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ARTICLE TYPE

Efficient Synthesis of 2,4-Disubstituted Quinolines: Calix[*n*]arene-Catalyzed Povarov-Hydrogen-Transfer Reaction Cascade

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A cascade process involving the Povarov reaction and hydrogen transfer catalyzed with *p*-sulfonic acid calix[4]arene was disclosed and afforded the synthesis of 2,4-disubstituted quinolines in good yields under appropriate conditions in a single pot process.

Introduction

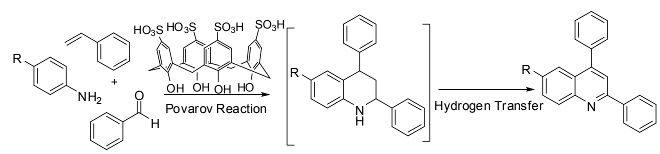
The quinoline nucleus is a common heterocyclic system found in natural and synthetic compounds, many of which have interesting biological properties.[1] Quinolines have generally been synthesized using classical reactions, including the Skraup,[2] Doebner-von Miller,[3] Friedländer,[4] Pfitzinger[5] and Combes syntheses.[6] Although many of these classical syntheses were developed many decades ago, they are still frequently used for the preparation of pharmaceutical agents and other new quinoline derivatives. Despite the many methods available, there are still limitations, especially with respect to obtaining an adequate variety of substituents on both rings.[7] Recent developments in the chemistry of quinoline derivatives have demonstrated that an acid catalyzed cycloaddition of the appropriate precursors could compete with the classical syntheses in terms of efficacy and speed.[8] The development of multicomponent reactions (MCRs) in this field has shown interesting advantages typical of an ideal reaction, such as atom and step economy, convergence, and exploratory power.[9]

Some 2,4-disubstituted quinolines have been reported as anthelmintics[10] and have been effective in the treatment of leishmaniasis, a widespread protozoan disease in tropical areas of South America.[11g] The synthesis of 2,4-disubstituted quinolines remains poorly explored[11], especially regarding synthetic methods involving MCRs.[12]

A typical multicomponent Povarov reaction can be used to prepare tetrahydroquinolines through the reaction of arylimines, which are generated *in situ* by the condensation of an amine and an aldehyde, with an electron-rich alkene. The tetrahydroquinolines that are formed may be transformed into quinolines by oxidation.[13] One example of this Povarov reaction utilizes an arylimine as the oxidant in the cascade process.[14]

The efficiency of the Povarov reaction is primarily associated with the nature of the alkene. The most commonly used alkenes are vinyl ethers because they are very nucleophilic.[15] The use of less nucleophilic alkenes, such as styrene and its derivatives, in the Povarov reaction has been rarely reported in the literature due to the lower reactivities of these alkenes compared with vinyl ethers.[13a,16]

Another important factor in the Povarov reaction is the catalyst employed. In recent years, our group and others have initiated the use of calix[*n*]arenes as catalysts in certain selective reactions,[17] including a Povarov reaction designed for the synthesis of julolidines.[18] Taking advantage of calix[*n*]arenes as catalysts, we report an unprecedented tandem multicomponent synthesis of 2,4-disubstituted quinoline derivatives via a Povarov reaction in this study. As shown in **Scheme 1**, the process involves initial production of the tetrahydroquinoline derivative catalyzed by *p*-sulfonic acid calix[4]arene (CX4SO_3H). This intermediate is then dehydrogenated *in situ* by the imine generated by condensation of aniline and aldehyde and/or the acetonitrile, used as the solvent, to afford the desired quinoline derivatives in a one pot process.



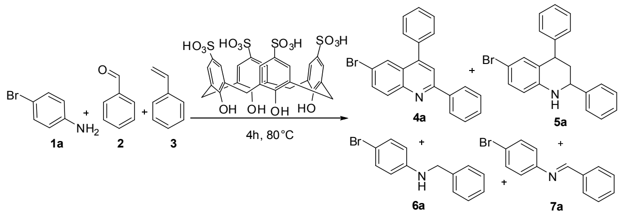
Scheme 1 Tandem Multicomponent Synthesis of 2,4-Disbustuted Quinoline Derivatives via a Povarov Reaction

Results and Discussion

For the initial investigation of the use of CX4SO_3H as a catalyst in this process, 4-bromoaniline (**1a**), benzaldehyde (**2**) and styrene (**3**) were employed as the substrates. The results for optimization of the solvent, reaction time and catalyst concentration are presented in **Table 1**. The use of acetonitrile provided the desired 2,4-disubstuted quinoline **4a** in 54% yield (**entry 1**).

Biodegradable green solvents, such as diethyl carbonate and ethyl lactate, and common solvents, such as tetrahydrofuran, dimethylsulfoxide and chloroform, did not provide good yields of the desired product (**entries 2-6**). With the exception of ethyl lactate, other solvents resulted in the formation of the imine **7a** in moderate to good yields (41-80%).

Table 1. Optimization of the Reaction Conditions[a]



Entry	Solvents	$CX4SO_3H$ (mol %)	Yield (%)[b]				
			4a	5a	6a	7a	Total[c]
1	CH_3CN	25	54	-	42	-	96
2	Diethyl Carbonate	25	-	5	-	74	79
3	Ethyl lactate	25	-	-	-	-	-
4	THF	25	-	-	-	60	60
5	DMSO	25	-	-		80	80
6	$CHCl_3$	25		8		41	49
7	Toluene	25	25	trace	-	50	75
8	H_2O	25	8	49[e]	6	25	88
9	EtOH	25	9	46[f]	7	30	92
10	-	25	17	10	15	40	82
11	CH_3CN	20	58	-	40		98
12	CH_3CN	10	59	-	33		92
13	CH_3CN	5.0	43	-			43
14	CH_3CN	2.0	40	-	36	5	81
15	CH_3CN	1.0	46		22	20	88
16	CH_3CN	0.5	5	-	-	78	83
17	CH_3CN[d]	10	62	-	32	-	94
18	CH_3CN[d]	1.0	65	-	34	-	99

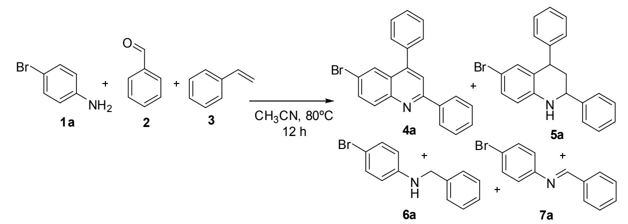
[a]The reaction of an aniline **1a** (1 mmol), benzaldehyde **2** (1.2 mmol), and styrene **3** (1.5 mmol) was performed at 80 ºC. [b]Isolated yield. [c]Sum of the % yields of **4a**-**7a**.[d]Reaction time of 12 hours. [e]Diastereomeric excess = 60% *cis*. [f]Diastereomeric excess = 58% *cis*.

When the reaction was carried out in toluene, water, ethanol or without solvent, mixtures of products **4a-7a** were obtained, including the desired quinoline in low yields (8-25%) (**entries 7-10**). As shown in **entries 8-9**, the use of polar protic solvents (ethanol and water) favored the formation of the intermediate tetrahydroquinoline in 46-49% yield.

The catalyst concentration was reduced to 1 mol% with only a slight decrease in the yield (**entries 11-16**); however, an increase in the reaction time led to an increase in the yield even with smaller amounts of catalyst (**entries 17-18**).

We further investigated the effect of the acid catalyst on the product distributions (Table 2). The use of a macrocycle consisting of six phenolic units, *p*-sulfonic acid calix[6]arene, ($CX6SO_3H$) afforded the desired quinoline in 63% yield, which was similar to the result obtained with $CX4SO_3H$ (65%). However, the use of the monomer 4-hydroxysulfonic acid (PHA) as the catalyst resulted in only a 12% yield of the desired quinoline (**Table 2**, **entries 1-3**). These results indicate that the sulfonic and phenolic groups on the calix[*n*]arene structures are not solely responsible for its catalytic effect. Among the other Brønsted acids tested (**Table 2**, **entries 4-6**), only trifluoroacetic acid resulted in a yield comparable to those obtained with calix[*n*]arenes. However, the calix[*n*]arenes have the advantage of been easily recovered and reused.[17,18,19] Among the organic acids tested, lactic, oxalic and citric acids afforded the desired quinoline in 9%, 33% and 24% yields, respectively (**entries 7-11**).

Table 2. Effect of Different Brønsted Acid Catalysts on the Povarov Reaction[a]



Entry	Catalyst (mol %)[b]	Yield (%)[c]				
		4a	5a	6a	7a	Total[d]
1	$CX4SO_3H$ (1.0)	65	-	34	-	99
2	$CX6SO_3H$ (0.7)	63	8	18	7	96
3	PHA (4.0)	12	-	-	53	65
4	CF_3CO_2H (4.0)	64	-	33	-	97
5	CH_3CO_2H(4.0)	-	-	-	73	73
6	H_2SO_4 (2.0)	7	-	-	70	77
7	Lactic acid (4.0)	29	trace	58	-	87
9	Succinic acid (2.0)	-	-	8	30	38
10	Oxalic acid (2.0)	33	-	trace	40	73
11	Citric acid (1.3)	24	trace	50	trace	74

[a]The reaction of an aniline **1a** (1 mmol), benzaldehyde **2** (1.2 mmol), and styrene **3** (1.5 mmol) was performed at 80 °C. [b]The concentration of H^+ was kept constant. [c]Isolated yield. [d]Sum of the %yields of **4a-7a**.

To investigate the scope of this auto-tandem catalysis in a Povarov-hydrogen-transfer reaction cascade, several anilines were subjected to the optimized conditions (acetonitrile as the solvent, 1 mol% of $CX4SO_3H$, 80 ºC, 12 h). The results are provided in Figure 1.

The use of anilines with weak electron-withdrawing groups (**4a-4c**) or electron-donating substituents (**4d-4g**) resulted in better yields than the use of anilines with strong electron-withdrawing substituents (**4h-4i**). Quinolines that were di- and tri-substituted on the aniline component were also obtained (**4j-4l**). The reaction of *meta*-substituted anilines gave single regioisomers (**4m-4n)**.

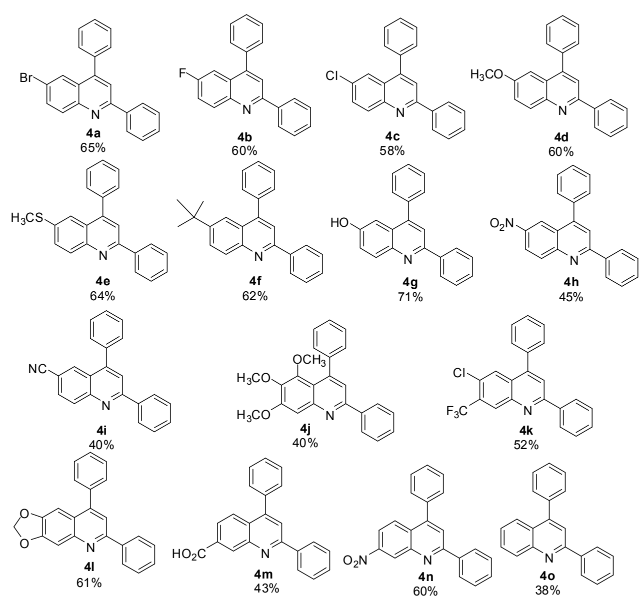
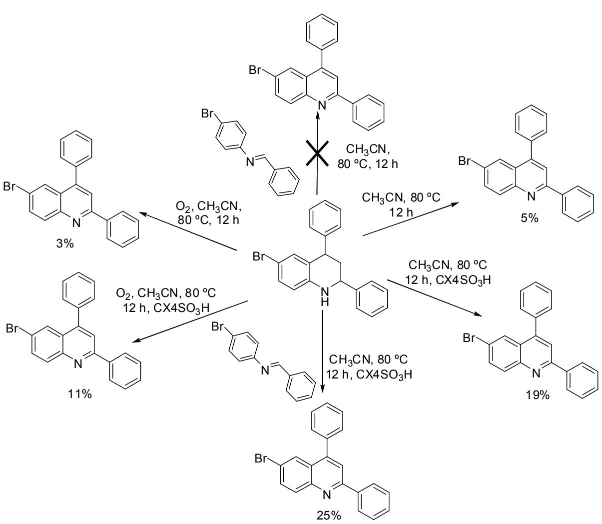


Fig. 1 The Scope of Auto-Tandem Catalysis in a Povarov Hydrogen-Transfer Cascade

As we have demonstrated so far, under the conditions described, the Povarov reaction can afford, in one pot, the corresponding quinoline instead of the commonly obtained 1,2,3,4-tetrahydroquinoline.[13] The oxidation of 1,2-dihydroquinoline has already been investigated in detail, and it has been demonstrated that this type of oxidation can be achieved through the use of oxygen, Fe^{3+}, and organic oxidants, such as benzaldehyde, imines and enones.[20] The disproportionation of 1,2-dihydroquinoline can also occur in the presence of HCl.[21] The aromatization of some Povarov adducts has been reported, but in such cases, oxidizing agents such as Br_2, DDQ and $NaIO_4$ were used.[13d] To the best of our knowledge, only one report on the successive dehydrogenation of Povarov-produced tetrahydroquinoline into quinoline has been reported, but in that case, the process was mediated by excess imine in the presence of acid.[13b] In our method, we used 1.0 equivalent of the aniline and 1.2 equivalent of the aldehyde. Therefore, if quinoline formation occurred through dehydrogenation mediated by the imine the maximum quinoline yield would be 33%, which is much lower than the yields observed in most instances. Thus, we hypothesized that acetonitrile is acting as a hydride acceptor. We then examined the details of the oxidation of the isolated tetrahydroquinoline (**Scheme 2**).

The oxidation of tetrahydroquinoline **5a** under an oxygen atmosphere at 80 ºC for 12 h in the absence of the catalyst results in less than 5% conversion to quinoline **4a**; however, in the presence of the catalyst, the conversion was 11%. On the other hand, a 25% conversion of tetrahydroquinoline **5a** to quinoline **4a** was observed at 80 ºC for 12 h in the presence of 1 equivalent of imine **7a** and $CX4SO_3H$ (1 mol%). However, in the absence of the catalyst, no hydrogen-transfer occurred. These results suggest that the imine acts as an oxidant and $CX4SO_3H$ acts as an auto-tandem catalyst activating two mechanistically distinct reactions in the Povarov hydrogen-transfer reaction cascade. To verify that the acetonitrile reaction solvent also acts as an oxidant, the reaction was conducted under the same experimental conditions but with an inert atmosphere; the conversion of tetrahydroquinoline **5a** to quinoline **4a** was 19%. This result indicates the participation of acetonitrile in the oxidation process, which had not previously been reported.



Scheme 2 Possible Oxidative Processes

After the tetrahydroquinoline is transformed into 1,2-dihydroquinolines *in situ,* it can be oxidized to the corresponding quinoline by a weak oxidizing agent. Based on the experimental results, we suggest that the first hydrogen-transfer might occur between the tetrahydroquinoline and acetonitrile or the imine. Further oxidation might proceed through disproportionation or hydrogen abstraction from the imine formed by the initial reduction of acetonitrile.

Checking the participation of acetonitrile, the reaction of tetrahydroquinoline **5a** was carried in deuterated acetonitrile (CD_3CN) in presence of $CX4SO_3H$ (1 mol%) and 1 equivalent of imine **7a**. The ^1H NMR spectrum (**Fig. 2b**) presents a signal in 4.3 ppm refers of CH_2 group due the reduction of imine **7a** to amine **6a**.

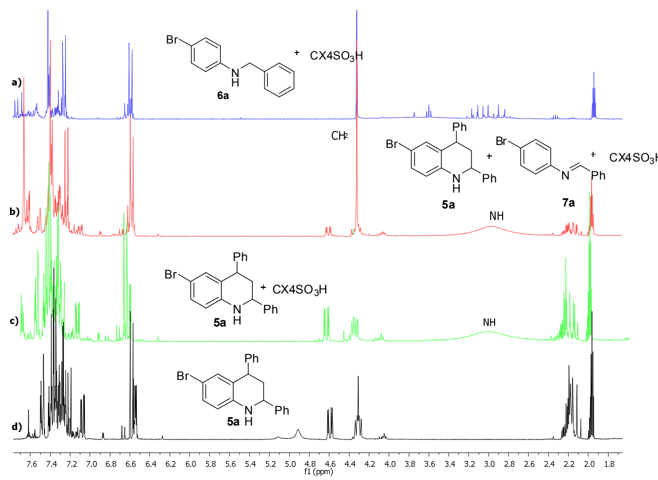


Fig. 2 a) ^1H NMR spectrum (300 MHz, CD_3CN) of 6a in presence of $CX4SO_3H$. b) ^1H NMR spectrum of reaction between 5a and 7a with $CX4SO_3H$. c) ^1H NMR spectrum of reaction of 5a in presence of $CX4SO_3H$. d) ^1H NMR spectrum of reaction of 5a in absence of $CX4SO_3H$.

As shown in **Figure 2** the ^1H NMR spectrum of reaction carried in presence of $CX4SO_3H$ (1 mol %) without the imine **7a** presents a large signal in 2.9 ppm (**Fig. 2c**). Whereas the ^1H NMR spectrum of tetrahydroquinoline **5a** maintained under the same reaction conditions but in absence of cataly and imine (**Fig. 2d**), not present this signal, we conclude that this signal is due to the reduction of acetonitrile that occurs only presence of catalyst.

Conclusions

In conclusion, we have developed a cascade process involving an efficient three-component reaction followed by oxidative aromatization for the synthesis of 2,4-disubstuted quinolines using *p*-sulfonic acid calix[4]arene ($CX4SO_3H$) as a catalyst. We have verified that in addition to the participation of the imine and oxygen, acetonitrile participates in the process of oxidizing the tetrahydroquinolines to quinolines. The developed method affords 2,4-disubstuted quinolines with electron donating or electron withdrawing groups from the aniline component. Further applications of this methodology are under investigation and will be reported in due time.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Including experimental data and characterization data (Melting point, IR, ^{1}H NMR, ^{13}C NMR and ESI-MS) for all compounds. See DOI: 10.1039/b000000x/

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