Organic & Supramolecular Chemistry

An Expedite Synthesis of Some Angularly Fused Novel 'U'-Shaped Tetracyclic Furophenanthraquinones Simulating ABCD Rings of Isotanshinone-II

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An expedite general synthesis of three angularly fused furophenantharquinones is described from 1-(2-furyl)-naphthalen-2-carbaldehyde derivatives. 1-(2-furyl)-naphthalen-2-carbaldehyde derivatives on sequential functional group transformation of the –CHO group afforded 2-[1-(2-furyl])-naphthalen-2-acetic acid derivatives in reasonably overall good yields. Cyclization of the carboxylic acids lead to the formation of furophenanthrenol derivatives. The phenolic intermediates were oxidized with Fremy's salt to furnish the condensed furophenanthraquinone derivatives in excellent yields. The synthesized compounds simulate the ABCD core nucleus of the naturally occurring isotanshinone-II isolated from *Salvia glutinosa*.

Introduction

Condensed furophenanthraquinones such as phenanthro[1,2-b] furan-10,11-dione and phenanthro[4,3-*b*]furan-4,5-dione derivatives, the S- and U-shaped furophenanthraquinones respectively (figure-1),[1] constitutes an important class of fused hetercyclic compounds as because of versatile biological activities of such compounds as well as natural occurrence in many Salvia species like Salvia *miltiorrhiza* Bunge, Salvia *columbaire*, Salvia *glutinosa* etc.[2] The crude dried root of Salvia *miltiorrhiza* Bunge (also known as *Dan Shen)*,[2] is used till date as herbal medicine in many countries largely for the treatment of various diseases such as cardiac and vascular disorder,[3] viral hepatitis,[3] hypertension,[3] inflammation,[4] cancer,[5] menstrual disorder,[3,6] miscarriage,[3,6] insomnia, urolithiasis, etc. with 1000 years of clinical applications.[2,5,7–9] *Dan Shen* is enriched with different lipophilic tetracyclic furoquinone diterpinoids such as Cryptotanshinone,[10,11] Nortanshinone,[12,13] Tanshindiol,[12,13] Tanshinone-I,[14] Tanshinone-IIA and Tanshinone-IIB[10,15,16a–d] etc. (Figure 2) supposed to be responsible for *Dan Shen's* broad spectrum pharmacological and pharmacokinetic activities and as a result a large number of studies on the synthesis of furo[1,2-b]phenathraquinones have been made in last few decades.[1,16–18]

Naturally occurring 'S'-shaped furoquinone was first extracted by Nakao and Fukushima[19] from *Dan Shen* as early as in 1934, while isotanshinone-II (naturally occurring 'U'-shaped tetracyclic furoquinone) and dihydroisotanshinone-II have been isolated in very negligible amount only in 1999 by Nagy and his coworkers[20] (Figure 1) from another salvia species (*Salvia glutinosa).* Consequently compared to large amount of synthetic and biological studies with 'S'-shaped furoquinone derivatives (Tanshinone-I and II derivatives),[17,18] in last few decades, relatively very few synthetic methodologies[17] are available so far for the synthesis of the isomeric 'U'-shaped tetracyclic furophenanthraquinones (phenanthro[4,3-b]furan-4,5-dione) derivatives. In most of the reported earlier synthesis of tetracyclic furophenanthraquinones A/AB/BC/ABC ring precursors[16–18] have been used as starting materials and the "D" ring *i.e* the furan moiety was developed at the later stage possibly due to labile nature of the furan ring under reactions conditions. Recently we have developed[1] a general and novel synthetic pathway for the preparation of tetracyclic 'S'-shaped furophenanthroquinone as well as the tricyclic analog (furonaphthoquinone) simulating ABCD and BCD rings of Tanshinone-I. The method has great potential for the synthesis of "U-shaped" furophenanthraquinones as well as their thiophene analogues[21] too. To explore the chemistry of non-natural furoquinones in this paper we have extended our methodology for synthesis of some novel phenanthro[4,3-b]furan-4,5-dione (the core nucleus of isotanshinone-II) and their 7-methyl and 8-methyl derivatives (the latter being the 3-demethylisotanshinone-II) (Figure 1 and Figure 2).

The retro synthetic approach reveals that 1-(2-furyl)-2-naphthaldehydes derivatives might be the suitable precursor for the synthesis of these 'U'-shaped tetracyclic furoquinones. These precursors in turn can be prepared from the substituted

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202100979

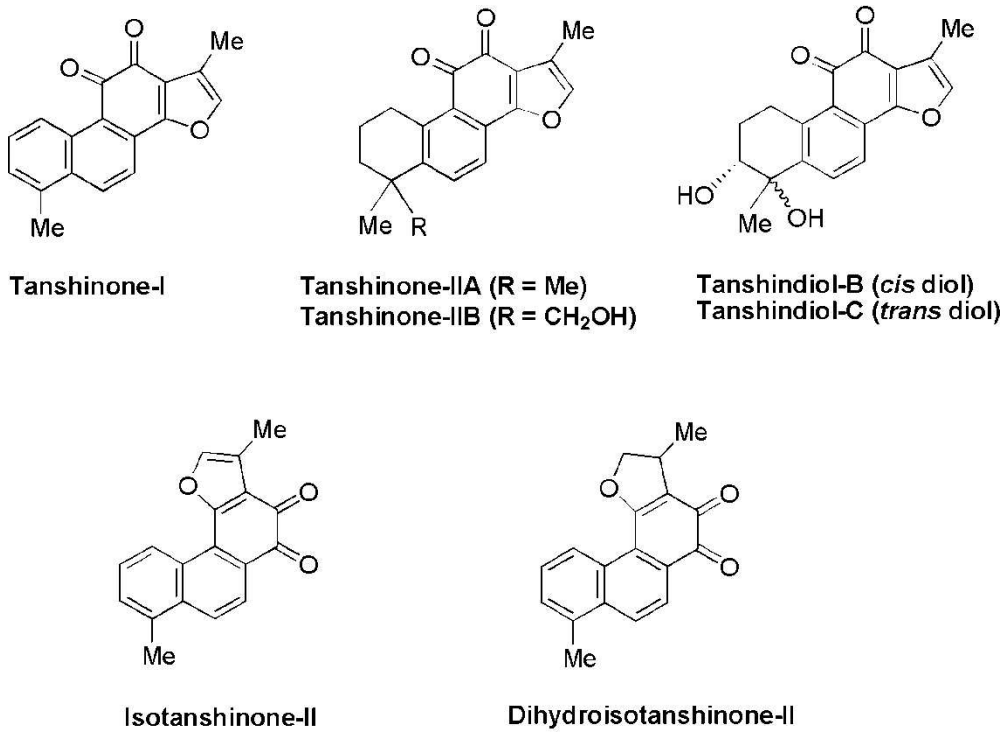


Figure 1. Representative condensed furophenanthraquinones isolated from salvia species.

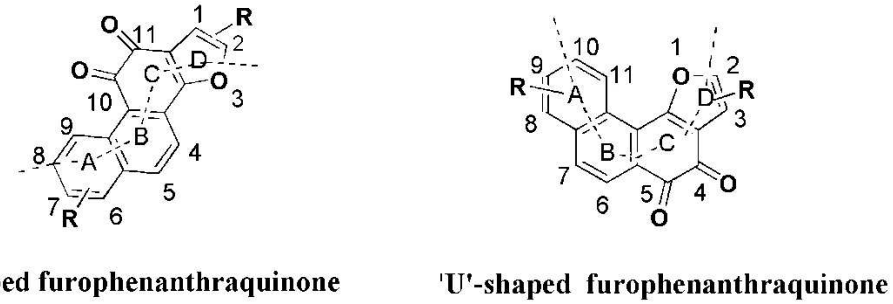


Figure 2. Core nucleus of 'S'- and 'U'-shaped furophenanthraquinones.

1-bromo-2-naphthaldehydes and furan-2-boronic acid (Figure 3) using Suzuki coupling reaction.

Results and discussions

Three novel phenanthro[4,3-b]furan-4,5-dione derivatives **9**(**a**–**c**) have been synthesized as per scheme-1. Synthesis of 3-demethylisotanshinone-II (**9b**) was achieved starting from 5-methyl-1-tetralone (**1b**). 1-bromo-3,4-dihydro-5-mehylnaphthalen-2-carbaldehyde (**2b**) was achieved (in 64% yield) from 5-methyl-1-tetralone (**1b**) by modified Vilsmeier-Haack reaction using PBr_3, DMF in $CHCl_3$ and the bromoaldehyde (**2b**) on aromatization with DDQ in refluxing benzene furnished 1-bromo-5-methylnaphthalen-2-carbaldehyde (**3b**) in 94% yield.

Compound (**3b**) was then subjected to Suzuki coupling reaction[22,23] with furan-2-boronic acid in presence of Et_3N and $Pd(PPh_3)_4$ (cat.) in DMF under inert atmosphere to produce 1-(2-furyl)-2-naphthaldehyde derivative (**4b**). The aldehyde (**4b**) on reduction with $NaBH_4$ in ethanol furnished the alcohol (**5b**) as colorless solid in 94% yield. Possibly the alcohol **5b** was present as a mixture of two atropisomer or rotamer (Figure 4) as indicated by ^{1}H NMR analysis of the compound **5b**. It was observed that two methyl signals appeared at δ 2.72(s) ppm and 2.73(s) ppm in the ratio 2:1 (total 3H) and the methylenic protons were also observed as two sets of signals at δ 4.66(s) ppm and 4.68(s) ppm respectively in the ratio 2:1 (total 2H).

Similar phenomenon was also found in ^{1}H-NMR of compound **6** or **7** prepared from the compound **5** in the sequential stage of the work. Functional group interconversion of the alcohol (**5b**) to the corresponding cyanide (**6b**) was carried out in two steps. In the first step the alcohol **5b** was treated with mesylchloride, *s*-collidine and LiCl, in DMF at 0 °C temperature

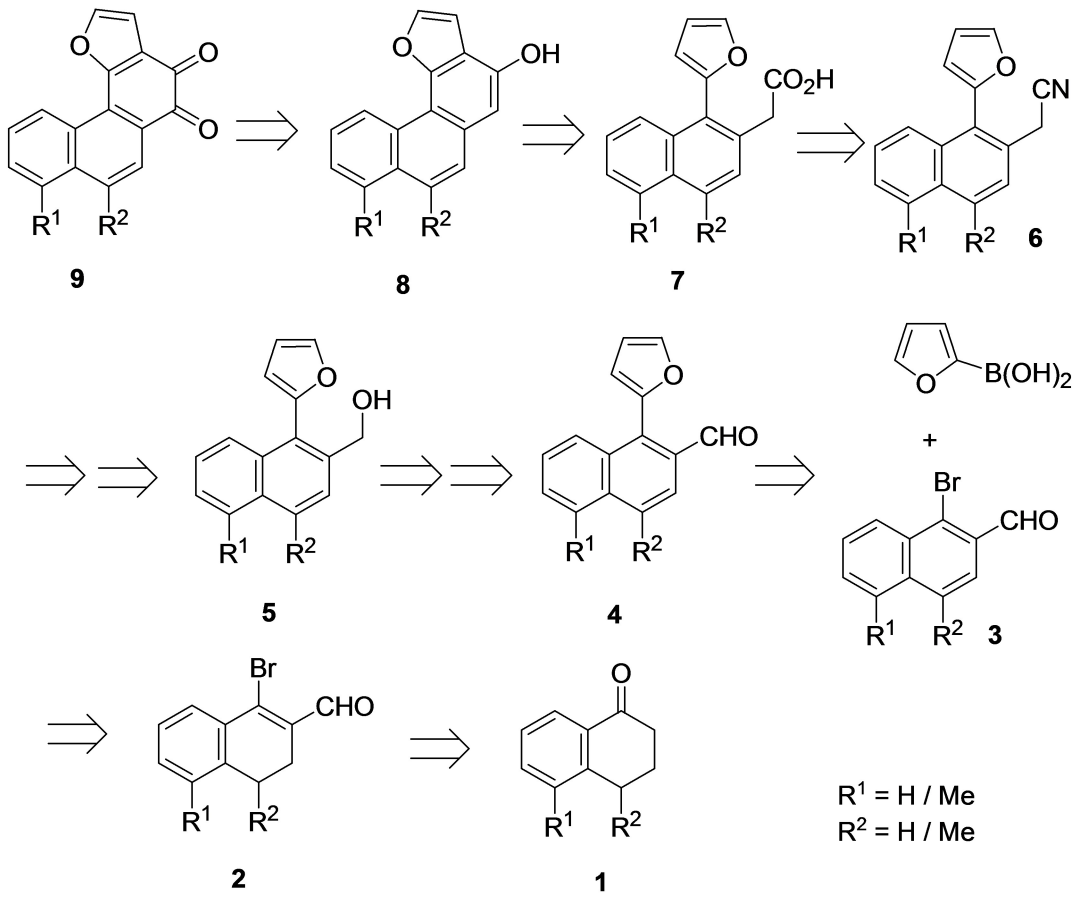


Figure 3. Retro synthetic pathway for phenanthro[4,3-b]furan-4,5-dione and derivatives.

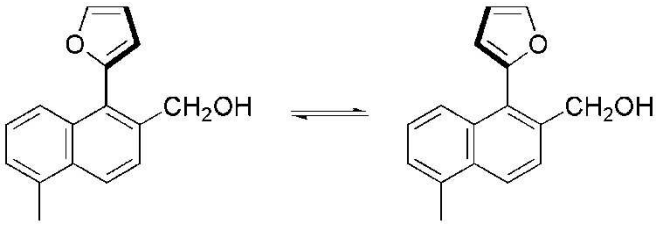
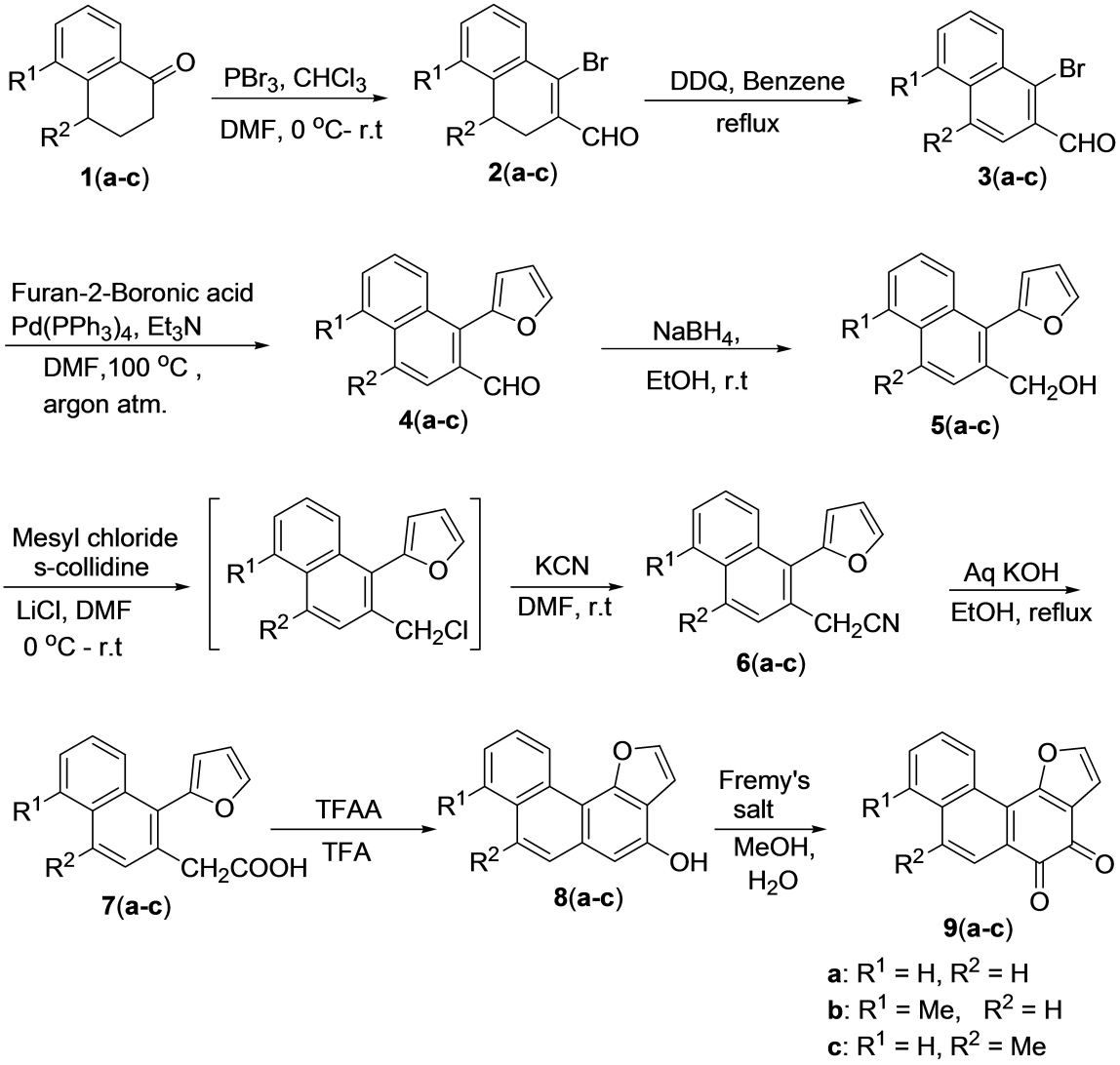


Figure 4. Atropisomerism or rotomerism of compound **5b**.

and then the resulting chloride was treated with KCN in DMF at room temperature to furnish the nitrile derivative (**6b**). Hydrolysis of the nitrile (**6b**) by aqueous-ethanolic KOH under reflux afforded the acid (**7b**) as colourless solid in 75% yield. The phenol **8b** was prepared in very good yield *via* cyclization of the acid **7b** with trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) at 0 °C to room temperature. Finally oxidation of the phenol with Fremy's salt [$(SO_3K)_2NO$] furnished *o*-quinone, 3-demethylisotanshinone-II (**9b**), as a deep violet solid in 80% yield (Scheme 1). Two other "U" shaped furophenanthraquinone derivative **9a** and **9c**, both hitherto unknown angularly fused condensed furoquinones were prepared starting from the corresponding bromoaldehyde **3a** and **3c** respectively following the similar sequence of reactions. Yield of the Products obtained in each step were good to excellent. Oxidation of the phenols **8a** and **8c** by Fremy's salt lead to the formation of corresponding furoquinones Phenanthro[4,3-*b*]furan-4,5-dione (**9a**) as a deep violet solid in 91% yield and 7-Methyl-phenanthro[4,3-*b*]furan-4,5-dione (**9c**) as a red solid in 94% yield respectively (Scheme 1). Structure of all the prepared compounds were established and characterized by usual spectroscopic technique (IR, ^{1}H-NMR, ^{13}C-NMR etc.) and mass spectrometry.

Conclusions

In conclusion, synthesis of some 'U'-shaped novel tetracyclic furophenanthraquinones have been achieved through a generalized method as developed in our laboratory. In this connection desmethylisotanshinone II has been achieved following the above described protocol. Naturally occurring 'U'-shaped tetracyclic fuoroquinone isotanshinone-II may be achieved by applying this method using 4-methylfuran-2-boronic acid and the bromoaldehyde **2b**. The boronic acid is not available commercially and now we are trying to develop a method for the synthesis of 4-methylfuran-2-boronic acid as a precursor for isotanshinone-II synthesis.



Scheme 1. Synthesis of 'U'-shaped tetracyclic furoquinones (the core nucleus **9a**, desmethyl isotanshinone II **9b** and it's 4-methyl analogue **9c**).

Supporting Information Summery

Detail experimental procedures, Characterization of different products and selected copies of NMR spectra of some important compounds have been included.

Acknowledgements

Financial help (project No.SR/S1/OC-30/2011) from DST-SERB, Govt. of India to Prof. G. K. Kar is gratefully acknowledged. Prof. Kar is also thankful to Presidency University for providing laboratory facilities and financial help through FRPDF grant. One of the author (KS) is grateful for CSIR-NET fellowship. Another author (AS) is thankful to UGC for providing leave to carry out the work under FIP program.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: desmethylisotanshinone-II · expedite Synthesis · Fremy's salt oxidation · Furophenanthrenol · Novel Furophenanthraquinone · Suzuki reaction

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Submitted: March 16, 2021
Accepted: June 9, 2021