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A facile one-pot synthesis of 2-(2-pyridyl)quinolines via Povarov reaction

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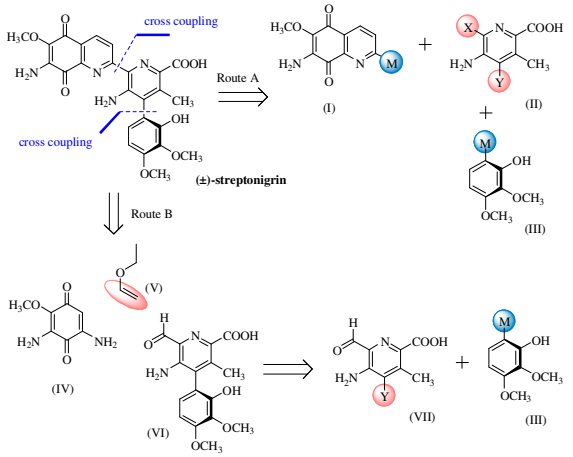
ABSTRACT

An efficient synthesis of 2-(2-pyridyl)quinolines was achieved via three-component Povarov reaction of aromatic aldehydes, anilines, and ethyl vinyl ether under boron trifluoride methyl etherate ($BF_3.O(CH_3)_2$) acid catalysis. The developed methodology for the preparation of 2-(2-pyridyl)-quinoline offers several advantages over previous methods including mild reaction conditions, easy work-up, a wide range of substrate applicability and products in good yields.

1. Introduction

Streptonigrin (Scheme 1) is an antitumor antibiotic produced by *Streptomyces flocculus*[1]. In 1963 Rao, Biemann, and Woodward established streptonigrin's tetracyclic pyridylquinolone structure based upon a brilliant combination of degradation and spectral studies[2]. Their original formulation was confirmed by X-ray crystallography[3]. In addition to its unique heterocyclic structure, streptonigrin has also been found to be produced by microorganisms via a novel biosynthetic pathway[4]. Highly substituted and functionalized 7-aminoquinoline-5,8-dione, has been shown to possess potent cytotoxic properties, broad spectrum antitumor activity, antiviral properties in vitro and in vivo,[5] and to display potent antimicrobial properties[6]. Streptonigrin has been investigated clinically as an anticancer drug, and although quite promising, severe bone marrow depression in treated patients has limited its widespread application in cancer chemotherapy[7]. Considerable effort has been made to prepare streptonigrin[8] as well as some analogues, with the ultimate goal being the preparation of a molecule having high activity but possessing attenuated toxicity[9].

In view of the importance of producing streptonigrin derivatives, several methods were developed for the synthesis of 2-(2-pyridyl)quinolines[10]. However, many of the synthetic protocols reported so far suffer from various disadvantages, including harsh reaction conditions, multistep reaction, expensive reagents lengthy reaction times, requirement of large amount of catalyst and low yield of desired products[11]. Although cross-coupling reactions are efficient for the preparation of bis-aryl[12] and bis-heteroaryl[13] compounds, the synthesis of 2-(2-pyridyl)quinolines by such procedures is neither widespread nor particularly efficient[14]. The most efficient synthesis of streptonigrin reported so far, accomplished by a cross coupling strategy (cf. route A, Scheme 1), serves to demonstrate the challenges associated with cross-coupling suitably substituted fragments[8]. Therefore, considering such limitations, an efficient protocol for the synthesis of streptonigrin-like molecules is required.



Scheme 1 Retrosynthetic analyses of streptonigrin

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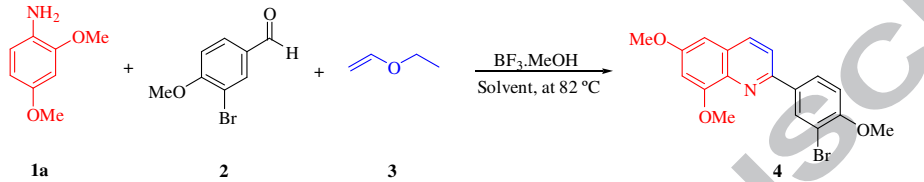
Multicomponent reactions (MCRs) have been steadily gaining importance in organic and medicinal chemistry[15]. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the synthesis of drug-like molecules with several degrees of structural diversity, since the combination of three or more building blocks in a single operation leads to a high combinatorial efficiency[16]. Among the large diversity of MCR is included the so called Povarov reaction[17]. This reaction involves a condensation of aniline with a carbonylic compound resulting in an imine that is further reacted with an electron-rich alkene to yield tetrahydroquinolies[18], quinolines[19] and julolidines[20]. Very recently an oxa-Povarov version resulting in the formation of chromans, have been reported[21]. Despite several synthetic applications of the Povarov reaction, to the best of our knowledge there is no systematic investigation on the preparation of 2-(2-pyridyl)quinolines via this method.

Following our recent effort on the synthesis of streptonigrin[8a,b] we describe herein a novel one-pot three-component efficient methodology for the synthesis of 2-(2-pyridyl)quinolones. We envisage that this protocol can be used for the preparation of several streptonigrin analogues, and ultimately, streptonigrin itself by the strategy outlined in Scheme 1 (route B)..

The multicomponent reaction employs an aniline, a benzaldehyde and ethyl vinyl ether together with boron trifluoride methyl etherate ($BF_3.O(CH_3)_2$) as catalyst.

Table 1
Screening of the solvent in one-pot synthesis of 2-(2-pyridyl)quinolines.



1a **2** **3** **4**

Entry	Solvent	Time (h)	Yield[b] (%)
1	Ethanol	24	54
2	Trifluoroethanol	24	63
3	Acetonitrile	24	81
4	Dimethylsulfoxide	24	64
5	Dimethoxyethane	24	63
6	Nitromethane	24	37
7	Without solvent	24	51

[a] Conditions: 2,4-dimethoxyaniline (1 mmol), 3-bromo-4-methoxybenzaldehyde (1 mmol), and ethyl vinyl ether 1.5 mmol), BF_3.MeOH acid (20 mol %) at was performed at 82 ºC. The progress of reaction was monitored by thin layer chromatography.
[b] Isolated yield.

In this work a preliminary investigation aiming to optimize the reaction conditions for producing 2-(2-pyridyl)quinolines was carried out. For a model reaction 2,4-dimethoxyaniline (**1a**), 3-bromo-4-methoxybenzaldehyde (**2**), and ethyl vinyl ether (**3**) were employed. In this case the benzaldehyde was used due to its lower costs compared with the pyridinecarbaldehyde. The results for optimization of the solvent, reaction time are presented in Table 1. In this case the catalyst employed was BF_3.MeOH previously reported as a catalyst for the Povarov reaction[22].

The polar protic solvents ethanol and trifluoroethanol were found to be the best solvents for the reaction affording the required product in moderate yields (54% and 63%) (Table 1, entries 1-2). In the non-protic solvents like dimethylsulfoxide and dimethoxyethane and under solvent-free condition, the desired product **4** was obtained in comparable yield with protic solvents (Table 1, entries 4-5 and 7, respectively). In contrast, the lowest yield was obtained using nitromethane as a solvent (entry 6) whereas the best yield (81%) was obtained using acetonitrile as solvent. The reaction was monitored by TLC analyses and the time required for its completion as evaluated by the consumption of the starting material was 24h (Tab. 1, entry 3). Based on such results all experiments were carried out for 24 hours.

Subsequently, we investigated the influence of the catalyst loading on the model reaction, employing acetonitrile as solvent. Initially at the catalytic loading of 20 mol % BF_3.MeOH, the reaction afforded 81% yield of the product **4** (Table 2, entry 1). An increase in catalyst concentration above 50% leads to a considerable decrease in yield of the required product **4** (Table 2, entries 3 and 4).

The best result for the reaction was obtained employing 30 mol % of the catalyst BF_3.MeOH, what afforded the product **4** in 88% yield (Tab. 2, entry 4).

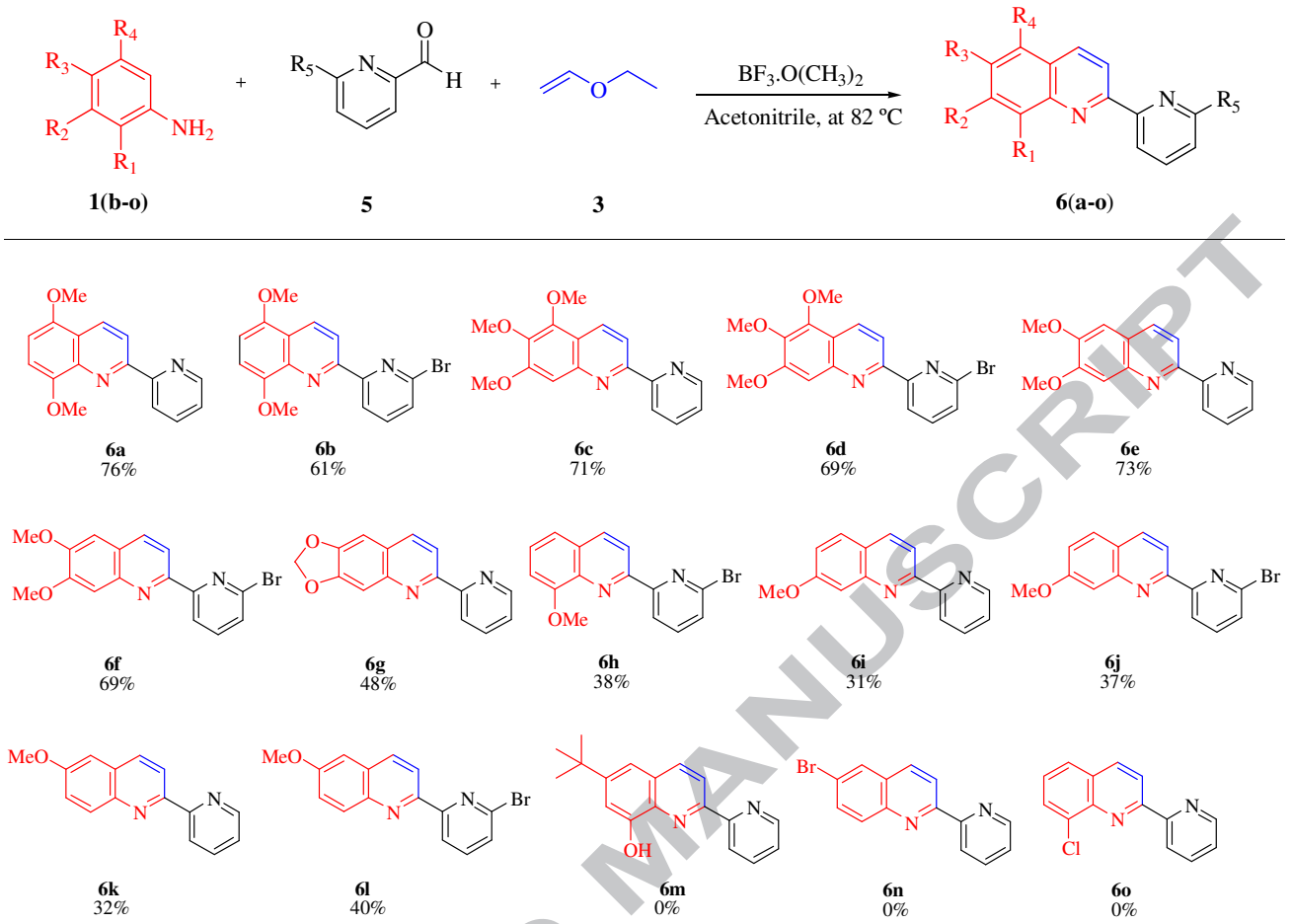
Table 2
Screening of the catalytic loading in one-pot synthesis of 2-(2-pyridyl)quinoline.

Entry	Catalyst (mol%)	Time (h)	Yield[b] (%)
1	BF_3.MeOH (20)	24	81
2	BF_3.MeOH (30)	24	88
3	BF_3.MeOH (50)	24	76
4	BF_3.MeOH (100)	24	58
5	**$BF_3.O(CH_3)_2$ (30)**	**24**	**92**

[a] Conditions: 2,4-dimethoxyaniline (1 mmol), 3-bromo-4-methoxybenzaldehyde (1 mmol), and ethyl vinyl ether (1.5 mmol), acetonitrile (4 ml) at was performed at 82 ºC. The progress of reaction was monitored by thin layer chromatography.
[b] Isolated yield.

In an attempt to improve yields and to check the effectiveness of the process, the reaction has been further investigated using $BF_3O.(CH_3)_2$, under the best condition found using the similar catalyst BF_3.MeOH. Although they are similar, we found that the product **4** was obtained in slightly higher yield (92%) with $BF_3O.(CH_3)_2$. A similar result has been previously reported[23] (Tab. 2, entry 5).

Having established the effectiveness of $BF_3.O(CH_3)_2$ as a catalyst, the scope of this reaction was then investigated using the optimized conditions (24 h, acetonitrile and 82 ºC).



Scheme 2 Multicomponent synthesis of 2-(2-pyridyl)quinolines derivatives via a Povarov reaction.

For this work, the reactivity of several anilines and aldehydes was explored (Scheme 2). It was found that anilines bearing electron-withdrawing groups failed to produce the desired quinolines (Scheme 2, compound **6n** and **6o**). Also, anilines containing bulky group, proved unreactive under these conditions. We ascribe the lack of reactivity in this case (Scheme 2, compound **6l**) to the steric hindrance. The use of aniline with weak electron-withdrawing groups or electron-donating substituents resulted in the corresponding quinolines in average to good yields (31–76%, Scheme 2, **6a-l**).

The best yields were obtained with di- and tri-substituted anilines bearing electron-donating group. Such groups make the pair of electrons on the nitrogen more available for the nucleophilic attack on the aldehyde carbonyl. In general all reactions proceeded well affording a wide range of pyridylquinoline in moderate to good yield (Scheme 2).

In conclusion, we have described a simple one-pot synthesis of 2-(2-pyridyl)quinolines in good yields starting from a diverse set of functionalized anilines and aldehydes, using $BF_3.(OCH_3)_2$ as catalyst.

The key advantages of the present method include mild reaction conditions, easy work-up, clean reaction profile, a wide range of substrate applicability, and good yields of products. We suggest that this method constitutes the shortest direct and atom efficient route for the preparation of new streptonigrin analogues for biological evaluation. Work in this area is in progress in our laboratory and will be reported elsewhere.

Acknowledgments

We thank the Brazilian agencies CNPq for research fellowships (CRB, LCAB, SAF) and FAPEMIG and CAPES for their financial support.

Supplementary Material

Supplementary data associated with this article can be found in the online version, at http://dx/doi.org/10.1016/j.tetlet.2015.x

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24. *General procedure for the synthesis of 2-(2-pyridyl)quinoline derivatives:* Into a 10 mL caped test tube, a mixture of anilines (1 mmol) and aromatic aldehydes (1 mmol) in acetonitrile (4 mL) was taken and left for stirring for 10 min at room temperature. Then ethyl vinyl ether (1.5 mmol) and the catalyst boron trifluoride methyl etherate (0.057 g, 30 mol %) were added successively into the above reaction mixture. Finally, the tube was sealed and maintained at 82 ºC (oil-bath) for 24 hours. The progress of the reaction was monitored by TLC until consumption of the reagents. After completion of the reaction, the catalyst was separated by dilution with 10 ml of $NaHCO_3$ and the crude product extracted with ethyl acetate (3 x 20 ml). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuum and the obtained product was purified by column chromatography using silica gel to afford the required quinoline. The product **(6a-l)** was eluted in ethyl acetate/3% aqueous ammonium hydroxide solution/hexane (25:3:72 v/v/v) in 31–76% yield after column chromatographic separation. Spectral data of some selected compounds:

2-(6-bromopyridin-2-yl)-5,8-dimethoxyquinoline (**6b)**: Yellow solid (0.210 g, 61%); mp 167-168 ºC; R_f (30% ethyl acetate/hexane v/v) 0.35; IR (KBr): 2999; 2937; 2831, 1582; 1474, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.08 (s, 3H), 6.78 (d, 1H, J = 8.5 Hz), 6.97 (d, 1H, J = 8.5 Hz), 7.52 (dd, 1H, J = 7.8 Hz and J = 0.9 Hz), 7.71(t, 1H, J= 7.8 Hz), 8.58 (d, 1H, J = 8.8 Hz), 8.68 (d, 1H, J = 8.8 Hz), 8.70 (dd, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.41, 153.80, 149.61, 149.04, 141.66, 140.08, 139.47, 132.43, 128.60, 122.06, 121.15, 118.97, 107.96, 104.60, 56.61, 56.02; GC-MS, *m/z* : 346 (M+2); HRMS (ESI TOF-MS Calcd for $[C_{16}H_{14}BrN_2O_2]^+$: 345.0233, found 345.0126.

5,6,7-trimethoxy-2-(pyridin-2-yl)quinolone (**6c**): White solid (0.210 g, 71%); mp 147-148 ºC; R_f (30% ethyl acetate/hexane v/v) 0.30; IR (KBr): 3054; 2936; 2830, 1615; 1477, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H), 4.04 (s, 3H), 4.08 (s, 3H), 7.34 (m, 1H), 7.37 (s, 1H), 7.85 (dt, 1H, J = 7.9 Hz and J = 1.4 Hz), 8.39 (d, 1H, J= 8.7 Hz), 8.48 (dd, 1H, J = 8.7 Hz), 8.57 (m, 1H), 8.73 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 156.49, 156.20, 155.54, 149.46, 147.14, 145.52, 141.39, 137.24, 131.79, 124.21, 122.07, 119.62, 116.99, 104.37, 61.88, 61.52, 56.43; GC-MS, *m/z*: 297 (M+); HRMS (ESI TOF-MS Calcd for $[C_{17}H_{17}N_2O_3]^+$: 297.1234, found 297.1093.

5,8-dimethoxy-2-(pyridin-2-yl)quinolone (**6f**): Yellow solid (0.220 g, 64%); mp 193-194 ºC; R_f (30% ethyl acetate/hexane v/v) 0.28; IR (KBr): 3038; 2922; 2830, 1622; 1491, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.01 (s, 3H), 4.05 (s, 3H), 7.04 (s, 1H), 7.44 (s, 1H), 7.47 (d, 1H, J = 7.8 Hz), 7.66 (t, 1H, J= 7.8 Hz), 8.07 (d, 1H, J = 8.5 Hz), 8.37 (d, 1H, J = 8.5 Hz), 8.53 (d, 1H, J = 7.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.65, 152.56, 152.23, 150.19, 144.65, 141.42, 139.04, 134.95, 127.72, 124.17, 119.84, 117.36, 108.04, 104.88, 56.08, 55.99; GC-MS, *m/z* : 346 (M+2); HRMS (ESI TOF-MS Calcd for $[C_{16}H_{14}BrN_2O_2]^+$: 345.0233, found 345.0119.

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Povarov reaction for the synthesis of 2-(2-pyridyl)quinoline

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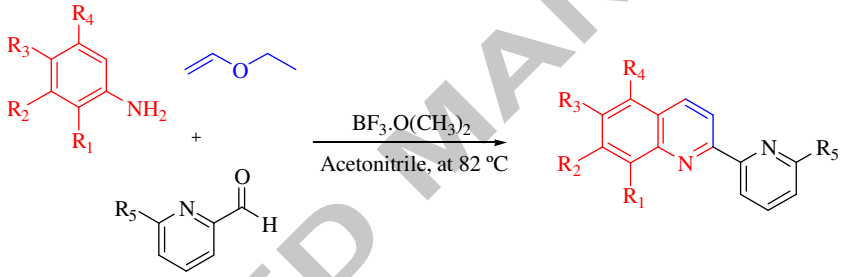
Carmindo Ribeiro Borel[a], Luiz Claudio Almeida Barbosa[a,b,]*, Célia Regina Álvares Maltha[a] and Sergio Antonio Fernandes[a]



Highlights

- ✓ An efficient synthesis of 2-(2-pyridyl)quinoline was achieved via Povarov reaction.
- ✓ Pyridinecarbaldehydes are converted in one step into quinoline derivatives.
- ✓ A short synthesis of streptonigrin core has been achieved via multicomponent reaction.