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Title Key: Silica sulphuric acid: a reusable solid acid catalyst …

Silica sulphuric acid: a reusable solid acid catalyst for the synthesis of Spiro[indoline-3,4'(1H') pyrano-[2,3-c]pyrazole]-2-one and Spiro[indoline -3,4'(1H')-pyrano- [2,3-c]pyran]-2-one

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Abstract

A three component reaction of isatins, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one or 4-hydroxy 6-methyl 2-pyrone for the synthesis of Spiro[indoline-3,4'(1H')-pyrano-[2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-one using silica sulfuric acid as a heterogeneous catalyst was described. Mild conditions, good to excellent yields and easy work-up are the main features of this method.

1. Introduction

Multi-component reactions (MCRs) effectively combine three or sometimes more reactants simultaneously in a one-pot synthesis. The process does not require the separation of intermediate products. These reactions constitute one of the best tools for modern organic synthesis because they can use most of the constituent atoms of several reactant molecules to form a product molecule.[1]These reactions are highly selective and are simply operated under mild conditions; some have been used industrially.[2] MCRs have been widely used in synthetic chemistry to form new carbon-carbon bonds.[3] Some examples of MCRs includes Biginelli,[4]Mannich,[5] Robinson,[6] Passerini,[7]and Ugi reactions, which have been widely used in synthetic, medicinal, and combinatorial chemistry.[8,9].

Heterocycles containing pyrazole rings are important compounds in synthetic and medicinal chemistry. Because the ring is a key moiety in various biologically active compounds. Pyrazole derivatives have been studied in the development of insecticides,

acaricides, fungicides, herbicides, dyes, and reagents because of their efficiency, low toxicity, unique reaction mechanisms, safety, lack of cross-resistance, and other characteristics.[9] Indole moiety the most well-known heterocycle, is an important active feature of a variety of natural products and medicinal agents.[10] Sharing of indole 3-carbon atom in the formation of spiroindole derivatives has been reported to greatly enhance the biological activity of the products.[11] Spirooxindoles exhibit a wide range of biological properties for example coerulescine, a simple spirooxindole found in nature, which displays a local anesthetic

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effect.[12] Spirocycles possess anticancer and antimicrobial activity.[13] They are also known to exhibit anticonvulsant, analgesic,[14] herbicidal,[15] fungicidal[16], and antibacterial properties.[17]As a result, several synthetic approaches have been developed for the synthesis of multi-stereogenic spirooxindoles.[18] Several MCRs have been used in various syntheses of spiro[indoline-3,40-pyrano[2,3-c]pyrazole] derivatives in the presence of InCl3,[19] TEBA,[20] TBAF,[21] L-proline,TEA,[22] C17H35COONa[23].

In this work, we frame a new eco-friendly multicomponent synthetic approach for the synthesis of Spiro[indoline-3,4'(1H')-pyrano-[2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-one derivatives using reusable catalyst under aqueous alcoholic medium. We reported is a simple, efficient and one-pot three-component protocol for the synthesis of Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-onederivatives in aqueous ethanol using silica sulphuric acid (SSA) as inexpensive and efficient catalyst.

2. Experimental

All the chemicals and reagents were purchased from Sigma Aldrich, Alpha Aiser and Spectrochem chemicals and used for the reactions without further purification.

Preparation of Catalyst

To Silica gel (60-120 mesh) (30.0 g) in two necked round bottom flask, chlorosulfonic acid (6.0 ml) was added dropwise in 30 minutes time interval. Rapidly generated HCl gas was neutralized by NaOH solution. Once the addition is over, the reaction mixture is shaken for another 30 minutes.[25] The separated solid is purified and used as catalyst.

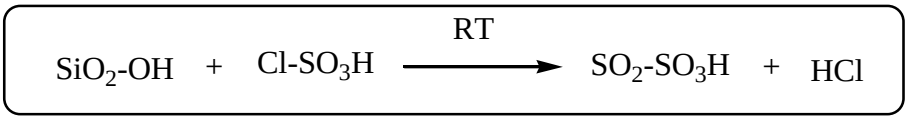
General procedure for the preparation of Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-one:

A mixture of isatin (1 mmol), malononitrile (1.1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) or 4-hydroxy 6-methyl 2-pyrone (1 mmole) and SSA (10 mol%) in water : ethanol (5 mL) was refluxed for an appropriate period of time. After completion of the reaction (monitored by TLC), the catalyst was separated by filtration. The solvent was removed and the products (4a-l) were purified by recrystallization from EtOH.

Spectral Data:

6'-Amino-5'-cyano-3'-methyl-1'-phenylspiro [indoline-3, 4'(1'H)-pyrano-[2, 3-C]pyrazole]-2-one (4a): White solid. Mp: 219–220°C; 1H NMR(300MHz, DMSO-d6): δH (ppm) 1.545 (s, 3H, CH3), 6.94-6.96(m, 1H, Ar-H), 7.017-7.033 (s, 1H, Ar-H), 7.054-7.134 (m, 1H,Ar-H), 7.192-7.273 (m, 1H, Ar-H), 7.289-7.312 (m, 1H, Ar-H), 7.340-7.359 (m 1H, Ar-H), 7.59(s, 2H, NH2), 7.78-7.802(m, 2H, Ar-H), 10.756(s, 1H, NH) ; HRMS (ES+) calculated for $C_{21}H_{17}N_5O_2$(M+H)+ 371 found m/z 370.

6'-Amino-5'-cyano-3'-methyl-1'-phenylspiro [indoline-3, 4'(1'H)-pyrano-[2,3-C]pyran]-2-one (4l): White solid.1H NMR (200MHz, DMSO-d6): δH (ppm) 2.247 (s, 3H, CH3), 6.352-6.354(s, 1H, Ar-H), 6.667-6.684 (d, 1H, Ar-H), 7.509(s, 2H, NH2), 7.523-7.527 (d, 1H, Ar-H), 7.539-7.543 (d, 1H, Ar-H), 10.705(s, 1H, NH).



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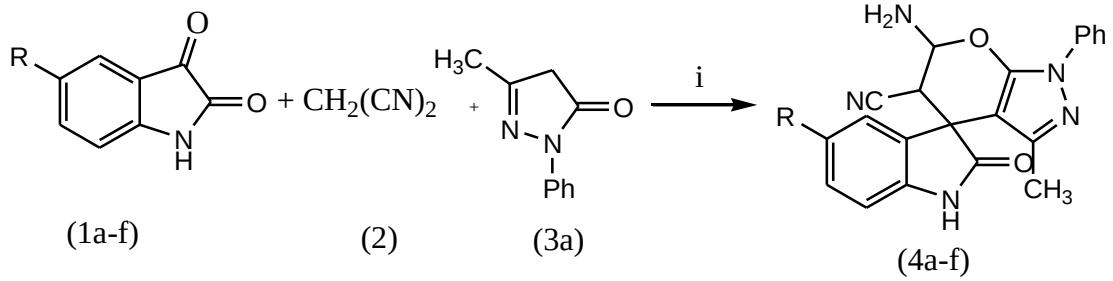
3. Results and discussion

As it can be seen that, the best results were obtained by performing the reaction in presence of 10 mol% of SSA at 80-90^{0}C in 50%aqueous ethanol. Thereafter, a series of reactions were carried out using diversely substituted isatins under identical reaction conditions. All these isatins underwent three-component reaction with malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one or 4-hydroxy 6-methyl 2-pyrone to produce Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-one derivatives in good to excellent yields (entries a-l, Table 2) .

Due to our interest in using solid catalysts in the synthesis of heterocycles[24], we describe an efficient and facile protocol for the synthesis of Spiro[indoline-3,4'(1H')-pyrano-[2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-one derivatives from various isatins(1a-f), malononitrile(2) and 3-methyl-1-phenyl-2-pyrazolin-5-one(3a) (Scheme 1) or 4-hydroxy 6-methyl 2-pyrone(3b) (Scheme 2) using reusable and safe catalyst silica sulphuric acid in aqueous ethanol (1:1) at 80-90^{0}C .

Scheme 1:



(1a-f) (2) (3a) (4a-f)

Scheme 1: Reagent and conditions: i) 10 mol % SSA, EtOH: H_2O (1:1), 80-90^{o}C, 40-60min, 84-94%.

In present year, the major strategies used for the synthesis of pyrano pyrazole derivatives include reusable catalyst and eco-friendly conditions. Recently, the use of environmentally friendly and economically viable solid acids is increasing continuously because of their high catalytic activities, reusability and environmental benefits by non-toxicity. Among them, silica sulphuric acid is a well-known and widely used solid acid catalyst in synthetic organic chemistry. It has received considerable attention because of its ease of handling, good reactivity, recyclability, experimental simplicity, non-toxicity, cost effectiveness and water compatibility and supports for a wide variety of reactions. The present work was performed by using this catalyst for the synthesis of Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]- 2-one derivatives. However, SSA could be reused for the reaction and was collected by simple work up process. Another aspect in this work was the use of water–ethanol as a solvent mixture in the ratio of 1:1.

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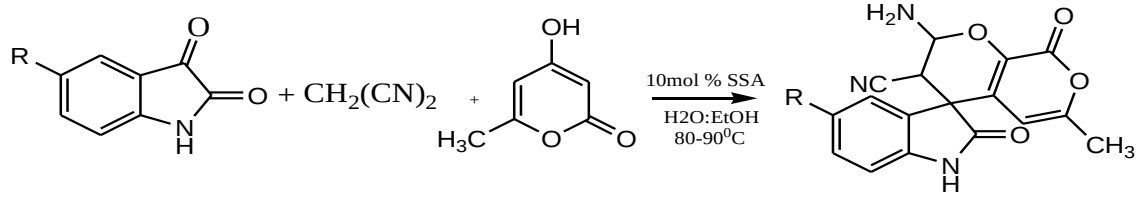
Scheme 2:



(1a-f) (2) (3b) (4g-l)

Scheme 2: Reagent and conditions: i) 10 mol % SSA, EtOH: H_2O (1:1), 80-90°C, 40-60min, 84-94%.

To investigate the scope and limitation of this process, various isatins and 2-pyrazolin-5-ones or 4-hydroxy 6-methyl 2-pyrone were examined under the same conditions. In all cases, the reaction proceeded smoothly to afford corresponding spiropyranyloxindoles in good to excellent yields. The results are shown in Table 1.

Table 1: Optimisation of reaction conditions:

Entry	Solvent	Catalyst	Temperature (°C)	Time (min.)	Yield (%)
1	50% EtOH	5 mole%	80-90	100	80
2	**50% EtOH**	**10 mole%**	**80-90**	**40**	**94**
3	50% EtOH	15 mole%	80-90	60	90
4	H_2O	10 mole%	80-90	110	65
5	EtOH	10 mole%	80-90	50	90
6	CH_3CN	10 mole%	80-90	100	65
7	CH_2Cl_2	10 mole%	40	140	70

Table 2: Synthesis of Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-oneby SSA.

Entry	R	3a/3b	Time (min.)	Yield (%)
4a	H	3a	48	84
4b	5-Br	3a	45	90
4c	5-Cl	3a	40	94
4d	5-OCH_3	3a	46	90
4e	5-CH_3	3a	48	92
4f	5-I	3a	53	88
4g	H	3b	43	83
4h	5-Br	3b	47	92
4i	5-Cl	3b	42	91
4j	5-OCH_3	3b	50	87
4k	5-CH_3	3b	54	88
4l	5-I	3b	52	90

3. Conclusion:

In summary, the reaction between isatins, malononitrile and 3-methyl-1-phenyl-2- pyrazolin-5-one or 4-hydroxy 6-methyl 2-pyrone using silica sulfuric acid as a catalyst provides a simple and efficient one-pot synthesis of Spiro[indoline-3,4'(1H')-pyrano-[2,3-c]pyrazole]-2-one and Spiro[indoline-3,4'(1H')-pyrano- [2,3-c]pyran]-2-one derivatives. The use of green and recyclable catalyst, high yield of products and simple workup procedure makes the present method valuable contributing in accordance with green chemistry principles.

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