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Sodium Bismuthate: An Efficient Catalyst for the One-pot Synthesis of Biologically Active Spiro[4*H*-pyran] Derivatives under Solvent-free Conditions

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Abstract

An efficient sodium bismuthate ($NaBiO_3$) synthesis of biologically active spiro[4*H*-pyran] derivatives has been accomplished via one-pot three-condensation of isatin/acenaphthequinone, malononitrile and different reagents including 1,3-dicrbonyl compounds, α-naphthol and 4-hydroxycumarin under solvent-free conditions. The notable advantages of the present procedure are: eco-friendly, environmentally benign nature, low-cost and non-toxic catalyst, simplicity of operation with no necessity of chromatographic purification steps, short reaction times, good to high yields and solvent-free conditions.

Keywords: *Sodium bismuthate ($NaBiO_3$), Spiro[4H-pyran] derivatives, Biologically active compounds, Solvent-free conditions, One-pot operation.*

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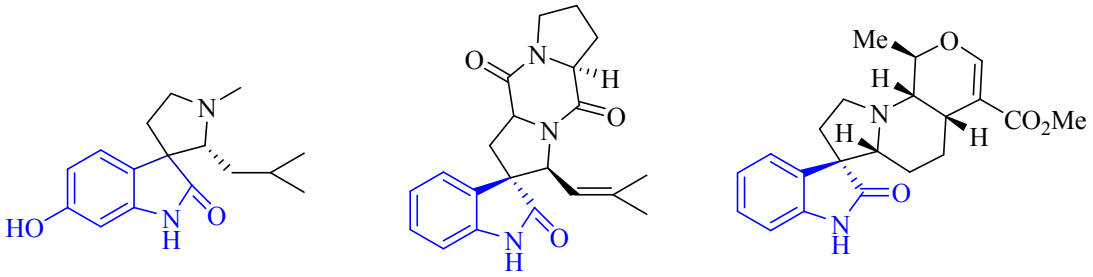
Introduction

In the recent years, the spiro[4*H*-pyran] derivatives have attracted considerable attention in organic synthesis because of their biological (Figure1) and pharmacological properties for example anticancer [1], anticonvulsant [2], fungicidal [3], antibacterial [4], anti HIV [5], antimalarial [6], antitubercular [7], antimicrobial [8], in addition these spirocycles are MDM2 inhibitor [9], progesterone receptor modulator [10].



Elacomine Spirotryprostatin B Pteropodine

Figure 1. Some alkaloids containing heterocyclic spirooxindole unit.

Recently, Multi component domino reactions (MCRs) [11-18] has become to one of the best approach for economical and efficient synthesis of organic compounds. The special advantages of multi-component reactions are including simple work-up, atom-economy, mild and environmentally friendly, low-cost, one-pot for the synthesis of organic compounds. Therefore, our recent studies focused on developing of multi-component reactions.

Thus, a number of procedures for the synthesis of spiro[4*H*-pyran] derivatives have been reported such as carbon-SO_3H [19], [Bmim]BF_4 [20], urea-choline chloride [21], porcine pancreas lipase [22], sulfated choline based heteropolyanion [23], Et_3N [24], CsF [25], triethanolamine [26], L-proline [27], ethylenediamine diacetic acid [28], β-Cyclodextrin [29], $InCl_3$ [30]. Some of disadvantages these methodologies are toxic and expensive catalysts and solvents, long time reactions, low yields and difficulty work-up.

Due to the above considerations and our interest in the development of synthesis of spiro[4*H*-pyran] derivatives we have studied of the development of clean, simple and environmentally friendly approaches for the synthesis of these fused heterocyclic compounds and finally, we have reported a simple, mild and economical protocol for one-pot

three-component reaction of isatin/acenaphthequinone, malononitrile and different reagents including 1,3-dicrbonyl compounds, α-naphthol and 4-hydroxycumarin under thermal and solvent-free conditions in the presence of sodium bismuthate as a mild and efficient catalyst with good to high yields and short reaction times. The most important advantages of the present procedure are one-pot, environmental friendly, solvent-free conditions, eco-friendly, simple operational procedures, mild, non-toxic and inexpensive catalyst. Furthermore, one of the source of environmental pollutions is the usage of organic solvents under reflux conditions and the need for column chromatography to purity the products. In this work, the products were obtained through simple filtering with no need column chromatographic separation.

Experimental

Material and methods

Melting points all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with DMSO-d_6 as solvents. In this article, all reagents and solvents were purchased from Merck, Fluka and Acros chemical companies were used without further purification.

*General procedure for preparation of spirooxindole and spiroacenaphthylene derivatives (**4a-g**) and (**8a-f**)*

A mixture of isatin/acenaphthequinone (1.0 mmol), malononitrile (1.0 mmol) and different reagents including [1,3-dicrbonyl compounds, α-naphthol and 4-hydroxycumarin] (1.0 mmol) in the present of sodium bismuthate ($NaBiO_3$) as a mild and environmentally benign nature catalyst under thermal and solvent-free conditions was heated for the appropriate time. After completion of the reaction (by thin layer chromatography, TLC) the mixture was cooled to room temperature the solid products were filtered and then were recrystallized from ethanol to give pure compounds (**4a-g**) and (**8a-f**). The catalyst is solvable in ethanol and catalyst was removed from the reaction mixture. The products have been characterized by melting points and ^{1}H NMR spectroscopy. Spectra data of selected and known products are represented below:

*2-Amino-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-spiro[chromene-4,3-indoline]-3-carbonitrile (**4a**)*

Pale yellow powder; m.p. 291-293 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.00 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.07-2.19 (2H, m, CH_2), 2.50-2.57 (2H, m, CH_2), 6.79 (1H, d, *J*=7.2 Hz, ArH), 6.89 (1H, t, *J*=7.2 Hz, ArH), 6.98 (1H, d, *J*=6.8 Hz, ArH), 7.13 (1H, t, *J*=6.4 Hz, ArH), 7.22 (2H, s, NH_2), 10.38 (1H, s, NH).

*2-Amino-2,5-dioxo-5H-spiro[indoline-3,4-pyrano[3,2-c]chromene]-3-carbonitrile (**4d**)*

Pale yellow powder; m.p. > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.83 (2H, s, NH_2), 7.19-7.26 (2H, m, ArH), 7.52 (2H, d, *J*=10.4Hz, ArH), 7.60 (1H, t, *J*=10.4Hz, ArH), 7.70 (1H, s, ArH), 7.79-7.85 (1H, m, ArH), 8.47 (1H, dd, *J*=10.4Hz, *J*=10.4Hz, ArH), 10.71 (1H, s, NH).

*2-Amino-7,7-dimethyl-5-chloro-2,5-dioxo-5,6,7,8-tetrahydro-spiro[chromene-4,3-indoline]-3-carbonitrile (**4f**)*

Pale yellow powder; m.p. >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.03 (6H, s, CH_3), 2.16 (2H, s, CH_2), 2.55-2.58 (2H, m, CH_2), 6.81 (1H, d, *J*=10.8Hz, ArH), 7.12 (1H, s, ArH), 7.20 (1H, dd, *J*=10.8 Hz, *J*=10.8 Hz, ArH), 7.35 (2H, s, NH_2), 10.57 (1H, s, NH).

*2-Amino-5-chloro-2,5-dioxo-5H-spiro[indoline-3,4-pyrano[3,2-c]chromene]-3-carbonitrile (**4g**)*

Pale yellow powder; m.p. > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.89 (1H, m, ArH), 7.27 (2H, s, NH_2), 7.73-7.76 (4H, m, ArH), 7.95 (1H, dd, *J*=10.8Hz, *J*=10.8Hz, ArH), 8.47 (1H, dd, *J*=10.8Hz, *J*=10.8Hz, ArH), 10.84 (1H, s, NH).

*2-Amino-7,7-dimethyl-2,5,6,7,8-tetrahydro-2H-spiro[acenaphthylene-1,4-chromene]-3-carbonitrile (**8a**)*

Yellow powder; m.p. 267-269 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.02 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.04-2.13 (1H, m, CH_2), 2.50-2.51 (1H, m, CH_2), 2.63 (2H, s, CH_2), 7.32 (2H, s,

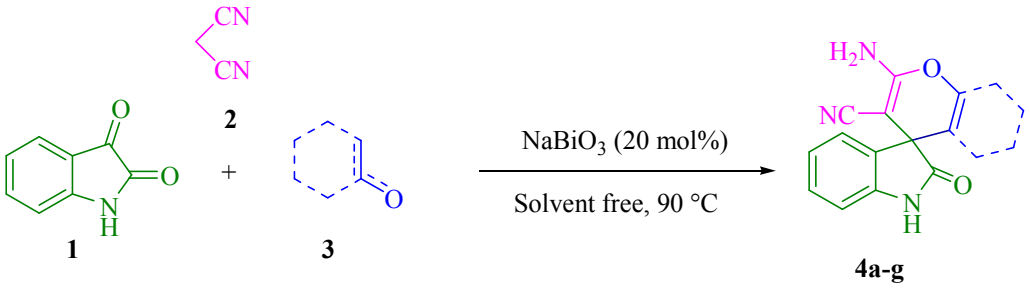
NH_2), 7.37-7.85 (6H, m, ArH).

5-Acethyl-2-Amino-6-methyl-2-oxo-2H-spiro[acenaphthylene-1,4-pyran]-5-carbonitrile ***(8e)***

Yellow powder; m.p. > 300 °C;^{1}H NMR (400 MHz, DMSO-d_6): 1.13 (3H, t, *J*=9.6 Hz, $COCH_3$), 1.92-2.53 (3H, m, CH_3), 7.96 (2H, s, NH_2), 7.67-8.47 (6H, m, ArH).

Results and discussion

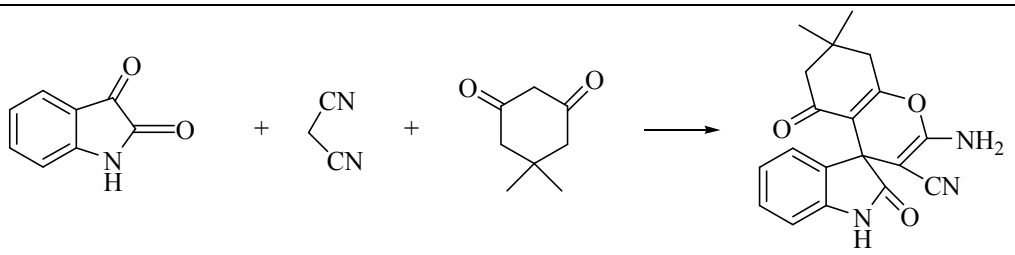
An efficient catalyst for economical, simple and one-pot synthesis of biologically active spirooxindole derivatives via isatin (**1**, 1.0 mmol), malononitrile (**2,** 1.0 mmol) and different reagents including 1,3-dicrbonyl compounds, α-naphthol and 4-hydroxycumarin (**3,** 1.0 mmol) in the present of sodium bismuthate ($NaBiO_3$) as a catalyst under thermal and solvent-free conditions is reported (Scheme 1).



Scheme1. Synthesis of spirooxindole derivatives.

In order to optimized the reaction conditions, the synthesis of compound **4a** (Table 1, entry 1) was used as a model reaction. The effect of different amount of catalyst on the reaction has been studied in method. No product could be detected in the absence of the catalyst even after 12h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The best amount of catalyst was 20 mol % (0.055 g) (Table 1, entry 5). The higher amount of catalyst did not increase the yields products (Table 1, entry 6).However, the higher yield of product is obtained with 20 mol % of catalyst and the results are summarized in Table 1.

Table 1. Optimization of the reaction condition for the synthesis of spiro[4*H*-pyran-3,3-oxindole] [a].

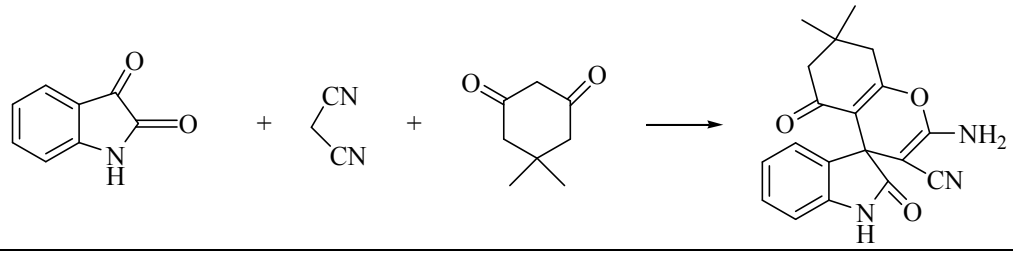


Entry	$NaBiO_3$ (mol %)	Time (h)	Product	Isolated Yields (%)
1	Catalyst free	12	4a	Not product
2	5	10	4a	42
3	10	6	4a	56
4	15	6	4a	69
5	**20**	**4**	**4a**	**80**
6	25	4	4a	82

[a] Reaction condition: isatin, malononitrile, dimedone and sodium bismuthate was heated at 90 °C for the appropriate time.

Also, the effect of temperature on the reaction has been investigated. No product could be detected in room temperature conditions (Table 2, entry 1). The reaction was investigated by changing temperature from 40-110 °C and the high yield of product is obtained in 90 °C temperature (Table 2, entry 5). The yields of product at different temperature are reported in Table 2.

Table 2. Effect of the reaction temperature on the synthesis of **4a** [a].

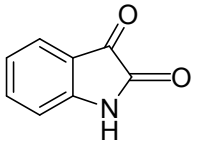
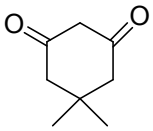
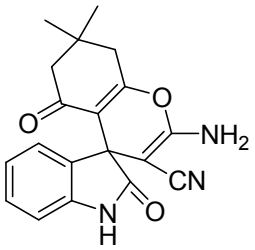
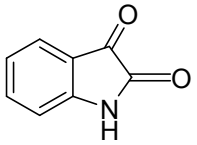
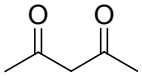
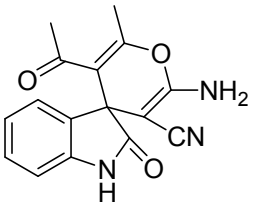
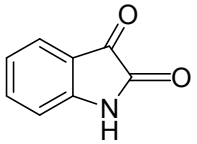
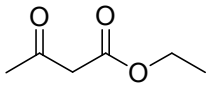
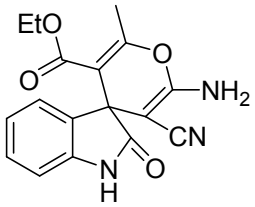
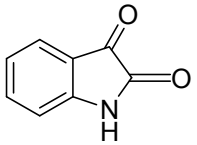
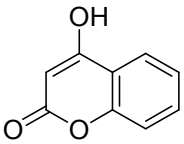
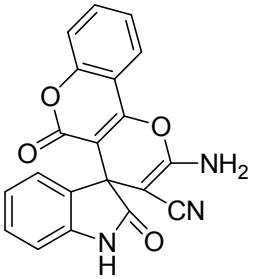
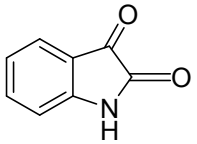
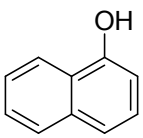
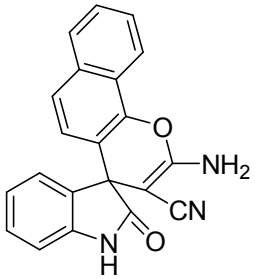


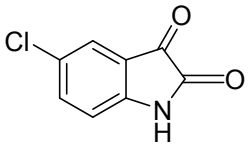
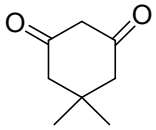
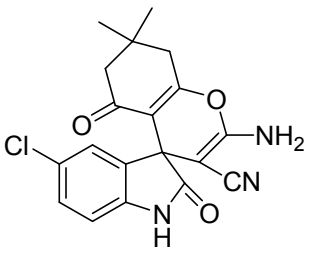
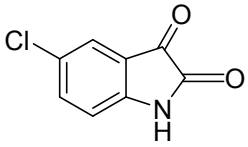
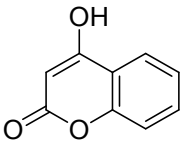
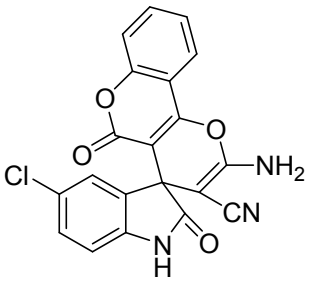
Entry	Temperature (°C)	Time (h)	Isolated Yields (%)
1	r.t.	12	Not product
2	40	6	23
3	60	6	47
4	80	4	68
5	90	4	80
6	110	4	81

[a] *Reaction condition: isatin, malononitrile, dimedone (1:1:1) with sodium bismuthate (20 mol %) was heated under various temperatures for the appropriate time.*

In order to study of this procedure, we have synthesized one-pot, three condensation reaction of isatin (1.0 mmol), malononitrile (1.0 mmol) and different reagents including [1, 3-dicrbonyl compounds, α-naphthol and 4-hydroxycumarin] (**7**, 1.0 mmol) (1.0 mmol) in the present of sodium bismuthate (20 mol %) as a mild catalyst under thermal and solvent-free conditions and the results are shown in Table 3.

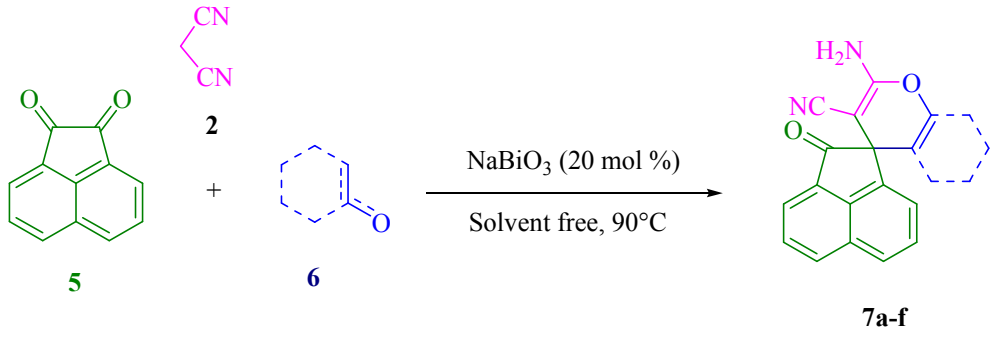
Table 3. Sodium bismuthate catalyzed synthesis of spiropyrans.

Entry	Isatin	3	Product	Time (h)	Yield % [a]
1			 **4a**	4	80 [20]
2			 **4b**	4	83 [19]
3			 **4c**	6	82 [20]
4			 **4d**	6	75 [21]
5			 **4e**	4	79 [21]

6			 **4** **f**	4	83 [25]
7			 **4** **g**	6	72 [23]

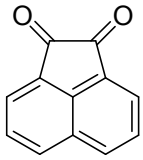
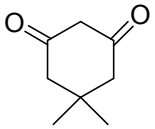
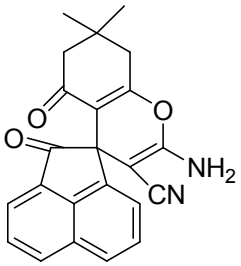
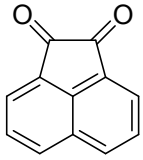
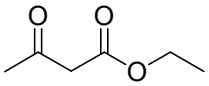
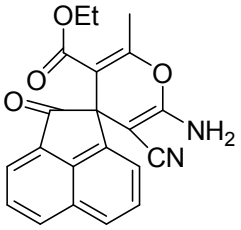
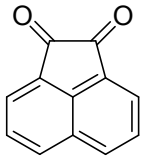
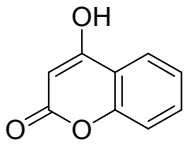
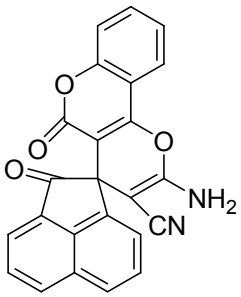
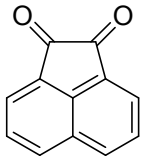
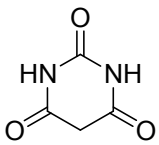
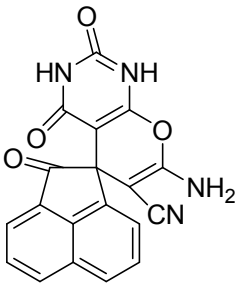
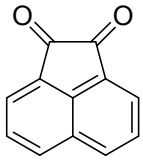
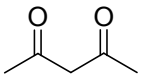
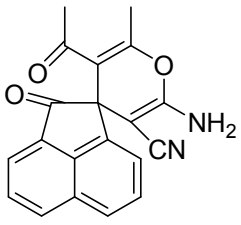
[a] *Isolated yield.*

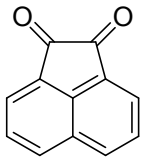
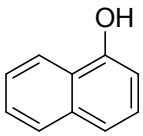
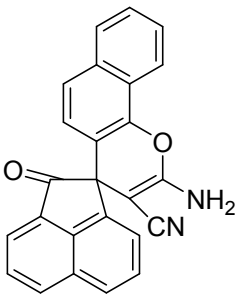
After the successful synthesis of spirooxindole derivatives, we turned our attention to the synthesis of spiroacenaphthylene derivatives via acenaphthequinone (**5**, 1.0 mmol), malononitrile (**6**, 1.0 mmol) and different reagents including [1,3-dicrbonyl compounds, α-naphthol and 4-hydroxycumarin] (**7**, 1.0 mmol) in the present of sodium bismuthate (Scheme 2) and these compounds have synthesized under similar conditions in good yields. The results are shown in Table 4.



Scheme 2. Synthesis of spiroacenaphthylenes derivatives.

Table 4. Sodium bismuthate catalyzed synthesis of spiroacenaphthylenes.

Entry	Acenaphthoquinone	6	Product	Time (h)	Yield % [a]
1			 **7a**	5	82 [24]
2			 **7b**	6	78 [24]
3			 **7c**	6	76 [24]
4			 **7d**	5	73 [24]
5			 **7e**	4	84 [24]

6			 **7f**	4	78 [24]

[a] *Isolated yield.*

Comparison of catalytic ability some of catalysts reported in the literature for the synthesis of spiro[4*H*-pyran] derivatives are shown in Table 5. This study reveals that sodium bismuthate shown its extraordinary potential to be an alternative cheap, cost effective, eco-friendly, efficient catalyst for the synthesis of these compounds, in addition to the use of solvent-free conditions with good to high yield and short reaction times in the reaction are the notable advantages this present methodology.

Table 5. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of spiro[4*H*-pyran] derivatives [a].

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	Carbon-SO_3H	EtOH, Reflux	3h/81	[19]
2	lipase	EtOH,, heating	3h/94	[22]
3	Et_3N	EtOH, Reflux	4h/80	[24]
4	β-Cyclodextrin	H_2O, heating	5h/90	[29]
5	$InCl_3$	MeCN, Reflux	90 min/75	[30]
6	$NaBiO_3$	Solvent-free, heating	4h/80	This work

[a] Based on the three-component reaction of isatin, malononitrile, dimedone.

Conclusion

In summary, sodium bismuthate as an efficient and eco-friendly catalyst for the one-pot synthesis of bioactive spiro[4*H*-pyran] and spiroacenaphthylene derivatives under thermal and solvent-free conditions with good to high yields and short reaction times is studied. The notable advantages the present methodology are low-cost, non-toxic catalyst, eco-friendly, mild, one-pot, highly efficient, environmental benign nature, simplicity of operation with no necessity of chromatographic purification steps and solvent-free conditions.

Acknowledgments

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