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Povarov-Reductive Amination Cascade to Access 6-Aminoquinolines and Anthrazolines

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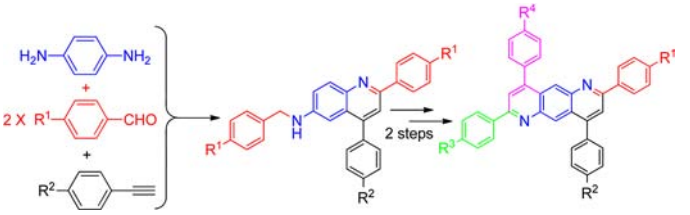
ABSTRACT



A new strategy is reported for the synthesis of 6-aminoquinoline derivatives *via* a tandem Povarov reaction, dihydroquinoline oxidation, and imine reduction. These products allow access to symmetrical as well as unsymmetrical tetraarylpyrido[2,3-*g*]quinolines, potentially useful organic electronics.

Nitrogen containing heterocycles are ubiquitous scaffolds in many natural products and biologically potent molecules. The quinoline nucleus, a privileged substructure, is present in an array of natural compounds[1] and functional materials[2] and is found to have extensive biological properties such as antimalarial,[3] anti-HIV,[4] anticancer,[5] and antituberculosis.[6] Particularly, aminoquinolines act as fluorophores[7] and have been studied as potential organic semiconductors.[8] Owing to their importance in multidisciplinary fields, syntheses of these heterocycles have attracted the interest of synthetic chemists.

Since the first report by Skraup in 1880,[9] several methods have been developed for the synthesis of the quinoline nucleus. The Povarov reaction, an inverse electron demand hetero-Diels–Alder reaction, has proven to be one of the convenient methods for the synthesis of 2,4-disubstituted tetrahydroquinolines.[10] This reaction is an excellent example of multicomponent reactions with high atom economy in organic synthesis. Multicomponent and tandem or cascade reactions are found to be efficient when compared to traditional stepwise linear synthesis because they often offer excellent atom economy leading to reduction of waste.[11] Several groups have reported the synthesis of 2,4-disubstituted quinolines with alkynes as dienophiles in a Povarov protocol followed by either an aerobic oxidation or using an additional oxidant. Imines, the substrate for the Povarov reaction, are known to act as an oxidant to produce quinolines from di- and tetrahydroquinolines, and the

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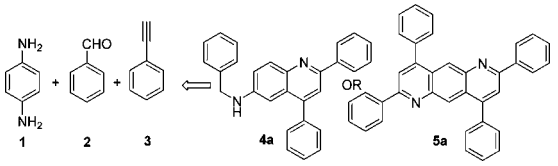
corresponding amine would be a byproduct.[12] Takasu and co-workers reported the synthesis of quinolines *via* a Povarov reaction and hydrogen transfer reaction using triflic imide as an autotandem catalyst.[13]

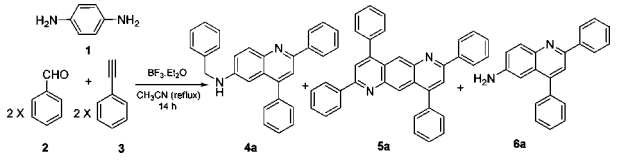
Recently, Gaddam et al. reported the synthesis of isomeric ellipticine derivatives *via* a Povarov reaction with an imine as an oxidant.[14] When the imine acts as an oxidant, an equimolar amount of amine and aldehyde substrates are exhausted which directly affects the atom economy of the reaction. To the best of our knowledge, synthesis of privileged 6-aminoquinoline derivatives is not reported in the literature *via* a tandem multicomponent approach. With our continued interest in multicomponent reactions for the synthesis of heterocyclic compounds,[15] we envisioned that the synthesis of 6-aminoquinolines can be achieved *via* a Povarov reaction and intramolecular hydrogen transfer. In the present study, we wish to report the unprecedented tandem multicomponent synthesis of 6-aminoquinoline derivatives *via* a Povarov reaction, dehydrogenation, and imine reduction sequence (Scheme 1) and their subsequent use in the synthesis of symmetrical and unsymmetrical anthrazolines or pyrido[2,3-*g*]quinolines.

Scheme 1. Retroanalysis for *N*-Benzyl-6-amino-2,4-diphenylquinoline



With the use of 1,4-phenylenediamine (**1**), benzaldehyde (**2**), and phenylacetylene (**3**) as our model Povarov reaction substrates, we were interested in understanding the kinetics of the reaction — whether the Povarov cycloaddition is a kinetically controlled process and if it outcompetes the dehydrogenation/hydrogenation reaction or if these processes happen in tandem. It should be noted that dehydrogenation and concomitant hydrogenation reactions, which lead to aromatization of the quinolone ring, are secondary processes which occur after the initial Povarov reaction. If the Povarov cycloaddition is the faster process then the *bis*-Povarov product 2,4,7,9-tetraphenylpyrido[2,3-*g*]quinoline (**5a**) of 1,4-phenylenediamine (**1**) should be isolated as the major product. However, if the aromatization of the quinoline ring is the dominating process (thermodynamic control), then 6-benzylamino-2,4-diphenylquinoline (**4a**) should be isolated as the major product (Scheme 1). Upon conducting this reaction with the substrate stoichiometry required for the *bis*-Povarov product (**5a**) in the presence of $BF_3 \cdot Et_2O$ (5 mol %) in refluxing acetonitrile for 14 h, compound **4a** was isolated in 32% yield (Scheme 2). In addition to **4a**, the *bis*-Povarov product (**5a**, traces) and the mono-Povarov product 2,4-diphenylquinolin-6-amine (**6a**, 18% yield) were also identified in the product mixture. Surprisingly, *N*,*N*′-dibenzyl-1,4-phenylene diamine, the transfer hydrogenation product from the diimine, was not detected in the reaction mass. Thus, it became clear that the Povarov cycloaddition followed by the dehydrogenation and hydrogenation reaction is the major process occurring under the employed conditions. Also, the isolation of compound **6a** was a surprise based on the amount of benzaldehyde used; the corresponding benzylideneimine (Schiff base) would have been a more reasonable product from which **6a** is likely a decomposition product. It was realized that the formation of **4a** required substrates **1**, **2**, and **3** in the ratio 1:2:1 as opposed to the 1:2:2 requirement for the *bis*-Povarov reaction. At this point we decided to optimize the conditions for the formation of *N*-benzyl-6-amino-2,4-diphenylquinoline (**4a**) by varying the substrate stoichiometry, solvent, catalyst, temperature, and time. The results are summarized in Table 1.

Scheme 2. Reaction of Diamine with Benzaldehyde and Acetylene Using $BF_3 \cdot Et_2O$



When substrates **1**, **2**, and **3** in a ratio of 1:2:1.5 were reacted in the presence of $BF_3 \cdot Et_2O$ (5 mol %) in acetonitrile at reflux for 14 h, compound **4a** was isolated in 36% yield (Table 1, entry 1). Prolonging the reaction times did not help to improve the yields. By increasing the catalyst loading to 20%, the yield of **4a** increased to 44% (Table 1, entry 2). Along with **4a**, **5a** (7%) and **6a** (21%) were also isolated from this reaction. However, a further increase in the catalyst loading resulted in an inseparable mixture of compounds. Several other Lewis and Bronsted acids, namely aluminum chloride ($AlCl_3$), *p*-toluenesulfonic acid (*p*-TSA), trifluoroacetic acid (TFA), and acetic acid were also screened as catalysts. $AlCl_3$ and *p*-TSA resulted in poor yields of **4a** (Table 1, entries 3–4). Use of TFA as a catalyst resulted in a mixture of components with trace amounts of the desired compound **4a** (Table 1, entry 5), and no desired product was observed in the case of acetic acid (Table 1, entry 6). Transition metal triflates have proved to be efficient Lewis acid catalysts for the synthesis of several important biologically active heterocyclic

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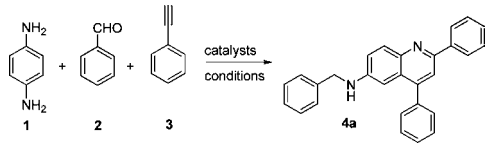
molecules because of their distinct properties such as moisture insensitivities, stability, reusability, and high catalytic activity.[16] They have also been used efficiently for the synthesis of quinoline derivatives;[15b] therefore we decided to screen the effectiveness of $Sc(OTf)_3$, $Cu(OTf)_2$, $Y(OTf)_3$, and $Yb(OTf)_3$ (Table 1, entries 7−10). $Yb(OTf)_3$ was found to be the most effective (Table 1, entry 10) as compared to all the catalysts studied.

Table 1. Optimization of Reaction Conditions for the Synthesis of **4a**[a]



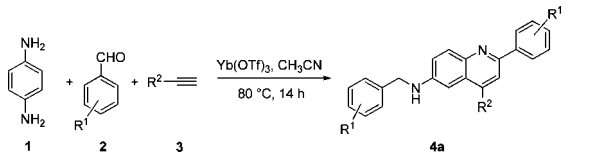
entry	catalyst	solvent	yield (%)[b]
1	BF_3-Et_2O	CH_3CN	36
2	BF_3-Et_2O	CH_3CN	44[c]
3	$AlCl_3$	CH_3CN	22
4	*p*-TSA	CH_3CN	18
5	CF_3CO_2H	CH_3CN	trace
6	CH_3CO_2H	CH_3CN	ND[d]
7	$Sc(OTf)_3$	CH_3CN	39
8	$Cu(OTf)_2$	CH_3CN	22
9	$Y(OTf)_3$	CH_3CN	29
10	**$Yb(OTf)_3$**	CH_3CN	**48**
11	CAN[e]	CH_3CN	16
12	cyanuric chloride	CH_3CN	12
13	$Yb(OTf)_3$	1,4-dioxane	15
14	$Yb(OTf)_3$	toluene	ND[d]
15	$Yb(OTf)_3$	DCE[f]	18
16	$Yb(OTf)_3$	DMF[g]	ND[d]
17	$Yb(OTf)_3$	DME[h]	trace

[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), **3** (1.5 mmol), catalyst (0.05 mmol), solvent (3.0 mL), 80 °C, 14 h. [b] Isolated yields. [c] Catalyst (20 mol %). [d] Not detected. [e] Ceric ammonium nitrate. [f] 1,2-Dichloroethane. [g] *N,N*-Dimethylformamide. [h] 1,2-Dimethoxyethane.

The high reactivity of $Yb(OTf)_3$ is generally attributed to the smaller radius of the Yb^{3+} cation and higher oxophilic nature.[15a,16] Ceric ammonium nitrate and cyanuric chloride were found to be less effective (Table 1, entries 11, 12). We investigated the effect of different solvents such as 1,4-dioxane, toluene, 1,2-dichloroethane (DCE), *N,N*-dimethylformamide (DMF), and dimethoxyethane (DME) (Table 1, entries 13−17) on the yield of **4a** using $Yb(OTf)_3$ as the catalyst. The yield of **4a** was found to be best in CH_3CN compared to all solvents tested (Table 1, entry 10). Although our optimization efforts led to improvement in the amount of the isolated yield of desired compound **4a**, we were unable to find the conditions that exclusively formed **4a** while eliminating the formation of other products from competing reactions.

Subsequently, we proceeded to explore the scope of the developed tandem multicomponent reaction for the synthesis of *N*-arylmethyl-6-amino-2,4-diarylquinolines, and the results are summarized in Table 2. Initially, the reaction of different aromatic aldehydes with 1,4-phenylenediamine and phenylacetylene was studied.

Table 2. Substrate Scope for Tandem Synthesis of *N*-Arylmethyl-6-amino-2,4-diphenylquinolines[a]



entry	R^1	R^2	product	yield (%)[b]
1	H	C_6H_5	**4a**	48
2	4-CH_3	C_6H_5	**4b**	38
3	4-OCH_3	C_6H_5	**4c**	26
4	3,4,5-OCH_3	C_6H_5	**4d**	57
5	4-Cl	C_6H_5	**4e**	28
6	4-F	C_6H_5	**4f**	27
7	3-NO_2	C_6H_5	**4g**	41
8	4-NO_2	C_6H_5	**4h**	38
9	H	4-$nC_4H_9C_6H_4$	**4i**	57[c]
10	3-NO_2	4-$nC_4H_9C_6H_4$	**4j**	39
11	H	4-$nC_5H_{11}C_6H_4$	**4k**	32[c]
12	4-CH_3	4-nC_5H_{11} C_6H_4	**4l**	32[c]
13	4-OCH_3	4-$nC_5H_{11}C_6H_4$	**4m**	42[c]
14	4-Cl	4-$nC_5H_{11}C_6H_4$	**4n**	34[c]
15	4-F	4-nC_5H_{11} C_6H_4	**4o**	37[c]
16	3-NO_2	4-$nC_5H_{11}C_6H_4$	**4p**	48
17	H	4-$OCH_3C_6H_4$	**4q**	61
18	4-CH_3	4-$OCH_3C_6H_4$	**4r**	38
19	3-NO_2	4-$OCH_3C_6H_4$	**4s**	52

[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), **3** (1.5 mmol), $Yb(OTf)_3$ (0.05 mmol), acetonitrile (3.0 mL), 80 °C, 14 h. [b] Isolated yields. [c] BF_3-Et_2O (20 mol %) used instead $Yb(OTf)_3$.

The results demonstrated that a wide range of aldehydes with electron-donating and -withdrawing groups participated in this tandem process to give the corresponding *N*-arylmethyl-6-amino-2,4-diarylquinolines (**4a**−**h**) in moderate to good yields (Table 2, entries 1−8). Unexpectedly, 3,4,5-trimethoxybenzaldehyde resulted in a higher yield (Table 2, entry 4) compared to tolualdehyde and anisaldehyde (Table 2 entries 2−3). 4-Fluoro- and 4-chlorobenzaldehyde produced moderate yields (Table 2, entries 5−6). Compared to 4-nitrobenzaldehyde, 3-nitrobenzaldehyde gave better yields of corresponding *N*-arylmethyl-6-aminoquinolines (Table 2, entries 8−7). Similarly, 4-butyl- and 4-pentylphenyacetylenes reacted smoothly with different aldehydes and 1,4-phenyldiamine to give reasonable yields of *N*-arylmethyl-6-amino quinolines (**4i**−**p**) (Table 2, entries 9−16). 4-Methoxyphenylacetylene also reacted efficiently to produce corresponding *N*-arylmethyl-4-(4-methoxyphenyl)-2-phenylquinolin-6-amines (**4q**−**s**) in reasonable yields (Table 2, entries 17−19). Further improvement in the yield of compounds of series **4** may be achieved by the use of molecular sieves as a moisture sponge along with further optimization of reaction conditions. Phenylacetylene and

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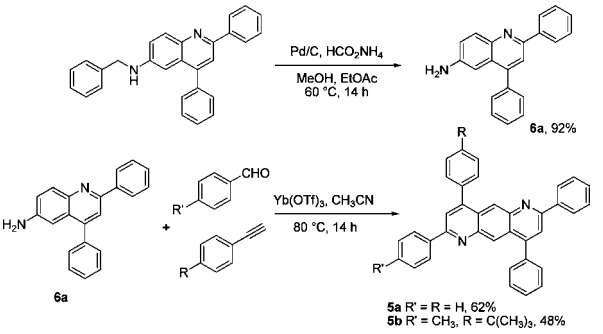
three of its electron-donating analogs were employed in this study as alkyne substrates. We believe that arylacetylenes bearing electron-withdrawing groups will also result in the smooth formation of corresponding *N*-arylmethyl-6-amino-2,4-diarylquinolines because Povarov and Povarov-type reactions with arylacetylenes and arylacetylene equivalents bearing electron-withdrawing groups are reported to work well.[17]

As expected for 6-aminoquinoline derivatives,[7] most compounds in series **4** were found to be highly flourescent. Visually, the fluorescence appeared to be dependent on the aromatic substituents, but no further experiments were conducted to ascertain their emission maxima and quantum yields at this time. The 4-nitro derivative (**4h**) was found to be nonflourescent.[18]

Having synthesized a variety of *N*-arylmethyl-6-amino-2,4-diarylquinolines (**4a**–**s**), we wondered if these compounds can be appropriately modified to produce symmetrical and unsymmetrical *bis*-Povarov products, i.e. anthrazolines. Removal of the *N*-benzyl group from **4a** using palladium on charcoal and ammonium formate gave easy access to 2,4-diphenyl-6-aminoquinoline (**6a**) in excellent yield (92%). Furthermore, compound **6a** was subjected to the Povarov reaction using $Yb(OTf)_3$ as a catalyst (Scheme 3) to produce anthrazoline derivatives. We were able to synthesize symmetrical and unsymmetrical anthrazolines with reasonable yields (62% and 48% for **5a** and **5b**, respectively). It should be noted that the anthrazoline derivatives have potential applications as organic semiconductors.[19] These heterocycles are generally synthesized from complex starting materials.[19b,20] Thus, our method for direct access to 6-aminoquinoline derivatives provides an easy access for these important heterocycles from simple and commercially available starting materials. It should also be noted that the synthesis of unsymmetrical anthrazoline derivatives has been an unmet challenge so far.

Scheme 3. Synthesis of Anthrazoline Derivatives



In summary, we have developed a novel approach for the synthesis of *N*-arylmethyl-6-amino-2,4-diarylquinolines *via* a tandem reaction of 1,4-phenylenediamines, aryl aldehydes, and aryl acetylenes. Removal of the *N*-benzyl group on a representative molecule by catalytic hydrogenation resulted in 6-amino-2,4-diphenylquinoline, which was utilized in making symmetrical and unsymmetrical anthrazoline derivatives. Further mechanistic studies and the application of the developed procedure are currently in progress.

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Supporting Information Available. Experimental procedure, characterization data and copies of the ^1H and ^{13}C NMR of the synthesized compounds **4a**–**s**, **5a**–**b**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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