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A Simple Approach to Access Tricyclic Spiro Dihydrofurans in a One Pot Reaction

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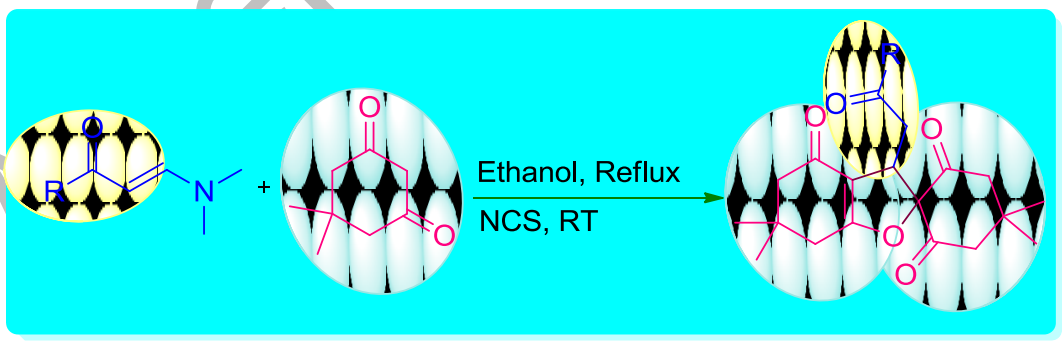
Abstract

A simple and efficient one pot protocol is accomplished to access tricyclic spiro dihydrofurans (**4**) by the reaction of β-enamino ketones (**1**) and dimedone (**2**) in ethanol followed by sequential addition of N-chloro succinimide (NCS) at ambient temperature for the first time. The Selectivity in desired product formation in good yields is the advantage of this protocol.

Graphical Abstract



KEYWORDS: *β*-Enamino ketones, Dimedone, N-Chloro succinimide, Spiro dihydrofurans

INTRODUCTION

Furan scaffolds occupy a prominent position in modern heterocyclic chemistry.[1] Among these class of compounds; dihydrofurans are one of the important compounds generally found naturally occurring substances.[2] Specifically, spiro dihydrofurans are prevalent in diverse class of natural products having biological importance and pharmaceutical.[3] Further, synthetic spirocycles with a spiro furan frame work has drawn significant attention owing to their antibacterial,[4] antitumor[5] and hypocholesterolemic activities.[6,7]

Based on the importance of these compounds, numerous methods have been reported for the synthesis of spiro dihydrofurans. For example, three step reaction of cyclic 1,3-diones with aldehydes involving addition, halogenaton and cyclodehydrohalogenation[8] gave the spiro dihydrofurans. Sahu's group[9] reported by reacting aldehydes and dimedone using iodine and ammonium acetate. Further, some more reports found on the synthesis of spiro dihydrofurans promoted by 1,4-diazabicyclo[2.2.2]octane (DABCO),[10] Dess-Martin Periodinane (DMP) and tetraethyl ammonium bromide.[11] Furthermore, molecular iodine and dimethylaminopyridine mediated reaction of aldehydes with dimedone and 1,3-indanedione independently through ball-milled approach[12] selectively gave spiro dihydrofuran and cyclopropane derivatives. On the other hand, ceric ammonium nitrate mediated 1,3-dipolar cycloaddition of 1,3-diketones with exocyclic alkenes[13] gave spiro

dihydrofuran oxindole derivatives. Additionally, a pseudo multi-component electro chemical synthesis of spiro dihydrofurans was reported by C.Yao and coworkers.[14] However, most of them are from benzaldehyde and cyclic 1,3-dione and uses either a base, combination of bases or organic solvents which are derived from non-renewable resources.

In order to come out with an alternate approach and also based on our ongoing research program on synthesis of new bioactive molecules[15] and utilization of β-enamino ketones, we have come out with a simple methodology for the synthesis of tricyclic spiro dihydrofurans by a novel, efficient and one pot reaction from β-enamino ketones for the first time. In fact, *β*-Enamino ketones were reported to use in the preparation of different kind of heterocyclic building blocks in organic chemistry. For example, Perumal et al., reported the synthesis of highly functionalized tetrahydroquinolines by a four component domino reaction involving *β*-enamino ketones.[16] Further, it was also used in synthesizing the substituted pyridines and dihydro-6*H*-quinolin-5-ones along with 1,3-diketone and ammoniumacetate.[17]

On the other hand, multi component reactions (MCRs) have become a powerful tool in organic synthesis because of their atom economy, multiple bond forming efficiency, convergence etc. These features are important aspects from the green chemistry point of view.[18] In this context, MCRs based on "bio-solvents" such as ethanol which is produced from renewable resources[19] is an increasingly important parameter as it is one of the best alternate to hazardous solvents owing to the EHS (Environment, Health,

Safety) properties such as increased biodegradability or reduced ozone depletion potential.[20] With this idea, we report herein, a novel protocol to access tricyclic spiro dihydrofurans starting from β-enamino ketones and dimedone followed by sequential addition of N-chlorosuccinimide (NCS) in ethanol and the results are as follows.

RESULTS AND DISCUSSION

Initially, β-ketoenaminone (**1a**) was prepared by condensing acetophenone and dimethyl formamide dimethyl acetal (DMF-DMA) in xylene by a literature procedure.[21] Thus obtained compound **1a** was reacted with dimedone in ethanol under reflux condition and obtained di-enol compound (**3a**) (Scheme 1).

By looking at the structure of **3a**, we conceptualized the possible formation of a spiro furan skeleton from **3a**. On this account, initially, compound **3a** was treated with NCS at room temperature. Interestingly, the desired spiro furan product **4a** was obtained in 86% yield exclusively. Earlier, when **3a** was refluxed in acetic acid, a bicyclic product was obtained. Notably, the same compound when refluxed in toluene in presence of trifluoroacetic acid gave xanthenes.[19b] Structure of **4a** was confirmed by the spectral data. It is interesting to mention that, the ^{1}H NMR of compound **4a** (recorded in 500 MHz) was found to be quite complex especially from δ 2.19 to 2.75 and 3.23 to 3.60 ppm even after purification. However, entire signal pattern was found to be same at par with the similar compound reported.[12] To confirm it further, a spectra was recorded in high resolution (700 MHz) and also observed to be the same. Then we presumed that the complexity may be due to methylene protons between dihydrofuran ring on one side and

benzoyl group on the other side. These two characteristic methylene protons were resonating at δ 3.56 and 2.35 ppm as doublets of doublet by coupling with the dihydrofuran ring proton. Except this, all other signals were clearly comparable with aforesaid report. Surprisingly, the same compound gave a very clean ^{13}C NMR where four carbonyl carbon signals were observed at δ 203.6, 201.2, 199.0, 194.1 ppm (four clear signals) and the methylene carbon which is attached to dihydrofuran ring and carbonyl carbon on either side resonating at δ 38.6 ppm, rest of the signals are at a par with reported data. Finally, the structure of compound **4a** was also unambiguously confirmed by X-ray crystallography (Fig-1).[22]

Enticed by the exclusive formation of **4a**; studies were directed to prepare **4a** in a one pot reaction. Accordingly, the compound **1a** was reacted with dimedone followed by sequential addition of NCS in toluene and obtained the desired product **4a**. Further, solvent scrutiny studies (table-1) pronounced that, ethanol medium gave the enhanced yields 88%. Having obtained the compound **4a** in a one pot reaction in ethanol, reactions were also carried out in ethanol and water solvent mixtures (entry 11 & 12) also. However, there was no progress in the reaction after formation of **3a.** On the other hand, formation of **4a** was observed in combination of ethanol and water medium in decreased yields. Next, studies were conducted to optimize the NCS ratio to determine the best optimal reaction condition. However, best yields were obtained in ethanol with 1.0 equivalent of NCS (table 1, entry 3). Alternately, a reaction was also conducted by replacing NCS with NBS and NIS independently and observed the decrease in yields. (Table-1& Scheme 2)

Fascinated by formation of **4** in one pot reaction in high yields, scope and generality of this protocol was next explored (Scheme 2). To our satisfaction, this protocol demonstrated wide scope as a range of enamino ketones were highly compatible under these set of reaction conditions and provided **4** in high yields. Electronic and steric nature of enamino ketones has shown no influence on the reaction efficiency. However, nominal variations in the yield were observed. Compounds bearing electron withdrawing groups gave near to 90 % yields. Whereas, electron donating groups gave up to 85% yields. This method was found to be mild enough to be compatible with the enamino ketones bearing naphthalene and hetero rings such as furan, thiophene and gave excellent yields up to 88% yield (**4m-o**). Further, reaction with 1,3-cyclohexanedione under similar reaction conditions gave xanthenes[19b] whereas, with acetyl acetone no reaction was observed.

A plausible mechanism was proposed for the formation of **4a** where the active methylene functional of diketone initially attack on β-carbon of enamino ketone in Michael fashion to give **A** (elimination of *N*,*N*-dimethylamine in the form of gas was observed by dipping the outlet vent of the reaction flask in water and also confirmed with litmus paper during the course of the reaction). Subsequently, attack of second molecule of diketone on β-carbon of **A** lead to dienol compound **3a** (isolated). Next, addition of chloronium ion [15b,15c] from NCS at active methylene carbon followed by attack of lone pair electrons from hydroxy functional and successive dehydrohalogenation gives 4',4',6,6-tetramethyl-3-(2-oxo-2-phenylethyl)-6,7-dihydro-3*H*-spiro[benzofuran- 2,1'-cyclohexane]-2',4,6'(5*H*)-trione(**4a**) (Scheme 3).

CONCLUSIONS

In conclusion, we have developed a new protocol to accomplish the synthesis of tricyclic spiro dihydrofurans in a three component one pot reaction in ethanol at ambient temperature for the first time. This simple and efficient protocol is an alternate to the existing methodologies which may find good utility.

EXPERIMENTAL

General

Melting points were measured by CINTEX programmable melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ recorded on AVANCE-300 MHz, 400 MHz, 500 MHz and 700 MHz spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as the internal standard. Mass spectra were recorded in ESI spectrometers. All high resolution mass spectra were recorded on QSTAR XL hybrid ms/ms system (Applied Bio systems/MDS sciex, foster city, USA), equipped with an ESI source (IICT, Hyderabad). TLC was performed on Merck 60 F-254 silica gel plates. The chemicals used in this work were obtained from commercial channels and were used without purification.

General Procedure For The Synthesis Tricyclic Spiro Dihydrofurans (4)

To a round bottomed flask equipped with a reflux condenser and stopper was added β-keto enaminone viz (E)-3-(dimethylamino)-1-aryl prop-2-en-1-one derivatives (**1**, 2.85 mmol), dimedone (**2**, 5.71 mmol), ethanol (10 mL) and was heated to reflux while

stirring. After refluxing reaction mixture for 5 to 6 hours, the homogenous mass was allowed to come down to room temperature and to this was added NCS (2.7 mmol) and continued the stirring at RT open to air for 1 hour. After completion of reaction as indicated by TLC, the separated solid was filtered, washed with water (2×5mL) followed by hexane (2×5mL) and was purified by flash column chromatography to get pure products **4**.

4',4',6,6-Tetramethyl-3-(2-Oxo-2-Phenylethyl)-6,7-Dihydro-3H-Spiro[Benzofuran-2,1'-Cyclohexane]-2',4,6'(5H)-Trion (4a).

Isolated as a white solid; Yield 88%; m.p.148-149°C; IR (KBr) ν_{max}: 2959, 1734, 1708, 1671, 1631, 1467, 1397, 1246, 1143, 1041, 938, 770, 694 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 4.14 (d, *J* = 9.9 Hz, 1H), 3.65-3.60 (m, 1H), 3.56 (dd, *J* = 19.0, 1.9 Hz, 1H), 3.30-3.23 (m, 1H), 2.75-2.69 (m, 1H), 2.57-2.46 (m, 3H), 2.35 (dd, *J* = 16.2, 3.1 Hz, 1H), 2.29-2.19 (m, 2H), 1.21 (s, 3H), 1.16 (s, 6H), 0.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6, 201.2, 199.0, 194.1, 176.8, 135.9, 133.7, 128.6, 128.0, 111.5, 97.8, 53.0, 51.2, 49.8, 43.3, 38.6, 37.3, 34.2, 30.5, 30.2, 28.6, 28.4, 26.7 ppm; ESI-MS: m/z 409 $[M+H]^+$; HRMS (ESI) Anal. calcd. for $C_{25}H_{29}O_5$ m/z 409.2009 $[M+H]^+$, found 409.2003.

SUPPLEMENTARY DATA

Experimental procedures, characterization and Spectral data for all the synthesized compounds and X-ray diffraction crystallographic data for the compound **4a** which has been deposited on CCDC with deposition number **1450194** can be available free of

charge at www.ccdc.cam.ac.uk/conts/retrieving.html[or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033;

email: www.ccdc.cam.ac.uk/data_request/cif.

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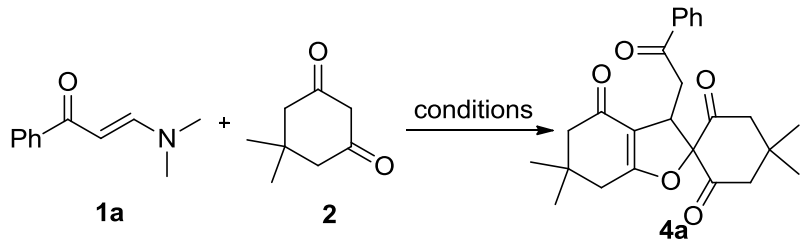
[22] CCDC **1450194** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html[or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033;

email: www.ccdc.cam.ac.uk/data_request/cif.

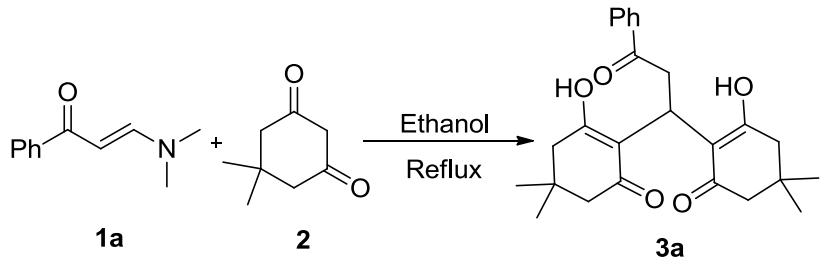
Table 1. Optimization of reaction conditions for the synthesis of tricyclic spiro dihydrofuran (4a).[a]



S. No	Solvent	Additive	Temp	Quantity	Yield (%)
1	Toluene	NCS	Reflux	1 eq	86
2	MeOH	NCS	Reflux	1 eq	86
3	EtOH	NCS	Reflux	1 eq	88
4	Acetonitrile	NCS	Reflux	1 eq	84
5	Ethyl acetate	NCS	Reflux	1 eq	80
6	1,2-DCE	NCS	Reflux	1 eq	83
7	EtOH	NCS	Reflux	0.5 eq	55
8	EtOH	NCS	Reflux	1.2 eq	88
9	EtOH	NBS	Reflux	1 eq	75
10	EtOH	NIS	Reflux	1 eq	86
11	EtOH,H_2O (1:1)	NCS	Reflux	1 eq	80
12	EtOH,H_2O (1:2)	NCS	Reflux	1eq	77

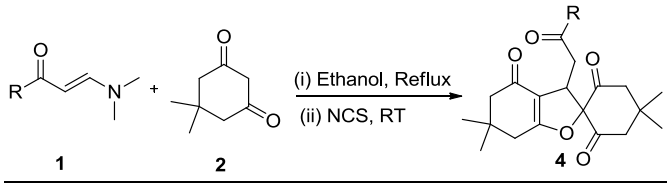
[a;] Reaction conditions: β-ketoenaminone (2.8 mmol) and dimedone (5.7 mmol) in solvent (10 ml) refluxed for 5 hours then followed by sequential addition of N-halo succinimide (halo = Cl, Br, I) at RT. Yields refer to isolated pure products.

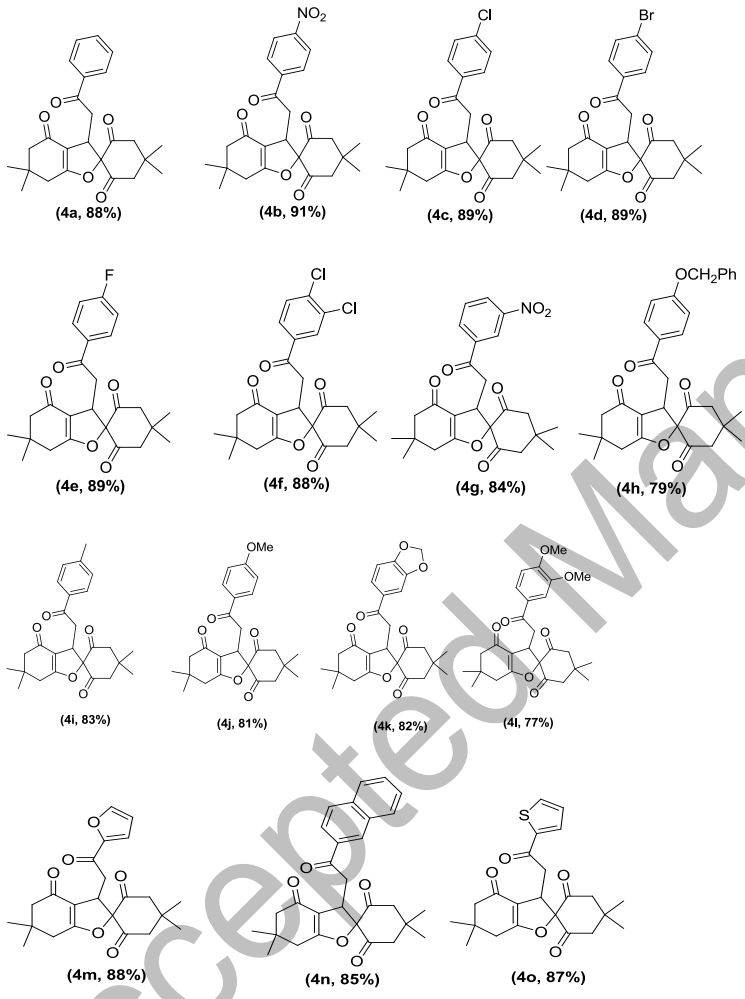
Scheme 1. Preaparation of 2,2'-(3-oxo-3-phenylpropane-1,1-diyl)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3a**).



1a **2** **3a**

Scheme 2. Preparation of tricyclic spiro dihydrofuran derivatives (4).[a]





[a]Reaction conditions: β-ketoenaminone (2.8 mmol) and dimedone (5.7 mmol) in ethanol (10 ml) reflux for 5 hours then followed by sequential addition of NCS (2.8 mmol) at RT. Yields refer to pure products after flash column chromatography.

Scheme 3. Plausible mechanism for formation of compound (**4a**).

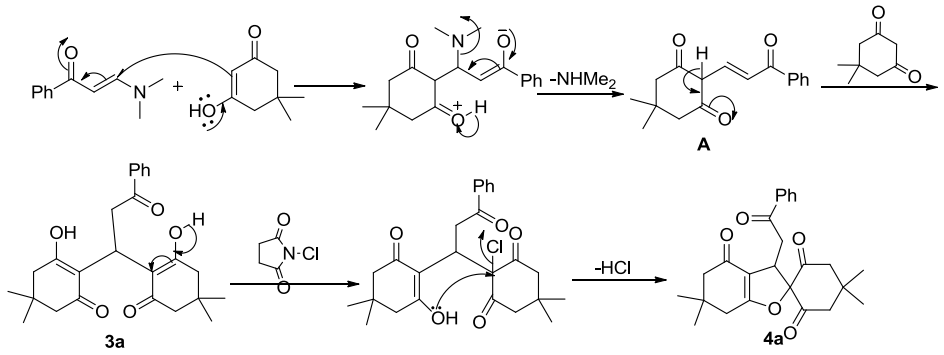


Figure 1. Crystal structure of the compound 4a (ORTEP diagram of compound 4a).