Domino Oxidation–Michael Reactions of Catechols with Barbituric Acid Derivatives in Water: An Efficient Synthesis of Polycyclic Pyrimidinones

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Abstract: The oxidative coupling reaction of catechols with barbituric acid derivatives, mediated by ferricyanide, has been investigated in aqueous solution. The results indicate that the barbituric acid derivatives participate in Michael-type addition reactions with in situ generated ortho-benzoquinones, in a domino fashion, to afford a variety of polycyclic pyrimidinones. The method provides a one-step, rapid and efficient procedure for synthesizing a range of polycyclic pyrimidinones of biological significance.

Key words: catechols, quinines, Michael additions, domino reactions, polycycles

The development of efficient, simple and straightforward chemical processes and methodologies for the synthesis of widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis. Pyrimidinone derivatives continue to be of great interest due to their wide range of biological activities and have been widely used in medical applications as sedative, hypnotic and local anaesthetic drugs. 3,4 Pyrimidine-2,4,6-(1H)-triones are useful in chemical transformations and have been used as organic oxidizers, and as intermediates to oxadeazaflavines, which are used as biomimetic models of the 5-deazaflavine coenzyme. The importance of these compounds has motivated many workers to synthesize a number of highly substituted pyrimidinone derivatives and numerous methods have been developed for their preparation. A literature survey reveals that, in contrast to the widely studied, monocyclic pyrimidinones (I), relatively few papers have reported the synthesis of either polycyclic benzofuro[2,3-d]pyrimidinones (II) or dispiropyrimidinones (III) (Figure 1).

To the best of our knowledge, only a few methods for the preparation of polycyclic pyrimidinones have been developed through electrochemical routes and there have been no reports on the synthesis of such compounds via efficient and simple chemical procedures.

In a continuation of our efforts to develop more versatile methodologies for the synthesis of catechol-annulated heterocycles, herein we wish to describe a simple, convenient and straightforward protocol for the synthesis of fused pyrimidinones using ferricyanide as a mild, homogeneous oxidizing agent.

In this new approach, oxidation of catechols 1a–d, bearing electron-donating or -withdrawing groups, in the presence of barbituric (3a), 1,3-dimethylbarbituric (3b) or 1,3-diethyl-2-thiobarbituric acid (3c) as possible nucleophiles, has been performed in water using potassium ferricyanide. The present work has led to the development of a facile, one-pot oxidation–Michael addition sequence which allows access to the dispiropyrimidin-2,4,6-(1H,3H,5H)-triones (7a–h) and the benzofuro[2,3-d]pyrimidin-2,4-(1H,3H)diones (7i–j), from simple and inexpensive precursors, in good yields and high purity.

Figure 1 Structures of mono- and polycyclic pyrimidinones

In our earlier work, comparison of the values of $E^\circ$, evaluated from the midpoint potential between the anodic and cathodic peaks ($E_{\text{mid}}$) for catechol $[(0.26 + 0.07)/2 = 0.165]$ and potassium ferricyanide $[(0.24 + 0.15)/2 = 0.195]$, using cyclic voltammetry, revealed that potassium ferricyanide was a suitable agent for mild oxidation of catechols in the presence of nucleophiles. Such systems could selectively oxidize catechols to their corresponding ortho-benzoquinones without any effect on the nucleophiles. When catechol (1a; 1 mmol) was treated with potassium ferricyanide (4 mmol) in an aqueous solution containing barbituric acid derivatives (3a–c; 1 mmol) and sodium acetate (pH 6.8, 0.2 M), fused pyrimidinones (7a–c) were obtained in good yields (Scheme 1). In more basic solutions, the anionic forms of catechols that arose through an acid-dissociation reaction was enhanced and the coupling of these species with ortho-quinones interfered in the Michael addition reaction of barbituric acid derivatives (3a–c) with ortho-quinones. In other words, in aqueous solutions containing 0.2 M sodium acetate, any...
hydroxylation23–25 or dimerization26 reactions take place too slowly to interfere with the synthesis of pyrimidinone derivatives. The proposed mechanism for oxidation of 1a, in the presence of 3a–c, is presented in Scheme 1.

According to our results, it seems that, upon oxidation of 1a to ortho-quinone 2a, an intermolecular 1,4-addition (Michael) reaction of anions 4a–c with 2a leads to the formation of intermediates 5a–c. The oxidation of these intermediates (5a–c) is easier than the oxidation of the starting parent molecule (1a), by virtue of the presence of an electron-donating group, and gives intermediates 6a–c. These intermediates can form the final products of the reaction (7a–c) through a cyclization process. Though the final products could also be oxidized at a lower potential than the starting compound (1a), such over-oxidation of 7a–c was circumvented during the preparative reaction because of the insolubility of the products in the water/sodium acetate medium. As can be seen, there is an oxidation/intermolecular Michael addition/oxidation/intermolecular Michael addition sequence in this one-pot oxidative coupling reaction of 1a with 3a–c, leading to the formation of the dispiropyrimidinones 7a–c (Scheme 1, Table 1, entries 1–3).

![Scheme 1 Possible mechanism and tentative intermediates proposed for the synthesis of pyrimidinones 7a–h](image)

Examining the scope and generality of the developed protocol and the influence of structural variation of the catechol ring on the reaction sequence, we studied the reaction of barbituric acid derivatives with catechols bearing a methyl (1b), methoxy (1c) or carboxylic (1d) group at either the C-3 or C-4 position. The oxidation of 1b and 1c, in the presence of 3a–c as nucleophiles in sodium acetate solution, proceeded in a similar fashion to that of 1a (Scheme 1). The existence of a methyl or methoxy group at the C-3 position of these compounds probably causes relevant Michael acceptors (2b and 2c) to be attacked by 4a–c at the C-4 and/or C-5 positions to yield two types of product in each case. Since, for the ortho-quinones 2b and 2c, C-5 is more electropositive, we suggest that 2b and 2c are selectively attacked at this position, leading to the for-
decarboxylation, leads to the formation of the final product
molecular Michael addition reaction of barbituric acids
that of sodium acetate solution, proceeds in a different manner to
pling reaction of Michael addition sequence in the one-pot oxidative cou-
lecular Michael addition/oxidation/intramolecular

Interestingly, oxidation of 3,4-dihydroxybenzoic acid
Table 1, entries 4–9).

Possible mechanism and tentative intermediates in the synthesis of pyrimidinones
Scheme 2

In conclusion, we have described a simple, convenient
and versatile protocol for the preparation of a series of
polycyclic pyrimidinones via the domino oxidation/
Michael addition reaction of commercially available starting
materials in aqueous solution. This method is applicable
to both electron-rich as well as electron-deficient catechols. The attractive features of this process are mild
reaction conditions, short reaction times, large-scale synthesis, simple and rapid isolation of the products and high
to excellent yields. We believe that the ready availability of starting materials and the experimental simplicity gives
this procedure great potential. In addition, we hope that because of the diversity of this method, it could be adapted
for use in heterocyclic chemistry in order to synthesize and screen libraries of related biologically important poly-
cyclic pyrimidinones.

All materials and solvents used for synthesis and purification were of analytical reagent grade. Infrared spectra were recorded on a Bruker Vector 33 spectrophotometer using a drop-casting technique on NaCl plates and are reported in wavenumbers (cm⁻¹). ¹H NMR and ¹³C NMR spectra were all recorded in DMSO-d₆ on a Bruker (500 MHz) or a Jeol (90 MHz) spectrometer. Mass spectra and exact masses were recorded on a MAT 8200 Finnigan high-resolution mass spectrometer (70 eV); the latter employed a mass of 12.0000 for carbon. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F₂₅₄ 0.2 mm plates and visualized using UV light.

Synthesis of Polycyclic Pyrimidinones; General Procedure
To a stirred solution of 3a–c (1 mmol) in distilled H₂O (20 mL) containing AcONa (2 mmol), was added potassium ferricyanide (4 mmol) and the mixture was stirred at r.t. for 2 min. A solution of catechols (1a–d; 1 mmol) in distilled H₂O (10 mL) containing AcONa (2 mmol) was prepared and added dropwise to the stirred solution. The reaction mixture was kept at r.t., with occasional stirring, for the time indicated in Table 1, until the reaction was complete (monitored by TLC). The solution became dark and precipitates formed. At the end of the reaction, a few drops of AcOH were added and the mixture was placed in a refrigerator overnight. The solids formed were collected by filtration and recrystallized (acetone–H₂O). The crystals were washed with ethanol, dried in vacuum and were used for analytical and spectroscopic studies.

Selected characterization data for some pyrimidinones prepared are given below.

Compound 7b
Amorphous, beige solid.

¹H NMR (DMSO-d₆, 500 MHz): δ = 3.27 (s, 12 H, NCH₃), 6.59 (s, 4 H, H₁), 9.32 (s, 4 H, OH).

¹³C NMR (DMSO-d₆, 125 MHz): δ = 28.9, 57.5, 113.1, 123.3, 146.2, 150.9, 169.2.

MS (EI): m/z (%) = 524.1 (19), 467.2 (12), 410.1 (80), 382.1 (100), 325.1 (9), 268 (67), 240 (17), 199.1 (18), 143 (19), 60.5 (11).

HRMS (EI): m/z calcd for C₂₄H₂₀N₄O₆: 524.1179; found: 524.1183.
Compound 7d
Amorphous, brown solid.

$^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ = 1.90 (s, 6 H, CH$_3$), 6.82 (s, 2 H, H$_2$), 8.81 (s, 2 H, OH), 10.00 (s, 2 H, OH), 11.84 (s, 4 H, NH).

$^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ = 28.9, 57.5, 110.1, 113.1, 122.5, 123.1, 123.3, 146.2, 150.9, 169.2.

MS (EI): $m/z$ (%) = 496.1 (12), 410.1 (22), 365 (25), 322 (35), 296 (35), 207 (80), 199 (100), 162 (45), 124 (84), 77.2 (85).

HRMS (EI): $m/z$ calc for C$_26$H$_{24}$N$_4$O$_{10}$: 496.0866; found: 496.0864.

Compound 7e
Amorphous, beige solid.

IR (KBr, neat): 3441, 2923, 2855, 1746, 1701, 1577, 1502, 1464, 1376, 1295, 1218, 1116, 1072 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$, 90 MHz): $\delta$ = 1.85 (s, 6 H, CH$_3$), 3.32 (s, 12 H, NCH$_3$), 6.81 (s, 2 H, H$_2$), 8.84 (s, 2 H, OH), 9.65 (s, 2 H, OH).

MS (EI): $m/z$ (%) = 552 (20), 495 (6), 438 (30), 410 (39), 322 (10), 296 (100), 240 (10), 212.1 (12), 164 (22), 77.2 (9).

HRMS (EI): $m/z$ calc for C$_{26}$H$_{24}$N$_4$O$_{10}$: 552.1492; found: 552.1486.

Compound 7g
Amorphous, brown solid.

IR (KBr, neat): 3374, 3015, 2925, 2854, 1746, 1701, 1653, 1521, 1457, 1376, 1300, 1226, 1056 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$, 90 MHz): $\delta$ = 3.24 (s, 3 H, NCH$_3$), 3.46 (s, 3 H, NCH$_3$), 7.05 (s, 1 H, Har), 7.12 (s, 1 H, Har), 9.21 (br, 2 H, OH).

HRMS (EI): $m/z$ (%) = 584 (52), 513.3 (10), 470.2 (43), 408.1 (18), 380.1 (35), 340.1 (42), 280.1 (39), 213 (25), 199.1 (100), 138 (19), 91.1 (79).

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References