RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

RSC Advances

COMMUNICATION

A facile catalyst-free synthesis of 2-vinylquinolines via direct deamination reaction occurring during Mannich synthesis

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

DOI: 10.1039/x0xx00000x

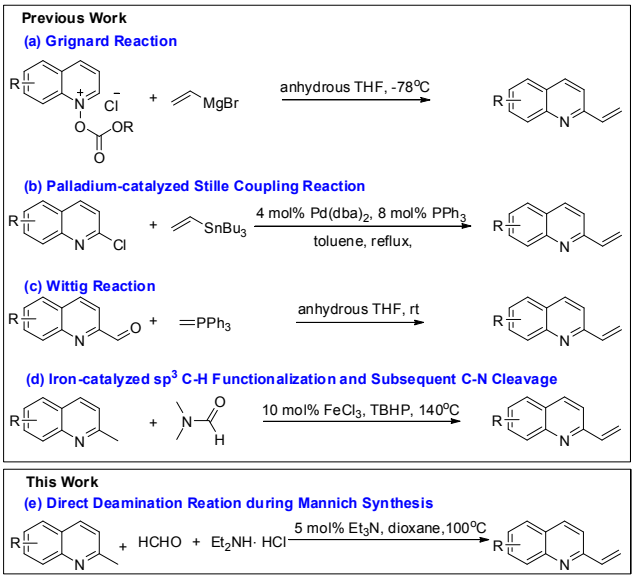
www.rsc.org/

[#]Jichao Xiao, [#]Ye Huang, Zilan Song and Wenhua Feng*

A facile catalyst-free method for the synthesis of 2-vinylquinolines via direct deamination reaction during Mannich synthesis has been developed. Instantaneous hydrogen transfer via a six-membered ring intermediate is proposed as a key step for the direct deamination reaction. This reaction strategy tolerates a broad substrate scope and provides a high-efficient way to synthesize 2-vinylquinolines with adequate yields.

2-vinylquinolines are not only ubiquitous structural motifs in biologically relevant molecules,[1] but also valuable intermediates in organic synthesis[2] and drug discovery.[3] Conventional methods for the synthesis of 2-vinylquinolines include (Scheme 1): iron-catalyzed sp^3 C-H functionalization and a subsequent C-N cleavage reaction between 2-methylquinolines and *N,N*-dimethylformamide;[4] Grignard reaction between vinylmagnesium bromide and *N*-oxyisobutyl-oxycarbonylquinolinium chloride at low temperature;[5] Stille coupling reaction between 2-chloroquinoline and tri(n-butyl)vinylstannane;[6] Wittig reactions between 2-quinaldehyde and methyl triphenyl phosphonium bromide.[7] However, all these reported methods possess some shortcomings, such as low yield,[6,7] harsh reaction conditions,[4,5] numerous steps,[5,7] and the use of organometallic compounds,[4,5,6] etc. Therefore, it is necessary to develop a simple, efficient and catalyst-free method to synthesize 2-vinylquinolines.

The deamination reaction following Mannich synthesis has also been recognized as an efficient strategy for producing vinyl derivatives. Various vinyl derivatives derived from the Mannich bases of aldehydes, α,β-unsaturated aldehydes, ketones, acetylenes, oximes have been produced via the deamination reaction.[8] The deamination reaction involves the elimination of a primary or secondary amine from a prepared Mannich base or of a tertiary amine from the prepared quaternary ammonium salt of Mannich base which is more reactive. In the industrial process for the synthesis of LTD4 receptor antagonists Montelukast, 2-vinyl-7-chloroquinolines has been prepared through Mannich reaction of 7-chloro-2-methylquinoline followed by Hofmann elimination of the quaternary salt of Mannich base. However, the overall yield was just 45% from 7-chloro-2-methylquinoline and the procedure is complicated and time-consuming.[3] In rare cases when the substrates were ketones, the deamination reaction could occur directly during Mannich synthesis, but with special conditions.[9,10] Undoubtedly, it provides a higher yield and shorter synthetic route because the Mannich base formed in the reaction is neither isolated nor quaternized, but directly eliminated to produce vinyl derivatives. However, the yield in the previous attempt for the synthesis of 2-vinylquinolines via direct deamination reaction occurring during Mannich synthesis was just under 2%.[11] Here, we reported a method for the rapid synthesis of 2-vinylquinolines via direct deamination reaction with great yield and simple process.



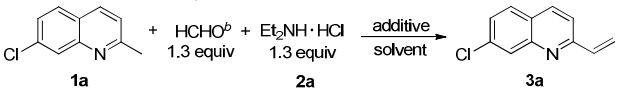
Scheme 1. Reported synthesis methods of 2-vinylquinolines

*Department of New Drug Research and Development, Institute of Materia Medica, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China. Email:fwh@imm.ac.cn; Tel:+86-10-8315-8977
[#] These authors contributed equally to this work.
† Electronic Supplementary Information (ESI) available: Synthetic procedures and characterization data; See DOI: 10.1039/x0xx00000x

Initially, the reaction of 7-chloro-2-methylquinoline (**1a**) with formaldehyde solution and diethylamine hydrochloride was chosen as a model reaction to optimize the reaction conditions. After a number of attempts, we found that 7-chloro-2-methylquinoline, formaldehyde solution and diethylamine hydrochloride reacted together with 5 mol % Et_3N in dioxane at 100°C gave the best result, that the reaction was completed after only half an hour with a high isolated yield of 95% (Table 1, entry 3). The addition of catalytic amount of Et_3N was important for the reaction yield that the yield dropped to 58% in the absence of Et_3N (Table 1, entry 1). Meanwhile, the accurate loading of the Et_3N was also essential that slightly reduced yields were obtained when loadings of Et_3N were below or above 5 mol % (Table 1, entries 2 and 4). Both the reaction yield and the reaction speed were correlated with temperature that, along with temperature decreased, both yield of desired product **3a** and reaction speed decreased, but yield of Mannich base increased (Table 1, entries 5-9). When the reaction was executed at room temperature (25 °C), only Mannich base was obtained at a low yield of 40% after 48 hours (Table 1, entry 9). These results also suggested that Mannich base was produced first for the following formation of the desired 2-vinylquinolines **3a**. Meanwhile, we could infer that the energy barrier for the deamination reaction is higher than for the formation of the Mannich base, because only Mannich reaction happened but no deamination reaction was detected at room temperature. Other inorganic bases, organic bases and coupling reagent DCC were also examined as catalyst and we found that only the reaction yield with K_2CO_3, LiOH and pyridine (Table 1, entries 13, 16 and 19) were comparable with Et_3N. Other bases, such as NaOH, KOH, DBU, C_2H_5ONa and DCC (Table 1, entries 10-12, 14, 15, 17) did not improve the yield obviously compared with the reaction without any catalyst (Table 1, entry 1). When equimolar amount of acids were added, the product was just Mannich base again, but the reaction yield and speed was much higher than reaction at room temperature (Table 1, entries 20, 21). This reminds us that the conversion of Mannich base to desired product **3a** could not proceed when the micro-environment is acidic. Finally, the influence of the reaction solvent was explored. Much lower reaction yields and slower reaction speed were obtained when the reaction was performed in other organic solvents (Table 1, entries 22–27). The lower yield might result from either the relatively lower reflux temperature or the difference of solvent polarity.

Next, the scope of various amine hydrochlorides **2** in the deamination reaction was investigated. The reaction efficiency was not significantly influenced by the alkyl substituents of the amine hydrochlorides (Table 2, entries 1-3). When dimethylamine hydrochloride was used in the reaction, **3a** was obtained in an isolated yield of 88% which is slightly lower than diethylamine hydrochloride. Worse than dimethylamine hydrochloride, dipropylamine hydrochloride and diisopropylamine hydrochloride provided **3a** in 79% and 62% yield, respectively. The lower yield with diisopropylamine hydrochloride than with dipropylamine hydrochloride reminds us the steric effects might play an important role in the reaction efficiency. In addition, neither Mannich reaction nor deamination reaction happened when the amine hydrochlorides substrate was dibenzylamine hydrochloride.

Table 1. Optimization of Reaction Conditions[a]

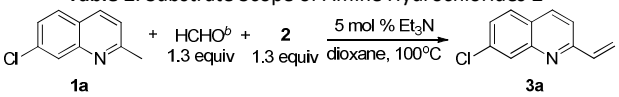


1a 2a 3a

Entry	Additive (mol %)	Solvent	t(°C)	Time(h)	Yield(%)[c]
1	-	dioxane	100	1	58
2	Et_3N (3)	dioxane	100	1	82
3	**Et_3N (5)**	**dioxane**	**100**	**0.5**	**95**
4	Et_3N (10)	dioxane	100	1	85
5	Et_3N (5)	dioxane	90	1.5	92
6	Et_3N (5)	dioxane	80	3.5	89
7	Et_3N (5)	dioxane	70	5	55
8	Et_3N (5)	dioxane	60	14	33
9	Et_3N (5)	dioxane	25	48	MB[d]
10	NaOH (5)	dioxane	100	5.5	70
11	KOH (5)	dioxane	100	5.5	65
12	Na_2CO_3 (5)	dioxane	100	2	74
13	K_2CO_3 (5)	dioxane	100	1.5	92
14	DCC (5)	dioxane	100	1.5	75
15	DBU (5)	dioxane	100	1	77
16	LiOH (5)	dioxane	100	1	91
17	C_2H_5ONa (5)	dioxane	100	1	74
18	KOBu-t (5)	dioxane	100	1.5	87
19	pyridine (5)	dioxane	100	1	91
20	HCl (5)	dioxane	100	3	MB[e]
21	H_2SO_4 (5)	dioxane	100	3	MB[e]
22	Et_3N (5)	EtOH	reflux	5	68
23	Et_3N (5)	CH_3OH	reflux	9	40
24	Et_3N (5)	CH_2Cl_2	reflux	18	73
25	Et_3N (5)	THF	reflux	18	45
26	Et_3N (5)	DMF	100	1.5	55
27	Et_3N (5)	DMSO	100	1.5	46

[a]Reaction conditions: **1a** (0.5 mmol), HCHO (0.65 mmol) and diethylamine hydrochloride (0.65 mmol) react in various solvents (1 mL) at various temperatures. [b]HCHO is formaldehyde solution. [c]Isolated yield. [d]The Mannich base was obtained in 40% yield after reaction for more than 48 hours, no vinyl product. [e]The Mannich base was obtained in 90% yield after reaction for 1 hour, no vinyl product.

Table 2. Substrate Scope of Amine Hydrochlorides **2**[a]



1a 3a

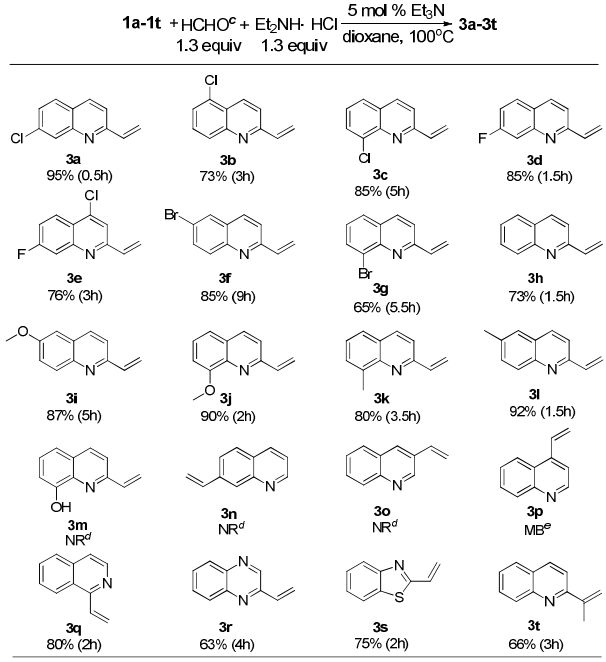
Entry	**2**		Time(h)	Yield(%)[c]
1	Me_2NH·HCl	**2b**	3	88
2	$(n\text{-Pro})_2NH$·HCl	**2c**	5	79
3	$(i\text{-Pro})_2NH$·HCl	**2d**	1.5	62
4	Bn_2NH·HCl	**2e**	>24	NR[d]

[a]Reaction conditions: **1a** (0.5 mmol), HCHO (0.65 mmol) and **2b-2e** (0.65 mmol) react in dioxane (1 mL) at 100 °C. [b]HCHO is formaldehyde solution. [c]Isolated yield. [d]No reaction happened.

Under the optimized reaction condition, the scope of the reaction substrates was then investigated. As shown in Table 3,

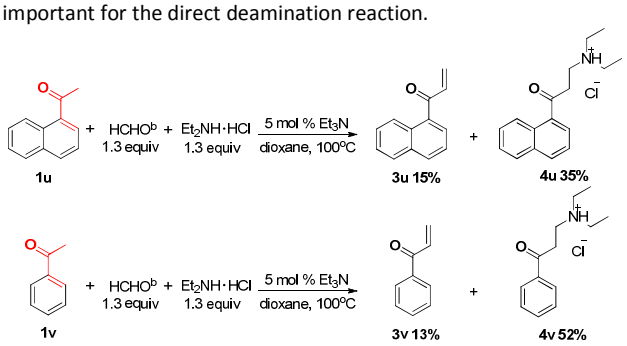
various substrates (**1a-1t**) were employed in the reaction. Electron-withdrawing substituents such as 7-chloro (**3a**), 5-chloro (**3b**), 8-chloro (**3c**), 7-fluoro (**3d**), 4-chloro-7-fluoro (**3e**), 6-bromo (**3f**), 8-bromo (**3g**), and electron-donating substituents such as 6-methoxy (**3i**), 8-methoxy (**3j**) were all well tolerated in the present reaction condition to afford the desired 2-vinylquinolines. Among them, the isolated yield of 8-bromo (**3g**) was the lowest which is 65%, but was still quite acceptable. When both position 6 or position 8 and position 2 were modified with methyl group, the methylene was only introduced to the methyl group at position 2 to produce **3k** and **3i**. The regioselectivity reminds us the importance of the inductive effect of nitrogen atom. Besides, when 3-methylquinoline, 4-methylquinoline and 7-methylquinoline were used as substrates, no desired products (**3n-3p**) were detected. However, their reaction results were different that no reaction happened when either 3-methyl or 7-methyl was used, but product of Mannich reaction could be isolated when 4-methylquinoline was used. In contrast, when 1-methylisoquinoline whose methyl group and nitrogen atom have switched place was used in the reaction, the desired product **3q** was still obtained in high isolated yield. These results indicate that the relationship between the relative positions of methyl group and nitrogen atom could affect the inducing effect of nitrogen atom. Interestingly, different from other substitutes at position 8, 8-hydroxyl failed to undergo the deamination reaction, which may be owing to the interference from the hydroxyl to the electron transfer of the adjacent nitrogen atom by hydrogen-bonding interaction. In order to further extend the scope of the deamination reaction, 2-methylquinoxaline, 2-methylbenzothiazole, and 2-ethylquinoline were also evaluated as substrates, and they all provided their corresponding products under the optimized condition in acceptable yields (**3r-3t**).

Table 3. Substrate Scope of **1**[a]



[a]Reaction conditions: **1a-1t** (0.5 mmol), HCHO (0.65 mmol), diethylamine hydrochloride (0.65 mmol) react in dioxane (1 ml) at 100 °C. [b]Isolated yield. [c]HCHO is formaldehyde solution. [d]NR: no desired products isolated. [e]MB: Only Mannich reaction happened.

In order to investigate the precise mechanism for the direct deamination reaction happening instead of common Mannich reaction, control experiments were performed. When the substrate are 1-acetonaphthone and acetophenone, whose structures are similar as 2-methyquinoline, the major products become Mannich base **4u** and **4v** and only 15% and 13% vinyl products were obtained respectively under the optimized condition (Scheme 2). The reaction difference between 1-acetonaphthone, acetophenone and 2-methylquinoline reflects the substrate selectivity of the direct deamination reaction and provides important clues for the mechanism study. It indicated that not all the Mannich base was able to be directly converted to the product of deamination reaction in such a high yield and high rate, as mentioned in previous reports.[8] The participation of neighbouring nitrogen atom was important for the direct deamination reaction.

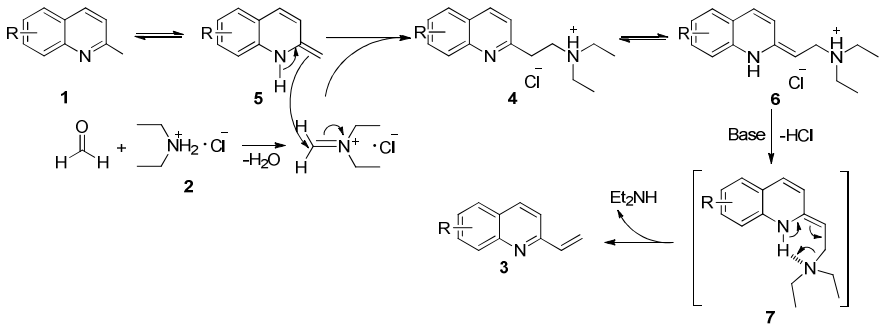


Scheme 2. Reactions between 2-acetonaphthone, formaldehyde solution and diethylamine hydrochloride

Based on the experimental results above, we proposed that the deamination reaction occurs through a six-membered ring intermediate **7** as shown in Scheme 3. First, Mannich base **4** was formed through Mannich reaction among the enamine tautomer **5** of 2-methylquinoline **1**, formaldehyde solution and diethylamine hydrochloride. Then, unprotonated form of intermediate **6**, which is isomer of Mannich base **4**, was generated after the addition of base, followed by instantaneous hydrogen transfer to finally produce the stable 2-vinylquinoline **3**. Because the hydrogen transfer provides an extra conjugated double bond to stabilize the structure, the equilibrium tends to the direction of deamination instead of providing Mannich base. And according to the mechanism we proposed, protonated nitrogen atom is unable to interact with the hydrogen atom of the enamine, therefore only Mannich base was obtained when acid was added (Table 1, entries 20, 21) and significantly lower yield was obtained when no base was added (Table 1, entry 1).

In conclusion, we have developed a simple catalyst-free method for the synthesis of 2-vinylquinolines via direct deamination reaction during Mannich synthesis. Although the procedure of this one-pot synthesis is analogous to the classical Mannich reaction, by suitable choice of substrates and optimization of reaction conditions, the vinyl product instead of Mannich base is the direct product isolated from the process. The substrate scope is pretty wide that a series of 2-vinylquinolines could be obtained from

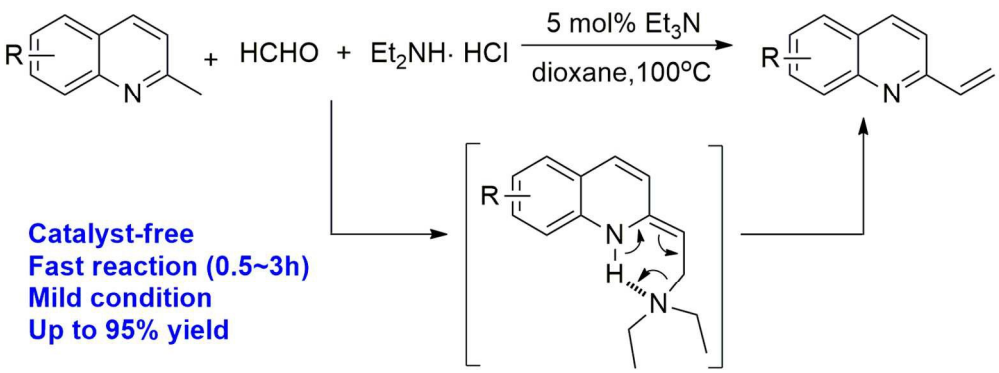
cheap, readily available 2-methylquinolines with adequate yields. Owing to the high-efficiency and simplicity, the present reaction procedure appears to be superior to previous reported methods for the synthesis of 2-vinylquinolines. Further work on expanding this strategy toward the synthesis of other styrylquinoline compounds is currently underway.



Scheme 3. Proposed mechanism for the direct deamination reaction

Notes and references

1. (a) A. Fournet, A. A. Barrios, V. Munoz, R. Hocquemiller, A. Cave´ and Bruneton, *J. Antimicrob. Agents Chemother.,* 1993, **37**, 859; (b) J. F. Mouscadet and D. Desmaele, *Molecules*, 2010, **15**, 3048; (c) W. Cieslik, R. Musiol, J. E. Nycz, J. Jampilek, M. Vejsova, M. Wolff, B. Machura and J.Polanski, *Bioorg. Med. Chem.*, 2012, **20,** 6960; (d) M. Rams-Baron, M. Dulski, A. Mrozek-Wilczkiewicz, M. Korzec, W. Cieslik, E. Spaczynska, P. Bartczak, A. Ratuszna, J. Polanski and R. Musiol, *PloS one,* 2015, **10**, e0131210.
2. (a) M. Lautens, A. Roy, K. Fukuoka, K. Fagnou and B. Martin-Matute, *J. Am. Chem. Soc.*, 2001, **123,** 5358; (b) R. D. Ferguson, N. Su and R. A. Smith, *Tetrahedron Lett.,* 2003, 44, 2939; (c) W. J. Drury, N. Zimmermann, M. Keenan, M. Hayashi, S. Kaiser, R. Goddard and A. Pfaltz, *Angew. Chem. Int. Ed.*, 2004, **116**, 72; *Angew. Chem. Int. Ed.* 2004, **43**, 70; (d) T. P. Glushenko, V. I. Goncharov and A. V. Aksenov, *Chem. Heterocycl. Compds.,* 2008, **44**, 973; (e) G. M. Schaaf, S. Mukherjee and A. G. Waterson, *Tetrahedron Lett*., 2009, **50**, 1928.
3. R. D. Larsen, E. G. Corley, A. O. King, J. D. Carroll, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang and R. J. Zamboni, *J. Org. Chem.*, 1996, **61**, 3398.
4. Y. Li, F. Guo, Z. Zha and Z. Wang, *Chem.-Asian J.*, 2013, **8**, 534;
5. M. A. Fakhfakh, X. Franck, A. Fournet, R. Hocquemiller and B. Figadère, *Tetrahedron Lett*., 2001, **42**, 3847.
6. J. Y. Legros, G. Primault, M. Toffano, M. A. Rivière and J. C. Fiaud, *Org. Lett.*, 2000, **2**, 433.
7. M. A. Fakhfakh, X. Franck, A. Fournet, R. Hocquemiller and B. Figadère, *Synth. Commun.*, 2002, **32**, 2863.
8. M. Tramontini and L. Angiolini, *Mannich bases: chemistry and uses.* CRC Press Inc., U.S.A., 1994.
9. (a) J. L. Grass, *Tetrahedron Lett*., 1978, **32**, 2955; (b) J. L. Grass, *Tetrahedron Lett*., 1978, **24**, 2111.
10. S. J. deSolms, *J. Org. Chem.*, 1976, **41**, 2650.
11. V. Boekelheide and A. L. Sieg, *J. Org. Chem.*, 1954, **19**, 587.



128x47mm (300 x 300 DPI)