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A new process of multicomponent Povarov reaction–aerobic dehydrogenation: synthesis of polysubstituted quinolines

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ABSTRACT

A new domino process of three-component Povarov reaction and aerobic dehydrogenation was developed toward the synthesis of polysubstituted quinolines. 2,4-Disubstituted-8-nitroquinolines, which are important precursors for the synthesis of antimalarial primaquine drug-like molecules, were prepared conveniently by this method in moderate to good yields. Brönsted acid ($HClO_4$)-modified montmorillonite was found to be a crucial catalyst in promoting the procedure.

The Povarov reaction,[1] a class of inverse electron demand Diels–Alder reaction of *N*-arylimines with appropriate dienophiles, has gained popularity as a powerful approach to prepare tetrahydroquinolines in diversity- and target-oriented synthesis (DOS & TOS) of *N*-polyheterocycles including alkaloids. Although less explored, the use of alkyne in this reaction to synthesize dihydroquinolines has been documented.[2] To offer the synthesis of quinolines via Povarov reaction, tetrahydro/dihydro-quinoline products are oxidized subsequently. These oxidation processes are normally accomplished by (1) in situ-reduction of excess imine under specific hydrogen transfer catalysis,[3] (2) using excess harsh oxidizing/dehydrogenating agents[2c,3b–d,4] in chlorinating solvents and (3) pyrolytic or acid-catalyzed eliminations[4b,5] (e.g., dehydrosulfonation and dehydropyrrolidinonation) followed by oxidation. In these Povarov reaction processes to access quinolines, the selection of appropriate catalyst was found to be crucial as the catalyst should be capable of promoting the in situ imine formation (in case of multicomponent Povarov), imino Diels–Alder reaction, hydrogen transfer process to imine and/or be compatible to the harsh oxidation. In addition, the 2-azadiene- and dienophile-behaviors of *N*-arylimines and the easy susceptibility of aldimines toward hydrolysis and polymerization under acidic conditions can cause competing side reactions in Povarov reaction processes. These shortcomings hinder the Povarov reaction route in reflecting its efficiency to prepare quinolines.

Recently, the catalytic aerobic dehydrogenation[6] in oxidation of functional groups and the construction of heterocyclic scaffolds have received immense attention because of their green chemistry aspects. The Povarov reaction and subsequent aerobic dehydrogenation to access quinolines will thus eliminate the use of harsh oxidizing agents and chlorinating solvents or excess imines and result in the protocol's simplicity. To the best of our knowledge, there is no report of aerobic oxidative Povarov reaction to synthesize quinolines. An attempted aerobic dehydrogenation by TfOH (1 equiv) in Povarov reaction route to access quinoline was unsuccessful.[3a]

Quinoline nucleus is a common heterocyclic scaffold found extensively in natural products, many of which possess interesting biological properties.[7] There are currently used in several quinoline antimalarial drugs. Quinoline compounds have been found to exhibit a wide range of pharmaceutical activities like antimalarial, antileishmanial, antituberculosis, anti-HIV, antibacterial, antifungal, and anticancer.[8] Although many methods including classical reactions and their modifications,[9] transition metal-catalyzed protocols[10] and radical methods[11] are known to synthesize quinolines, the recent focus with particular interest of drug discovery research is directed toward the development of new process for the synthesis of quinolines possessing relevant substitutions and functionalities that can be modified to useful pharmacophores.

The Domino, tandem/cascade, and multicomponent reactions (MCR)[12] offer the atom-saving and economic bond-forming and structural change, convergent synthesis and the feasibility of introducing maximum chemical diversity elements in one chemical event. Thus, they are increasingly used in organic synthesis.

With this backdrop, the development of multicomponent aerobic oxidative Povarov reaction to prepare quinolines is of immense value. Herein, we present a new domino process of $HClO_4$-modified montmorillonite-promoted three-component

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Povarov reaction–aerobic dehydrogenation, which provides the synthesis of polysubstituted quinolines relevant to pharmaceuticals, especially antimalarials (Scheme 1).

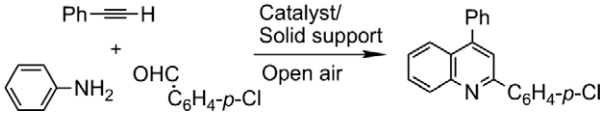
We envisaged that the selection of a catalyst could be the key in chemoselective-activation of reactants toward three-component Povarov reaction and the aerobic dehydrogenation in domino mode and to minimize the possible competing reactions. The superior activation of reactants and chemoselectivity in reactions mediated by heterogenized-catalysts are well known.[13,14] Initially, we decided to study the solid supported Povarov reaction under open air, using SiO_2/montmorillonite containing 15 mmol % (mol per weight) of Lewis acids/Brönsted acids.[14] *p*-Chlorobenzaldehyde, aniline, and phenylacetylene were chosen as model substrates (Table 1).

The screening of catalysts in this multicomponent hetero Diels–Alder reaction-aerobic oxidation revealed that Brönsted acid-modified montmorillonite showed better activity than Brönsted acid non-covalent heterogenized on silica gel, while Lewis acids adsorbed on montmorillonite or SiO_2 exhibited similar activities. In general, montmorillonite modified with Brönsted acids are more active than those modified with Lewis acids. In the activation of montmorillonite with different acids, ($HClO_4$, HBF_4, and HCl), $HClO_4$–montmorillonite ($HClO_4$–Mont.) showed the highest activity. The natural K-10 Mont. activated at 100 °C for 72 h under vacuum without modification by treating with Lewis/Brönsted acid was found to lower the reaction rate and yield (41%, entry 8, Table 1), and the reaction using *o*-nitroaniline (in place of aniline) resulted 2-(4-chlorophenyl)-8-nitro-4-phenylquinoline in poorer yield (21% vs 56%). These indicate that the acid modification by perchloric acid of montmorillonite enhances its activity for promoting the reaction. To examine the plausible higher activity of $HClO_4$–Mont., we also performed the solution phase reactions. It is well recognized that water as a solvent accelerates multicomponent and cycloaddition reactions and the presence of dissolved oxygen in water can favor the aerobic dehydrogenation. But in our investigations, the reaction catalyzed by $HClO_4$, phosphomolybdic acid, $CeCl_3$ and $ZrCl_4$ in water at same temperature (70 °C) were found to be very slow and unsuccessful (Table 1, entries 14–17). Prolonging the reaction in the case of $HClO_4$ caused the formation of a complex mixture of products. Use of EtOH as the solvent in the reaction catalyzed by $ZrCl_4$ did not also improve the yield. $Sc(OTf)_3$ and $InCl_3$, which were demonstrated[1a] as efficient catalysts in Povarov reactions, have also been found ineffective (Table 1, entries 19 and 20). All together, these imply that montmorillonite modified with perchloric acid possess the superior catalytic activity toward the three-component Povarov reaction and aerobic dehydrogenation in domino fashion. When the reaction was done under oxygen atmosphere in place of open air, it increased the yield slightly from 65% to 69% (Table 1, entry 7 vs entry 13). The reaction performed under nitrogen resulted in a complex mixture of products containing desired quinoline in 39% yield as revealed by HPLC. Aniline (1 equiv), aldehyde (1 equiv), alkyne (1.5 equiv), and 15 mmol % (mol/w) of $HClO_4$–Mont. were found to be optimum to provide the best results. The reaction procedure was simple and straightforward.[15]

Interestingly, the versatile polysubstituted and medicinally relevant quinolines were prepared by this process in moderate to good yields (Table 2). The diverse elements could be introduced into quinoline ring at 2- and 4-positions and the substitutions in aromatic amines used. 8-Nitroquinolines are known to be important precursors for synthesis of primaquine drug-like molecules, and primaquines with 2- and 4-ring relevant substitutions were reported to possess higher radical curative antimalarial activity compared to that of primaquine.[16] Recent studies have exploited that the introduction of 2-*tert*-butyl into quinoline ring of primaquine offers the tremendous improvement in its blood-schizontocidal antimalarial activity.[8a,16a] The reported syntheses of these 8-nitroquinolines involve the drawbacks of use of harsh conditions, expensive reagents, and multiple reaction steps.[16,17] In contrast, this new milder convenient method offers in one-step the preparation of targeted 8-nitroquinolines in good yields (Table 2, entries 9–14). Moreover, the multicomponent nature of the process and the easy accessibility of starting materials (versatile aldehydes and amines are commercially available and alkynes can be prepared from aldehydes in one-step) bestow the opportunity of synthesis of focused library of relevant substituted 8-nitroquinolines. The well known advantages of using heterogenized catalysts in organic synthesis are their remarkable thermal, mechanical, and chemical stabilities especially under oxidizing conditions, easy handling and low toxicity, facile separation from reaction mixture through filtration, and recyclability. In the present protocol, $HClO_4$–Mont. showed its recyclable efficiency up to three times (65%, 61%, 55% yields, entry 1, Table 2). These attributes of the process make it synthetically useful.

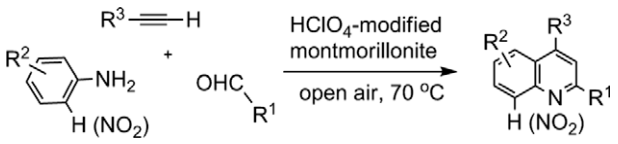
Since the process involves the Povarov reaction (an inverse electron demand hetero Diels–Alder reaction), the higher yield-formation of quinolines from anilines or aldehydes with electron-withdrawing groups is reasonable. The aliphatic alkynes (hexyne and octyne), which are not sufficiently electron-rich dienophiles, did not undergo the [4+2]-cycloaddition with *N*-arylimines. In

Table 1
Screening of catalysts and reaction conditions[a]



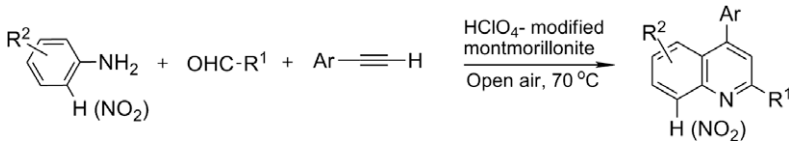
Entry	Catalyst/solid support	Solvent (T °C)	Yield[b] (%)
1	$HClO_4$–SiO_2	25	9
2	$HClO_4$–SiO_2	70	17
3	$ZrCl_4$–SiO_2	70	45
4	$CeCl_3$–SiO_2	70	25
5	$HClO_4$–Mont.	25	28
6	HBF_4–Mont.	25	7
7	$HClO_4$–Mont.	70	65
8	Natural K-10 Mont.	70	41
9	HBF_4–Mont.	70	30
10	HCl–Mont.	70	33
11	$CeCl_3$–K-10 Mont.	70	30
12	$ZrCl_4$–K-10 Mont.	70	50
13	$HClO_4$–Mont.	70	69[c]
14	$HClO_4$	H_2O, 70	15
15	Phosphomolybdic acid	H_2O, 70	10
16	$CeCl_3 \cdot 7H_2O$	H_2O, 70	NR
17	$ZrCl_4$	H_2O, 70	NR
18	$ZrCl_4$	EtOH, 70	NR
19	$Sc(OTf)_3$ (20 mol %)	EtOH, 70	NR
20	$InCl_3$ (10 mol %)	MeCN, 70	16

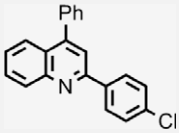
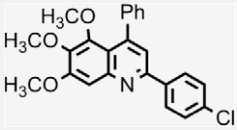
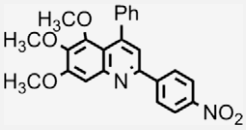
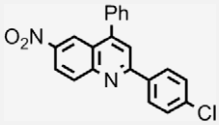
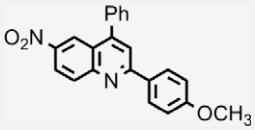
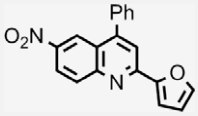
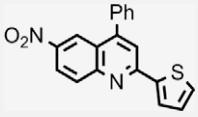
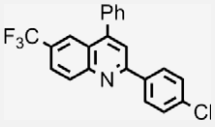
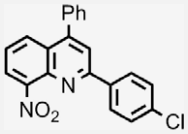
[a] Aldehyde (1 mmol), amine (1 mmol), alkyne (1.5 mmol), and catalyst (0.3 mmol) for solid-supported and solution phase reactions and 2 g of solids for solid-supported reactions were used, Each experiment was done with 30 mmol % equiv. Lewis/Brönsted acids, NR: no reaction after 14 h. For incomplete reactions, yields are noted for reactions continued for 14 h.
[b] Isolated yields.
[c] Reaction was done under oxygen.



Scheme 1. Domino process of Povarov reaction–aerobic dehydrogenation.

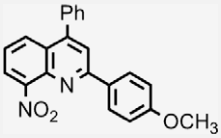
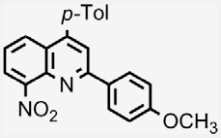
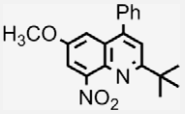
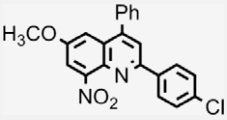
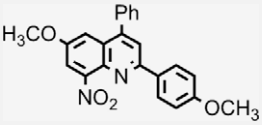
Table 2
Synthesis of polysubstituted quinolines[a]



Entry	Product	Time (h)	Yield[b] (%)
1		4	65
2		4	42
3		4	68
4		4	74
5		3	81
6		5	53
7		5	48
8		5	46
9		6	56

(*continued on next page*)

Table 2 (*continued*)

Entry	Product	Time (h)	Yield[b] (%)
10		6	58
11		6	51
12		6	41
13		6	66
14		6	61

[a] Products were characterized by ^{1}H and ^{13}C NMR, mass and IR spectroscopy, and confirmed by elemental (C, H & N) analysis.
[b] Isolated yields.

some cases, the incomplete reaction conversion and the aerial oxidation of reactants resulted in low yield formation of products.

In general, $HClO_4$-acidified montmorillonite exhibited its crucial catalytic role in promoting the Povarov reaction–aerobic dehydrogenation. Its increased activity favoring the domino process of imine formation-[4+2]-cycloaddition-aerobic dehydrogenation resulting in the formation of quinoline is plausible due to the enhanced effective surface area, increased Hammett acidity (H_0) value of Brönsted acid and Clay's favorable structural change caused by acidification and incorporation of ClO_4^-.[18]

In conclusion, we have developed a novel $HClO_4$-modified montmorillonite-promoted domino process of multicomponent Povarov reaction–aerobic dehydrogenation to provide the synthesis of polysubstituted quinolines relevant to pharmaceuticals, especially antimalarials. The exploration of $HClO_4$-modified montmorillonite as a privileged catalyst in this method predicts its potential use for promoting various multicomponent hetero Diels–Alder reactions and possible successive aerobic dehydrogenation in domino mode to afford the synthesis of heterocyclic scaffolds. Further investigations in this area and the focused library synthesis to find out potential antimalarial agents are ongoing in our laboratory.

Acknowledgments

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References and notes

1. (a) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721–2750; (b) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670; (c) Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSR. Ser. Khim.* **1963**, 953–956.
2. (a) Kikuchi, S.; Iwai, M.; Fukuzawa, S. *Synlett* **2007**, 2639–2642; (b) Baudelle, R.; Melnyk, P.; Deprez, B.; Tartar, A. *Tetrahedron* **1998**, *54*, 4125–4140; (c) Bortolotti, B.; Leardini, R.; Nanni, D.; Zanardi, G. *Tetrahedron* **1993**, *49*, 10157–10174.
3. (a) Zhao, Y.-L.; Zhang, W.; Wang, S.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 4985–4988; (b) Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451–7456; (c) Hirashita, T.; Kawai, D.; Araki, S. *Tetrahedron Lett.* **2007**, *48*, 5421–5424; (d) Shindoh, N.; Tokuyama, H.; Takasu, K. *Tetrahedron Lett.* **2007**, *48*, 4749–4753.
4. (a) Sridharan, V.; Avendano, C.; Menendez, J. C. *Tetrahedron* **2007**, *63*, 673–681; (b) Savitha, G.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 3589–3593.
5. (a) Demaude, T.; Knerr, L.; Pasau, P. *J. Comb. Chem.* **2004**, *6*, 768–775; (b) Kouznetsov, V. V.; Bohorquez, A. R. R.; Saavedra, L. A.; Medina, R. F. *Mol. Divers.* **2006**, *10*, 29–37; (c) Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSR. Ser. Khim.* **1964**, 2221–2222.
6. (a) Chen, Y.; Qian, L.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330–9333; (b) Samec, J. S. M.; Ell, A. H.; Baeckvall, J. *Chem. Eur. J.* **2005**, *11*, 2327–2334.
7. Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223–246.
8. (a) Jain, M.; Khan, S. I.; Tekwani, B. L.; Jacob, M. R.; Singh, S.; Singh, P. P.; Jain, R. *Bioorg. Med. Chem.* **2005**, *13*, 4458–4466; (b) Lilienkampf, A.; Mao, J.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2009**, *52*, 2109–2118; (c) Chen, S.; Chen, R.; He, M.; Pang, R.; Tan, Z.; Yang, M. *Bioorg. Med. Chem.* **2009**, *17*, 1948–1956.
9. (a) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141–161; (b) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon press: Oxford, 1996; Vol. 5, pp 167–243; (c) Das, B.; Krishnaiah, M.; Laxminarayana, K.; Nandankumar, D. *Chem. Pharm. Bull.* **2008**, *56*, 1049–1051; (d) Panda, K.; Siddiqui, I.; Mahata, P. K.; Ila, H.; Junjappa, H. *Synlett* **2004**, 449–452.

10. (a) Arcadi, A.; Aschi, M.; Marinelli, F.; Verdecchia, M. *Tetrahedron* **2008**, *64*, 5354–5361; (b) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873–6877.
11. Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G.; Ruggieri, F. *J. Org. Chem.* **1992**, *57*, 1842–1848.
12. (a) Guchhait, S. K.; Madaan, C. *Synlett* **2009**, 628–632; (b) Guchhait, S. K.; Madaan, C.; Thakkar, B. S. *Synthesis* **2009**, 3293–3300; (c) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2008**, *43*, 5474–5489; (d) Colombo, M.; Peretto, I. *Drug Discovery Today* **2008**, *13*, 677–684; (e) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131–163.
13. For synthetic use of heterogenized catalyst: (a) Corma, A. *Chem. Rev.* **1997**, *97*, 2373–2419; (b) Shaterian, H.; Yarahmadi, H.; Ghashang, M. *Tetrahedron* **2008**, *64*, 1263–1269; (c) Das, B.; Thirupathi, P.; Kumar, R. A.; Laxminarayana, K. *Adv. Synth. Catal.* **2007**, *349*, 2677–2683.
14. Lewis acid/protic acid adsorbed on SiO_2 and Brönsted acidified montmorillonite were prepared following this letter: Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896–1897.
15. *Representative synthesis of 2-(4-chlorophenyl)-4-phenylquinoline* (Table 2, entry 1): A mixture of 4-chlorobenzaldehyde (0.14 g, 1 mmol), aniline (0.09 g, 1 mmol) and phenylacetylene (0.15 g, 1.5 mmol) in DCM (1 mL) was adsorbed on 2.0 g of $HClO_4$–Mont. (15 mmol %, mol/w) and it was made as a free flowing powder. The solid mixture was then stirred under open air at 70 °C for 4 h. The organic compounds were extracted from the solid support by stirring with EtOAc (3 × 25 mL) and DCM (25 mL). All organic solutions were combined and concentrated under reduced pressure. The column chromatographic purification of crude product over silica gel (mesh size: 60–120) eluting with EtOAc–petroleum ether (60–80) afforded 2-(4-chlorophenyl)-4-phenylquinoline (205 mg, 65%) as a white solid; mp 98–100 °C; MS (ESI) *m*/*z*: 316.4 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.57 (m, 8H), 7.73–7.79 (m, 2H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 2H), 8.24 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.8, 125.6, 125.8, 126.4, 128.4, 128.5 (2 CH), 128.8 (2 CH), 128.9 (2 CH), 129.5 (2 CH), 129.6, 130.1, 135.5, 138.0, 138.3, 148.8, 149.4, 155.5; IR (KBr) ν_{max} = 1591, 1488, 1275, 1092 and 831 cm^{-1}; Anal. Calcd for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.66; H, 4.61; N, 4.29.
16. (a) Jain, M.; Vangapandu, S.; Sachdeva, S.; Singh, S.; Singh, P. P.; Jena, G. B.; Tikoo, K.; Ramarao, P.; Kaul, C. L.; Jain, R. *J. Med. Chem.* **2004**, *47*, 285–287; (b) LaMontagne, M. P.; Blumbergs, P.; Smith, D. C. *J. Med. Chem.* **1989**, *32*, 1728–1732; (c) Carroll, I. F.; Berrang, B.; Linn, C. P. *J. Med. Chem.* **1985**, *28*, 1564–1567.
17. (a) Case, F. H.; Brennan, J. A. *J. Org. Chem.* **1954**, *19*, 919–922; (b) Sarma, R.; Prajapati, D. *Synlett* **2008**, *19*, 3001–3005.
18. Rodríguez, Y. M. V.; Beltrán, H. I.; Vázquez-Labastida, E.; Linares-López, C.; Salmón, M. *J. Mater. Res.* **2007**, *22*, 788–800.