ABSTRACT

The thesis entitled “Total Synthesis of Mitochondrial NADH Oxidase Inhibitor Circumdatin H, Opium Alkaloid Noscapine and Development of New Methodologies in Organic Synthesis” has been divided into three chapters.

**Chapter I:** First total synthesis of mitochondrial NADH oxidase inhibitor (-)-circumdatin H and its novel quinazolinone analogues

**Chapter II:** Synthetic studies and improved process for the synthesis of opium alkaloid noscapine

**Chapter III:** This chapter is further divided into **two** sections

*Section A:* Synthesis of 2,5-diamino-1,4-benzoquinone

*Section B:* Synthesis of anticancer agent (±)-monastrol and its analogues
Chapter I
First total synthesis of mitochondrial NADH oxidase inhibitor (-)-circumdatin H and its novel quinazolinone analogues

Introduction

Recently, a new group of quinazolinones fused to benzodiazepines were isolated from Aspergillus ochraceus extracts and they exhibited very interesting biological activities such as antitumor, antifungal, antibiotic activities. (-)-Circumdatin H 1a (Figure 1), was isolated from a fungus culture broth of Aspergillus ochraceus, and it was found to be inhibitor of the mammalian mitochondrial integrated electron transfer chain (mitochondrial NADH oxidase inhibitor) with IC$_{50}$ values of 1.5 ± 0.1 µM. The structure of (-)-circumdatin H was determined by comparison of its $^1$H NMR, $^{13}$C NMR spectral data and 2D NMR experiments with those of other known circumdatins, The stereoc hemistry at C-19 of 1a was tentatively assigned by comparison of the sign of the optical rotation value of 1a with that of other circumdatins.

![Figure 1](image)

1a: Circumdatin H

Quinazolinones, 3-(2-carbomethoxyphenyl)-2-methyl-4(3H)-quinazolinone 2 (Figure 1) was newly isolated natural product from Aconitum pseudo-laeve var. erectum Nakai (Ranunculaceae), and are pharmacologically active as sedative hypnotic drug [methaqualone 3 (Figure 1)], antitussive (chloroqualone) and anticonvulsant (piriqualone). In addition, quinazolinone derivatives are also possesses antimalarial, antibacterial, antidiabetic and anticancer activity.

Present work

In continuation of our ongoing program on synthesis of pyrrolobenzodiazepines as cytotoxic agents, now we have focused our attention on total synthesis of benzodiazepine
fused biologically active natural products. In this connection, we have undertaken the synthesis of (-)-circumdatin H and its analogue for studying structure activity relationship. We report the first total synthesis of mitochondrial NADH oxidase inhibitor (S)-(−)-circumdatin H and its analogue by chiron approach and unambiguously assigned and confirm the absolute configuration of natural (S)-(−)-circumdatin H as 19(S). We also report a new method utilized for the synthesis of 3-(2-carbomethoxyphenyl)-2-methyl-4(3H)-quinazolinone, methaqualone and their novel analogues.

**Figure 2:** Retro synthetic analysis of circumdatin H and its analogue

Retro synthetic analysis of (−)-circumdatin H revealed two possible synthetic strategies, one is path-A; and another one is path-B (Figure 2).

**Synthesis of circumdatin H analogue via quinazolinone intermediate (path-A):**

Synthesis of circumdatin H analogue initially started from the commercially available anthranilic acid and L-proline [(S)-pyrrolidin-2-carboxylic acid]. Methylantranilate 13a was prepared quantitatively by methylation of anthranilic acid with dimethyl sulfate. N-Boc-L-proline 9 was prepared from L-proline and di-tert-butyl dicarbonate. Amide 14 was prepared by the condensation reaction of methylantranilate 13a with N-Boc-L-proline 9 under essential neutral conditions by using HOBT, and DCC in dry THF in 73% yield. Compound 14 was subjected to hydrolysis with 10% aqueous LiOH solution in a (2:1) mixture of MeOH
and THF for over night afforded benzoic acid 15 in 94% yield. Cyclization of compound 15 to 2-\((\text{-N-tert.} \text{butyloxy carbonyl})\)-L-prolinyl-amino)-benzo\([d][1,3]\)oxazin-4-one 5 was achieved in 95% yield, in the presence of N,N’-carbonyldiimidazole (CDI) in dry THF at room temperature for 1 h (Scheme 1).

Scheme 1

\[
\begin{align*}
\text{CO}_2\text{CH}_3 & \quad + \quad \text{CO}_2\text{H} \\
13\text{a} & \quad \text{HOBt, DCC} \\
\text{THF, 0}^\circ\text{C - r.t.} & \quad \rightarrow \\
14 & \quad 10\% \text{ aq. LiOH, MeOH : THF (2:1)}
\end{align*}
\]

Cyclocondensation reaction of compound 5 with methyl anthranilate 13a in refluxing pyridine, or in the presence of ZnCl\(_2\) resulted, complex mixture of carbonaceous compounds. Where as the cyclocondensation reaction of 2-methyl-benzo\([d][1,3]\)oxazin-4-one 17a with o-toluidine 13b in pyridine at 150 °C for 3 h afforded the desired product 3 in 13% yield.

Tetra-n-butylammonium bromide (TBAB) is an inexpensive readily available ionic liquid has been used as homogeneous catalyst in various organic transformations, and in view of its inherent properties like environmental compatibility, operational simplicity, non corrosive nature; we have used TBAB for the first time in the cyclocondensation reaction of various benzoazin-4-ones with amines.

Scheme 2

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{(CH}_3\text{CO})_2\text{O} \\
16\text{a} & \quad \text{reflux, 3 h} \\
\text{17a} & \quad \text{H}_2\text{N} \quad \text{13b} \\
\text{TBAB, 120}^\circ\text{C, 60 min.} & \quad \rightarrow \\
\text{3} & \quad \text{(CH}_3\text{CO})_2\text{O}
\end{align*}
\]

2-Methyl-benzo\([d][1,3]\)oxazin-4-one 17a was prepared from anthranilic acid by reaction with acetic anhydride at reflux temperature, and it was used immediately in the next step. Cyclocondensation reaction of freshly prepared 17a with equivimolar amounts of o-toluidine 13b and TBAB at 120 °C under N\(_2\)-atm. the reaction was completed within 60 minutes and resulted expected product methaqualone 3 in 83% yield (Scheme 2).
We attempted the synthesis of newly isolated quinazolinone alkaloid 2. Compound 17a upon reaction with equimolar amount of methylantranilate 13a in the presence of TBAB at 120 °C under N2-atm. for 60 minutes, after completion of reaction the reaction mixture was diluted with ethyl acetate, extracted with 2% aq. NaHCO3 solution and the organic layer was purified by silica-gel column chromatography to give 2 in 69% yield (over two steps) as a pale yellow solid (Scheme 3).

Scheme 3

2-Methyl-bnezo[d][1,3]oxazin-4-ones 17a-d were prepared from corresponding anthranilic acids 16a-d by the reaction with acetic anhydride at reflux temperature. The amines; o-toluidine 13b, (R)-(+-)1-phenylethylamine 13d were readily available where as methylantranilate 13a was prepared by esterification of anthranilic acid, and 3,4-dimethoxyphenethylamine 13c was prepared from veratraldehyde.

Scheme 4

Veratraldehyde 18 upon reaction with nitromethane and piperidine acetate (Henry reaction) in benzene afforded β-nitrostyrene 19 in 72% yield, followed by reduction with LAH in THF afforded 3,4-dimethoxyphenethylamine 13c in 52% yield (Scheme 4).

Scheme 5
Anthranilic acids 16b and 16c are prepared from vanillic acid as below; compound 22 was prepared from vanillic acid 20 by methylation followed by nitration. Base hydrolysis of ester 22 using 10% aqueous NaOH solution in 1:1 mixture of water and 1,4-dioxane afforded nitrobenzoic acid 23 in 96% yield. Compound 23 upon reduction using H₂-Pd/C (5%) at 1 atm. pressure in methanol at room temperature resulted 2-amino-4,5-dimethoxybenzoic acid 16b in 88% yield (Scheme 5).

Scheme 6

Methyl vanillate 24 was prepared from vanillic acid 20 by esterification using methanol and catalytic amount of sulfuric acid in 94% yield. Ester 24 upon reaction with propargyl bromide using K₂CO₃ in acetone afforded ether 25 in 81% yield. Ether 25 upon regioselective nitration using 70% HNO₃ resulted nitro compound 26 in 70% yield. Compound 26 upon ester hydrolysis using 10% NaOH solution in water in a 1:1 mixture of 1,4-dioxane and water afforded acid 27 in 94% yield. Compound 27 upon reduction using iron in acetic acid afforded compound 16c in 43% yield (Scheme 6).

To study the feasibility and applicability of this reaction process we have prepared various 2,3-disubstituted quinazolin-4-ones 28a-h by the cyclocondensation reaction of 4H-3,1-benzoazin-4-ones 17a-d and amines 13a-d using TBAB at 120 °C (Scheme 7).

Scheme 7

28a: R’=R’’=R’’’=H; R= (R)-(+) 1-phenylethylamine
28b: R’=R’’=R’’’=H; R= 3,4-dimethoxyphenethylamine
The success of the synthesis of compound 2, 3 and various 2,3-disubstituted-3H-quinazolin-4-ones 28a-h mediated by TBAB encouraged us to pursue the synthesis of circumdatin H analogue. Freshly prepared benzo[d][1,3]oxazin-4-one 5 upon reaction with equimolar amount of methylanthranilate 13a using TBAB under N₂-atm. at 120-160 °C for 6 h resulted (±)-circumdatin H analogue 29 in 52% yield, and a homo-coupled byproduct dione 30 in 12% yield (Scheme 8).

Scheme 8

During the course of reaction enantiomeric erosion was encountered and resulted (±)-circumdatin H analogue 29 in racemic form. To overcome the racemization, we switched over to another route. Alternatively, we have followed another approach of path-A starting from anthranilic acid for the synthesis of circumdatin H analogue via quinazolinone intermediate route.

Compound 8 was prepared from anthranilic acid 16a by the reaction with thionyl chloride followed by methylanthranilate 13a in 46% yield. Compound 8 upon condensation reaction with N-Boc-L-proline 9, DCC and HOBT in dry THF afforded the triamide 7 in 57% yield. Compound 7 was treated with 3 equiv. of HMDS and four equiv. of I₂ in DCM at room temperature for 48 h, then the reaction mixture was washed with 5% Na₂S₂O₅.5H₂O solution in water and the resulting reaction mixture was purified by silica gel column chromatography resulted only in the isolation of Boc-deprotected 2-[[2-(L-prolinyl)-benzoylamino]-benzoic
acid methyl ester 32 as sole product instead of expected quinazolinone compound 4 (Scheme 9). We felt the need to develop an alternate route for the synthesis of circumdatin H.

**Scheme 9**

![Chemical structures](image)

**Synthesis of (-)-circumdatin H and its analogue via Eguchi aza-Wittig protocol (path-B):**

**Scheme 10**

![Chemical structures](image)

First, we planned to synthesize (-)-circumdatin H analogue 1b starting from the anthranilic acid 16a and chiral starting material L-proline 34. Isatoic anhydride 33 was prepared from anthranilic acid using ethyl chloroformate and triethylamine. Dione 11 was prepared from the reaction of isatoic anhydride 33 with L-proline 34 in DMSO in 82% yield (Scheme 10).

**Scheme 11**

![Chemical structures](image)

Anthranilic acid 16a upon diazotization using aqueous NaNO₂, followed by nucleophilic substitution of azide using NaN₃ resulted 2-azido benzoic acid 35 in 77% yield (Scheme 11). Compound 35 was converted into 2-azido-benzoyl chloride 12b by the reaction of thionyl
chloride resulted 12b, and it was immediately used in the next step. Dione 11 in dry THF was acylated with freshly prepared 2-azidobenzoyl chloride 12b using triethylamine and DMAP at 20 °C under N₂-atm. gave crude 10b as brownish syrup, which was used immediately for the next step (Scheme 12).

Scheme 12

\[
\begin{align*}
\text{11} + \text{12b} & \xrightarrow{\text{Et₃N, DMAP}} \text{10b} \\
\text{10b} & \xrightarrow{(n-Bu)₃P, benzene} \text{1b}
\end{align*}
\]

The azide derivative 10b was treated with tributylphosphine at 60 °C in dry benzene under N₂-atm. afforded (S)-(−)-circumdatin H analogue 1b in 63% yield over two steps (Scheme 12). Compound 1b exhibited a specific rotation of -128.60° (c 0.5, MeOH).

2-Amino-5-methoxybenzoic acid 16e in a solution of aq. 25% HCl was diazotized with NaNO₂, and the resulted reaction mixture was treated with sodium azide afforded pure 2-azido-5-methoxy-benzoic acid 36 in 95% yield.

Scheme 13

\[
\begin{align*}
\text{16e} & \xrightarrow{1) \text{25% HCl, water, NaNO₂, -5 - 0 °C, 30 min.}} \text{36} \\
\text{36} & \xrightarrow{2) \text{urea, NaN₃, -5 - 0 °C to r.t. overnight}} \text{12a}
\end{align*}
\]

Compound 36 upon treatment with thionyl chloride resulted benzoyl chloride 12a, and it was used immediately in the next step. Dione 11 was acylated with compound 12a in dry THF using triethylamine and DMAP at 20 °C under N₂-atm. afforded crude 10a, which was used immediately in the next step. Crude compound 10a in dry benzene was treated with (n-Bu)₃P at 60 °C under N₂-atm. afforded (-)-circumdatin H 1a in 73% yield (35.03% overall yield starting from anthranilic acid over four steps) (Scheme 14). (-)-Circumdatin H was fully characterized by the analysis ¹H NMR, ¹³C NMR and DEPT, IR, HR-MS spectral data, and they are identical with the authentic data.
We assigned the stereochemistry of natural and synthetic (-)-circumdatin H at C-19 as C-19(S) without ambiguity by synthesis of (-)-circumdatin H starting from S-proline, and based on sign of optical rotation of natural and synthetic (-)-circumdatin H 1a $\left[\alpha\right]_D^{\circ}$ -130.77 (c 0.078, MeOH), and its analogue 1b $\left[\alpha\right]_D^{\circ}$ -128.60 (c 0.5, MeOH).

Chapter II
Synthetic studies and improved process for the synthesis of opium alkaloid noscapine

Introduction

Noscapine 37 is a naturally occurring phthalideisoquinoline alkaloid obtained from opium. It has been used orally in humans as an antitussive drug. Noscapine inhibits the progression of murine lymphoma, melanoma, and human breast tumors implanted in nude mice with little or no toxicity to the kidney, heart, liver, bone-marrow, spleen, or small intestine and does not inhibit primary humoral immune responses in mice.

Figure 3

37: (-)-α-(1R, 9S)-Noscapine

However, noscapine is available from natural source, in view of environmental issues and the increasing demand for noscapine, we felt the need to develop a synthetic route and process development is essential for the synthesis of noscapine. Herein, we report a synthetic process for the synthesis of noscapine at multigram scale by zinc-promoted reductive coupling reaction of cotanine iodide 41 with 3-bromomeconine 48 as the key step.
**Present work**

In continuation of our program on the synthesis of biologically active natural products, we undertook the synthesis and process development of an antitussive drug and anticancer agent of opium alkaloid noscapine. Synthesis of noscapine was achieved in three different methods (method A-C), and method-C was developed into multigram scale level.

**Scheme 15**

Initially, for our synthetic experiments cotarine 38 was prepared from (-)-α-noscapine 37 by oxidative degradation with 18% nitric acid in 96% yield, and opianic acid 39 in 89% yield.

**Method A:**

In this method, meconine 40 was prepared from opianic acid 39 by the reaction with NaBH₄ in EtOH in 74% yield (Scheme 16).

**Scheme 17**

A solution of cotarine 38 and meconine 40 in ethanol was refluxed for 4 h then the crude product was purified by silica gel column chromatography afforded (±)-α/β-noscapine 37a/b in 0.25% yield (Scheme 17).
Method B:

In this method, for the conversion of cotarnine 38 to cotarnine iodide 41, we have developed a novel method without using any organic solvents, indeed in water. Cotarnine 38 was dissolved in equimolar amount of aq. 1N HCl, and was treated with two equivalents of potassium iodide gave cotarnine iodide 41 in 93% yield (HPLC 98% pure).

Scheme 18

Meconine 40 upon treatment with LDA followed by cotarnine iodide 41 in THF at – 70 °C for 18 h, and the reaction mixture was purified by silica gel column chromatography afforded (±)-α/β-noscapine 37a/b in 2.3% yield (Scheme 19).

Scheme 19

Due to the low yield and the cost of reagents, we have switched over to the alternate method.

Method-C:

In this method, meconine 40 was prepared from 2,3-dimethoxybenzoic acid 43, using conc. HCl and 37% aqueous formaldehyde solution at 95 °C for 20 minutes. Then the reaction mixture was cooled to 10 °C and the separated solid was filtered to give over alkylated byproduct 44 in 12% yield. The filtrate was diluted with ice cold water afforded a crude product of meconine 40 and recrystallized from water gave pure meconine 40 in 33% yield (HPLC 97% pure) (Scheme 20).

Scheme 20
During the recrystallization of crude meconine in water, the byproduct 44 was converted into an alcohol 45. Formation of alcohol 45 from byproduct 44 was confirmed by converting the byproduct 44 into alcohol 45 by boiling the compound 44 in water for 30 minutes.

**Scheme 21**

Alcohol 45 was acetylated using Ac$_2$O/pyridine at room temperature resulted, acetyl derivative 46.

**Scheme 22**

Meconine 40 upon bromination with NBS in CCl$_4$ using catalytic amount of benzoyl peroxide at reflux temperature for 6.5 h, resulted 3-bromomeconine 48 (>99% pure by $^1$H NMR) in 99% yield (Scheme 22). Formation of 4-bromomeconine 49 was excluded by performing the bromination reaction under neutral conditions.

To a solution of cotarine iodide 41 and 3-bromomeconine 48 in CH$_3$CN under N$_2$-atm was added zinc dust and stirred at -10 °C to 0 °C for 2 h and at room temperature for 26 h. After completion of reaction, solvent was removed, diluted with DCM and was treated with 10% aqueous NaHCO$_3$ and the insoluble solid was filtered. From the filtrate, organic layer was separated and concentrated to give crude (±)-α/β-noscapine 37a/b.
The crude (±)-α/β-noscapine 37a/b was boiled with methanol and insoluble solid was filtered to afford a solid of 1\textsuperscript{st} crop. Methanolic mother liquor was cooled to room temperature for 2 h; separated solid was filtered to give 2\textsuperscript{nd} crop solid. After removal of 2\textsuperscript{nd} crop, the resulted methanolic mother liquor was kept at 20 °C for 48 h and the separated solid was filtered to give 3\textsuperscript{rd} crop solid (Scheme 23).

The solid of 1\textsuperscript{st} crop was dissolved in aqueous solution of 1N HCl at room temperature, insoluble material was filter off, which was characterized as a dimer of meconine 51. The acidic filtrate was basified with an aqueous solution of 12.5% NH\textsubscript{3} at 10 °C, resulted precipitate was filtered to give pure (±)-α-noscapine 37a in 56% of isolated yield (HPLC >99% pure; chiral HPLC shown the presence of (-)-α-noscapine and (+)-α-noscapine in 1:1 ratio). The overall yield of (±)-α-noscapine 37a starting from meconine over two steps was 55% or starting from cotarnine over two steps was 52%.

The 3\textsuperscript{rd} crop was purified (as 1\textsuperscript{st} crop) by acid base treatment to give pure (±)-β-noscapine 37b in 31% of isolated yield (HPLC >99% pure; chiral HPLC shown the presence of (-)-β-noscapine and (+)-β-noscapine in 1:1 ratio). The overall yield of (±)-β-noscapine 37b starting from meconine over two steps was 30% or starting from cotarnine over two steps was 29%.
Attempts were made to get the diastereoselectivity under developed coupling reaction conditions using 10 mol% of chiral auxiliary. Use of dihydrocinchonine, (-)-sparteine, or L-prolinol as chiral auxiliaries could not succeed in achieving required diastereoselectivity.

Resolution of (±)-α-noscapine 37a into (-)-(1R, 9S)-α-noscapine and its enantiomer of (+)-(1S, 9R)-α-noscapine was attempted using various chiral acid resolving agents including L- (+)-tartaric acid, (S)- (+)-mandelic acid, (R)-( +)-4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide, (R)-(−)-mandelic acid, (1S)-( +)-10-camphorsulfonic acid, (1S)-( +)-3-bromocamphorsulfonic acid, (1R, 3S)-( +)-camphoric acid, D-( +)-malic acid, di-p-toluoyl-D-tartaric acid, cholic acid, L-(−)-3-phenylacetic acid, (1R, 3R, 4R, 5R)-(−)-quinic acid, naproxen, S-fenavaleric acid were attempted. Most of the chiral acids did not form diastereomeric salt with (±)-α-noscapine 37a. Some of the chiral acids formed a protinated salt of (±)-α-noscapine. While some of them formed diastereomeric salt with (±)-α-noscapine, but they did not crystallized.

Chapter III: This chapter is further divided into two sections.

Section A: Synthesis of 2,5-diamino-1,4-benzoquinone.

Introduction

The natural product terreusinone 52 (Figure 5), isolated from the marine algicolous fungus Asperigillus terreus, was detected to possess UV-A absorbing activity with an ED₅₀ value of 70 µg/mL.

![Figure 5](image)

2,5-Diamino-1,4-benzoquinone 53 (Figure 5) is an integral structure of naturally occurring biologically active compounds such as terreusinone 52. It is also an integral structure of synthetic drug benzoquinonium chloride, a skeletal muscle relaxant drug. It is a useful intermediate for the preparation of many industrial dyestuffs. 2,5-Diamino-1,4-benzoquinone 53 derivatives especially 2,5-aziridinyl-1,4-benzoquinone was found to form interstrand crosslink DNA, and it was cytotoxic in vitro.
Present Work

We attempted the synthesis of terreusinone having a dipyrrolo-1,4-benzoquinone moiety. Retro synthetic analysis of terreusinone 52 revealed two fragments; of which one is 2,5-diamino-1,4-benzoquinone 53 and another one is an aliphatic fragment 54 (Figure 5). The present work describes a novel and efficient method for the synthesis of 2,5-diamino-1,4-benzoquinone 53 based on the hydrogenolysis of 2,5-diamino-3,6-dibromoquinone 58 over palladium-on-charcoal.

1,4-Benzoquinone 55 was prepared from p-hydroquinone using CrO$_3$ in acetic acid and water. Benzoquinone 55 upon bromination in acetic acid gave tetrabromo-1,4-hydroquinone 56 (bromanillic acid) in 85% yield. Bromanillic acid 56 upon oxidation using CrO$_3$ in acetic acid afforded tetrabromo-1,4-benzoquinone 57 (bromanil) in 95% yield. Bromanil 57 upon treatment with ammonia in ethanol at reflux temperature for 8 h, gave 2,5-diamino-3,6-dibromoquinone 58 in 74% yield (Scheme 24).

Scheme 24

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\begin{center}
\includegraphics[width=\textwidth]{Scheme24.png}
\end{center}
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Hydrogenolysis of 2,5-diamino-3,6-dibromoquinone 58 with catalytic amounts of 5% palladium on charcoal at 45 psi in methanol at ambient temperature. Subsequent base hydrolysis with triethylamine in methanol-water (1:1) resulted in the formation of 2,5-diamino-1,4-benzoquinone 53 as bright reddish-brown crystalline solid in 82% yield; and the overall yield was 48.99% starting from benzoquinone 55 in four steps (Scheme 24). (Synthesis 2007, 187-189).
Section B: Synthesis of anticancer agent (±)-monastrol and its analogues

Introduction:

In recent years 3,4-dihydropyrimidin-2(1H)-ones 59 (DHPMs) scaffolds displays a fascinating array of pharmacological and therapeutic properties such as antibacterial, antihypertensive and neuropeptide (NPY) antagonists. 4-(3-Hydroxyphenyl)-2-thione derivative (±)-monastrol 59g was found to possess mitotic kinesin Eg5 inhibitor activity.

Figure 6

![Chemical Structure of (±)-Monastrol]

59g: (±)-Monastrol

Present work

Due to our interest on synthesis of biologically active compounds, we targeted the synthesis of anticancer agent (±)-monastrol 59g (Figure 6) and its analogues for studying structure activity relationship. Use of potassium dodecatungstocobaltate trihydrate (K₅CoW₁₂O₄₀·3H₂O) an environmentally benign, reusable heteropoly acid catalyst for a wide variety of organic transformations by our group as well as others, prompted us to explore the potential of K₅CoW₁₂O₄₀·3H₂O as catalyst for one-pot three component heterocyclocondensation process. We report the synthesis of Biginelli compounds by the one-pot three-component condensation of aryl aldehyde, alkyl acetoacetate and urea or thiourea promoted by K₅CoW₁₂O₄₀·3H₂O (0.01 equiv. or 1.0 mol%) under solvent-free conditions at 80 °C in excellent yields (Scheme 25).

Scheme 25

![Scheme 25]

In a typical experimental procedure, a mixture of aldehyde 60, β-keto ester 61, urea 62 and K₅CoW₁₂O₄₀·3H₂O (1 mol%, 0.01 equiv.), was heated at 80 °C for appropriate time (30-
90 minutes). The reaction mixture was poured onto crushed ice and the precipitated solid was filtered to give crude product of 59. The crude product 59 was dissolved in boiling EtOH and the insoluble catalyst was filtered. Filtrate was cooled to room temperature and the separated crystals were filtered to give analytically pure DHPMs 59 in excellent yields (Scheme 25). The filtered catalyst was (quantitatively recovered) reactivated by heating the catalyst at 80 °C for 2 h and it was reused for three times without considerable loss of activity.

This method offers several advantages including high yields, short reaction times, and a simple work-up procedure; moreover the catalyst was recovered and reused for several times without loss of activity. Furthermore, the present procedure is readily amenable to parallel synthesis and the generation of combinatorial dihydropyrimidinone libraries.

Figure 7

Condensation of 2-hydroxybenzaldehyde with ethyl acetoacetate and urea in presence of K₅CoW₁₂O₄₀.3H₂O resulted diazatricyclo compound 59s (Figure 7) in place of expected DHPM. Condensation of 4-methoxybenzaldehyde with ethyl trifluoroacetoacetate 61e and urea in presence of K₅CoW₁₂O₄₀.3H₂O resulted hexahydropyrimidine 59t (Figure 7) in place of expected DHPM. (Heterocycles 2006, 68, 1217-1224).