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COMMUNICATION

Construction of quinoline ring via a 3-component reaction in water: crystal structure analysis and H-bonding patterns of a 2-aryl quinoline

T. Ram Reddy,[a,b] L. Srinivasula Reddy,[a,b] G. Rajeshwar Reddy,[a] Kaviraj Yarbagi,[a] Y. Lingappa,[b] D. Rambabu,[c,e] G. Rama Krishna,[d] C. Malla Reddy,[d] K. Shiva Kumar,[e] Manojit Pal[e,*]

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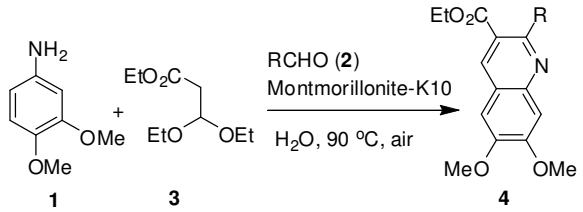
Montmorillonite K-10 mediated green and one-pot synthesis of 2-substituted quinolines has been accomplished *via* a 3-component reaction of aniline, aldehydes and ethyl 3,3-diethoxypropionate in the presence of air oxygen in water. The crystal structure analysis and H-bonding patterns of one compound prepared is presented.

Development of efficient and environmental friendly synthetic methodologies for the commonly used small organic molecules is one of the major challenges in modern organic synthesis. Quinolines, because of their numerous pharmacological properties are often considered as widely used *N*-heterocycls in both academia and pharmaceutical industries.[1,2] It is not surprising that a number of methods have been developed for the construction of quinoline ring including Skraup, Doebner-Miller, Doebner, Combes or Pfitzinger syntheses.[2] Though very effective, many of these methods however, often involve the use of various acids or reagents that are not environmentally compatible, produce a large amount of waste and require longer reaction times. The multicomponent domino reactions are known to afford structurally complex and diversity based molecules in a single step operation that ensures high atom economy as well as good overall yields.[3] We envisioned that a similar strategy for the construction of functionalized quinoline ring would not only be beneficial for the development of a simpler and straightforward method[4] but also might increase the chances of achieving a greener synthetic route. In continuation of our interest in quinoline derivatives[5] of potential pharmacological interest we now wish to report a one-pot synthesis of 2-substituted quinoline-3-carboxylate esters[6] *via* 3-component reaction of aniline (**1**), aldehydes (**2**) and ethyl 3,3-diethoxypropionate (**3**) in the presence of montmorillonite K-10 as a green and reusable catalyst and air oxygen in water (Scheme 1). In view of the known antimicrobial activities of quinolines[1] we expected that the present class of compounds would show relevant pharmacological properties.



Scheme 1. Green synthesis of quinolines *via* a MCR

In our initial study, the reaction of aniline **1a**, 3,4-diflouro benzaldehyde (**2a**) and ester **3** was carried out in water in the presence of *p*-toluenesulfonic acid (*p*-TSA) and air at 90 ºC when the corresponding quinoline **4a** was isolated in 41% yield (entries 1, Table 1). The use of other Lewis acids such as $ZnCl_2$, $TiCl_4$ and $SnCl_4$ was examined but was found to be less effective as the expected product **4a** was isolated in 10-30% yield (entries 2-4, Table 1). We then examined the use of montmorillonite K-10 (entry 5, Table 1). To our satisfaction, the reaction proceeded well affording the desired product in 83% yield within 5h. To test the recyclability of the catalyst, Montmorillonite-K10 was recovered by simple filtration and reused when **4a** was isolated without significant loss of its yield. The yield of **4a** was found to be 80, 77 and 75 after 1st, 2nd and 3rd recovery and resue of the catalyst. The use of lower quantity of montmorillonite K-10 decreased the product yield (entry 6 and 7, Table 1) whereas the reaction did not proceed in the absence of catalyst indicating the key role played by the catalyst (entry 8, Table 1). While water was used as a solvent in all these cases, other solvents such as EtOH (entry 9, Table 1), DMSO, DMF, acetonitrile, and toluene however was found to be less effective in the present MCR. Thus, a combination of Montmorillonite-K10 in water was found to be optimal for the preparation of **4a.**

To test the generality and scope of this green MCR a range of aldehydes (**2**) were employed under the optimized reaction conditions[7a] (Table 2). Various electron donating e.g. F, Cl,

[a]*Custom Pharmaceutical Services, Dr. Reddy's Laboratories Limited, Bollaram Road Miyapur, Hyderabad 500 049, India.*

[b]*Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, Andhra Pradesh, India.*

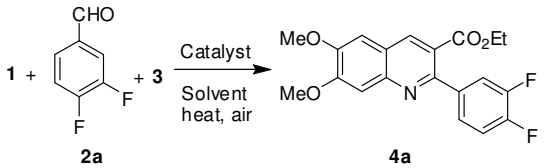
[c]*Department of Chemistry, K. L. University, Vaddeswaram, Guntur 522 502, Andhra Pradesh, India.*

[d]*Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal, 741252, India.*

[e]*Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad, 500046, India. E-mail: manojitpal@rediffmail.com*

†Electronic Supplementary Information (ESI) available: Experimental Procedures, spectral data and copies of NMR for all new compounds. CCDC 864149. For ESI See DOI: 10.1039/b000000x/

Table 1. Effect of reaction conditions on the MCR of **1**, **2a** and **3**.[a]



2a **4a**

Entry	Catalyst	Solvent	%Yield[b,c]
1.	*p*-TSA (2.5 mol%)	H_2O	41
2.	$ZnCl_2$(2.5 mol%)	H_2O	15
3.	$TiCl_4$ (2.5 mol%)	H_2O	30
4.	$SnCl_4$ (2.5 mol%)	H_2O	10
5.	Montmorillonite-K10 (50% w/w)	H_2O	83 (80)[d]
6.	Montmorillonite-K10 (20% w/w)	H_2O	41
7.	Montmorillonite-K10 (0.5% w/w)	H_2O	28
8.	No catalyst	H_2O	0
9.	Montmorillonite-K10 (50% w/w)	EtOH	35

[a]All the reactions were carried out using **1** (0.98 mmol), **2a** (1.07 mmol) and **3** (2.45 mmol) in a solvent at 90 °C for 5 h in the presence of air. [b]With respect to the aniline **1** used. [c]Isolated yield. [d]Recovered Montmorillonite-K10 was used.

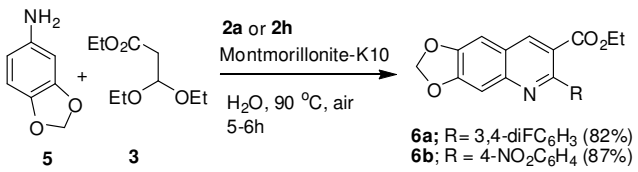
Br, Me and OMe (entries 1-7, Table 2) or electron withdrawing groups e.g. NO_2 and CF_3 (entries 8 and 10, Table 2) present on the aryl ring of aldehydes were well tolerated. The reaction proceeded well irrespective of the substituents present in aldehydes employed (entry 9 vs 1-7, 8 & 10, Table 2). The use of heteroaromatic and aliphatic aldehydes were also successful and afforded the desired quinolines in good yields (entries 11-13, Table 2). We then examined the use of other aniline in place of **1**. Thus, benzo[*d*][1,3]dioxol-5-amine (**5**) was reacted with **3** and aldehyde **2a** or **2h** smoothly to give the desired product **6a** or **6b** in good yield (Scheme 2). The use of 1,1-diethoxyethane in place of **3** was also examined *via* the reaction of **1** along with **2i** when the desired product[7b] was isolated in 70% yield. While all the new compounds synthesized were well characterized by spectral (NMR, IR and MS) data the molecular structure of a representative compound **4j** was established unambiguously by single crystal X-ray diffraction (Fig. 1).[8] The compound **4j** crystalizes in the monoclinic $P2_1/c$ space group with one molecule in the asymmetric unit (Z=0, Z' = 2) (Figure 2). While the molecule in the asymmetric unit as such had no conventional functional groups to form H-bonding the ethyl ester and trifluoro groups present however were responsible for the formation of weak inter molecular H-bonding. The inversion related molecule in the asymmentric unit forming the dimer synthon through C-H···O interactions is shown in Fig. 2. They formed channels with above one molecule and below one molecule *via* C-H···F interactions and are stabilised by aromatic C-H···π interactions. These interactions propagated in 3D network packing along ac axis as shown in Fig. 3.

Mechanistically, the reaction seems to proceed (Scheme 3) *via in situ* generation of (i) an imine from the aniline (**1**) and aldehyde (**2**) and (ii) a 3-hydroxy acrylate from ethyl 3,3-diethoxypropanoate (**3**) under mild acidic conditions employed. The Mannich reaction between the imine and 3-hydroxy acrylate derivative followed by intramolecular cyclization afforded the 1,2-dihydroquinoline intermediate which on subsequent oxidation in the presence of air oxygen provided the desired product.[9] The role of air oxygen was further confirmed by the isolation of ethyl 2-(3,4-difluorophenyl)-6,7-dimethoxy-1,2-dihydroquinoline-3-carboxylate when the MCR of **1**, **2a** and **3** was carried out strictly under inert atmosphere maintaining the other conditions same as presented in entry 5 of Table 1.

Table 2. Synthesis of 2-substituted quinolines (**4**)[a] (Scheme 1)

Entry	**2**; R =	Time (h)	Products (**4**)	% yield[b]
1	**2a;** 3,4-diFC_6H_3	5	**4a**	83
2	**2b;** 4-FC_6H_4	6	**4b**	82
3	**2c;** 4-ClC_6H_4	7	**4c**	74
4	**2d;** 2-BrC_6H_4	5	**4d**	75
5	**2e;** 4-BrC_6H_4	5	**4e**	81
6	**2f;** 3,4-diMeC_6H_3	7	**4f**	82
7	**2g;** 4-$MeOC_6H_4$	10	**4g**	75
8	**2h;** 4-$NO_2C_6H_4$	5	**4h**	87
9	**2i;** Ph	9	**4i**	78
10	**2j;** 4-$CF_3C_6H_4$	5	**4j**	89
11	**2k;** thiophen-2-yl	6	**4k**	81
12	**2l;** furan-2-yl	8	**4l**	71
13	**2m;** Me	6	**4m**	62

[a]All the reactions were carried out using aniline **1** (0.98 mmol), aldehyde **2** (1.07 mmol), ethyl 3,3-diethoxypropionate **3** (2.45 mmol) and Montmorillonite K-10 (75 mg) in water at 90 °C in the presence of air. [b]Isolated yields.



Scheme 2. Synthesis of quinolines **6a-b**

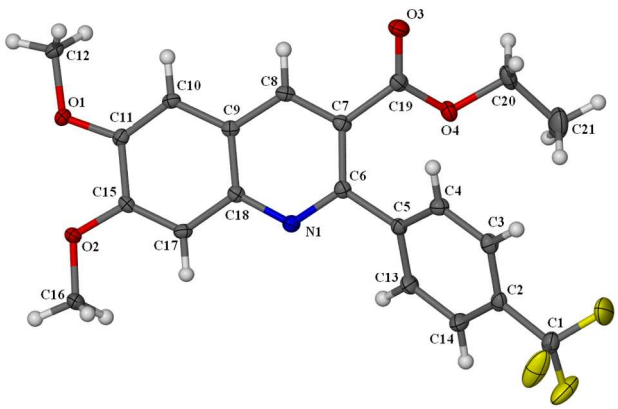


Fig. 1.ORTEP representation of compound **4j** (Thermal ellipsoids are drawn at 50% probability level).

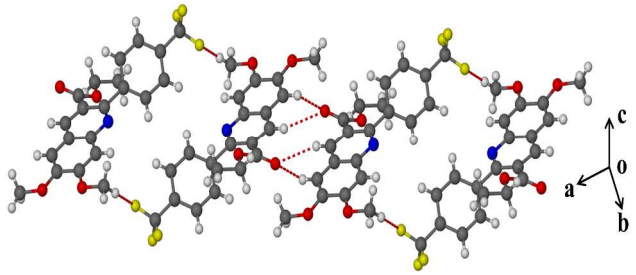


Fig. 2. The hydrogen bonding pattern in the molecule **4j**.

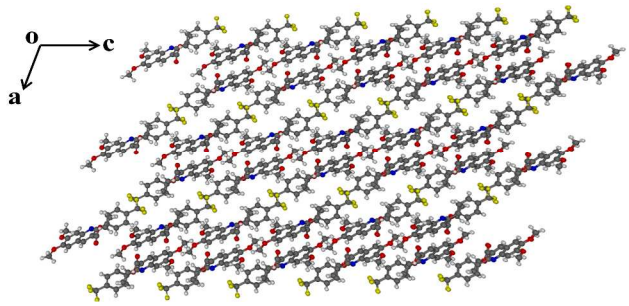
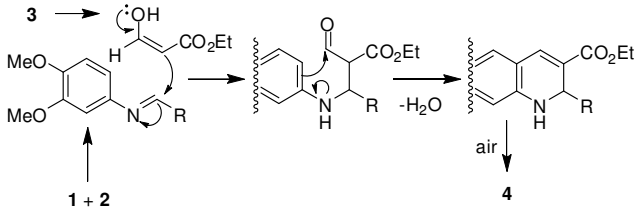
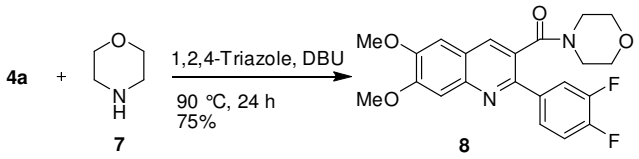


Fig. 3. The molecular arrangement along ac axis in molecule **4j**.



Scheme 3. Proposed reaction mechanism

To demonstrate the further scope of this MCR, structure elaboration of quinoline **4a** was carried out *via* the reaction with morpholine (**7**) in the presence of 1,2,4-triazole to give the corresponding amide **8** (Scheme 2). Some of the quinolines (**4**) synthesized were teseted for their inhibitory properties against Mycobacterium tuberculosis H37Rv chorismate mutase (CM) *in vitro*.[10] Compound **4a** and **4b** showed 30% inhibition of CM when tested at 50 µM.



Scheme 2. Structure elaboration of quinoline **4a**.

In conclusion, a direct and one-pot synthesis of 2-substituted quinolines of potential medicinal interest has been accomplished *via* a 3-component reaction in water in the presence of air oxygen. Montmorillonite K-10 was identified as a green and reusable catalyst in this MCR. The methodology could be useful in constructing a diversity based library of small molecules related to quinoline framework.

TRR thanks Dr V. Dahanukar and analytical group of DRL.

Notes and references

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7. (a) General procedure for the synthesis of quinoline **4**: A mixture of Montmorillonite K-10 (75 mg), an appropriate aniline **1** (0.98 mmol), ethyl 3,3-diethoxypropionate **3** (466 mg, 2.45 mmol) and an aldehyde **2** (1.07 mmol) in pure water (7.5 mL, 5 times vol w. r. t. aniline) was stirred at 90 °C for the time mentioned in Table 2 in the presence of air. After completion of the reaction (indicated by TLC), the mixture was cooled to room temperature and filtered. The filtrate was extracted with EtOAc (3 x 5 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-hexane to give the desired product. (b) K. V. Rao, *J. Heterocyclic Chem.* 1975, **12**, 725.
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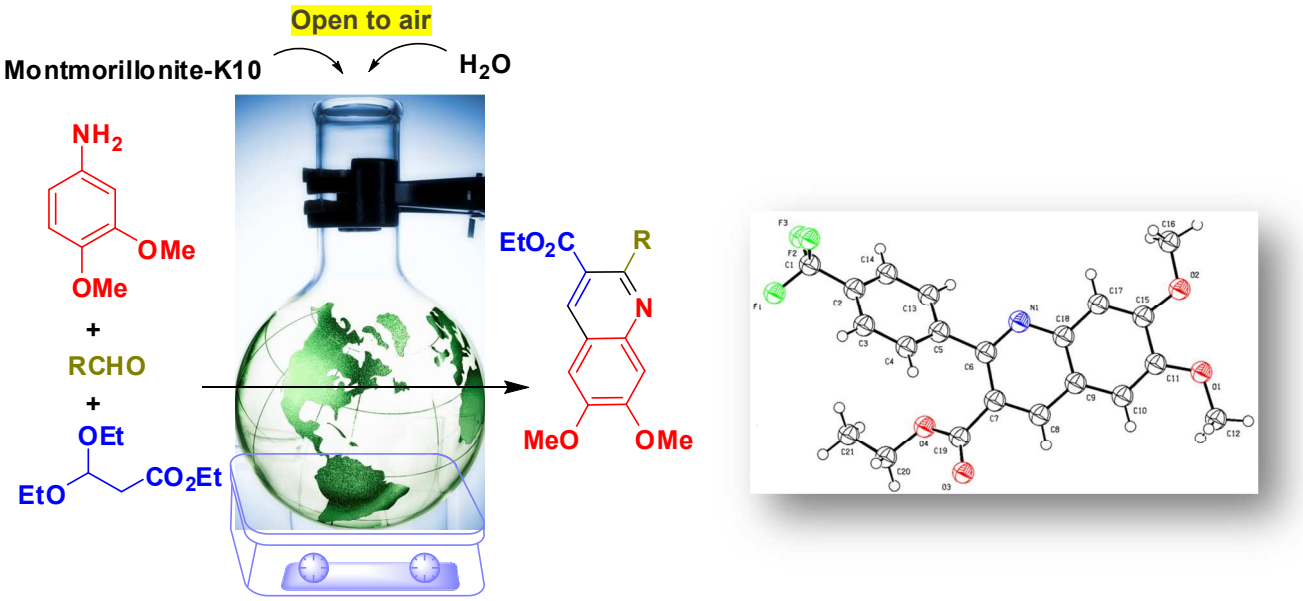
Graphical Abstract



We describe green synthesis of 2-substituted quinolines *via* a 3-component reaction in water along with the crystal structure analysis of a 2-arylquinoline.