a dual role, that is, as a reactant as well as a catalyst. Accordingly, the reaction of isatoic anhydride (**1**), cyclohexyl amine (**2b**) and glyoxylic acid was used as a model reaction to establish the optimized reaction condition (Table 1). The reaction was initially performed in polar and protic solvents such as MeOH, EtOH and *n*-BuOH at their refluxing temperatures when the desired product **3b** was isolated in moderate to good yields (entries 1–3, Table 1). The reaction was almost suppressed in chloroform (entry 4, Table 1) but proceeded well in toluene (entry 5, Table 1). In all these cases the duration of the reaction was 8–50 h. We then examined the use of PEG-400 and to our surprise the reaction reached to completion within 12 min affording the high yield of **3b** (entry 6, Table 1). The reaction time was marginally reduced to 10 min when the reaction was performed under neat microwave irradiation (entry 7, Table 1). However the yield of **3b** was decreased (entry 6 vs 7, Table 1) due to the formation of an unknown side product. Being an inexpensive, polar, nontoxic and high boiling solvent, PEG has several advantages over other commonly used organic solvents. We therefore used the reaction condition of entry 6 in Table 1 for further studies.

Table 1
Reaction of **1**, **2b** and glyoxylic acid under various conditions[a]



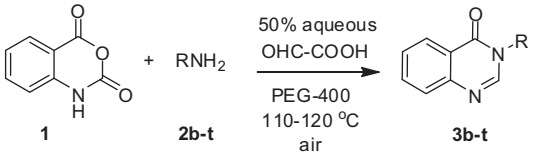
Entry	Solvent/temp	Time	Yield[b] (%)
1	MeOH/65 °C	48–50 h	44
2	EtOH/80 °C	48–50 h	52
3	*n*-BuOH/115 °C	8–10 h	76
4	$CHCl_3$/60 °C	48–50 h	10
5	Toluene/110 °C	20–22 h	70
6	PEG-400/110–120 °C	12 min	94
7	Neat[c]/120 °C	10 min	82

[a] Reactions were performed by using a mixture of **1** (1.0 equiv), **2b** (1.1 equiv) and glyoxylic acid (50% w/w in water) (1.1 equiv) in a solvent (3 mL) under open air.
[b] Isolated yield.
[c] Reaction was performed under microwave irradiation (300 W).

A range of aliphatic and aromatic amines as well as ammonia were reacted with **1** under optimized conditions (Table 2). The aliphatic amines may contain groups like alkyl, cycloalkyl, alkylaryl etc., (entries 1–3 and 5–12, Table 2) whereas the aromatic amines may contain various substituents like alkyl, haloalkyl, alkoxy, morpholino etc., on the aromatic ring (entries 13–19, Table 1). The reaction proceeded well in all these cases affording the desired 3-substituted quinazolin-4(3*H*)-ones (**3**) in good yields.

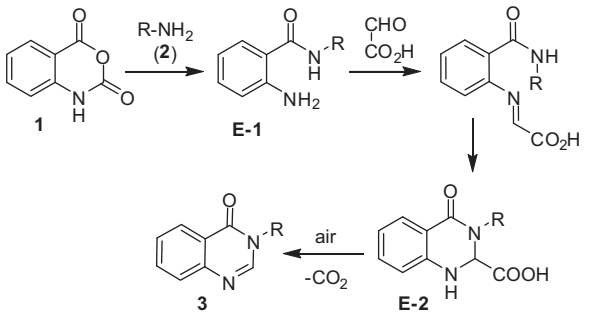
A plausible mechanism for the step-wise formation of 3-substituted quinazolin-4(3*H*)-ones (**3**) is shown in Scheme 2. The reaction of isatoic anhydride (**1**) with amine (**2**) affords the *o*-amino benzamide intermediate **E-1** which on reaction with glyoxylic acid gives the cyclic intermediate **E-2**. This step seemed to proceed via an imine formation between the $-NH_2$ group of **E-1** and the aldehyde moiety of glyoxylic acid[16] followed by intramolecular cyclization. The glyoxylic acid seemed to play a dual role, that is, as a reactant and a catalyst in this step. An oxidative decarboxylation of **E-2** in the presence of aerial oxygen affords the desired product **3**.[17]

Table 2
Synthesis of 3-substituted quinazolin-4(3*H*)-ones (**3**)[a]



Entry	Amine (**2**); R=	Time (min)	Products (**3**)	Yield[b] (%)
1	**2b**; Cyclohexyl	12	**3b**	94
2	**2c**; Cyclopropyl	15	**3c**	92
3	**2d**; Cycloheptyl	12	**3d**	90
4	**2e**; H[c,d]	8	**3e**	96
5	**2f**; Me[c,e]	8	**3f**	96
6	**2g**; n-Bu[c]	10	**3g**	94
7	**2h**; $CH_2(CH_2)_2OMe$	18	**3h**	93
8	**2i**;	20	**3i**	85
9	**2j**; CH_2Ph	22	**3j**	86
10	**2k**; $CH_2C_6H_4F$-*p*	25	**3k**	81
11	**2l**; $CH_2C_6H_4OMe$-*p*	22	**3l**	91
12	**2m**; CH(Me)Ph-(*S*)	25	**3m**	88
13	**2n**; Ph	20	**3n**	82
14	**2o**; C_6H_4Me-*p*	20	**3o**	84
15	**2p**; $C_6H_4Bu^t$-*p*	25	**3p**	89
16	**2q**; $C_6H_4CF_3$-*p*	30	**3q**	78
17	**2r**; C_6H_4Cl-*p*	30	**3r**	76
18	**2s**; C_6H_4OMe-*p*	25	**3s**	88
19	**2t**; C_6H_4(morpholino)-*p*	30	**3t**	83

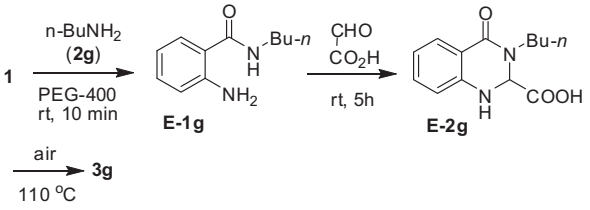
[a] Reaction was performed by using a mixture of **1** (1.0 equiv), **2b–t** (1.1 equiv) and glyoxylic acid (50% w/w in water) (1.1 equiv) in PEG-400 (3 mL) under open air.
[b] Isolated yield.
[c] Reaction was performed in a closed vessel without removing air.
[d] 28% aqueous NH_4OH was used.
[e] 40% aqueous $MeNH_2$ was used.



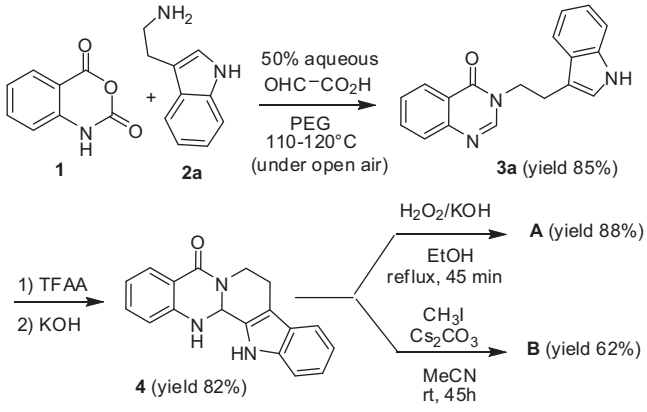
Scheme 2. Proposed reaction mechanism for the formation of **3**.

To gain further evidence on the proposed mechanism, the isatoic anhydride **1** was reacted with the amine **2g** in PEG-400 at room temp for 10 min (Scheme 3) when the amino amide intermediate **E-1g** was formed that was isolated and characterized by ^{1}H NMR, MS and HRMS. Then the glyoxylic acid was added and the mixture was stirred at room temp for 5 h. We were able to detect the formation of the intermediate **E-2g** that was supported by MS and HRMS data (see ESI). However, we failed to isolate pure **E-2g** due to its quick conversion to **3g** during the removal of PEG-400 at elevated temperature. Nevertheless, all these studies indicated the intermediacy of **E-1** and **E-2** in the present reaction.

Having developed a novel and catalyst-free rapid synthesis of 3-substituted quinazolin-4(3*H*)-ones we then applied this methodology for the synthesis of our target natural products, that is, rutaecarpine (**A**) and evodiamine (**B**) (Scheme 4). Thus isatoic anhydride (**1**) was reacted with tryptamine (**2a**) and glyoxylic acid in PEG-400 at 110–120 °C for 15 min under open air to give the desired product **3a** in 85% yield. The compound **3a** on treatment with TFAA followed by KOH afforded 13b,14-dihydrorutaecarpine **4** in 82% yield.[1a,18] Treatment of **4** with alkaline H_2O_2 afforded **A** in 88% yield whereas reaction of **4** with MeI in the presence of Cs_2CO_3 provided **B** in 62% yield. Notably, earlier attempts to convert **4** directly to **A** using oxidative coupling reagents such as $Hg(OAc)_2$, $FeCl_3$ and $Pb(OAc)_4$ were not successful as complex reaction mixtures were obtained in all these cases.[1a] Thus the present effort represents the first example of successful conversion of **4** into **A** and the method does not require the use of any metal catalyst. It is also mention worthy that our approach of converting **4** into **B** has not been explored earlier. Overall, our strategy of synthesizing **A** and **B** via a common intermediate **4** seemed to be attractive and may find a wide usage.



Scheme 3. Reaction of isatoic anhydride **1** with amine **2g**.



Scheme 4. Synthesis of rutaecarpine (**A**) and evodiamine (**B**).

In conclusion, we have demonstrated for the first time the use of glyoxylic acid in the reaction of isatoic anhydride with various amines to furnish a novel and metal catalyst-/microwave-free rapid synthesis of 3-(un)substituted quinazolin-4(3*H*)-ones. The glyoxylic acid played a dual reactant/catalyst role in this reaction which proceeded via the cleavage of a C–C bond. The potential of this methodology has been realized in developing a shorter, common and economical route to two known alkaloids, for example, rutaecarpine and evodiamine.

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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.2014.09.011.

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16. While the participation of carboxylic acid moiety (as described under microwave irradiation earlier, see Ref. 15) of glyoxylic acid in this step cannot be ruled out completely, this appeared to be less likely due to the (a) higher reactivity of the aldehyde moiety, (b) detection of **E-2** in the reaction mixture (see the text) and (c) absence of microwave irradiation.
17. In an alternative pathway the reaction may proceed via an initial formation of imine (resulted from the reaction of amine **2** with the glyoxylic acid) which on subsequent reaction with **1** may furnish **3**. However, we failed to detect the formation of this imine during the reaction even after several attempts.
18. While the synthesis of **4** was claimed by Horvath-Dora and Clauder earlier [see: Horvath-Dora, K.; Clauder, O. *Acta Chim. Acad. Sci. Hung.* **1975**, *84*, 93 (*Chem. Abstr.* **1975**, *82*, 171273)] the real structure of the **4** was corrected by Bergman and Bergman later (see: Bergman, J.; Bergman, S. *Heterocycles* **1981**, *16*, 347, see also Ref. 1a).