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

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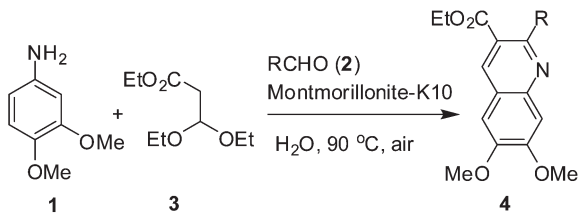
Montmorillonite K-10 mediated green and one-pot synthesis of 2-substituted quinolines has been accomplished *via* a 3-component reaction of aniline, aldehydes and ethyl 3,3-diethoxypropionate in the presence of air oxygen in water. The crystal structure analysis and H-bonding patterns of one compound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

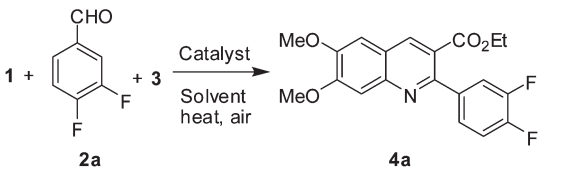
Development of efficient and environmentally friendly synthetic methodologies for the commonly used small organic molecules is one of the major challenges in modern organic synthesis. Quinolines, because of their numerous pharmacological properties, are often considered as widely used *N*-heterocycles in both academia and the pharmaceutical industry.[1,2] It is not surprising that a number of methods have been developed for the construction of a 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 a 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* a 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.

In our initial study, the reaction of aniline **1a**, 3,4-difluoro benzaldehyde (**2a**) and ester **3** was carried out in water in the presence of *p*-toluenesulfonic acid (*p*-TSA) and air at 90 °C when the corresponding quinoline **4a** was isolated in 41% yield (entry 1, Table 1). The use of other Lewis acids such as



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

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



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 K-10 (50% w/w)	H_2O	83 (80)[d]
6	Montmorillonite K-10 (20% w/w)	H_2O	41
7	Montmorillonite K-10 (0.5% w/w)	H_2O	28
8	No catalyst	H_2O	0
9	Montmorillonite K-10 (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 K-10 was used.

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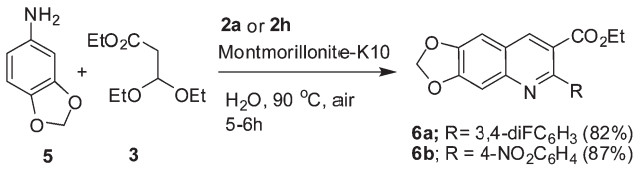
Table 2 Synthesis of 2-substituted quinolines (**4**)[a] (Scheme 1)

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**.

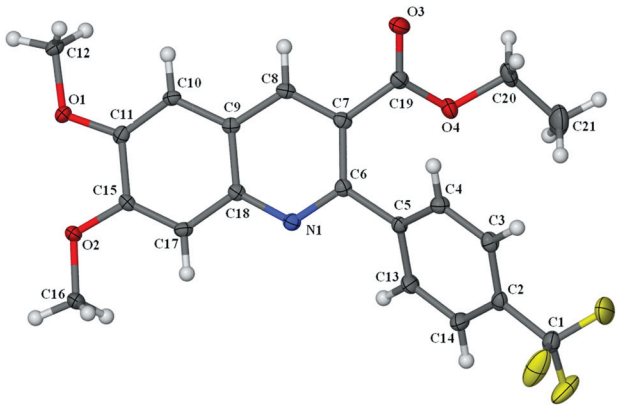


Fig. 1 ORTEP representation of compound **4j** (thermal ellipsoids are drawn at 50% probability level).

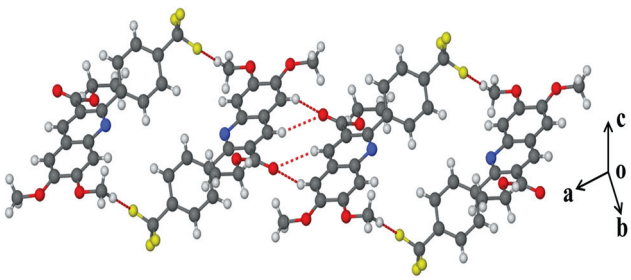


Fig. 2 The hydrogen bonding pattern in molecule **4j**.

$ZnCl_2$, $TiCl_4$ 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 5 h. To test the recyclability of the catalyst, montmorillonite K-10 was recovered by simple filtration and reused when **4a** was isolated without significant loss of yield. The yield of **4a** was found to be 80, 77 and 75 after 1st, 2nd and 3rd recovery and reuse of the catalyst. The use of a lower quantity of montmorillonite K-10 decreased the product yield (entries 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 were found to be less effective in the present MCR. Thus, a combination of montmorillonite K-10 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, 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 the aldehydes employed (entries 9 *vs.* 1–7, 8 and 10, Table 2). The use of heteroaromatic and aliphatic aldehydes was also successful and afforded the desired quinolines in good yields (entries 11–13, Table 2). We then examined the use of other anilines in place of **1**. Thus, benzo[*d*][1,3]dioxol-5-amine (**5**) 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** crystallizes in the monoclinic $P2_1/c$ space group with one molecule in the asymmetric unit ($Z = 4$, $Z' = 1$) (Fig. 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 intermolecular H-bonding. The inversion related molecule in the asymmetric unit forming the dimer synthon through C–H···O interactions is shown in Fig. 2. They formed channels with one molecule above and one molecule below *via* C–H···F interactions and are stabilised by aromatic C–H···π interactions. These interactions propagated in 3D network packing along the *ac* plane 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 the 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

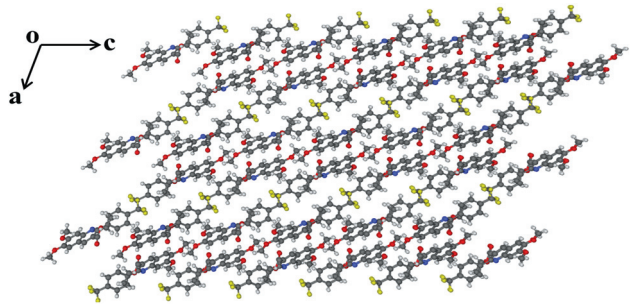
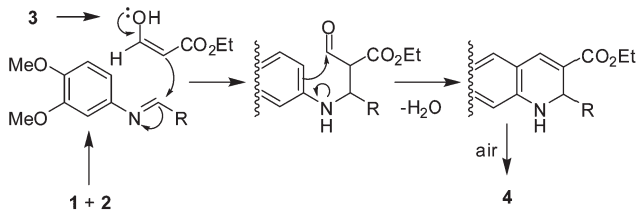
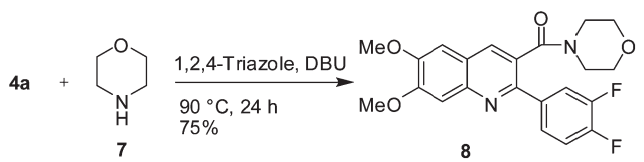


Fig. 3 The molecular arrangement along the *ac* plane in molecule **4j**.



Scheme 3 Proposed reaction mechanism.



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

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 as presented in entry 5 of Table 1.

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 4). Some of the quinolines (**4**) synthesized were tested for their inhibitory properties against *Mycobacterium tuberculosis* H37Rv chorismate mutase (CM) *in vitro*.[10] Compounds **4a** and **4b** showed 30% inhibition of CM when tested at 50 μM.

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 the quinoline framework.

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Notes and references

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6 For selected synthesis, see: (*a*) M. Balasubramanian, J. G. Keay, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 5, p. 245; (*b*) J. P. Michael, *Nat. Prod. Rep.*, 1997, **14**, 605; (*c*) K. Kobayashi, R. Nakahashi, A. Shimizu, T. Kitamura, O. Morikawa and H. Konishi, *J. Chem. Soc., Perkin Trans.*, 1999, **1**, 1547; (*d*) C. Mitsos, A. Zografos and O. Igglessi-Markopoulou, *Chem. Pharm. Bull.*, 2000, **48**, 211; (*e*) J. N. Kim, H. J. Lee, K. Y. Lee and H. S. Kim, *Tetrahedron Lett.*, 2001, **42**, 3737; (*f*) S. Sakaguchi, A. Shibamoto and Y. Ishii, *Chem. Commun.*, 2002, 180.

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 × 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. Heterocycl. Chem.*, 1975, **12**, 725.

8 Crystallographic data (excluding structure factors) for **4j** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 864149 (see also ESI†).

9 The air oxygen has been reported to act as an effective oxidant for aromatization of hydroquinolines, see: S.-Y. Tanaka, M. Yasuda and A. Baba, *J. Org. Chem.*, 2006, **71**, 800.

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