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Transition-metal-free solid phase synthesis of 1,2-disubstituted 4-quinolones *via* regiospecific synthesis of enaminones†

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Abstract: Transition-metal-free step-economical solid phase synthesis of 1,2-disubstituted 4-quinolones has been developed *via* novel regiospecific synthesis of enaminones. Notably, wide range of enaminones were synthesized by silica-supported solid-phase reaction in good to excellent yields. The transformation of enaminones to 1,2-disubstituted 4-quinolones and *N*-methyl-2-aryl-4-quinolone alkaloid was achieved in high yield by alumina-supported solid phase reaction. In addition, all the synthesized compounds were isolated directly in pure form from the reaction mixture by easy workup procedure.

Introduction

In the view of environmental and economic consciousness, the development of solid phase and transition-metal free reactions has been given much attention in pharmaceutical industry. These type of reactions offers remarkable advantages such as operational simplicity, avoid of metal contamination in the products, no work-up, minimum use of energy and save manpower, thus rendering the transformations more environmentally friendly. Therefore, pharmacists as well as chemists[1] are frequently involving in the development of greener strategies to replace the toxic and flammable organic solvents by solid supports such as inorganic oxides; alumina or silica on which the organic compounds get adsorbed. Transition metal catalysed reactions are most common tool in the formation of C-C, C-N, C-O and C-S bonds in conventional organic synthesis. Particularly, bulk drug manufacturing industries are distinctly use transition-metals to access required products hence, these metals have the possibility of adsorption with the product in higher concentration and cause health risks in humans such as oxidative damage of DNA,[2] apoptosis,[3] allergic dermatitis[4] and inhibit the activity of steroidogenic enzymes.[5] The purification of active pharmaceutical ingredient from transition metal catalyst will be the major concern and this need unnecessary protocols.[6] Therefore, environmental friendly transition metal free, solid phase approach is highly desirable for the synthesis of bioactive molecules.

In consideration of the biological importance of 4-quinolones as antimalarial,[7] anticancer,[8] antimicrobial agents[9] and also exist as a high pharmacological profile alkaloids (Fig. 1),[10] many synthetic strategies have been reported to construct 1,2-disubstituted 4-quinolones.[11] Enaminones are one of the most common synthons have been utilised to access 4-quinolones which include palladium or copper catalyzed cyclization of alkynones (Method A), chalcones (Method B) and enaminones (Method C) as shown in Scheme 1. However, existed synthetic routes of both enaminones and 1,2- disubstituted 4-quinolones associated with significant disadvantages such as using expensive transition-metal catalyst and corrosive acids, cumbersome procedure, and harsh reaction conditions. More importantly, none of the above reported methods afforded deceptively simple looking 2-benzoyl substituted 4-quinolone scaffolds.

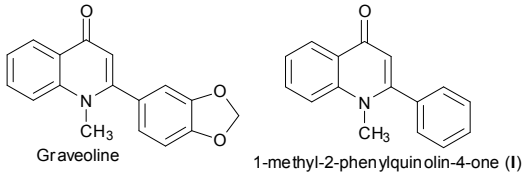

Fig. 1 Naturally occurring biologically active 1,2-disubstituted 4-quinolones

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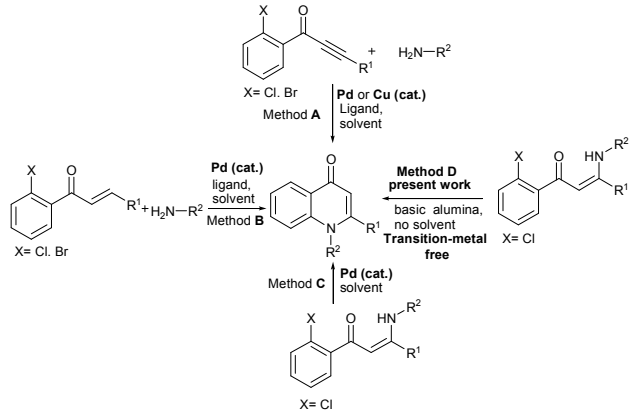
‡Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme 1 Synthetic approaches for 1,2- disubstituted 4-quinolones.

To tackle the above mentioned problems we envisage a new synthetic protocol to synthesize 1,2-disubstituted 4-quinolones and their synthon, enaminones.

Enaminones (Type A-C) (Fig. 2) are an important building blocks for the construction of heterocycles in the field of medicinal chemistry. Enaminones of type A and B (Fig. 2) were utilized largely in the synthesis fused quinolines,[12] pyrroles,[13] pyrimidines,[14] imidazoles,[15] thiazoles,[15] indoles,[16] pyrazoles,[17] triazoles,[18] aminoalcohol[19] and 4-quinolones[20] whereas, Type C enaminones are less explored in synthetic chemistry.[21] Because of these wide applications, enaminones are become a versatile precursors in organic and medicinal chemistry.

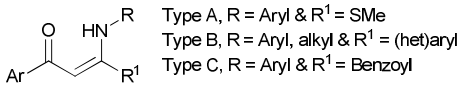
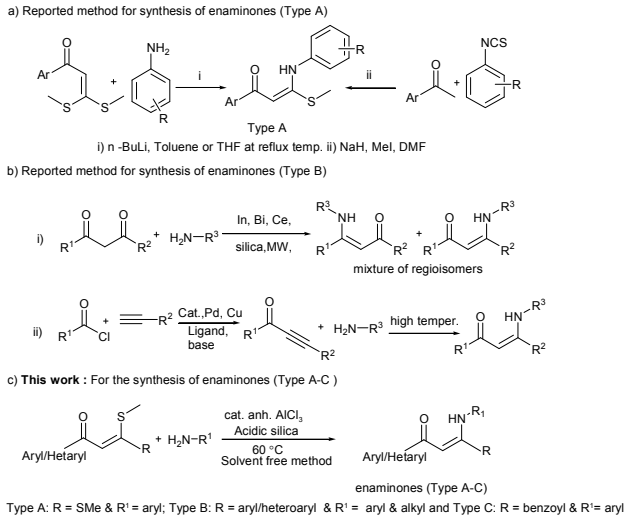


Fig. 2 Types of enaminones

A very few methods were reported for the synthesis of type A enaminones by reaction of aryl substituted ketene *S,S*-acetals with aromatic amines in presence of stoichiometric amount of strong base under reflux conditions.[12a,22] (Scheme 2, a). Various methods were available in the literature for the preparation of enaminones of type B by reacting amines with *β*-dicarbonyl compounds,[23] *α,β*-ynones,[24] monothio-*β*-diketones,[20] (Scheme 2, b). Besides, few other methods were reported as hydrolysis of amidines[25] and the reaction of *β*-dicarbonyl compounds with amines by using microwave,[26] solvent free,[27] ionic liquid,[28] ultra sound[29] and water medium[30] conditions. Similarly, the synthesis of type C enaminones were reported by amination of *α,β*-unsaturated *γ*-dicarbonyl compounds,[31] diaroylacetylenes,[21b] *α*-tosyloxy acetophenones,[32] phenacyl pyridiniumbromides[33] and 2-methylthio-substituted-1,4-enediones.[34] Majority of these methods for the synthesis of enaminones (Type A-C) suffer from major disadvantages like use of stoichiometric amount strong base, high temperature, formation of isomeric mixture of enaminones, laborious synthetic routes to access starting material in presence of toxic solvents limit the utility of these protocols.



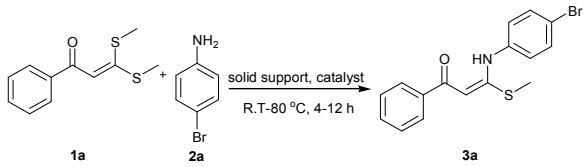
Scheme 2 Synthetic methods for enaminones

In continuation of our ongoing research towards the development of new facile synthesis of both enaminones and biologically active 4-quinolones and to overcome the synthetic challenge with above mentioned limitations, here we have successfully developed robust transition-metal free, solid phase greener synthetic strategy (Scheme 1, Method D and Scheme 2, C). All the synthesised compounds were isolated directly in pure form from the reaction mixture by easy workup procedure.

Results and discussion

In the beginning of our optimization reaction studies towards the synthesis of enaminones, ketene *S*, *S*-acetal (**1a**) and aniline (**2a**) were chosen as model substrates. These substrates were adsorbed on 5 volumes of neutral silica (60-120 mesh size) heated at 80 °C for 12h, did not afford desired Ketene *N*, *S*-acetal (**3a**) (Table 1, entry 1) and addition of Lewis acid anh. $ZnCl_2$ (0.5 equiv.) was not affected the reaction (entry 2). Addition of more Lewis acidic anhydrous $AlCl_3$ (0.05 equiv.) under similar reaction conditions afforded the desired enaminone (**3a**); albeit in low yield (20%, entry 3). Further attempts to improve the yield by using basic or neutral alumina were not successful (entry 4 & 5). To view the influence of acidic property of solid support on a reaction, we adsorbed both the reactants (**1a** & **2a**) on acidic alumina at 80°C afforded the desired product in 25% yield (entry 6). The reaction using combination of acidic silica with 0.03 eq. anh. $AlCl_3$ at 60°C afforded **3a** in 78% yield (entry 7). Further to check the efficiency of other oxophilic Lewis acid catalyst on a reaction, we used 0.03 equiv. of $SnCl_2.2H_2O$ results enaminone **3a** in 84% yield within 4h at room temperature (entry 8).

Table 1 Optimization of reaction conditions

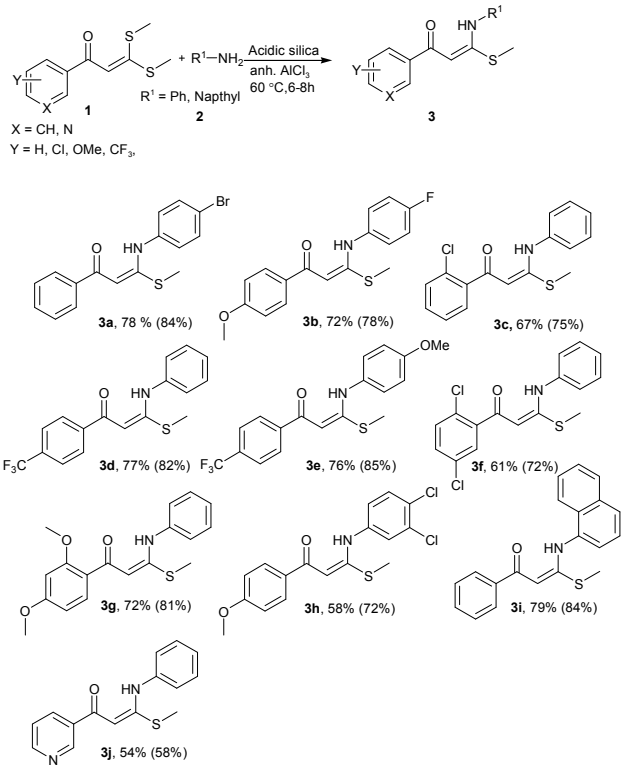


Entry[a]	Solid support	Catalyst	Time(h)	Temp. (°C)	Yield[b](%)
1[c]	neutral silica	-	12	80	0
2[c]	neutral silica	anh. $ZnCl_2$	12	80	0
3	neutral silica	anh. $AlCl_3$	12	80	20
4[c]	basic alumina	anh. $AlCl_3$	12	80	0
5	neutralalumina	anh. $AlCl_3$	12	80	10
6	acidic alumina	anh. $AlCl_3$	12	80	25
7	**acidic silica**	**anh. $AlCl_3$**	**6**	**60**	**78**
8	**acidic silica**	**$SnCl_2.2H_2O$**	**4**	**R.T**	**84**

[a]**1a** (2.0 mmol), **2a** (2.6 mmol), solid support (5 vol. w.r.t 1a), catalyst (0.03 equiv.), room temperature to 80 °C; [b]isolated yields; [c]Starting substrates were recovered

The substrate scope of solid phase reaction protocol (Table 1, entry 7 & 8) was examined by applying to various aryl (heteroaryl) ketene *S,S*- acetals with different aromatic amines (Table 2). The electron donating -OMe substituents (**1b**, **1g**, **1h**), and electron withdrawing substituents such as -Cl, -CF_3, (**1c**, **1d**, **1f**) on phenyl ring of ketene *S, S*-acetals were competent afford to the desired products in high yield (58-79%). A noteworthy example was reaction of aniline with ketene *S, S*-acetals having pyridine entity (**1j**) was also proceeded well afforded **3j** in good yield (54%).

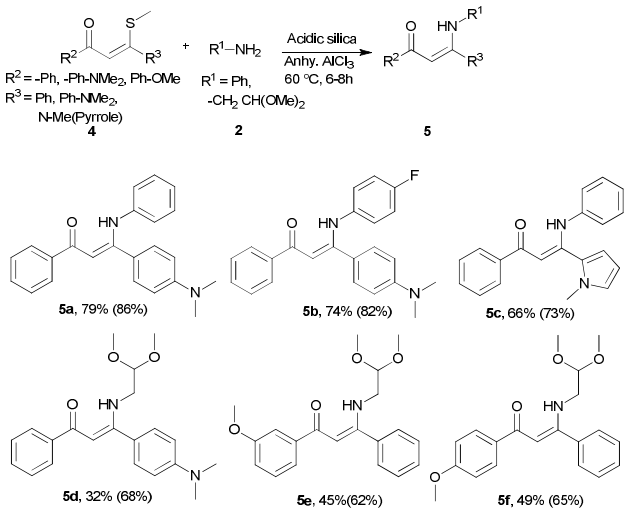
Table 2 Synthesis of Ketene *N, S*-acetal (Enaminones, Type-A)[a]



Reaction conditions: **1** (2.0 mmol), **2** (2.6mmol), acidic silica (5 vol. w.r.t 1), anh. $AlCl_3$ (0.03 equiv.), 60 °C, 68 h. [a] yields in parentheses were obtained in the presence of $SnCl_2.2H_2O$ (0.03 equiv.) at R.T for 4 -6 h.

To see the efficiency of solid phase reactions towards the synthesis of enaminones, we continued our study by reacting aromatic amines (**2**) to unsymmetrical substituted *β*-(methylthio)-*β*-(het)arylenones (**4**) (Table 3) [20,35] on both the stabilised solid phase (Table 1, entry 7 & 8). The substrates **4a** & **4b** affords the product **5a** & **5b** in excellent yield (79 & 74%), whereas heterocyclic substituent at β-position of enone (**4c**) gives the product (**5c**, 66%) in good yield. Aliphatic amines (**2d**-**f**) were also gave enaminones (**5d**-**f**), in low to satisfactory yield (32-49%). But in presence of 0.05 equiv. anhydrous $AlCl_3$ the yield of **5e** and **5f** is increased to 58 and 63 % respectively, after stirring at 60 ° C for 24 h and the yield of **5d** remains unchanged in use of higher equivalent (0.1 equiv. anh. $AlCl_3$), of catlyst.

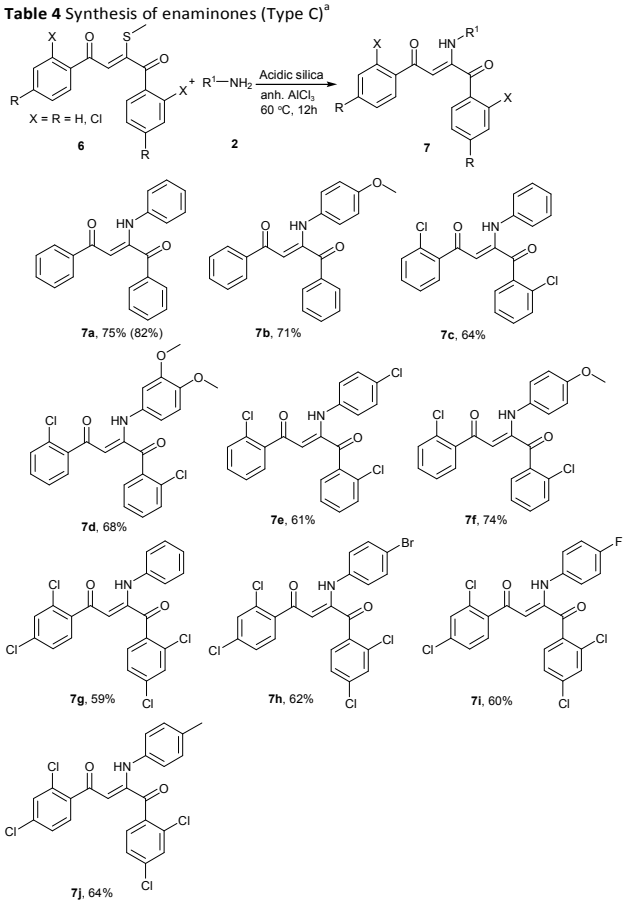
Table 3 Synthesis of enaminones (Type-**B**)[a]



Reaction conditions: **4** (2.0 mmol), **2** (2.6 mmol), acidic silica (5 vol. w.r.t 4), anh. $AlCl_3$ (0.03 equiv.), 60 °C, 6-8 h. [a] yields in parentheses were obtained in the presence of $SnCl_2.2H_2O$ (0.03 equiv.) at R.T, for 6 h to afford 5 a-c & for 18-22 h to afford 5 d-f.

Further we extend our process to synthesize another important class of building block, such as type C enaminones (Table 4). The starting substrates (**6**) were accessible easily from readily available aryl methyl ketones.[36] The reaction of **6a** & **2a** proceeded smoothly using stabilized condition (Table 1, entry 7) afforded the product **7a** in 75% yield (Table 4) after 12 h, but the reaction condition acidic silica with $SnCl_2.2H_2O$ (Table 1, entry 8) require temperature 70 °C to give the product **7a** (yield 82 %, Table 4). Since these enaminones were investigated for the synthesis of biologically important 4-quinolones, we are selecting the optimized reaction condition acidic silica/ anh. $AlCl_3$ (Table 1, entry 7) for the synthesis of differently substituted enaminones of type C. The anilines having electron donating group afforded enaminones in high yield as compared to the anilines having electron withdrawing group (**7c**-**7f**). Further, screening of substrates **6c**-**6j** reveal that, the more electron withdrawing groups on **6** decreases the amount of formation of **7c**-**7j**.

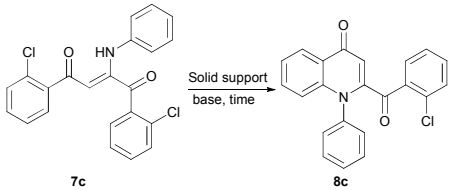
Table 4 Synthesis of enaminones (Type C)[a]



Reaction conditions: **6** (2.0 mmol), **2** (2.6 mmol), acidic silica (5 vol. w.r.t 6), anh. $AlCl_3$ (0.03 equiv.), 60 °C, 12 h. [a] yield in parentheses were obtained in the presence of $SnCl_2.2H_2O$ (0.03 equiv.) at 70 °C for 8 h.

In an attempt to explore a suitable combination of solid support and base for cyclization of enaminone (**7c**) to access 1-aryl 2-benzoyl 4-quinolones (**8c**). We initially examined neutral alumina in presence of 2 equiv. anh. K_2CO_3 as base at 90 °C for 8 h, afforded the product **8c**; albeit in low yield (15%, Table 5, entry 1). The various combinations of acidic silica, neutral silica and basic alumina with different stoichiometric amount of bases did not give satisfactory results (entry 2-7). Further, use of basic alumina as a solid support with 3 equiv. anh. Cs_2CO_3 gave **8c** in 55% yield (entry 8). Finally, the combination of basic alumina with 2 equiv. K_2CO_3 at 90 °C for 8 h was proved to be the best condition, **7c** undergoes intramolecular cyclization afforded **8c** in optimum yield (78%, entry 9).

Table 5 Optimization of reaction on different solid support

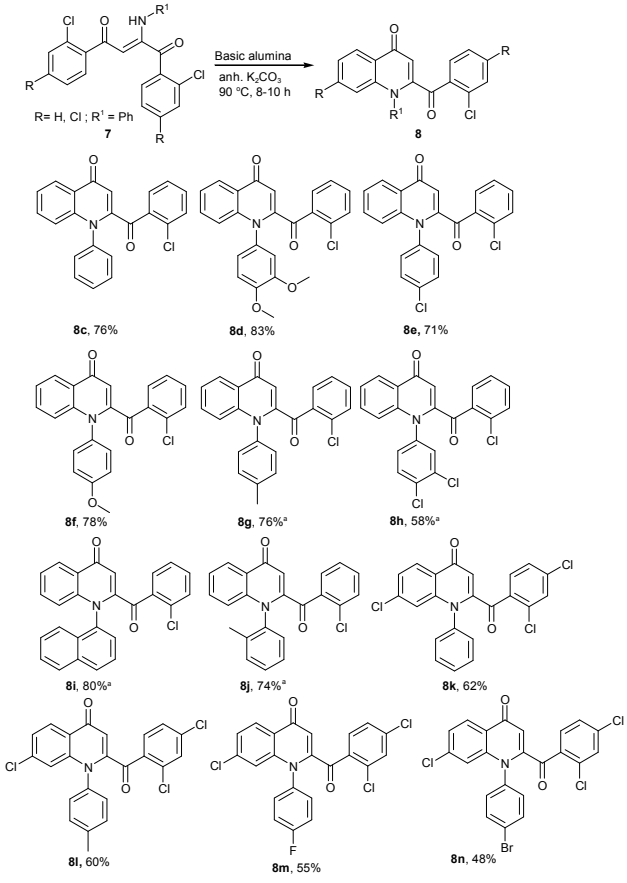


Entry[a]	Solid support	Base	Time (h)	Yield (%)[b]
1	neutral alumina	2 equiv. K_2CO_3	8	15
2	neutral alumina	5 equiv. K_2CO_3	12	20
3	neutral silica	3 equiv. K_2CO_3	12	10
4	neutral silica	3 equiv.Cs_2CO_3	12	8
5	acidic silica	3 equiv.Cs_2CO_3	12	0
6	basic alumina	-	-	0
7	basicalumina	2 equiv. LiOH	12	0
8	**basicalumina**	**3 equiv.Cs_2CO_3**	**12**	**55**
9	**basic alumina**	**2 equiv. K_2CO_3**	**8**	**78**

[a]**7c** (1.0 mmol), solid support (5 vol. w.r.t 7c), base, 90 °C, 8-12 h. [b]isolated yields.

Having established the optimal conditions, we screened different types enaminones **7** (Table 6) for cyclization towards 1-aryl 2-benzoyl 4-quinolones (**8c**-**n**). The electronic property of substituent on aromatic amines influences the product yield. For instance, substrates **7d** and **7f** having electron donating substituents (-OMe) on anilines gives 1,2-disubstituted quinolones (**8d** and **8f)** in higher yield than **7e** having electron withdrawing substituents (-Cl). Similarly the enaminones **7k**-**n** having two extra -Cl atoms on aromatic ring of benzoyl moiety affords the desired product **8k**-**n** in moderate yield (48-62%).

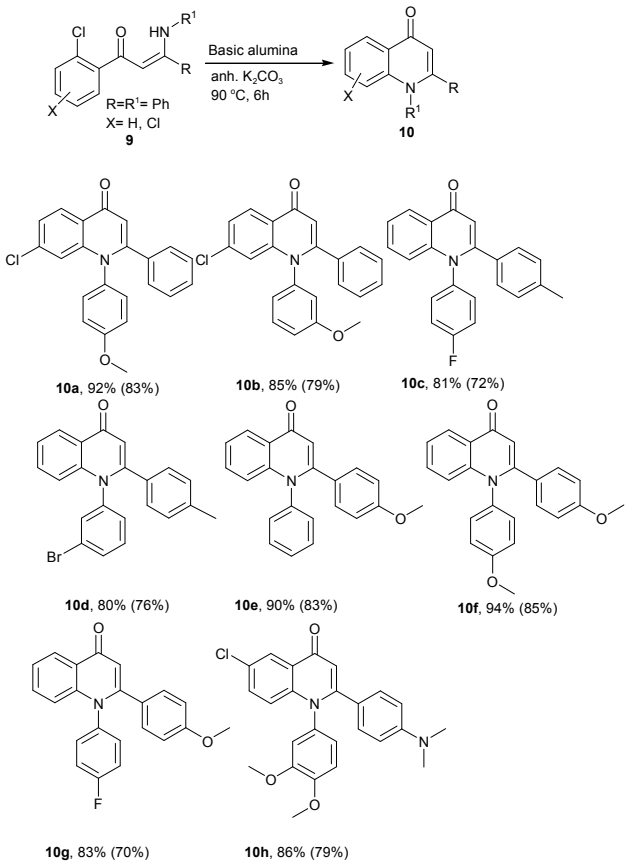
Table 6 Synthesis of 1-aryl 2-benzoyl 4-quinolone



Reaction conditions: **7** (1.0 mmol), basic alumina (5 vol. w.r.t 7), anh. K_2CO_3 (2 equiv.), 90 °C, 8-10 h. [a]Substrates **6** were directly used for the synthesis of 4-quinolones without purification of enaminones.

Under similar optimized conditions, the substrate **9** was adsorbed on basic alumina, adding 2 equiv. K_2CO_3 and heated at 90 °C with vigorous stirring for 6h, product **10a**-**h** obtained in higher yields (80-94%). The percentage of yields of the products were compared with our previous reported method ($Pd(OAc)_2$/anh.Cs_2CO_3 in DMF) and shown in parenthesis (Table 7).[20]

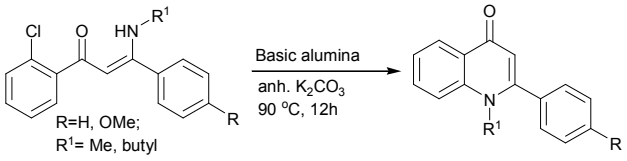
Table 7 Synthesis of 1,2 diarylsubstituted 4-quinolones



Reaction conditions: **9** (1.0 mmol), basic alumina (5 vol. w.r.t 10), anh. K_2CO_3 (2 equiv.), 90 °C for 6 h.

It became of our interest to cyclize the *N*-alkyl enaminones of type b (**11**) to 4-quinolone alkaloids (**12**) having high pharmacological profile and therefore we successfully synthesised the *N*-methyl-2-aryl-4-quinolone alkaloid (**12a**) found in family *Rutaceae* in comparable yield to the reported methods[37] from easily accessible enaminones by catalyst and solvent free method (Scheme 3).

Scheme 3 Synthesis of *N*-alkyl 2-aryl 4-quinolones

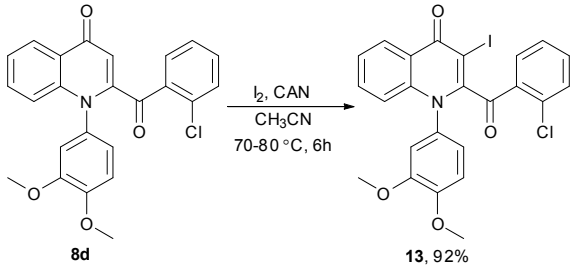


11 **12**

12a, 88% yield, R= H, R^1= Me,
12b, 86% yield, R=OMe, R^1= n-butyl,

Reaction conditions: **11** (1.0 mmol), basic alumina (5 vol. w.r.t 11), anh. K_2CO_3 (2 equiv.), 90 °C, 12 h.

To show the synthetic utility of 1-aryl 2-benzoyl 4-quinolones, **8d** was subjected for iodination using iodine and ceric ammonium nitrate (CAN) in acetonitrile solvent[38] obtained **13** in excellent yield (92%, Scheme 4). The structure of **11** was confirmed by single crystal X-ray analysis and it will be an important synthon in many transition-metal catalyzed coupling reaction to obtain synthetically useful scaffolds.[38]



8d **13**, 92%

Scheme 4 Iodination of **8d**

A single crystal of **13** with dimensions of 0.30 × 0.25 × 0.20 mm was chosen for X-ray diffraction studies. The crystal structure analysis showed that, the compound (**13**) crystallizes in orthrombic system under the space group Pbca, with cell parameters *a* = 8.7884(19) Å, *b* = 16.863(3) Å, *c* = 29.686(6) Å and *Z* = 8. The details of crystallographic information have been deposited at the CCDC NO 990917.[39]

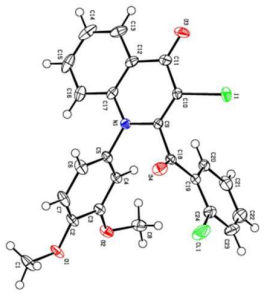
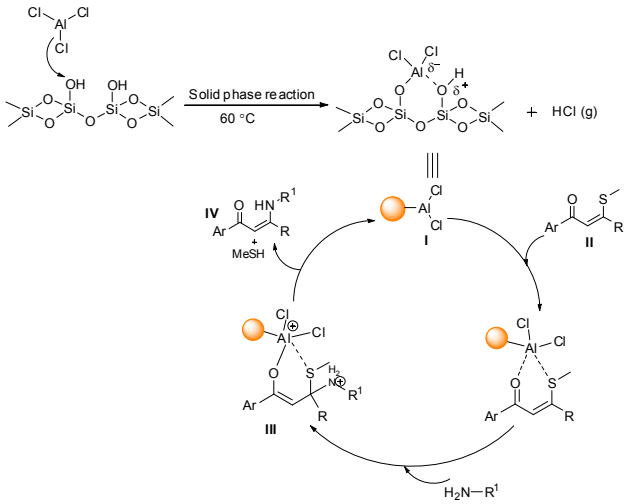


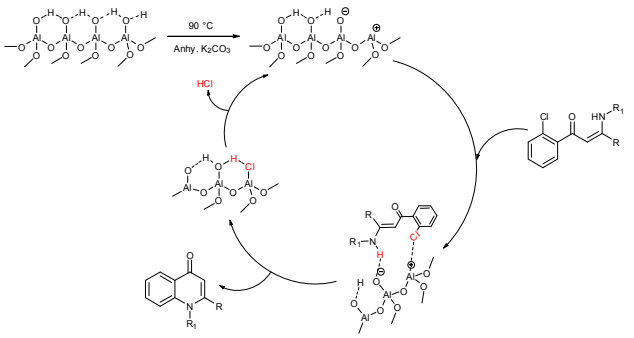
Figure 3 ORTEP diagram of the molecule **11** at 50 % probability

On the basis of above experimental details (Table **2, 3** & **4**) a possible mechanism is proposed in scheme **5**. Initially, the acidic silica reacts with anh. $AlCl_3$ at 60 °C generates the strong Lewis acidic sites ($SiOAlCl_2$) on the surface of silica (**I**). Then the starting substrate (**II**) will bound on the surface of (**I**) followed by the addition of amines at β-position of starting substrate provides (**III**). Finally the product (**IV**) will be released from surface with regeneration of (**I**).



Scheme 5. Proposed mechanism for enaminones formation.

On the basis of previous reports as alumina supported K_2CO_3 is hydrogen halide scavenger,[40] we proposed a possible mechanism for cyclization of type **C** enaminones in scheme **6**. On heating the basic alumina with anh. K_2CO_3 exposed the oxide and aluminium ions on surface to type C enaminones through a loss of water molecule. Thus these active site scavenge the hydrogen chloride from the enaminone adsorbed on the surface of alumina and it underwent the cyclization to 4-quinolones



Scheme 6. Proposed mechanism for cyclization of enaminones.

Conclusions

We have developed a new transition-metal-free method for the synthesis 1,2-disubstituted 4-quinolones and *N*-alkyl 2-aryl 4-quinolone alkaloids *via* regiospecific synthesis of three different types of enaminones by solvent free, greener, solid phase protocol in good to excellent yield. This is the first method reports synthetically challenging 2-benzoyl 4-

quinolones preparation in high yield. Our synthetic method is significant, due to less hazardous transition metal free reaction, solvent free (solid phase), easy work up procedures, high yield of the products.

Acknowledgements

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Notes and references

1 R. A. Sheldon, *Green chem.*, 2007, **9**, 1273-1283.
2 S. Stohsand and D. Bagchi, *Free Radic. Biol. Med.*, 1995, **18**, 321–336.
3 S. V. S. Rana, *J. Trace Elem. Med. Biol.*, 2008, **22**, 262–284.
4 P. Pillai, C. Pandya, N. Bhatt and S. S. Gupta, *Andrologia*, 2012, **44**, 92–101.
5 M. Chandel and G. C. Jain, *J. Environ. Occup. Sci*., 2014, **3**, 204-213.
6 (a) V. W. Rosso, D. A. Lust, P. J. Bernot, J. A. Grosso, S. P. Modi, A. Rusowicz, T. C. Sedergran, J. H. Simpson, S. K. Srivastava, M. J. Humora and N. G. Anderson, *Org. Process Res. Dev.*, 1997, **1**, 311–314; (b) C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889–900.
7 N. Mahmoudi, L. Ciceron, J. -F. Franetich, K. Farhati, O. Silvie, W. Eling, R. Sauerwein, M. Danis, D. Mazier and F. Derouin, *Antimicrob. Agents Chemother.*, 2003, **47**, 2636–2639.
8 R. E. Hawtin, D. E. Stockett, J. A. W. Byl, R. S. McDowell, N. Tan, M. R. Arkin, A. Conroy, W. Yang, N. Osheroff and J. A. Fox, *PLoS One*, 2010, **5**, 1–10.
9 M. M. Skugor, V. Stimac, I. Palej, D. Lugaric, H. C. Paljetak, D. Filic, M. Modric, I. Dilovic, D. Gembarovski, S. Mutak, V. E. Haber, D. J. Holmes, Z. I. Schoenfeld and S. Alihodzic, *Bioorg. Med. Chem.*, 2010, **18**, 6547–6558.
10 (a) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627–646; (b) A. P. Terezan, R. A. Rossi, R. N. A. Almeida, T. G. Freitas, J. B. Fernandes, M. F. Das, G. F. da Silva, P. C. Vieira, O. C. Bueno, F. C. Pagnocca and J. R. Pirani, *J. Braz. Chem. Soc.*, 2010, **21**, 882–886.
11 (a) V. O. Iaroshenko, S. Mkrtchyan and A. Villinger, *Synthesis*, 2013, **45**, 205–218; (b) R. Bernini, S. Cacchi, G. Fabrizi and A. Sferrazza, *Synthesis*, 2009, 1209–1219; (c) J. Shao, X. Huang, X. Hong, B. Liu and B. Xu, *Synthesis*, 2012, **44**, 1798–1808; (d) I. Takahashi, F. Morita, S. Kusagaya, H. Fukaya and O. Kitagawa, *Tetrahedron: Asymmetry*, 2012, **23**, 1657–1662; (e) T. Zhao and B. Xu, *Org. Lett.*, 2010, **12**, 212–215; (f) X. -D. Fei, Z. Zhou, W. Li, Y. -M. Zhu and J. -K. Shen, *Eur. J. Org. Chem.*, 2012, 3001–3008.
12 (a) P. K. Mahata, C. Venkatesh, U. K. Syam Kumar, H. Ila and H. Junjappa, *J. Org. Chem.*, 2003, **68**, 3966–3975; (b) Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu and Y. Gong, *Chem. Commun.*, 2010, **46**, 2145–2147; (c) X. -F. Xia, L. -L. Zhang, X. -R. Song, X. -Y. Liu and Y. -M. Liang, *Org. Lett.*, 2012, **14**, 2480–2483; (d) C. G. Savarin, J. A. Murry and P. G. Dormer, *Org. Lett*., 2002, **4**, 2071-2074.
13 (a) A. K. Gupta, H. Ila and H. Junjappa, *Synthesis*, 1988, 284–286; (b) A. K. Gupta, R. T. Chakrasali, H. Ila and H. Junjappa, *Synthesis*, 1989, 141–142; (c) R. -L. Yan, J. Luo, C. -X. Wang, C. -W. Ma, G. -S. Huang and Y. -M. Liang, *J. Org. Chem.*, 2010, **75**, 5395–5397.
14 V. Aggarwal, H. Ila and H. Junjappa, *Synthesis*, 1982, 65–68.
15 A. Rahman, H. Ila and H. Junjappa, *J. Chem. Soc. Chem. Commun.*, 1984, 430-431.
16 (a) S. Kumar, H. Ila and H. Junjappa, *J. Org. Chem.*, 2009, **74**, 7046–7051; (b) R. Bernini, G. Fabrizi, A. Sferrazza and S. Cacchi, *Angew. Chem. Int. Ed.*, 2009, **48**, 8078–8081; (c) J. -W. Sun, X. -S. Wang and Y. Liu, *J. Org. Chem*., 2013, **78**, 10560-10566.
17 J. J. Neumann, M. Suri and F. Glorius, *Angew. Chem. Int. Ed.*, 2010, **49**, 7790–7794.
18 G. Cheng, X. Zeng, J. Shen, X. Wang and X. Cui, *Angew. Chem. Int. Ed.,* 2013, **52**, 13265 –13268.
19 C. Cimarelli, S. Giuli and G. Palmieri, *Eur. J. Org. Chem.,* 2006, 1017–1022.
20 A. C. Vinayaka, M. P. Sadashiva, X. Wu, S. S. Biryukov, J. A. Stoute, K. S. Rangappa and D. C. Gowda, *Org. Biomol. Chem.*, 2014, **12**, 8555–8561.
21 (a) P. S. Silaichev, N. V. Kudrevatykh and A. N. Maslivets, *Russ. J. Org. Chem*., 2012, **48**, 253–256; (b) M. Adib, M. Mahdavi, A. Abbasi, A. H. Jahromi and H. R. Bijanzadeh, *Tetrahedron Lett.*, 2007, **48**, 3217–3220.
22 (a) T. Zhang, Y.-M. Jia, S.-J Yan, C.-Y Yu and Z.-T Huang, *Arkivoc*, 2009, 156–170 (b) W.-D. Rudorf, A. Schierhorn and M. Augustin, *Tetrahedron*, 1979, **35**, 551-556.
23 Z. -H. Zhang, L. Yin and Y. -M. Wang, *Adv. Synth. Catal.*, 2006, **348**, 184–190.
24 S. S. Palimkar, V. S. More and K. V. Srinivasan, *Synth. Commun.*, 2008, **38**, 1456–1469.
25 S. Fustero, M. G. Torre, B. Pina and A. S. Fuentes, *J. Org. Chem.*, 1994, **64**, 5551-5556.
26 (a) H. T. S. Braibante, M. E. F. Braibante, G. B. Rosso and D. A. Oriques, *J. Braz. Chem. Soc.,* 2003, **14**, 994-997; (b) B. Rechsteiner, F. T. Boullet and J. Hamelin, *Tetrahedron Lett*., 1993, **34**, 5071-5074.
27 Y. Gao, Q. Zhang and J. Xu, *Synth. Commun.,* 2004, **34**, 909-916.
28 (a) M. M. Khodaei, A. R. Khosropour and M. Kookhazadeh, *Can. J. Chem*., 2005, **83**, 209-212; (b) M. M. Khodaei, A. R. Khosropour and M. Kookhazadeh, *Synlett.,* 2004, **11**, 1980-1985.
29 C. J. Valduga, A. Squizani, H. S. Braibante and M. E. F. Braibante, *synthesis*, 1998, 1019-1022.
30 (a) H. A. Stefani, I. M. Costa and D. C. Silva, *synthesis*, 2000, **11**, 1526-1528; (b) A. R. Khosropour, M. M. Khodaei and M. Kookhazadeh, *Tetrahedron Lett.*, 2004, **45**, 1725-1728.
31 S. Seko and K. Miyake, *Synth. Commun*., 1999, **29**, 2487-2492.
32 O. Prakash, A. Batra, V. Chaudhri and R. Prakash, *Tetrahedron Lett*., 2005, **46**, 2877-2878.
33 M. Ghandi and A. H. Jamea, *Tetrahedron Lett*., 2011, **52**, 4005-4007.
34 C. Deng, Y, Yang, M. Gao, Y. -P. Zhu, A. -X. Wu, J. -R. Ma and G. -D. Yin, *Tetrahedron*, 2012, **68**, 3828-3834.
35 B. Raghava, G. Parameshwarappa, A. Acharya, T. R. Swaroop, K. S. Rangappa and H. Ila, *Eur. J. Org. Chem.,* 2014, 1882–1892.
36 (a) G. Yin, B. Zhou, X. Meng, A. Wu and Y. Pan, *Org. Lett*., 2006, **8**, 2245-2248; (b) G. Yin, Z. Wang, A. Chen, M. Gao, A. Wu and Y. Pan, *J. Org. Chem.,* 2008, **73**, 3377–3383.
37 (a) Y. J. Song, J. S. Choi and J. I. Lee, *Bull. Korean Chem. Soc*., 2013, **34**, 3117-3120; (b) K. E. Andersen, B. F. Lundt, A. S. Jorgensen and C. Braestrup, *Eur. J. Med. Chem*., 1996, **31**, 417-425; (c) F. C. Fuchs, G. A. Eller and W. Holzer, *Molecules*, 2009, **14**, 3814-3832.
38 (a) S. Venkataraman, D. K. Barange and M. Pal, *Tetrahedron Lett*., 2006, **47**, 7317-7322; (b) S. Shin, Y. Kim, K. Kim and S. Hong, *Org. Biomol. Chem*., 2014, **12**, 5719-5716.
39 http://www.ccdc.ac.uk/conts/retrieving.html

40 (a) M. Kodomari, S. Nawa and T. Miyoshi, *J. Chem. Soc. Chem. Commun.*, 1995, 1895-1896; (b) P. J. Kropp, G. W. Breton, S. L. Craig, S. D. Crawford, W. F. Durland, J. E. Jones and J. S. Raleigh, *J. Org. Chem.*, 1995, **60**, 4146-4152.

41 Preparation of enaminones type A, B & C (**3**, **5** & **7**): Appropriate substrate **1**, **4**, **6** (2 mmol), amine **2** (2.6 mmol) and 5 volume of acidic silica with respect to **1**, **4, 6** was grinded thoroughly using pestle and mortar (for liquid state reactants slurry was made using little amount of chloroform under reduced pressure), transformed to the oven dried 30 mL screw cap reaction vial with magnetic stir-bar followed by addition of anh. $AlCl_3$ (0.03-0.1 equiv.). The reaction mixture was stirred vigorously at 60 °C for time mentioned in the **table 2, 3 & 4**. After completion of reaction (monitored by TLC), crude reaction mass was directly transformed to column packed with silica gel, purified using ethyl acetate-hexane to give desired product (**3, 5 & 7**).

42 Preparation of 1,2 disubstituted 4-Quinolones (**8**, **10 & 12**): The enaminones **7**, **9, 11** (1 mmol) was added to mortar charged with basic alumina (5 volume), grind thoroughly for 5 min, transferred to dried 30 mL reaction vial with magnetic stir-bar followed by addition of anh. K_2CO_3 (2 equiv.). The reaction mixture was stirred vigorously at 90 °C for time mentioned in table **6**, **7 &** scheme 3. After completion of reaction, crude reaction mass was subjected for silica gel column chromatography without any workup gives the desired product **8**, **10 & 12**.

43 Note: The used alumina was first treated with boiling methanol for 30 min of stirring, filtered through Buchner funnel and washed with hot water followed by drying. Similarly, the used silica is stirred in a mixture of methanol and water (1:2) for 30-40 min. the silica gel was filtered through sintered glass funnel and dried at 110 °C for 16 h.