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α-Hydroxy acid as an aldehyde surrogate: metal-free synthesis of pyrrolo[1,2-*a*]quinoxalines, quinazolinones, and other N-heterocycles *via* decarboxylative oxidative annulation reaction†

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A metal-free and efficient procedure for the synthesis of pyrrolo[1,2-*a*]quinoxalines, quinazolinones, and indolo[1,2-*a*]quinoxaline has been developed. The key features of our method include the *in situ* generation of aldehyde from α-hydroxy acid in the presence of TBHP (*tert*-butyl hydrogen peroxide), and further condensation with various amines, followed by intramolecular cyclization and subsequent oxidation to afford the corresponding quinoxalines, quinazolinones derivatives in moderate to high yields.

Introduction

Pyrrolo[1,2-*a*]quinoxaline motifs are shown in a large number of natural products as well as in several molecules under clinical trials (Fig. 1). For example, the pyrrolo[1,2-*a*]quinoxaline core system is extensively utilized in pharmaceuticals due to its potential biological activities, including anti-bacterial, anti-infective, anti-inflammatory, anti-HIV, anti-malarial, 5-HTR affinity *etc.*[1] Furthermore, some of these derivatives have been utilized in electronic and optical fields.[2] Due to their structural prevalence, significant efforts have been devoted, and several synthetic strategies have been developed for the construction of these compounds.[3–5] Conventionally, 2-(1*H*-pyrrol-1-yl)aniline (**1a**) has been used as a starting material and is condensed with aldehydes[4e,f,m,n,p–s] or its equivalents to form the pyrrolo[1,2-*a*]quinoxaline derivatives.[4]

However, the existing methods suffer from several limitations in that they require tedious synthetic procedures, expensive transition metal catalysts, stoichiometric reagents, elevated temperatures, toxic solvents, and catalyst, *etc.* In addition to that, aldehydes are prone to convert into acids by aerial oxidation, which may cause decarbonylation, to avoid formation of additional side products inert condition required to carry out the experiment (Scheme 1).[6] Thus, it would be highly desirable to develop an environmentally benign method to synthesis of quinoxalines and its related derivatives.

Similarly, quinazolinone plays a major role in drugs and exhibits potential biological activities.[7] The substituted quinazolinones are associated with a range of biological and pharmacological activities such as an anti-inflammatory, anti-cancer, anti-fungal, anti-bacterial, *etc.* Additionally, numerous natural products contain the quinazolinone core unit, for example, L-Vasicinone, Rutaecarpine, Luotonin E, Bouchardatine, Tryptanthrin, and Methaqualone (Fig. 1).[8] Vast number of diverse methodologies has been developed during the past decades for the synthesis of these compounds.[9,10]

Decarboxylative coupling reaction has recently emerged as a green method to construct C–C bonds, in various reactions such as Heck, cross coupling, oxidative arylation, allylations, *etc.*,[11] However, most of the reactions utilized metal catalysts.[12] Due to expensive and toxicity of metal catalyst, it is highly required to design an environmentally benign method. Few reports were utilized the α-hydroxy acids as an aldehyde equivalent.[13] To the best of our knowledge there is no report related the direct synthesis of quinoxalines from α-hydroxy

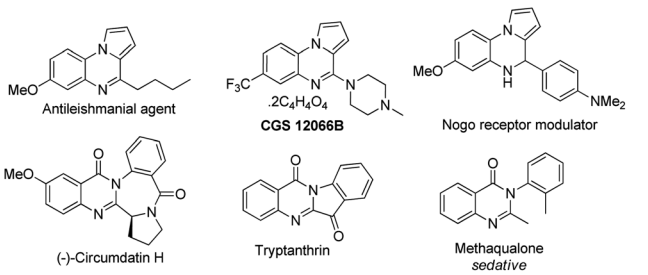

Fig. 1 Compounds containing pyrrolo[1,2-*a*]quinoxalines and quinazolinones.

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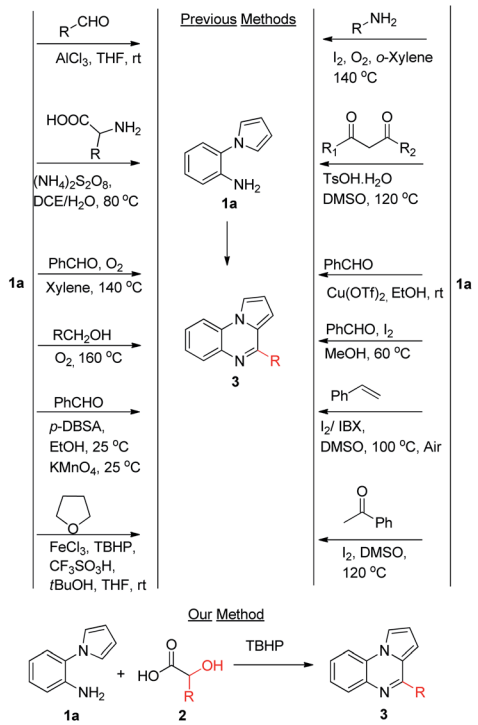


Scheme 1 Previous and our approaches.

acids as an aldehyde surrogate. In our efforts to develop privileged heterocycles *via* metal-free approaches,[14] herein we disclose a method to synthesize pyrrolo[1,2-*a*]quinoxalines and quinazolinones by utilizing α-hydroxy acids as aldehyde equivalent in the presence of TBHP.

Results and discussion

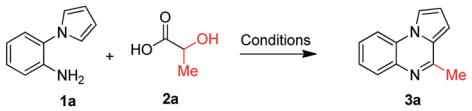
In our preliminary investigation, we selected 2-(1*H*-pyrrol-1-yl) aniline (**1a**, 1.0 equiv.) and lactic acid (**2a**, 5.0 equiv.) as model substrates to optimize the reaction condition, and the results are summarized in Table 1. By using $FeCl_3$ (30 mol%) as the catalyst and *tert*-butyl hydrogen peroxide (TBHP, 5.0 equiv., 70% in H_2O) as the oxidant in chloroform at 70 °C under the oxygen atmosphere, the corresponding pyrrolo[1,2-*a*]quinoxaline (**3a**) obtained in 23% yield (Table 1, entry 1).[4l] Replacing the catalyst to $CuSO_4$ given the similar result (entry 2). Surprisingly, absence of a metal catalyst successfully generated the expected product **3a** in 28% yield (entry 3). Furthermore, the product yield was increased to 52% when we, switched the solvent into dichloroethane (DCE, entry 4).

These above results encouraged us to screen various types of oxidants such as Oxone, sodium persulfate, and potassium persulfate, which unfortunately failed to form the desired product (entries 5–7). Similarly, replacing TBHP with other peroxide oxidants led to catalyze the reaction, albeit with slightly lower yields (entries 8–10). Gratifyingly, decreasing the equivalence of TBHP to 4.0 equiv. and increasing the temperature to 80 °C, **3a** was obtained in 76% yield (entry 12). To improve the yield of the product, the reaction was screened with various solvents such as DMSO, water, THF, toluene, and acetone (entries 13–17). But, unfortunately, other solvents failed to improve the yield of the reaction. Altering the temperature led to slightly lower the yield (entry 18). We concluded that the optimized conditions for the decarboxylative condensation followed by annulation reaction was **1a** (1.0 equiv.), **2a** (5.0 equiv.), and TBHP (4.0 equiv.) in DCE at 80 °C.

With the optimized reaction conditions in hand, we expanded the scope of the reaction and with various other hydroxyl acids and amine derivatives (Table 2). Different α-hydroxy acids were investigated with **1a** and equivalent products were obtained in moderate to good yields. When we moved from aliphatic equivalent to aryl equivalent; (here the mandelic acid, equivalent of benzaldehyde) was tolerated and furnished the expected product (**3b**) in good yield (56%).[3c] Likewise, aliphatic substituted hydroxy acids afforded the pyrrolo[1,2-*a*]quinoxaline derivatives in good yields. 2-Methyl-2-hydroxypropionic acid (2-methyllactic acid) equivalent of acetone, 2-methyl-2-hydroxybutanoic acid equivalent of 2-butanone underwent the reaction smoothly and provided the expected products (**3c** & **3d**) in moderate yields.[5b,d]

Interestingly, phenyllactic acid also produced the acetophenone derivative (**3e**, 65%) in good yield.[4o] This may be because benzylic protons are over-oxidized by TBHP. Moreover, the

Table 1 Optimization of reaction conditions[a]



S. no.	Solvent	Temp. (°C)	Oxidant (5.0 equiv.)	Time (h)	Yield[b] (%)
1[c]	$CHCl_3$	80	TBHP	20	23[e]
2[d]	$CHCl_3$	80	TBHP	20	24[e]
3	$CHCl_3$	80	TBHP	12	28[e]
4	DCE	70	TBHP	12	52
5	DCE	70	Oxone	36	NR
6	DCE	70	$Na_2S_2O_8$	36	NR
7	DCE	70	$K_2S_2O_8$	36	NR
8	DCE	70	H_2O_2	24	48
9	DCE	70	DTBP	24	<10
10	DCE	70	DCP	24	37
11	DCE	80	TBHP	12	63
12	DCE	80	TBHP[f]	12	76
13	DMSO	80	TBHP[f]	24	<10
14	H_2O	80	TBHP[f]	24	30
15	THF	80	TBHP[f]	24	NR
16	Toluene	80	TBHP[f]	24	33
17	Acetone	80	TBHP[f]	12	SR
18	DCE	90	TBHP[f]	10	71

[a] Reaction conditions: 2-(1*H*-pyrrol-1-yl)aniline **1a** (1.0 equiv.), lactic acid **2a** (5.0 equiv.), solvent 2.0 mL, stirred at mentioned temperature. [b] Isolated yield. [c] 30 mol% $FeCl_3$ used as a catalyst. [d] 30 mol% $CuSO_4$ used as a catalyst. [e] Performed under oxygen atm. [f] 4.0 equiv. of TBHP (*tert*-butyl hydrogen peroxide) used, DTBP: di-*tert*-butylperoxide, DCP: dicumyl peroxide, NR = no reaction, SR = side reaction.

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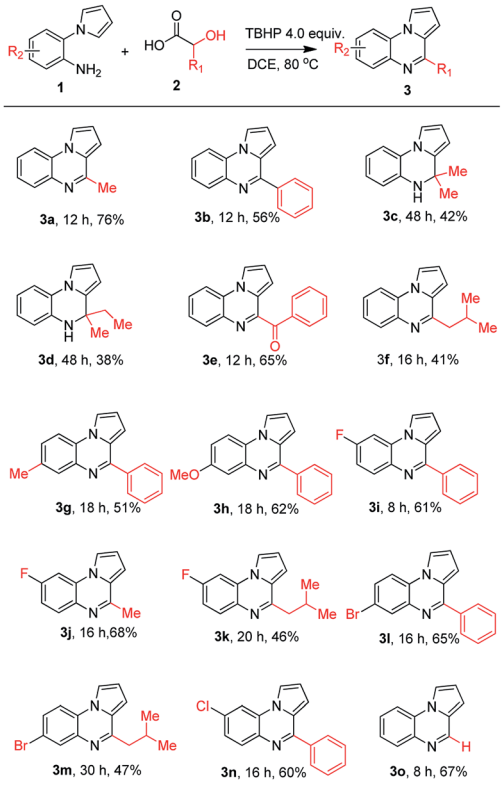
Table 2 Synthesis of pyrrolo[1,2-*a*]quinoxaline derivatives[a]



[a] Reaction conditions: all the reactions were performed using SM (1.0 equiv.), α-hydroxy acid (5.0 equiv.), TBHP (4.0 equiv.), and DCE (2.0 mL) stirred at 80 °C.

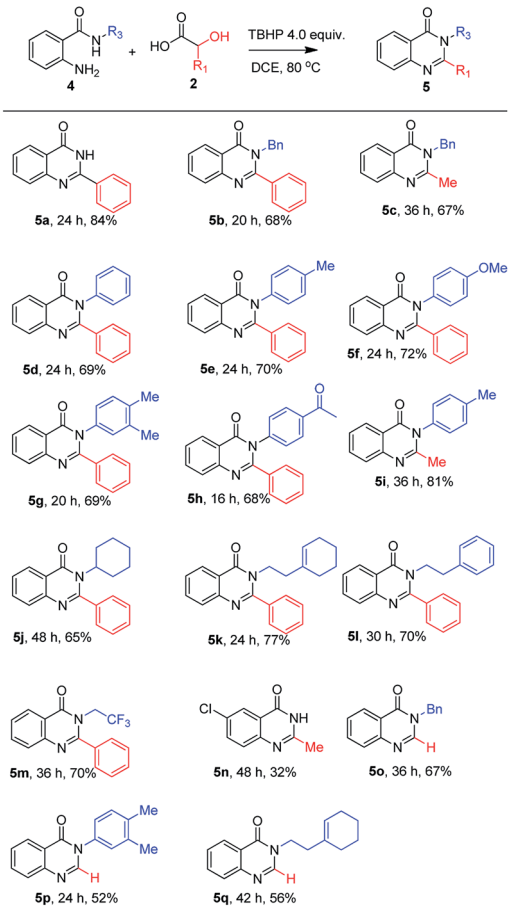
reaction of amine **1a** with leucic acid is an equivalent of 3-methylbutanal, smoothly underwent the reaction generated the corresponding product **3f** in moderate yield.[4h]

Later, we investigated various substituted aniline derivatives. Substrate containing methyl, and methoxy substituted aniline derivatives were compatible with this transformation and produced the respective products **3g**, **3h** in good yields.[3c] It was found that aniline containing the electron-withdrawing groups such as F, Br, and Cl could be amenable to the reaction, providing their equivalent products in good yields. Fluoro substituted amine was well tolerated under the present condition and afforded the corresponding quinoxalines in good yields. Both mandelic and lactic acid are furnishing the desired products **3i**, **3j** in good yields.[3c,5a] To synthesis products of **3a**, and **3j** acetaldehyde surrogate is required and acetaldehyde difficult to handle due to polymerization. Also, some of the reported methods are required either very high temperature, metal catalyst or strong acidic condition and so on.

Leucic acid also reacted smoothly and provided the final product **3k** in moderate yield. Similarly, both Br and Cl substituents furnish the corresponding products (**3l–n**) in good yields under the standard reaction condition.[5b] In general, isovaleraldehyde is required to condense with 2-pyrrolyl aniline to obtain the products **3f**, **3k**, and **3m**. But only one dihydro derivative was synthesized by using the above aldehyde.[5d] On the other hand, only product **3f** was previously synthesized by using equivalent amino acid (leucine).[4h] Besides, glycolic acid, which was used as a one-carbon source, also proven to be appropriate candidate, reacted quite well under the optimal reaction condition, and provided pyrroloquinoxaline **3o** in very good yield (67%).[4a]

Subsequently, we have expanded the scope of the decarboxylative condensation reaction with various anthranilamide derivatives and different α-hydroxy acids to synthesize quinazolinone derivatives. As shown in Table 3, we found that various functionalized anthranilamides successfully underwent this decarboxylative condensation to afford the expected products in good to excellent yields. For example, mandelic acid with anthranilamide produced the target product **5a** in excellent yield (84%).[10a] Substrates bearing *N*-benzyl efficiently engaged and produced the products **5b–c** in good yields.[9z,10b] A wide range 2-aminophenylbenzamides were synthesized which are compatible with standard conditions. Likewise, 2-amino-*N*-phenyl benzamide reacts with mandelic acid to generate the corresponding product **5d** in 69% yield.[10i]

Table 3 Synthesis of quinazoline derivatives[a]



[a] Reaction conditions: all the reactions were performed using SM (1.0 equiv.), α-hydroxy acid (5.0 equiv.), TBHP (4.0 equiv.), and DCE (2.0 mL) in stirred at 80 °C.

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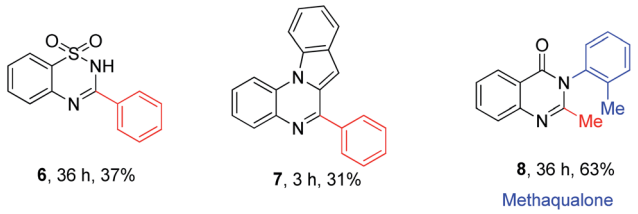
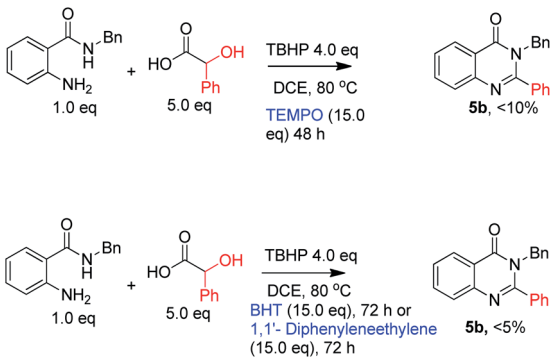


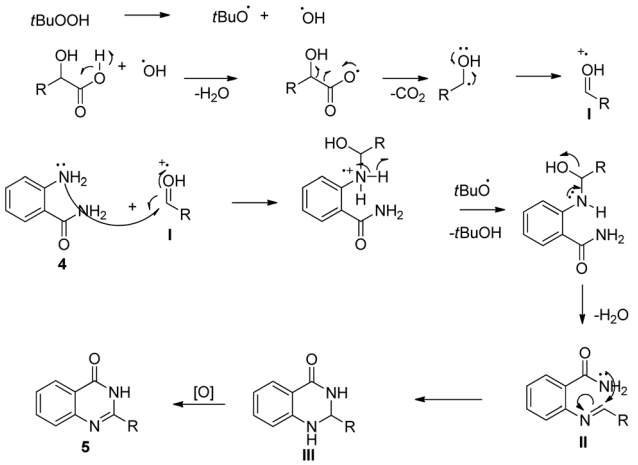
Scheme 2 Synthesis of other derivatives.

Further, similar results were obtained with phenyl ring containing methyl, methoxy, acetyl, dimethyl substituted anthranilamides which react with mandelic acid to afford expected quinazolinone derivatives (**5e–i**) in good yields.[10e,i,j] Also, *N-p*-tolyl-anthranilamide reacts with lactic acid to furnish the corresponding product **5i** in high yield as 81%.[10g] Besides, cyclohexyl, ethyl cyclohexene, ethylphenyl, trifluoroethyl protected amides also provided expected products (**5j–m**) in good yields.[10c,f,h] Similarly, the chloro substituted anthranilamide ring also delivered the product **5n** in moderate yield.[10d] Moreover, we applied the optimal condition to glycolic acid, which reacted with various 2-aminobenzamides to provide the expected quinazolinone products (**5o–q**) in good yields.[14b] To synthesis of substituted quinazoline derivatives such as **5o**, **5p**, and **5q**, the reported methods requires harsh reaction conditions such as higher temperature, toxic solvent, longer reaction time, and so on.

After investigating the scope with various anthranilamides, we next tested the generality of the decarboxylative condensation reaction with various amine partners (Scheme 2). For example, the 2-aminobenzenesulphonamide with mandelic acid produced the target sulfonamide condensed product **6** with moderate yield.[9x] The reaction between 2-(1*H*-indol-1-yl) aniline and mandelic acid under the optimized reaction condition produced indolo[1,2-*a*]quinoxaline (**7**) albeit in lower yield.[5b] Besides, under the standard conditions, we synthesized one of the best-selling sedative-hypnotic drug Methaqualone (**8**), which was obtained by the reaction between suitable substituted anthranilamide with lactic acid, which acts as an acetaldehyde equivalent to provide the natural product Methaqualone **8** in 63% yield.[14b]



Scheme 3 Control experiments.



Scheme 4 Possible reaction mechanism.

To gain more insight into the reaction mechanism, we have carried out the control experiments shown in Scheme 3. Mixing the reaction with the radical quencher TMEPO (15.0 equiv.) given the **5b** in less than 10% yield. Other radical scavengers such as BHT (15.0 equiv.) & 1,1-diphenylethylene (15.0 equiv.) both are completely inhibiting the reaction and less than 5% product only obtained. The above radical scavenger experiments reveal that the reaction occurs *via* radical formation.

Based on the experimental results, the possible mechanism for the formation of quinazolinone is depicted in Scheme 4. Initially, TBHP is fragmented into a *t*-butoxide radical and a hydroxyl radical. Then, the hydroxyl radical reacts with α-hydroxy acids to form the aldehyde equivalent **I** by the elimination of both CO_2 and H_2O. Then, the amine **4** reacts with **I** to afford the imine intermediate **II** *via* condensation with *t*-butoxide radical and yields water as a side product. The dihydro aminal **III** is generated from **II**, through intramolecular cyclization and product **5** is formed by oxidation.

Conclusion

We have developed a TBHP mediated, mild, and efficient approach to synthesis of various quinoxalines, quinazolinones, and indoloquinoxaline derivatives *via* decarboxylation followed by condensation using α-hydroxy acids as carbonyl source. The reaction proceeds in the absence of metal catalyst to afford the expected products in moderate to high yields. A series of substituted 2-amino benzamides are well suited in this process. Based on the control experimental results, a possible reaction mechanism suggests, the reaction occurs *via* radical mechanism. By utilizing this methodology, we have synthesized the bioactive natural product (Methaqualone) in good yield.

Experimental section

General information

^{1}H NMR spectra were recorded on a Jeol RESONANCE ECZ 400S (400 MHz). Chemical shifts are reported in ppm from

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tetramethylsilane (TMS) with the solvent resonance resulting from incomplete deuteration as the internal reference ($CDCl_3$: 7.26 ppm) or relative to TMS (δ 0.0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, dd = doublet of doublet, td = triplet of doublet), coupling constants (Hz), number of protons. ^{13}C NMR spectra were recorded on a Jeol RESONANCE ECZ 400S (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: 77.16 ppm). High-resolution mass spectrometry was performed with on LCQ Fleet-Thermo Scientifics. All reactant or reagent was purchased from Aldrich, TCI, Alfa Aesar and Acros, and were directly used without further purifications. Silica gel column chromatography was performed with Silica Gel of Kieselgel 60 F_{254} plate (Merck).

General procedure for the synthesis of heterocyclic compounds

A solution of 2-(1*H*-pyrrol-1-yl)anilines (1.0 equiv.) or 2-aminobenzamides (1.0 equiv.), α-hydroxy acids (5.0 equiv.), TBHP (70% in H_2O, 4.0 equiv.) and DCE (2.0 mL) was stirred at 80 °C for particular times (see the individual substrates at the manuscript). The reaction progress was monitored by TLC. Then, 10 mL of NH_4Cl was added to the reaction mixture and extracted with EtOAc (15 mL × 3). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel by using hexanes/ethyl acetate as eluent to afford the pure product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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