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DOI: 10.1039/C6NJ03907C

Journal Name

ARTICLE

Bioorganopromoted Green Friedländer : A versatile new Malic acid promoted solvent free approach to multisubstituted quinolines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The discovery of a new, malic acid promoted, eco-friendly Friedländer approach to varied multisubstituted quinolines is disclosed. To the best of our knowledge this is the first report on the use of malic acid, classified as one of the 12 biobased hot molecules by US Department of Energy, as an organopromoter in organic synthesis and includes many benefits like wide substrate scope, solvent free ambient reaction conditions, short reaction times, operational simplicity, cost effectiveness, high atom economy, and good to excellent yields, recylability of the organopromoter, making it a valuable green alternative to existing methods. The versatility and practicability of the developed method was further established by its successful application towards the targeted synthesis of few important quinoline molecules and successful scale up.

Introduction

Many of the traditional synthetic methodologies have wide applications but are not in consonance with green chemistry principles. However with the growing awareness for the need to prevent harm to the environment, the development of more environmentally acceptable processes in organic synthesis have become imperative.[1]

Friedländer,[2,3] a two component reaction (2-CR), between an o-acyl anilines and carbonyl compounds containing an α-methylene group to obtain polysubstituted quinolines, is one such important synthetic protocol which was discovered more than 100 years back, but remains as relevant as before.[3-5]

Quinoline is an important heterocyclic scaffold with immense applications in diverse fields ranging from material chemistry[6] to medicinal chemistry[7-14] (Figure 1). However nowhere its role is more well defined than in medicinal chemistry.[10] The prominence of quinoline motif in antimalarial drug development is well documented.[11] However in recent years quinolines have also gained recognition as an important privileged scaffold for the development of new therapeutics in other disease areas[12] particularly cancer[13] and tuberculosis.[14] As a consequence the discovery of more efficient and versatile new routes for the synthesis of quinolines remains of the hot areas in organic synthesis.[15,16] Though a variety of methods for the for the synthesis of quinolines are known,[3-5, 14,15] Friedländer annulation remains by far one of the most popular and useful methods for the synthesis of quinolines, as evidenced by the

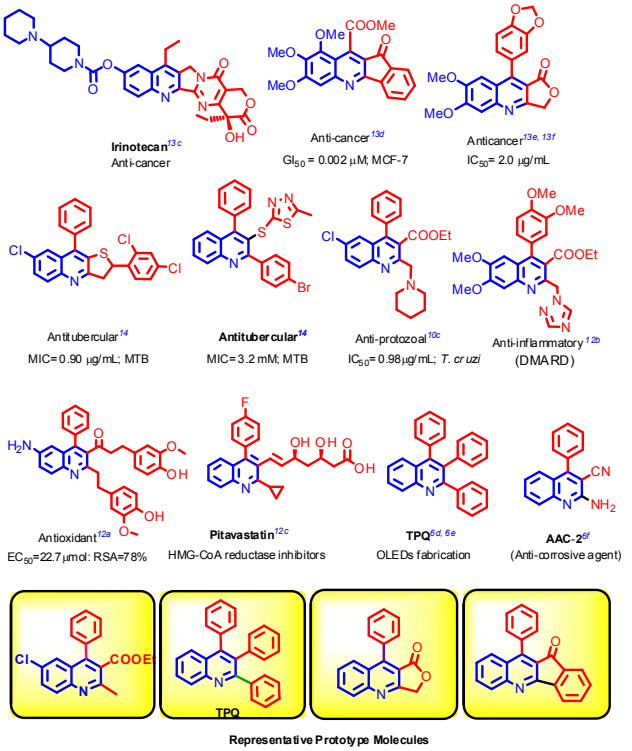

Figure 1. Some important 2,3,4-trisubstituted quinolines and synthesized prototypes from present work

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large number of recent reports on the Friedländer synthesis of quinolines. Friedländer annulation remains by far one of the most popular and useful methods for the synthesis of quinolines, as evidenced by the large number of recent reports on the Friedländer synthesis of quinolines.[5,18-20]

However, many of these Friedländer based approaches are not in consonance with the principles of green chemistry in as they involve the use of toxic catalysts, volatile organic solvents and harsh reaction conditions.5,18 This has prompted the search for eco-friendly Friedlander protocols leading to the development of a number of eco-compatible Friedlander approaches in recent years.[19,20] Though many of these methods are quite useful, they do suffer from drawbacks like use of expensive catalysts, high reaction temperature, long reaction times, operational complexity etc. To better illustrate this issue we examined two important eco-friendly methods reported in the literature. One report is that of C. Najera *et al* [19d] who used 1,1'-Binaphthalene-2,2'-diamine-derived prolinamide as organocatalyst. However this organocatalyst is highly expensive and not available commercially. Also the reaction time is quite long. Another important paper in this context is that of G-W. Wang and co-workers[20c] who reported the synthesis of polysubstituted quinolines in the presence of TsOH. However this method uses one equivalent of the organocatalyst at high temperature (100 °C).This necessitates the uninterrupted pursuit of better methods which are greener, more efficient and easier to operate.

Organocatalysis is one of the fastest growing areas in synthetic chemistry in the last few years, due to the innate benefits involved in using small organic molecules of biological origin as promoters, which are typically non-toxic, insensitive to moisture and air, cost-effective, easily available, efficient and selective.[21,22] Their potential advantages become all the more relevant in context of green synthesis since the real benefit of organopromoters is best realized when used in combination with green solvents or solvent free conditions.[23]

Organic acids of biological origin could serve as ideal green replacements[24] for mineral acid and metal or non-metal Lewis acid promoters in organic synthesis. However, surprisingly they remain largely under-utilized and underexplored.

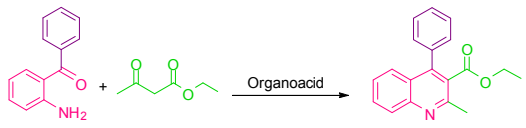
Malic acid, a C-4 dicarboxylic, α-hydroxy acid, is recognized as an important bioorganic molecule - listed as one of the 12 biobased hot molecules by US Department of Energy.[25-26] However its use in organic synthesis largely remains unexplored. The opening up of new possibilities for commercial production of malic acid, through microbial bioconversion of a cheap and abundant bio-renewable feedstock like glycerol, [27] could serve as a catalyst for exploration of organic acid as a green promoter and building block in chemical synthesis.

Consequently in our continued pursuit towards the development of novel green synthetic routes[28] for the construction of biologically important small heterocycles, we became interested in the design of a new eco-friendly, efficient and versatile, malic acid catalysed, Friedländer protocol for the synthesis of multisubstituted quinolines.

Results and Discussion

In our quest to design an ideal green methodology for the synthesis of polysubstituted quinolines using the Friedländer strategy, we decided to explore biobased organic acids as potential ecofriendly bioorganocatalyst for promoting this reaction.

Table 1. Screening of Organoacids



1 2 3

Entry	Organoacid (50 mol %)	Time (h)	Yield of 3[b] (%)[c]
1	Citric acid	4	79
2	Malonic acid	4.5	65
3	Tartaric acid	4	62
4	Benzoic acid	8	57
5	Cinnamic acid	8	50
6	Mandelic acid	7	61
7	Malic acid	1.2	85
8	Acetic acid	8	43
9	Oxalic acid	4	82
10	Ascorbic Acid	8	58
11	Succinic Acid	8	49
12	Fumaric Acid	8	58
13	No promoter	8	Trace

[a] All reactions were carried out with **1** (1 mmol) and **2** (1.1 mmol) in neat conditions under air; [b] M.P. of compound **3** was found to be 92-95 °C (Reported 93 °C) [17b]; [c] Isolated yields

We chose a model Friedländer experiment involving the reaction of 2-amino benzophenone with ethyl acetoacetate at 50 °C under solvent free conditions, for screening the efficacy of different organic acids as catalysts (Table 1). It was observed that among the 13 organic acids screened, malic acid gave the best result leading to the formation of the desired 2,3,4-

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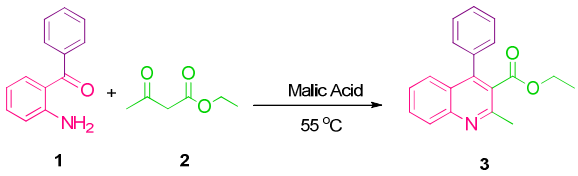
trisubstituted quinoline in 85 % yield in about 1.2 hours (Table 1, entry 7).

This superior performance of malic acid could be rationalised in terms of its structure. Malic acid being an alpha hydroxy acid is a stronger acid than normal carboxylic acids. Its chemical structure facilitates the formation of an internal hydrogen bond between the hydrogen at the hydroxyl group and one of the oxygen atoms of the carboxylic group. Due to the "occupation" of electrons of the carboxylic oxygen in the hydrogen bonding, the acidic proton is held less strongly, as the same electrons are used in bonding with hydrogen too. So the pK_a of malic acid is lower than its non-hydroxyl analogs.[29]

Table 2. Optimization of malic acid loading[a]



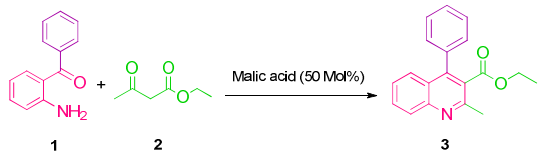
Entry	Malic acid (mol%)	Time(h)	Yield of 3 (%)[b]
1.	5	8	30
2.	10	8	45
3.	25	8	70
4.	50	2	96
5.	75	2	96
6.	100	2	96

[a] All reactions were carried out with 1 (1 mmol) and 2 (1.1 mmol) in neat conditions under air; [b] Isolated yields

Once malic acid had been identified as the best organoacid for promoting this reaction, we turned our attention towards optimization of the amount of malic acid needed for obtaining the best yield of quinoline **3**. A series of experiments were conducted using different quantities of malic acid wherein it was observed that use of 50 mol% malic acid gave the best result. While reducing the amount of malic acid led to a big decrease in yield and increase in reaction time (Table 2, entries 5 and 6) increased promoter loading led to no change in yield or time (Table 2, entries 1-3).

Next we investigated the effect of reaction temperature on the course of the reaction. It was observed that a 5 °C increase in temperature from 50 °C to 55 °C led to a marked increase in yield from 85% to 96% (Table 3, entry 4). On further increasing the temperature till 70 °C no marked change was noticed, however at higher temperatures a gradual decrease in yield, was observed (Table 3, entries 7 and 8).

Table 3. Optimization of reaction temperature[a]

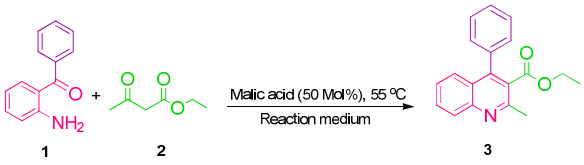


Entry	Temp (°C)	Time	Yield of 3 (%)[b]
1.	25	8 h	30
2.	40	8 h	45
3.	50	1.2 h	70
4.	55	55 min	96
5.	60	55 min	96
6.	70	45 min	96
7.	80	40 min	89
8.	100	35 min	85

[a] All reactions were carried out with **1** (1 mmol) and **2** (1.1 mmol) in neat conditions under air; b Isolated yields

Finally the model experiment was conducted in a variety of green solvents and in solvent free conditions in order to identify the best medium for carrying out this reaction (Table 4). From these set of experiments we observed that the reaction proceeds best in solvent less neat conditions (Table 4, entry 7).

Table 4. Identification of best reaction medium[a]



Entry	Reaction medium	Time (h)	Yield of 3 (%)[b]
1.	Water	8	Trace
2.	Water/CTAB	8	33
3.	Glycerol	8	21

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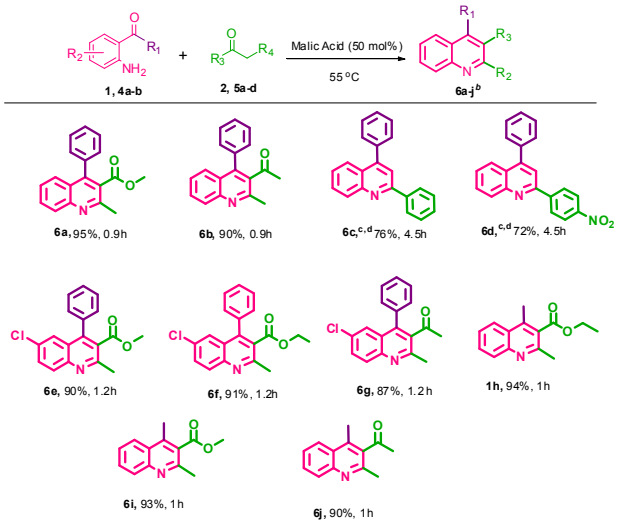
4.	PEG	8	Trace
5.	Ethanol: Water 4:1	8	67
6.	Ethanol	2	88
7.	Neat	0.9	96
8.	Methanol	4	82

[a] All reactions were carried out with **1** (1 mmol) and **2** (1.1 mmol) under air; [b] Isolated yields

With the optimized reaction conditions in hand we set out to examine the substrate scope of the developed synthetic strategy by reacting different *o*-acyl anilines and carbonyl compounds possessing an active α-methylene group. In all the cases the reaction proceeded smoothly and the corresponding polysubstituted quinolines were obtained in good to excellent yields (Table 5 and 6).

Table 5. Substrate scope for acyclic α-methylene compounds [a,b]

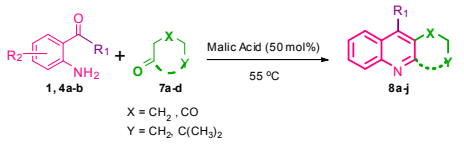


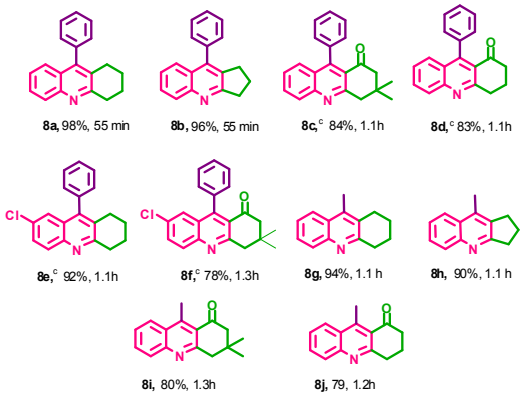
[a]All reactions were carried out with the respective o-acyl aniline 1, 4a or 4b (1 mmol) and respective α-methylene ketone 2 or 5a-d (1.1 mmol) in neat conditions under air; [b]All the synthesized quinolines (6a-j) are known in literature; Relevant literature references as well as melting points (for all solid compounds) are provided in Table S1 in ESI; [c]A few drops of ethanol was added to obtain the reaction mixture in form of a paste as both the starting materials were solid; [d]Reaction temperature 70 °C

The synthetic strategy worked equally well with both acyclic and cyclic α-methylene compounds (Table 5 and Table 6 respectively) while in the case of *o*-acyl anilines, use of 2-amino benzophenones generally led to higher yields as compared to 2-amino acetophenones (Table 5 and 6).

Next, we examined the possibility of recovery and recyclability of malic acid using the model reaction, under the optimized reaction conditions. Upon completion of the reaction, the reaction mixture was dissolved in EtOH (2mL) and cold water was added to it whence the solid product which separated out was filtered, washed with water and dried to obtain the quinoline product. The combined filtrate was now dried *in vacuo* and washed with a minimum amount of MeTHF to remove any

Table 6. Substrate scope for cyclic α-methylene compounds a,b





[a]All reactions were carried out with the respective o-acyl aniline 1, 4a or 4b (1 mmol) and respective α-methylene ketone 2 or 5a-d (1.1 mmol) in neat conditions under air; [b]All the synthesized quinolines (8a-j) are known in literature; Relevant literature references as well as melting points (for all solid compounds) are provided in Table S1 in ESI; [c]A few drops of ethanol was added to obtain the reaction mixture in form of a paste as both the starting materials were solid.

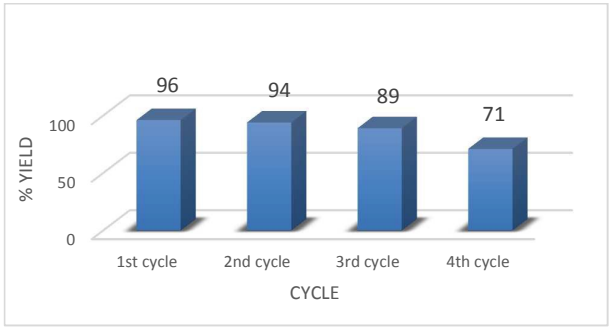


Figure 2. Recyclability of Malic acid

trace of residual reagents/product and the pure recycled malic acid so obtained was used for the next cycle. The recycled promoter could be reused multiple times with comparable efficiency without any further treatment. The recyclability of the promoter offsets the perceived disadvantage of the high catalyst loading needed for this reaction (Figure 2).

In order to test the versatility and robustness of the developed Friedlander protocol, we applied it for the synthesis of a few important quinoline molecules (Scheme 1).

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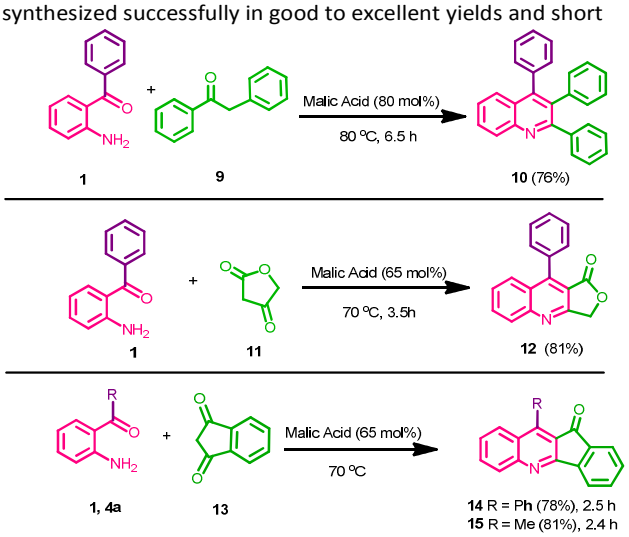
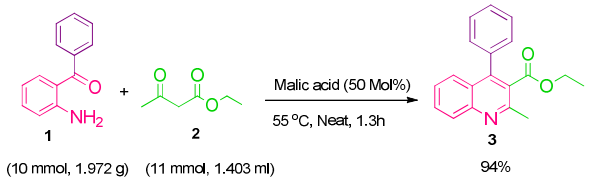
For this purpose we selected 2,3,4-Triphenyl Quinoline (**TPQ**)[6d, 6e] **10**, an important ligand used in synthesis of OLEDs, azapodophyllotoxin analogue[13e,13f,30] **12** and indeno[2,1*b*]quinolones[13d] **14** and **15** which are medicinally important molecules (Scheme 1). All the target molecules were synthesized successfully in good to excellent yields and short



Scheme 1. Targeted synthesis of TPQ 10, azapodophyllotoxin analogue 12 and indeno[2,1b]quinolines 14 and 15

reaction times. However marginally higher temperatures and higher promoter loading was required in these cases.

We also performed the model reaction on a multigram scale in order to ascertain the practicality of the develop methodology (Scheme 2). 2-amino benzophenone **1** (10 mmol, 1.972 g) was reacted with ethyl acetoacetate **2** (11 mmol, 1.403 ml), leading to which was obtained in 94% yield in about 1.3h. All the reactions including the scale up reaction were carried out using a common laboratory glasswares under air which demonstrates the operational ease of this method.

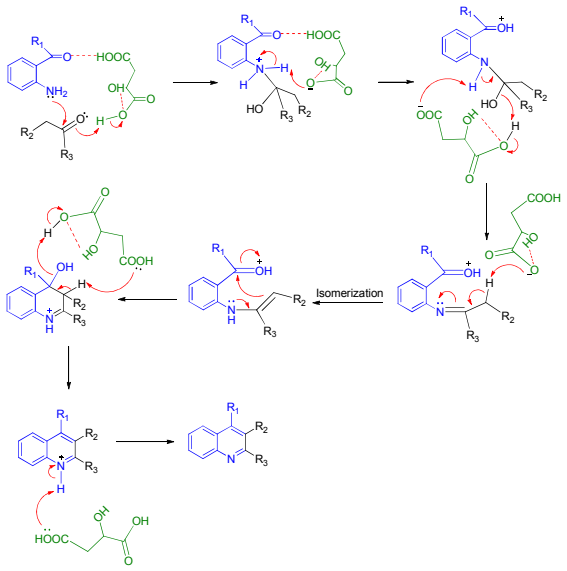


Scheme 2. Multigram synthesis of quinoline 3

A tentative mechanism for the synthesis of quinolines by the reaction of o-acyl anilines and α-methylene compounds using this method is depicted below.

Conclusions

In conclusion we have disclosed a new and efficient malic acid promoted, green Friedländer approach to diverse multisubstituted quinolines. To the best of our knowledge this is the first report on the use of malic acid - an easily available and cheap, promising bioorganic molecule as a catalyst in organic synthesis. Use of solvent free mild reaction conditions, ease of operation and workup, high atom economy, wide substrate tolerance, good to excellent yields and recyclability of the promoter are the other important hallmarks of the reported method. The successful application of the present method



Scheme 3. Plausible mechanism

towards the targeted synthesis of selected important quinoline molecules and its scale up to multi-gram scale further serve to make it a valuable green alternative to existing methods. Moreover the present work also highlights the latent possibilities of using hitherto unexplored biobased organic acids as alternative green promoters in organic synthesis.

Experimental Section

General remarks

All chemicals were reagent grade and purchased from Aldrich, Alfa Aesar, Merck, Spectrochem and Qualigens and were used without further purification. The reactions were monitored using pre-coated Aluminium TLC plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60 F-254). Column chromatography was performed using silica gel (60-120) and (100-200). NMR spectra were recorded on a Bruker Avance-II 400FT spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) in DMSO or $CDCl_3$ using TMS as an internal reference. Mass spectra (ESIMS) were obtained on a Waters UPLC-TQD mass spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer.Elemental analyses were carried out in a Thermo Scientific (FLASH 2000) CHN Elemental Analyser. Melting points were determined by open glass capillary method and were uncorrected.

General Experimental Procedure[abc]

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To a 50 mL round bottom flask were added *o*-acyl anilines (1 mmol), α-methylene ketone (1.1 mmol) and malic acid (0.5 mmol) and the resulting mixture was stirred at 55 °C under solvent free conditions. On completion of the reaction (TLC control), the reaction mixture was dissolved in EtOH (2mL) and cold water was added to it whence the solid product which separated out was filtered, washed with water and dried. The crude product was then recrystallized from a mixture of Et_2O/ hexane to obtain the pure quinolines.

[a]In those instances where required purity could not be achieved through recrystallization, column chromatography (100-200 mesh silica gel; EtOAc/Hexane) was performed to obtain the pure molecules.

[b]In case where quinolines were liquids, the reaction mixture was dissolved in EtOAc and washed with water. The EtOAc layer was separated and the aqueous fraction was extracted with EtOAc (3 x 3mL). The combined organic layers were dried over Na2SO4 and concentrated in vacuo to give the crude product which was subjected to column chromatography (100-200 mesh silica gel; EtOAc/Hexane) to afford the pure quinoline derivative.

[c]In those cases where both the *o*-acyl aniline and α-methylene ketone were solids, a few drops of ethanol was added so as to obtain the reaction mixture in form of a paste.

Acknowledgements

The authors are thankful to SAIF, PU, Chandigarh and SAIF, CDRI, Lucknow for spectral data. The authors also acknowledge the financial support from UGC, New Delhi in form of a major research project (Project No. 42-263/2013 (SR)), fellowships for Fatima Tufail, Swastika Singh and Mandavi Singh and a D.S. Kothari Postdoctoral Fellowship for Dr. Mohammad Saquib (Award No. F.4-2/2006 (BSR)/13-1030/2013(BSR). Jyoti Tiwari thanks CSIR, New Delhi for Junior Research Fellowship.

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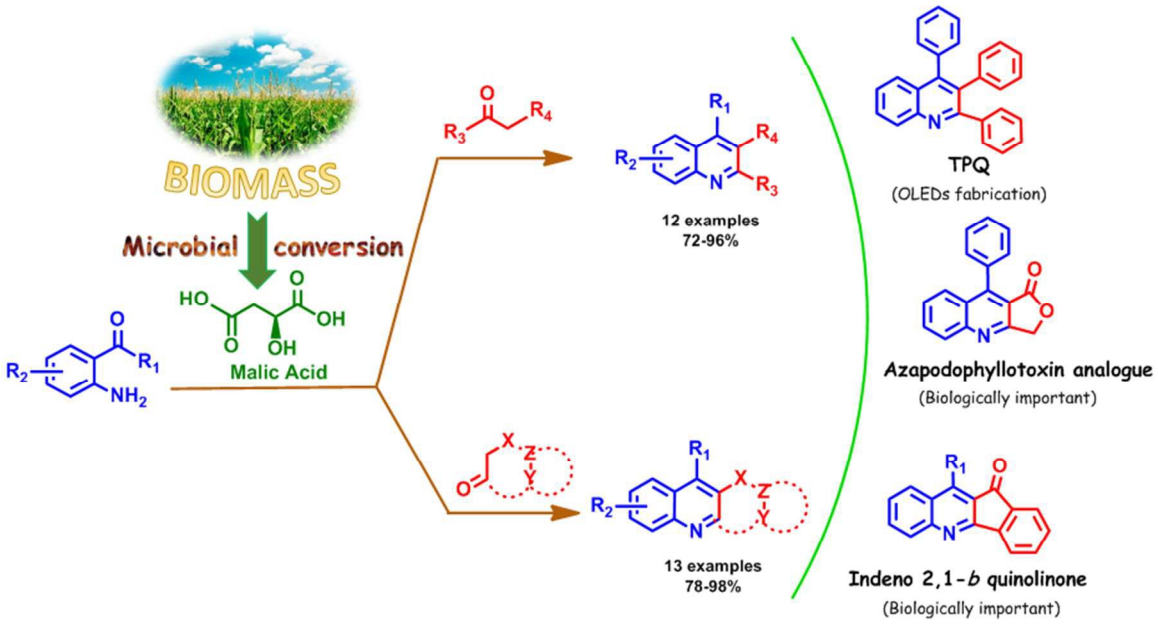

An efficient new method for the green synthesis of a variety of polysubstituted quinolines using the Friedländer approach is reported using malic acid as a catalyst in organic synthesis for the first time.