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ARTICLE

Expeditious synthesis of functionalized tricyclic 4-spiro pyrano[2,3-c]pyrazoles in aqueous medium using dodecylbenzenesulphonic acid as a Brønsted acid-surfactant-combined catalyst

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An efficient, three-component, one-pot synthesis of highly functionalized tricyclic 4-spiro pyrano[2,3-c]pyrazoles, incorporating medicinally privileged heterocyclic moieties, has been developed that involves the tandem Knoevenagel/Michael addition reaction followed by dehydrative cyclization of pyrazolone derivatives, cyclic 1,3-diketones and cyclic ketones, catalyzed by dodecylbenzenesulphonic acid (DBSA) as a Brønsted acid-surfactant-combined catalyst in aqueous media. The catalyst has found to be highly competent in accelerating this reaction that results in a considerable short reaction time, alleviating the need of high thermal energy. Wide substrate scope, high to excellent product yield, operational simplicity, absence of any hazardous organic solvent, mild reaction condition, simple work up procedure and easily available starting materials are the salient features of this protocol.

Introduction

Combination of diverse pharmacophores into a single molecular scaffold has revealed as a key strategy in design and synthesis of new drugs.[1] Accordingly development of synthetic protocols able to furnish molecular diversity and complexity from easily available and inexpensive starting materials has become one of the main goals for organic chemists. The knack of rapid introduction and expansion of molecular diversity by assembling three or more different reactants in a single chemical transformation makes multicomponent reactions (MCRs) a powerful tool to achieve this goal.[2] Over the past decades, several MCRs have been developed in order to synthesize pyran molecular scaffold and its spiro analogue since these classes of heterocyclic compounds are the key structural motif of various natural products possessing wide range of biological activities.[3] In addition, spirocyclic compounds are valuable precursors for the easy access of several cyclic molecules as they can undergo various rearrangement reactions due to the steric strain at quaternary carbon atom.[4]

The biological activity of a diversified spiro pyran molecular scaffold is greatly influenced due to the presence of other potent heterocyclic moieties within the same molecule.[5] Presence of multiple bioactive heterocyclic fragments in a single entity may increase the pharmacological activities because it might possess the properties of all moieties. Several methodology have been developed in order to construct diversified pyran molecular scaffolds and its spiro analogues, employing suitable active methylene compounds with various aldehydes and ketones.[6] Pyrazolone derivatives have been recognized as significant active methylene compounds since pyrazolone scaffold occurs in many drugs and synthetic products (e.g., phenazone, propyphenazone, ampyrone and metamizole) (Fig. 1a) which exhibit numerous biological activities.[7] In addition, pyrazole is a potent heterocycle which plays an important role in pharmaceutical and agrochemical industries.[8] On the other hand ninhydrin as well as isatin derivatives are major starting materials to form spiro functionality in different molecules since indan-1,3-dione moiety can be found as the core structure of medicinal scaffolds which displays hypolipidemic[9] and anti-inflammatory[10] activities. Moreover, many natural products (e.g., Uncarine, Isomitraphylline, Mitraphylline, Rynchophylline) (Fig. 1b) have the skeletal structure of oxindole and some synthetic compounds having oxindole unit possess several potent bioactivities.[11]

However, methods in order to synthesize polycyclic 4-spiro pyrano[2,3-c]pyrazoles are still limited.[12] Although, heterocycles with tricyclic pyran moieties have been acknowledged for their potent bioactivity as inhibitor of acetylcholinesterase,[13] γ-secretase,[14] anti-angiogenic activity against human umbilical vein endothelial cells.[15] In this context, it should be interesting to construct a diversified tricyclic spiropyran scaffold, possessing pyrazole, pyran and spiro functionality in single molecular entity, by utilizing a mild and environmentally benign protocol.

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MCRs in aqueous media have always greeted as water is eco-friendly[16] and in particular it has unique physical and chemical properties which may extend certain reactivity and selectivity normally unattainable by other commonly used organic solvents.[17] However, one major drawback of using water as a solvent is slower reaction rate of organic reactions due to the poor solubility of most organic substrates in water medium.[18] To overcome this problem surfactants are frequently used, as they can solubilize organic molecules or form colloidal dispersion with them by forming micelles in aqueous medium

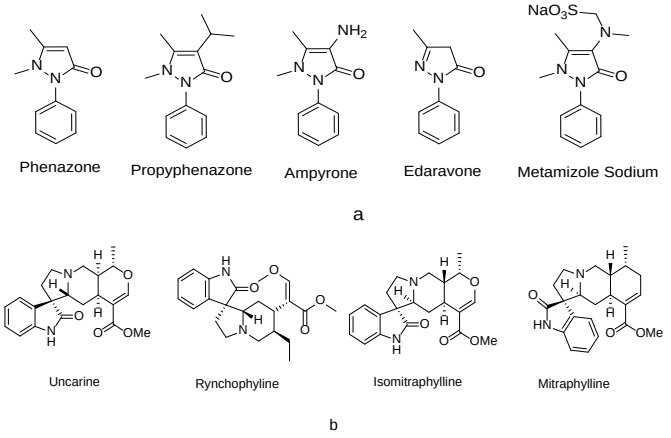
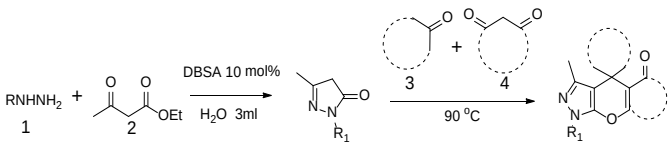


Fig. 1 (a) Some biologically active pyrazolone compounds, (b) Some natural products containing oxindole moiety

thereby diminishing the need of an organic co-solvent.[19] In recent years Brønsted acid-surfactant-combined catalyst (BASC), such as dodecylbenzenesulphonic acid (DBSA), has been found to be effective to catalyze various types of organic reactions in water medium.[20] The unique feature of BASC is, it can not only supply proton as an acid to activate the reactants but also solubilizes them by forming micelle or form a stable colloidal dispersion with them as a surfactant, resulting in an overall enhancement of the reaction rate.

In view of these important points and continuing our efforts on the development of new MCRs involving green methodologies,[21] herein we wish to report an efficient, one-pot, three component process for the synthesis of functionalized tricyclic 4-spiro pyrano[2,3-c]pyrazoles from the reaction between pyrazolone derivatives, cyclic 1,3-dicarbonyls and cyclic ketones (ninhydrin, isatin and 9,10-phenanthroquinone) in water medium at 90 ^{o}C in presence of DBSA as a Brønsted acid- surfactant-combined catalyst (scheme 1).



Scheme 1: Synthesis of tricyclic spiropyran derivatives

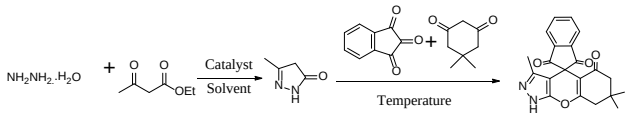
Result and discussion

Reaction conditions

In order to construct functionalized pyran structural motif several protocols can be found in literature where one of the active methylene compound is always acyclic.[22] However reactions where active methylene compounds are both cyclic, generally require harsh reaction conditions.[23] In the course of our studies, we were interested to utilize the surfactant as well as the Bronsted acid property of DBSA in exploration of a milder reaction protocol to afford tricyclic 4-spiro pyrano[2,3-c]pyrazoles. To begin with, hydrazine hydrate, ethyl acetoacetate, ninhydrin and dimedone were chosen as the model substrates for the proposed reaction. Initially hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol) were reacted in presence of DBSA (10 mol%) in water (3 ml) for 5 min then to it ninhydrin (1 mmol) and dimedone (1 mmol) were added subsequently and the reaction mixture was heated to 100 ^{o}C. The complete conversion of the starting materials was observed within 3 h as indicated by TLC (50% ethyl acetate in petroleum ether) and the product was isolated as a pale yellow solid in 80% yield (Table 1, entry 1). The structure of the product spiropyran (6a) was characterized by spectroscopic analysis (^{1}H NMR, ^{13}C NMR, IR). In addition, the single X-ray crystallographic analysis of the product also confirmed the identity of the desired tricyclic spiropyran structural motif (Figure 2a).

Based on this promising result, we have then investigated the effect on product yield by changing various experimental parameters in order to optimize the reaction conditions. The yield of the product was increased to 96% when the reaction was performed at 90 ^{o}C temperature (Table 1, entry 2). Use of 20 mol% of DBSA at 90 ^{o}C did not afford any further increase in the product yield, while use of 5 mol% of DBSA results in a decrease in the product yield (Table 1, entries 3 and 4). When 10 mol% of DBSA was employed at 80 ^{o}C the product was obtained in 55% yield (Table 1, entry 5). Curiously, when the reaction was performed in absence of any catalyst either in aqueous or organic solvent medium, no product was obtained even after allowing the reaction to proceed for a prolonged time (Table 1, entries 6-8), thereby indicating the essence of a catalyst for this typical reaction. In search of a more able reaction condition, the reaction was further carried out in presence of different catalysts. Various acid catalysts like acetic acid (AcOH), *p*-toluenesulfonic acid (PTSA), (*d,l*)-camphorsulphonic acid (*d,l*-CSA), and a polymer supported acid catalyst PEG-SO_3H were employed in aqueous medium as well as in organic solvent. AcOH, PEG-SO_3H and PTSA were failed to generate any considerable amount of product in aqueous medium (Table 1, entries 9-11). (*d,l*)-CSA was found to be inefficient catalyst for this reaction in ethanol, water and PEG-H_2O medium (Table 1, entries 12-14). The most efficient catalytic system was found to be the DBSA-water combination for this three-component reaction and the optimized reaction condition thus obtained carrying out the reaction at 90 ^{o}C using 10 mol% of DBSA as the catalyst in 3 ml of water (Table 1, entry 2).

Table 1 Optimization of reaction conditions



Entry	Catalysts	Solvent	Condition	Time (h)	Yield[a,b](%)
1	DBSA (10 mol%)	H_2O	100 °C	3	80
2	**DBSA (10 mol%)**	**H_2O**	**90 °C**	**3**	**96**
3	DBSA (20 mol%)	H_2O	90 °C	3	94
4	DBSA (5 mol%)	H_2O	90 °C	6	70
5	DBSA (10 mol%)	H_2O	80 °C	8	55
6	-	H_2O	reflux	24	_c
7	-	Peg-400	100 °C	24	_c
8	-	EtOH	reflux	24	_c
9	AcOH (0.5 ml)	H_2O	reflux	18	10
10	PEG-SO_3H	H_2O	100 °C	8	20
11	PTSA (10 mol%)	H_2O	100 °C	24	15
12	(*d*,*l*)-CSA (10 mol%)	EtOH	reflux	15	25
13	(*d*,*l*)-CSA (10 mol%)	H_2O	reflux	18	30
14	(*d*,*l*)-CSA (10 mol%)	H_2O-PEG-400 (2:1)	100 °C	8	50

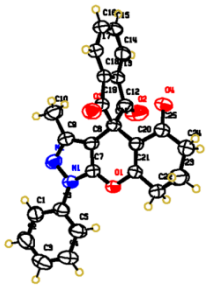
[a] all reactions are carried out with hydrazine hydrate (1 mmol), ethylacetoacetate (1 mmol), ninhydrin (1 mmol) and dimedone (1 mmol); [b] yield of isolated product; [c] the reaction failed to afford the desired product.

Substrate scope

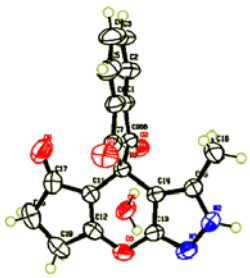
With this optimized condition in hand, we then investigated the scope and limitation of this reaction. Dimedone, cyclohexan-1,3-dione and cyclopentan-1,3-dione were employed successfully as the cyclic 1,3-dicarbonyls. A good range of hydrazine derivatives were reacted with ethyl acetoacetate to generate the corresponding pyrazolone derivatives in-situ. The protocol was found to be facile to produce a library of tricyclic indeno-4-spiro pyrano[2,3-c]pyrazoles (**6a-6j**) in good to excellent yields (Table 2). When isatin, 5-bromoisatin and 9,10-phenanthraquinone were employed in place of ninhydrin the reaction proceeded with the same efficiency and corresponding 4-spiro pyrano[2,3-c]pyrazoles (**7a-7l** and **8a-8c**) are obtained in good to excellent yields (Table 2). Careful observation of the reaction indicates that initially the reaction between ethyl acetoacetate and hydrazine derivatives in presence of DBSA in water medium afforded the pyrazolone derivatives which precipitated from the reaction medium, but after the addition of cyclic ketones and cyclic-1,3-dicarbonyls to the same medium followed by heating the reaction mixture at 90 °C, the initially developed turbidity of the reaction mixture became a colloidal dispersion as expected and ultimately get solubilized by forming micelle in aqueous medium or forming colloidal dispersion with them. From Table 2 it can be seen that the yield of the product is excellent in case of unsubstituted pyrazolone. Introduction of aromatic substituent on hydrazine part resulted in decrease of the product yield which may be due to the decrease in solubility of the initially formed pyrazolone derivatives in DBSA-water medium. In case of 9,10-phenanthraquinone, the desired 4-spiro pyrano[2,3-c]pyrazoles are obtained when the pyrazolone was unsubstituted. The completion of the reaction was monitored by TLC (50% ethyl acetate in petroleum ether). Crystallization of the crude product afforded the pure desired product while column chromatography of the crude product was performed in some cases.

The structures of the products were fully characterized by spectral analysis (^{1}HNMR, ^{13}CNMR, IR and HRMS). The structural motif of the compounds was fully established by means of single X-ray crystallographic analysis of the compounds **6a**, **6f**, **6i**, **7h** and **8c** (Fig. 2).

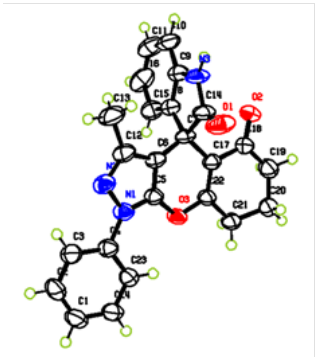
(a) Ortep diagram of single crystal of compound **6a** CCDC: 1031973



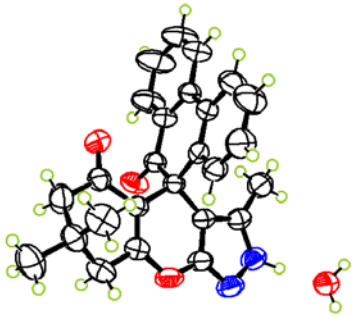
(b) Ortep diagram of single crystal of compound **6f** CCDC:1031971



(c) Ortep diagram of single crystal of compound **6i** CCDC:1031972



(d) Ortep diagram of single crystal of compound **7h** CCDC: 1039374



(e) Ortep diagram of single crystal of compound **8c** CCDC 1410076

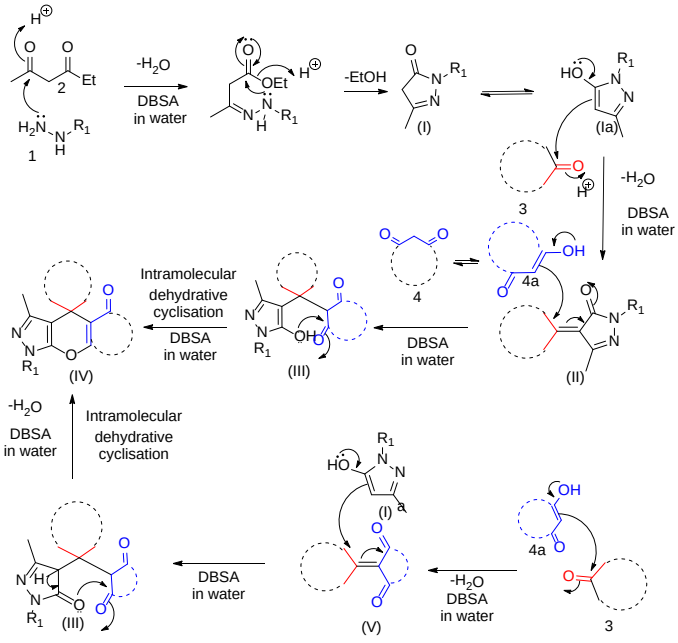
Fig. 2: Ortep diagrams of compounds **6a**, **6f**, **6i**, **7h** and **8c**

Reaction mechanism

Based on the above results, a plausible reaction mechanism[24] for this multicomponent reaction is depicted in scheme 2. Initially hydrazine derivative (**1**) reacted with ethyl acetoacetate (**2**) to form pyrazolone derivative (**I**) in presence of DBSA in water. Pyrazolone derivative can exist in tautomeric equilibrium with its enol form (**Ia**) which being inherently nucleophilic then undergoes Knoevenagel condensation with the cyclic ketone (**3**) (activated by getting proton from DBSA) to form the intermediate **II**. The intermediate **II** is an α,β-unsaturated ketone and further activation of it by proton causes a rapid reaction between **II** and the tautomeric form of the cyclic 1,3-dicarbonyls **4a** and results the formation of the intermediate **III** which then undergoes dehydrative cyclization facilitated by DBSA to generate the desired spiropyran product (**IV**). If initially **4a** undergoes Knoevenagel condensation with **3** then the intermediate **V** should be formed that should undergo Michael addition reaction with **Ia** to form **III**. **III** then follows the dehydrative cyclization pathway in order to generate the product **IV**.

We have tried to isolate intermediate **II** from the two-component reaction between pyrazolone (**I**) and isatin in presence of DBSA in water, and found that bis-pyrazolone (Fig. 3a) was formed. We also attempted a reaction between cyclohexan-1,3-dione and isatin, where tetraketone (Fig. 3b) was formed instead of intermediate **V**. These results revealed that intermediates **II** and **V** were both very reactive towards the subsequent reaction with pyrazolone and cyclohexan-1,3-dione respectively. Hence information on the relative rates of formation, as well as further reactions of **II** and **V** with cyclohexan-1,3-dione or pyrazolone respectively, could not be obtained and evaluated. Therefore, information on whether the multicomponent reactions proceeded through intermediate **II** or **V** could not be established in the current study.

We have taken the optical image of the reaction mixture (Fig. 4), that clearly shows the formation of micelle promoted by DBSA. The formation of micellar medium is attributed to the surfactant property of DBSA which make the reaction to occur inside the hydrophobhic interior and force the water molecules, produced as by products in several steps, to exit from the micelle. The rate of this three component reaction thereby highly assisted by the formation of the micellar medium.



Scheme 2. A plausible reaction mechanism for the formation of tricyclic spiropyran compounds

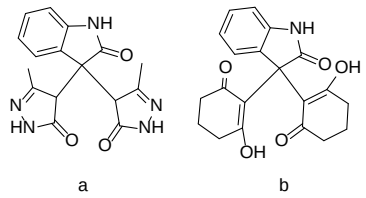


Fig. 3:(a) bis-pyrazolone (b) tetraketone

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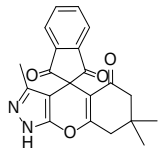
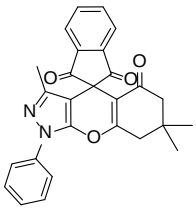
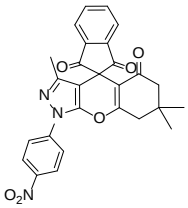
Table 2 Substrate scope for the synthesis of tricyclic 4-spiro pyrano[2,3-c]pyrazoles[a] 6, 7 and 8 (reaction time and yields of pure isolated products).



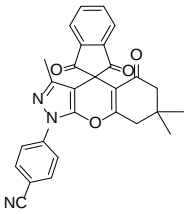
6a, 3 h, 96%



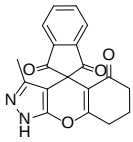
6b, 7 h, 87%



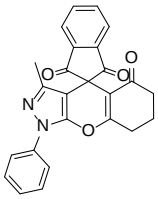
6c, 9 h, 82%



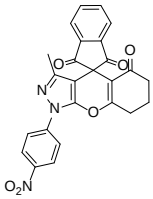
6d, 8 h, 86%



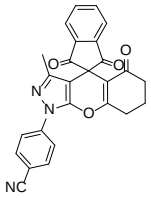
6e, 3 h, 95%



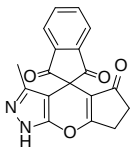
6f, 7 h, 88%



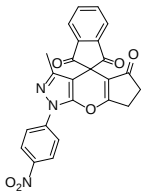
6g, 8 h, 83%



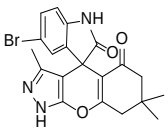
6h, 8 h, 87%



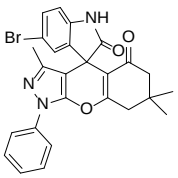
6i, 3 h, 94%



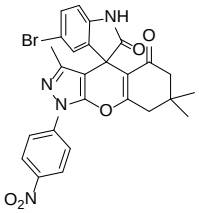
6j, 9 h, 78%



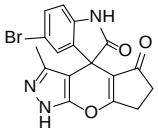
7a, 3 h, 93%



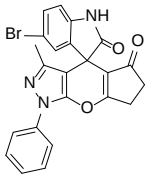
7b, 7 h, 86%



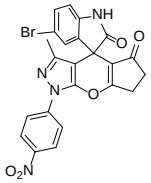
7c, 8 h, 80%



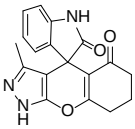
7d, 3 h, 94%



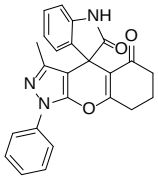
7e, 7 h, 84%



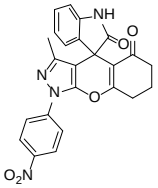
7f, 9 h, 78%



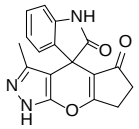
7g, 3 h, 94%



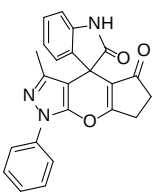
7h, 7 h, 88%



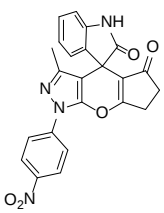
7i, 8 h, 82%



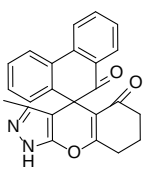
7j, 3 h, 92%



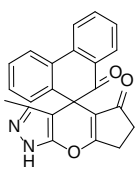
7k, 8 h, 86%



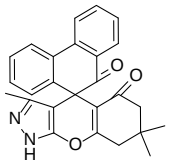
7l, 9 h, 79%



8a, 5 h, 78%



8b, 5 h, 75%



8c, 6 h, 76%

[a] Reaction conditions: ethyl acetoacetate (1 mmol), hydrazines (1 mmol), cyclic ketones (1 mmol) and cyclic 1,3-diketones (1 mmol) were reacted in presence of 10 mol% DBSA and 3 ml of water at 90 °C.

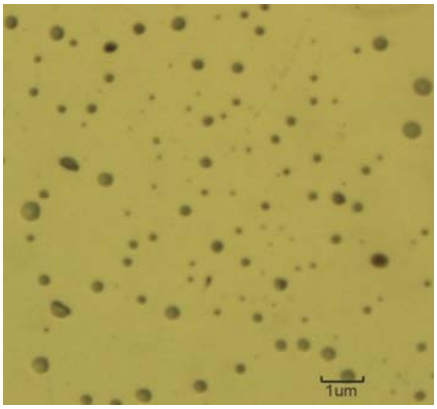


Fig. 4: Optical micrograph of the reaction mixture

Conclusion

In summary, dodecylbenzenesulphonic acid has been successfully used in the present study as an efficient Brønsted-acid surfactant combined catalyst for the synthesis of a series of tricyclic 4-spiro pyrano[2,3-c]pyrazole through one pot three-component reaction employing pyrazolone derivatives, cyclic ketones and cyclic 1,3-dicarbonyls in an aqueous medium at ambient temperature. This synthetic methodology is found to be mild, operationally simple, economical and environmentally benign and affords the target products in good yields.

Experimental procedure

To a mixture of 10 mol% of DBSA and 3 ml water taken in a 25 ml r.b. flask, hydrazine 1 (1 mmol) and ethyl acetoacetate 2 (1 mmol) were added and stirred under magnetic stirring for 5 min at rt. Then to this reaction mixture cyclic ketone 3 (1mmol) and cyclic 1,3-dicarbonyl 4 (1 mmol) were added and the whole mixture was then stirred at 90 °C for 3-9 h. After completion of the reaction (monitored by TLC), the mixture was cooled and poured into a mixture of 5 ml of cold saturated sodium bicarbonate solution containing 15 ml of cold brine. The resulting precipitate was filtered and washed with water (3×5 ml) and the precipitate was then crystallized from ethyl acetate-methanol (4:1) mixture to obtain the spiropyran in pure form. In case of substituted pyrazolone the precipitate was subjected to column chromatography (15-50% ethyl acetate in petroleum ether) to obtain the pure product. The isolated compounds were completely characterized by IR, ^{1}HNMR, ^{13}CNMR, HRMS and single X-ray crystallographic study.

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An eco-friendly multicomponent strategy has been developed to access a single tricyclic molecular scaffold possessing pyran, pyrazole and spiro functionalities.