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A new and efficient one-pot procedure for the synthesis of 2-styrylquinolines

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ABSTRACT

A one-pot combination of a modified Friedländer annulation and a Knoevenagel condensation provides 2-styrylquinolines in good to excellent yields. A variety of substrates are reacted in one-pot in the presence of 1-methylimidazolium trifluoroacetate ([Hmim]TFA).

Quinolines **1** and their derivatives are very important heterocyclic compounds because of their wide occurrence in natural products[1–3] and biologically active compounds.[4–9] A large variety of quinolines display interesting physiological activities and have found applications as pharmaceuticals and agrochemicals, as well as being general synthetic building blocks.[2] Among the various classes of quinolines, 2-styryl-substituted derivatives **2** form an important component of pharmacologically active compounds, associated with a wide spectrum of biological activities[10–24] such as HIV integrase inhibition.[17–24] In this respect, d'Angelo and coworkers reported that polyhydroxylated styrylquinolines, exemplified by **3**, are micromolar inhibitors of the third essential enzyme of HIV-1: integrase (IN), blocking replication of the virus in cell cultures and are themselves devoid of cytotoxicity (Fig. 1).[10–16]

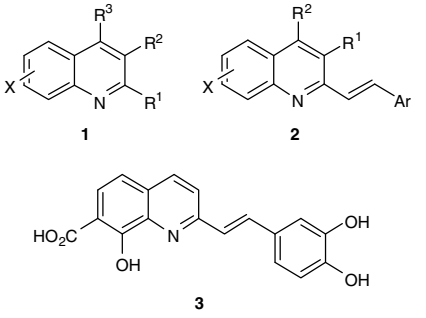
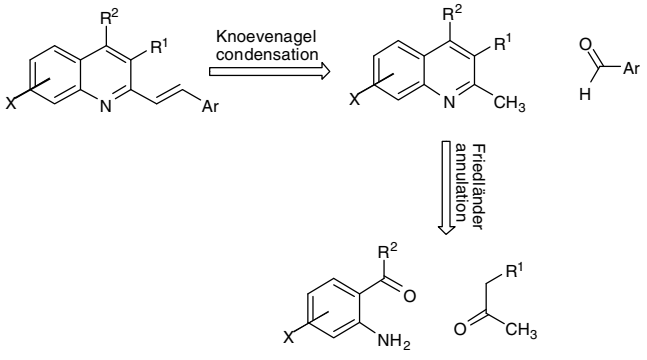


Figure 1.

The general method for the synthesis of these derivatives is via condensation of 2-methylquinolines with aromatic aldehydes under basic or acidic conditions.[17–24] Thus, 2-methylquinolines are key intermediates in the synthesis of 2-styrylquinolines. Friedländer annulation is one of the most simple and straightforward approaches for the synthesis of 2-methylquinolines.[25]

In this study, we have developed a novel and facile method for the synthesis of 2-styrylquinolines bearing different groups at the 3-position using the Friedländer reaction of a 2-aminoarylketone and a methylketone followed by Knoevenagel condensation with an aromatic aldehyde in the presence of 1-methylimidazolium



Scheme 1.

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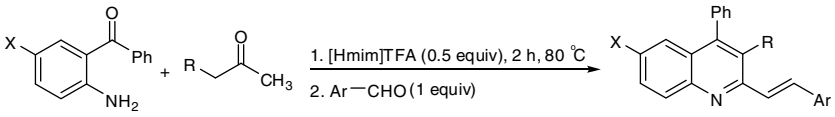
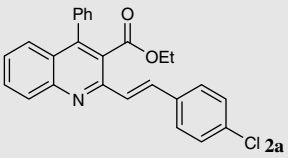
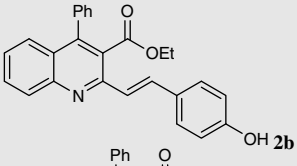
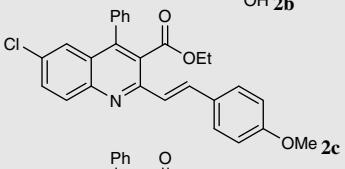
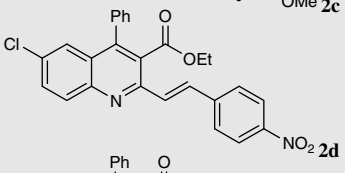
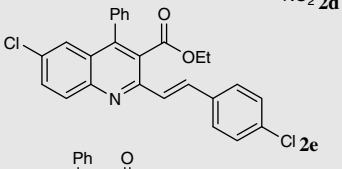
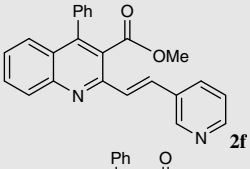
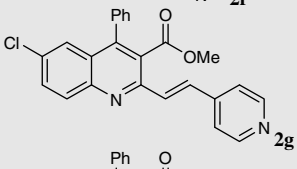
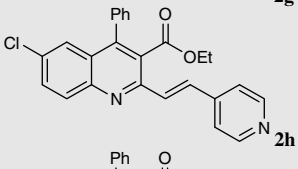
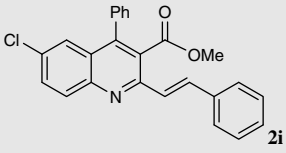
trifluoroacetate ([Hmim]TFA)[26] as a Brønsted acidic ionic liquid (IL) (Scheme 1).

We have reported previously [Hmim]TFA as an efficient acidic IL for the synthesis of heterocyclic compounds.[27,28] Also it was shown that [Hmim]TFA promoted the Knoevenagel condensation of CH-acids and aromatic aldehydes.[29] Thus, we decided to investigate the one-pot synthesis of 2-styryl-substituted quinolines in [Hmim]TFA. After extensive optimization, we found that the two steps could be carried out in a general and efficient one-pot process to afford a variety of 2-styrylquinolines.[30] As outlined in Table 1, addition of 0.5 equiv of [Hmim]TFA to a reaction mixture containing a 1:1 ratio of 2-aminoarylketone:methyl ketone at 80 °C for 2 h was optimal for the formation of 2-methylquinolines. Subsequent treatment with 1 equiv of aromatic aldehyde, followed by heating

Table 1
Synthesis of 2-styrylquinolines



Entry	X	R	Ar	Product	Yield[a] (%)
1	H	COOEt	4-ClC_6H_4	 **2a**	87
2	H	COOEt	4-HOC_6H_4	 **2b**	84
3	Cl	COOEt	4-$MeOC_6H_4$	 **2c**	81
4	Cl	COOEt	4-$O_2NC_6H_4$	 **2d**	84
5	Cl	COOEt	4-ClC_6H_4	 **2e**	82
6	H	COOMe	3-Pyridyl	 **2f**	78
7	Cl	COOMe	4-Pyridyl	 **2g**	80
8	Cl	COOEt	4-Pyridyl	 **2h**	78
9	Cl	COOMe	C_6H_5	 **2i**	82

[a] Isolated yield.

at 80 °C for 2 h, afforded 2-styryl-substituted quinolines in yields typically exceeding 78%.

Aromatic aldehydes carrying different functional groups reacted satisfactorily under the reaction conditions as can be seen in Table 1. Heteroaromatic aldehydes were equally amenable to these conditions with pyridine-3-carbaldehyde providing the corresponding 2-styrylquinoline in 78% yield. Prominent among the advantages of this new method are operational simplicity, good yields, short reaction times, and an easy work-up procedure without using any chromatographic methods. It is worthy to note that in previous reports, condensation of 2-methylquinolines and aromatic aldehydes is performed under harsh reaction conditions and requires long reaction times.

In conclusion, a new one-pot procedure for the synthesis of 2-styrylquinolines is described that utilizes a Friedländer reaction promoted by [Hmim]TFA, followed by a clean and rapid [Hmim]TFA-mediated Knoevenagel condensation to afford the corresponding styrylquinoline. To the best of our knowledge, this is the first report on the synthesis of styrylquinolines starting from commercially available 2-aminoarylketones and methyl ketones. [Hmim]TFA tolerated a range of aldehydes. In addition, this methodology is cost effective and amenable to large scale synthesis.

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Supplementary data

Experimental procedures and characterization data for compounds **2a**–**i** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.054.

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30. *Typical procedure for the synthesis of 2-styrylquinolines*: To a mixture of 2-amino-5-chlorobenzophenone (0.231 g, 1 mmol, 1.0 equiv), and methyl acetoacetate (0.116 g, 1 mmol, 1 equiv) was added 0.1 g (0.5 mmol, 0.5 equiv) of [Hmim]TFA, and the reaction mixture was heated at 80 °C. After 2 h, benzaldehyde was added and the reaction mixture was stirred for 2 h at 80 °C. After completion of the reaction, which was indicated by TLC (eluent: *n*-hexane/ethyl acetate:2/1), water was added to the mixture and the resulting solid was filtered. The crude product was recrystallised from EtOH to yield (*E*)-methyl 6-chloro-4-phenyl-2-styrylquinoline-3-carboxylate **2i** as a brown solid (0.327 g, 82%): mp 207–208 °C; IR (KBr): 1734 (C=O), 1209, 1062 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 3.62 (s, 3H), 7.39–8.61 (m, 15H, 13 Ar–H + 2CH); ^{13}C NMR (75 MHz, DMSO-d_6) 53.2 (CH_3), 122.1, 125.1, 126.5, 128.0, 128.3, 129.0, 129.5, 131.9, 132.2, 132.7, 134.3, 134.5, 143.1, 146.2, 150.3, 150.7, 167.1 (C=O); MS (EI, 70 eV): *m*/*z* (%): 399 (M^+, 40), 384 (100), 323 (50); Anal. Calcd for $C_{25}H_{18}NO_2Cl$: C, 82.17; H, 5.24; N, 3.83. Found: C, 82.22; H, 5.19; N, 3.89.