PART 4
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SECTION A

An Overview

ON SOME RECENT SYNTHETIC METHODS OF TETRAHYDROQUINOLINES BY THREE-COMPONENT POVAROV REACTIONS
INTRODUCTION

Heterocycles in general and quinolines in particular constitute ubiquitous scaffolds in pharmaceuticals, natural products and biologically active molecules. Quinoline substructure is a very privileged one and features in a large number of compounds with varied biological properties. Access to quinolines, particularly those which are polyfunctionalized ones, by multistep sequences is well-documented; however, some substitution patterns and functional group combinations necessitate long and difficult synthetic tour. On the other hand, a convenient approach for entry into densely functionalized quinolines is by way of multicomponent reaction (MRC) involving aromatic amines, aldehydes and activated vinyl ethers under acid catalysis. This version of original Povarov reaction, discovered in 1960s, was a [4+2] cycloaddition between aldimines with electron-rich alkenes under either protic or Lewis acid catalysis. It is mechanistically a formal inverse electron demand Diels-Alder (IEDDA) reaction between an 2-azadiene resulting from aniline and aldehyde and a vinyl ether, with subsequent double bond shift within the initial adduct to furnish a 1,2,3,4-tetrahydroquinoline (Scheme 1).

3 can be oxidized to quinoline. Povarov reaction is endowed with several advantageous features such as it is step- and atom-economic way of construction of diversely functionalized tetrahydroquinolines where two new C-C bonds, a new ring and three stereogenic centers are generated with the option of entry to their fully oxidized counterparts, viz. quinolines. The synthetic potential of this methodology was fully realized when one-pot three-component route of in situ formation of 2-azadiene was developed, making it eminently suitable for diversity-oriented synthesis. Variation with respect to all three components combined with applications of various kinds of Lewis and Bronsted acid catalysis under different reaction conditions (organic solvent at ambient as well as under reflux conditions, solventless...
conditions, use of aqueous medium) etc. vastly added to the synthetic usefulness of the reaction. This inverse electron demand hetero-Diels-Alder reaction has been extensively studied with use of different Lewis acids, such as BF$_3$·OEt$_2$, GbCl$_3$, InCl$_3$, TMSCl, ZrCl$_4$, CuBr$_2$, SbCl$_3$ and protic acids such as TFA, NH$_2$SO$_3$H and tungstophosphoric acid. The imino Diels-Alder reaction has also been successfully carried out using K-10 clay, Tf$_2$NH, Yb(OTf)$_3$, CAN, KHSO$_4$, I$_2$ and SmI$_2$. Herein, we present a brief overview of current status of investigation in this area which is relevant in the context of our related present work. The present overview covers the literature reports for the period 2004 to 2011.

**PRIOR ART**

**On Some Recent Synthetic Methods of Tetrahydroquinolines by Three-Component Povarov Reactions**

1. An efficient synthesis of pyrano and furoquinolines catalyzed by ZrCl$_4$

Anhydrous zirconium tetrachloride was found to be an efficient catalyst for the imino Diels–Alder reactions of N-benzylideneanilines with 3,4-dihydro-2H-pyran and 2,3-dihydrofuran to afford pyrano- and furo-[3,2-c]quinolines in good yields (Scheme 2).

The coupling constants of H-5 proton with H-4a ($J_{4a,5}$) in products 6 (5.2–5.8 Hz) and 7 (10.4–10.8 Hz) are consistent with cis- and trans-configurations, respectively. Besides, the coupling constant $J_{4a-10b}$ observed in all products viz. 2.7–2.9 Hz indicates the cis-junction between pyran and quinoline rings.
2. Copper (II) Bromide-catalyzed imino Diels-Alder reaction

Copper (II) bromide has been demonstrated to be an effective substoichiometric reagent for the imino Diels–Alder reaction \(^{10}\) between an imine (generated in situ) and an activated alkene in acetonitrile at ambient temperature (Scheme 3).

![Scheme 3](image)

3. One-pot synthesis of pyrano- and furanoquinoline derivatives catalyzed by tungstophosphoric acid

Tungstophosphoric acid (TPA) was observed to be an efficient catalyst for the synthesis of pyrano- and furanoquinolines through the imino Diels–Alder reaction involving one-pot coupling of benzaldehydes, anilines, and 3,4-dihydro-2H-pyran or 2,3-dihydrofuran \(^{14}\) (Scheme 4).

![Scheme 4](image)

4. Samarium diiodide-catalyzed one-pot aza Diels-Alder reaction

Three-component aza Diels-Alder reaction involving aromatic aldehydes, aromatic amine, and dihydropyran or dihydrofuran is effectively catalyzed by samarium diiodide afforded furo[3,2-c]- and pyrano-[3,2-c]quinoline derivatives in moderate to excellent yields \(^{21}\) (Scheme 5).
Notably, the m-isomer was obtained as the major product when the reaction was carried out in the absence of solvent.

5. One-pot synthesis of pyrano- and furanoquinoline derivatives catalyzed by SbCl₃

Antimony trichloride (SbCl₃) catalysed the inverse electron demand imino Diels–Alder reactions of in situ generated N-benzylidenes with 3,4-dihydro-2H-pyran and 2,3-dihydrofuran to afford pyrano- and furano[3,2-c]quinolines in good to excellent yields (Scheme 6).

It also catalyzed effectively the imino Diels–Alder reaction of in situ generated N-benzylidene-1-naphthylamine with 3,4-dihydro-2H-pyran and 2,3-dihydrofuran to afford the phenanthridine derivatives as a mixture of cis- and trans-isomers (Scheme 7).

A novel and efficient method for the synthesis of hexahydropyrano- and furo[3,2-c]quinolines was developed using catalytic amount molecular iodine$^{20b}$ (Scheme 8).

![Scheme 7]

A plausible reaction mechanism is given below (Scheme 9).

![Scheme 8]

7. Povarov reactions involving 3-aminocoumarins

Preformed or in situ generated 2-azadienes from the condensation of 3-aminocoumarins and aromatic aldehydes reacted with various electron-rich alkenes in the presence of Yb(OTf)$_3$ in acetonitrile to afford 1,2,3,4-tetrahydropyrido[2,3-c]coumarins$^{17}$ (Scheme 10). The ratios of the diastereomers formed were highly variable, although the overall yields were generally good. A concerted asynchronous inverse electron demand Diels Alder cycloaddition rather than a stepwise cyclization during the Povarov reaction has been proposed on basis of the observed solvent
effects including increase of yields with an increase of dielectric constant of the solvent.

A three-component one-pot version of this reaction, which involves \textit{in situ} formation of the 2-azadiene component (Scheme 11) afforded the same heterocyclic system using the same catalyst but required extended reaction time.
Some of these products were converted into the corresponding pyrido[2,3-c]coumarins upon treatment with bromine (Scheme 12).

One-pot synthesis of pyranobenzopyrans, furanobenzopyrans and tetrahydroquinolins: Povarov reaction catalyzed by KHSO₄

Potassium hydrogen sulfate (KHSO₄)-catalyzed one-pot three component coupling of aldehydes, anilines and electron rich dienophiles such as dihydropyran, dihydrofuran, and cyclopentadiene¹⁹ is reported to afford above heterocyclic systems (Scheme 13). With o-hydroxybenzaldehydes, the reaction is proposed to proceed via o-quinonemethides which underwent cycloaddition with cyclic and acyclic enol ethers to afford respective chromans. In contrast, the imine derivative is favored for benzaldehydes without o-hydroxyl group that acts as heterodiene and gave tetrahydroquinolines.
Cerium (IV) ammonium nitrate (CAN) is found to catalyze efficiently the three component coupling reaction of cinamaldehyde, aryl amine and electron-rich cyclic and noncyclic vinyl ether to afford the corresponding 2-styryl-1,2,3,4-tetrahydroquinolines.18 (Scheme 14)

9. Two-step synthesis of 2-styrylquinolines

Cerium (IV) ammonium nitrate (CAN) is found to catalyze efficiently the three component coupling reaction of cinamaldehyde, aryl amine and electron-rich cyclic and noncyclic vinyl ether to afford the corresponding 2-styryl-1,2,3,4-tetrahydroquinolines.18 (Scheme 14)
Treatment of diastereomeric mixtures of 2-styryl-1,2,3,4-tetrahydroquinolines in benzene with 2 equiv of DDQ under mild conditions (room temperature) afforded mixtures of isomeric styrylquinolines (Scheme 15).

10. Cascade Povarov-hydrogen transfer reaction
The reaction of electron-rich olefins and excess amount of imines in the presence of triflic anhydride under warming conditions\textsuperscript{16} afforded substituted tetrahydroquinolines -s and quinolines in a single operation (Scheme 16).
Generation of quinolines may be explained on the basis of the auto-tandem catalysis where aromatization of tetrahydroquinolines occurred by transferring their hydrogen atom to the starting imine. The one-pot synthesis of quinolines by a catalytic Povarov reaction followed by DDQ oxidation is also reported (Scheme 17).