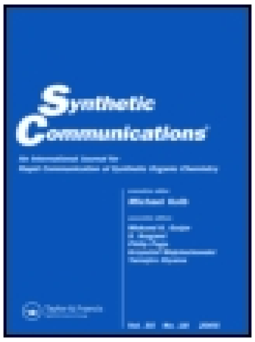

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Ultrasound assisted synthesis of diversely functionalized tetrahydro-1H-indole-4(5H)-one using Brønsted base silica sodium carbonate (SSC) as a catalyst under solvent-free conditions

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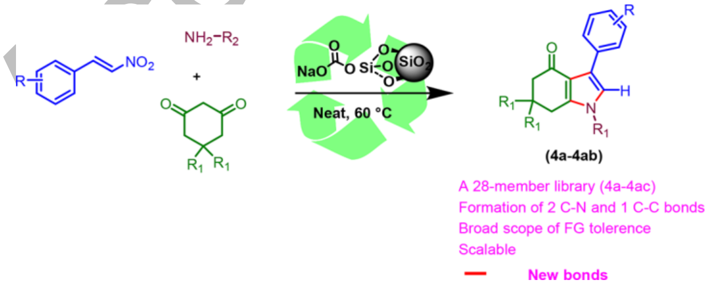
Abstract

An ultrasound promoted an environmentally benign and efficient procedure has been developed for the synthesis of biologically active tetrahydro-1H-indol-4(5H)-one using heterogeneous Brønsted base silica sodium carbonate (SSC) as a catalyst under solvent-free condition. In comparison to the conventional methods, this efficient green protocol provides remarkable advantages such as good to excellent yields, shorter reaction time, low cost, easy work-up procedure and bypass for use of hazardous transition metal catalysts and organic solvent.

GRAPHICAL ABSTRACT



KEYWORDS: Silica sodium carbonate (SSC), Brønsted base, tetrahydro-1H-indol-4(5H)-one, Ultrasound**,** solvent-free

INTRODUCTION

Polysubstituted indole derivatives represent an important class of nitrogen containing heterocycles ubiquitous in a number of biologically active natural products. As a representative of this class of compounds, the tetrahydro-1H-indol-4(5H)-one scaffold serving as a valuable starting material for indole-based compounds.[1–5] In addition, derivatives bearing this core are of considerable pharmacological interest and possess an array of biological activities including HSP90 inhibition,[6] soluble guanylate cyclase inhibition,[7] kv 1.5 blocking,[8] anti-psychotic,[9] GABAA-α[9] receptor ligands,[10] antiproliferation and aurora kinase inhibition.[11] Indolone is a prominent structural unit found in several natural products and pharmaceutically active compounds and acts as a precursor to indole.[12–14, 38–39]

Owing to their versatile biological activities, extensive synthetic efforts have been devoted for the construction of polysubstituted indole. The classical methods such as the Fischer-type indole synthesis [15] provide rapid access to substituted indole from phenylhydrazine and an aldehyde or ketone compounds. Furthermore there are several methods available for the synthesis of indole derivatives using transition metal as a catalyst for instance, radical cyclization,[16] nickel-catalyzed alkylation,[17] palladium-catalyzed C–H functionalization[18-19] reactions. On the other hand, recently non-metal catalyzed method also has been developed for the synthesis of substituted indoles from cyclic 1,3-dicarbonyl, amine and nitroolefins involving intramolecular cyclization.[20]

Although the known methodologies have convenient protocols with good to high yields, the reported methods still suffered from shortcomings, such as long reaction times, expensive catalyst, low yields, toxic solvents, high temperature and the use of non-recyclable catalysts. Thus, the development of efficient and environmentally benign protocol using a recyclable catalyst and solvent-free condition for the synthesis of tetrahydro-1H-indol-4(5H)-one derivatives is still desirable and in demand.

The use of green solvents [21–22] or solvent-free [23] conditions, non classical energy sources such as microwaves, [24] ultrasound [25–27] and infrared, [28] eco-friendly reagents and catalysts [29] are among the alternatives to improve the greenness of the synthesis of indoles. Ultrasound-assisted organic synthesis is a green approach and a superior technique employed for the organic reactions leading to suppression of side products, improved rate of reaction, milder conditions and easier handling and formation of pure products in prominent yields.[30–31] Moreover ultrasound promoted, especially when either one of the substrates or the products is a liquid and can be used as the solvent of the reaction are particularly welcome.

In the recent years, heterogeneous catalysts have found increased application in an organic synthesis[32] as they are efficient, easily recovered and recycled. In this context silica sodium carbonate (SSC) is synthetically useful as an efficient Brønsted base was found in organic reactions. Because sodium carbonate is inorganic Brønsted base, it is widely used as a catalyst in the organic reactions. Nevertheless, it is easily soluble in aqueous medium, so that reuse and separation from the reaction mixture are tedious and inconvenient. On the other hand silica sodium carbonate (SSC) is silica supported Brønsted base (Fig. 1). The unique feature of SSC, over conventional basic catalysts is ease of handling, stability, recyclability, cost effective, tunable Brønsted basicity. It could be successively used in multicomponent reactions [33–34].

In the last few years we have developed greener methodologies to prepare novel heterocyclic compounds combining two or more of the Green Chemistry Principles, using heterogeneous catalysts under solvent-free conditions and energy-efficient protocols.[35–36] Herein, we wish to report a simple and useful synthetic protocol, ultrasound assisted synthesis of tetrahydro-1H-indol-4(5H)-one by employing SSC as a catalyst through one-pot three-component condensation reaction of nitroolefin (**1**), cyclic 1,3-diketones (**2**) and amine (**3**) under solvent-free condition at 60 °C as shown in (Scheme 1).

RESULT AND DISCUSSION

Initially, to investigate the reaction conditions, we carried out the reaction between 1-fluoro-4-((E)-2-nitrovinyl)benzene (**1a**, 1 mmol), 5,5-dimethylcyclohexane-1,3-dione (**2a**, 1mmol) and 3-methoxybenzenamine (**3a**, 1 mmol) in the absence of the catalyst under solvent-free condition as a model. In the absence of catalyst we could not isolate any desired product even after 14 h stirring (Table 1, entry 1).

After that we investigated by utilizing different catalysts under both conventional heating and ultrasonication conditions without solvent. Catalysts such as $FeCl_3$, $Y(OAc)_3.H_2O$, $GaBr_3$, and sodium carbonate either completely impede the reaction or diminish the yield of the product (Table 1, entries 2–5). In order to develop a viable approach, the model reaction was investigated by employing different silica supported heterogeneous catalyst such as CAN-SiO_2, $BF_3.SiO_2$, TiO_2-SiO_2, $FeCl_3.SiO_2$, $Cu(OTf)_2.SiO_2$ and $ZnCl_2.SiO_2$ and obtained moderate product yields (Table 1, entries 6–11). Subsequently the reaction was performed in the presence of SSC and we obtain the desired product (**4a**) in high yield (Table 1, entry 12). Moreover, The optimal molar loading of SSC was determined by performing the model reaction using 2, 2.5, 3, 3.5, 4 and 4.5 mol % of SSC in neat condition and 53, 62, 75, 80, and 89% yields were obtained, respectively; (Table 1, entries 13–18). Increasing the amount of catalyst above 4 mol % had no effect on yield and reaction time. The effect of solvent on the model reaction was studied in both conventional and ultrasonication conditions using 4 mol % of SSC in different solvents. The reaction was also studied at varying temperature (40, 50, 60 and 80 °C). The optimum conversion of reactants to product was achieved when reaction was under solvent-free condition at 60 °C. Further the frequency of ultrasonication bath was also studied with 10KHz, 20KHz, 30KHz and 40KHz. It showed that 20KHz frequency was sufficient for this reaction. One more reaction was carried out using plain silica as a catalyst to find out the exact role of silica in the reaction system. But we haven't observed any product formation even after 12 h of reaction time. So the role of silica as heterogenous support in this modified silica supported catalyst is demonstrated (Table 1, entry 29). Hence, the product yield and the rate of reaction, both are mutually dependent on the nature and quantity of the catalyst, frequency of ultrasonication.

The recyclability of the SSC catalyst was also established by running the same model reaction in five cycles with recovered SSC and obtained **4a** in 89, 87, 85, 85, and 83% product yield. This proved that efficiency of the catalyst can be used for the multiple usage purpose without much loss of its efficiency (Table1, entry 12). From all these observations (Table1), we concluded that 4 mol % of the SSC catalyst, 60 °C and solvent-free conditions under ultrasonication (20 KHz) are best optimized conditions for this synthesis of tetrahydro-1H-indol-4(5H)-one derivative (**4a-4ac**).

In order to explore the scope and limitations of the SSC catalysis, the protocol was extended to other examples, under the optimized conditions. To our delight, we found this transformation to be very general for a wide range of amine, conjugated nitroolefins and two cyclic 1,3-dicarbonyl, providing easy access to densely substituted tetrahydro-1H-indol-4(5H)-one derivatives **4**. Aromatic as well as aliphatic amines displayed good reactivity in this reaction. On the other hand a different functional groups substituted at the aromatic ring of the nitroolefin were tolerated. We also employed two different cyclic 1,3-dicarbonyl substrates, such as 5,5-dimethylcyclohexane-1,3-dione and cyclohexane-1,3-dione, producing tetrahydro-1H-indol-4(5H)-one in good to excellent yields.

To further demonstrate the advantage of this method, we attempted to scale-up synthesis of tetrahydro-1H-indol-4(5H)-one (**4a**) use of 1-fluoro-4-((E)-2-nitrovinyl)benzene (**1a**) with 5,5-dimethylcyclohexane-1,3-dione (**2a**) and 3-methoxybenzenamines (**3a**). These reagents were subjected to the reaction under ultrasonication for 50 min. and 86% yield was afforded (Scheme 2).

Presumably the reaction seems to proceed through following mechanistic pathway as presented in (Fig. 2). The catalyst SSC appears to play a key role as Brønsted base in the reaction and accelerates the reaction to helps in the formation of the intermediate β-enamino carbonyl (**A**) which then undergoes Michael reaction with nitroolefin (**1**) to give intermediate **B.** Intermediate **B** undergoes *in-situ* formation of aldehyde (**C**) by Nef reaction followed by intramolecular cyclization leading to the final products **4a-4ac.**

CONCLUSION

Silica sodium carbonate (SSC), proved to be an effective, selective and reusable catalyst for the green synthesis of tetrahydro-1H-indol-4(5H)-one derivatives under ultrasonic in solvent-free condition. Besides, being a simple procedure, the SSC catalyst was easily recycled and reused. The use of solvent-free condition allows the use of sonication to accelerate the reaction from hours to only a few minutes. The low toxicity of SSC allied to an atom-economic reaction. The bypass the solvents and use of sonication are features which make this new, silica supported sodium carbonate protocol, a green alternative method to access tetrahydro-1H-indol-4(5H)-one selectively.

EXPERIMENTAL

Chemicals were purchased from Aldrich and Alfa Aesar Chemical Companies. NMR spectra were recorded in parts per million (ppm) in $CDCl_3$ on a Jeol JNM ECP 400 NMR instrument using TMS as internal standard. Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument.

Two Step Preparation Of SSC

STEP-1

Silica sodium carbonate was prepared by adopting the literature K. Eskandari, B. Karami et al. [34]. To a 250mL round bottom flask equipped with a reflux condenser, in which the hose interface was connected to a pot of water, 10 g of silica gel 60 (63–200 μm) that was previously dried at 120 °C for 6 h was added. Then 40 mL of thionyl chloride was added dropwise to this flask which was perched in an ice bath (caution). After the addition of thionyl chloride, the reaction mixture was removed from the ice bath and stirred for 0.5 h in room temperature and 48 h under reflux conditions. Afterwards, the reaction mixture was filtrated to obtain silica chloride.

STEP-2

To a stirred 250 mL round bottom flask containing 10 g of sodium bicarbonate and 25 mL of n-hexane under reflux conditions, 10 g of silica chloride (after drying at 120 °C for 6 h) was added. After 24 h, the reaction mixture was filtrated to separate the catalyst and the solid product was washed with 50 mL of distilled water ten times, using 5 mL each time until filtrate became quite neutral, in order to remove the remaining sodium bicarbonate. Finally, dryid at 100 °C for 12 h, to afford SSC.

General Procedure For The Synthesis Of Tetrahydro-1H-Indol-4(5H)-One At Ultrasound (4a-4c)

To a 10 mL vessel was added nitroolefins (**1**, 1 mmol), cyclic 1,3-dicarbonyl (**2**, 1mmol), amine (**3**, 1 mmol) and SSC (4 mol%), the reaction was carried out under ultrasound (20 KHz). The resulting solution was sonicated with an US probe for the time indicated in Table 2. The progress of reactions were checked by thin layer chromatography (TLC) using hexane/ethyl acetate as an eluent. After completion of the reaction, the mixture was washed with ethyl acetate and filtered to recover the catalyst. The filtrate was evaporated, and the crude product was purified by flash column chromatography on silica gel (200−300mesh) with ethyl acetate and hexane as eluent to afford the product **4**. The SSC catalyst was reused by the way of addition of ethyl acetate to the reaction mixture and filtration followed by drying in a vacuum oven every time. The spectral and analytical data of the model representative compound is given here:

***3-(4-Fluorophenyl)-6,7-Dihydro-1-(3-Methoxyphenyl)-6,6-Dimethyl-1H-Indol-4(5H)-One* (4a)**

Yield 89 %; off-white solid; Mp: 130-132; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 6H, $2CH_3$), 2.42 (s, 2H, CH_2), 2.67 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.84(s, 1H, ArH), 6.87 (s, 1H, ArH), 6.92 (d, *J*=7.7 Hz, 1H, ArH), 6.97 (d, *J*=8.4 Hz, 1H, ArH), 7.03 (t, *J*=8.6 Hz, 2H, ArH), 7.41 (t, *J*=8.1 Hz, 1H, ArH), 7.63-7.66 (m, 2H, ArH), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.53, 35.44, 37.53, 53.23, 55.70, 111.50, 113.51, 114.72, 114.93, 117.18, 117.55, 121.79, 124.31, 130.37, 130.45, 139.58, 143.51, 160.84, 163.31 (C-F, d, *J* = 246 Hz), 193.84; HRMS (ESI, m/z): calcd for $C_{23}H_{22}FNO_2$ $(M+H^+)$ 363.1634, found: 363.1633.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra, HRMS data for all compounds. This material can be found via the “Supplementary Content” section of this article’s webpage.

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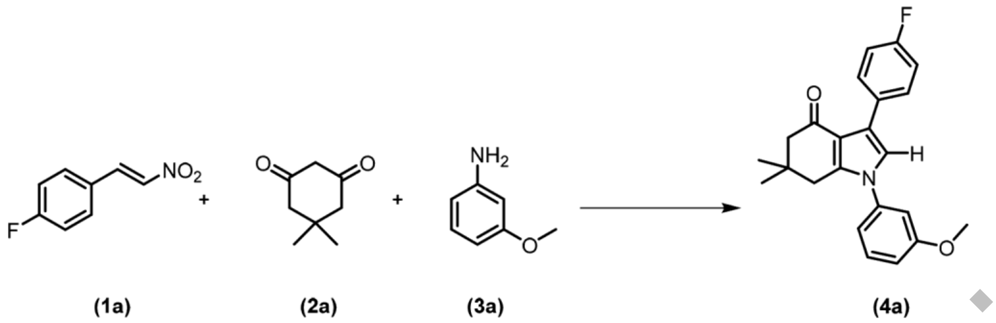
Table 1. Optimization of reaction conditions in the synthesis of **4a**[a]

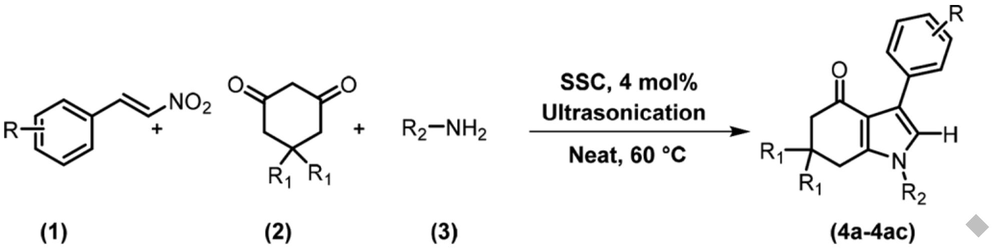


Entry	Catalyst (mol%)	Solvent	Temp (°C)	Conventional		Ultrasound (20 KHz)	
				Time (min)	Yield[b] (%)	Time(min)	Yield[b] (%)
1	-	Neat	60	840	-	300	-
2	$FeCl_3$ (5)	Neat	60	280	30	156	55
3	$Y(OAc)_3.H_2O$ $_3$ (5)	Neat	60	260	35	152	50
4	$GaBr_3$ (5)	Neat	60	245	45	122	55
5	Na_2CO_3 (5)	Neat	60	200	50	110	65
6	CAN-SiO_2 (5)	Neat	60	245	60	91	70
7	$BF_3.SiO_2$ (5)	Neat	60	290	55	80	61
8	TiO_2-SiO_2 (5)	Neat	60	324	45	123	58
9	$FeCl_3.SiO_2$ (5)	Neat	60	270	35	140	60
10	$Cu(OTf)_2.SiO_2$ (5)	Neat	60	190	45	90	62
11	$ZnCl_2.SiO_2$ (5)	Neat	60	266	50	110	55
12[c]	SSC (5)	Neat	60	190	70	45	89, 87, 85,

							85, 83
13	SSC (2)	Neat	60	251	40	65	53
14	SSC (2.5)	Neat	60	240	45	60	62
15	SSC (3)	Neat	60	230	51	58	75
16	SSC (3.5)	Neat	60	292	65	52	80
17	SSC (4)	Neat	60	190	70	78	89
18	SSC (4.5)	Neat	60	190	70	78	89
19	SSC (4)	H_2O	60	310	60	146	76
20	SSC (4)	[bmim][Cl]	60	251	22	139	34
21	SSC (4)	Toluene	60	263	35	141	42
22	SSC (4)	Ethanol	60	253	55	112	67
23	SSC (4)	Neat	40	285	62	110	72
24	SSC (4)	Neat	50	240	65	90	74
25 [d]	SSC (4)	Neat	80	190	68	55	82
26 [e]	SSC (4)	Neat	60	240	52	78	61
27 [f]	SSC (4)	Neat	60	150	62	65	84
28	SSC (4)	Neat	60	140	65	55	86
29	Silica gel (5)	Neat	60	720	NR	720	NR

[a]Reaction between 1-fluoro-4-((E)-2-nitrovinyl)benzene (**1a**, 1 mmol), 5,5-dimethylcyclohexane-1,3-dione (**2a**, 1mmol) and 3-methoxybenzenamine (**3a**, 1 mmol); [b]Isolated yield; [c]Catalyst was reused five times; [d, e] and [f] Ultrasonication reactions carried out with 10, 30 and 40KHz frequency respectively.

Table 2. Ultrasound-assisted synthesis of tetrahydro-1H-indol-4(5H)-one derivatives[a]



Entry	R	R_1	R_2	Product	Time (min)	Yield (%)[d]
1	4-F	CH_3	$3\text{-}OCH_3C_6H_4$	**4a**	45	89
2	4-F	CH_3	$4\text{-}CH_3C_6H_4$	**4b**	35	88
3	4-F	CH_3	$3\text{-}CH_3C_6H_4$	**4c**	40	88
4	4-F	CH_3	$2\text{-}CH_3C_6H_4$	**4d**	42	87
5	$3,4\text{-}OCH_3$	CH_3	$2\text{-}CH_3C_6H_4$	**4e**	51	88
6	$3,4\text{-}OCH_3$	CH_3	$3\text{-}CH_3C_6H_4$	**4f**	50	88
7	H	CH_3	$4\text{-}CH_3C_6H_4$	**4g**	22	92
8	H	CH_3	$3\text{-}OCH_3C_6H_4$	**4h**	35	90
9	H	CH_3	$3,4\text{-}CH_3C_6H_3$	**4i**	42	87
10	H	CH_3	$2,5\text{-}CH_3C_6H_3$	**4j**	53	85
11	H	CH_3	$3,5\text{-}CH_3C_6H_3$	**4k**	36	87
12	H	H	$2\text{-}CH_3C_6H_4$	**4l**	32	92[39]
13	H	CH_3	$3\text{-}CH_3C_6H_4$	**4m**	40	87
14	H	CH_3	$2\text{-}CH_3C_6H_4$	**4n**	36	89[39]
15	H	H	$3\text{-}CH_3C_6H_4$	**4o**	46	87
16	H	H	$4\text{-}CH_3C_6H_4$	**4p**	30	86

17	H	H	3,4-$CH_3C_6H_3$	**4q**	48	84
18	H	H	2,5-$CH_3C_6H_3$	**4r**	52	85
19	4-OCH_3	CH_3	4-$OCH_3C_6H_4$	**4s**	50	84
20	4-OCH_3	CH_3	4-$CH_3C_6H_4$	**4t**	42	89
21	4-OCH_3	CH_3	3-$OCH_3C_6H_4$	**4u**	55	87
22	4-OCH_3	CH_3	2-$CH_3C_6H_4$	**4v**	36	87
23	4-OCH_3	CH_3	3-$CH_3C_6H_4$	**4w**	50	87
24	H	CH_3	2,3-dihydro-1H-indene-5yl	**4x**	25	88
25	4-FC_6H_4	CH_3	cyclohexyl	**4y**	39	79
26	4-OCH_3	CH_3	cyclohexyl	**4z**	40	82
27	H	CH_3	3-methoxypropyl	**4ab**	58	76
28	H	CH_3	Ph	**4ac**	25	92[20,39]

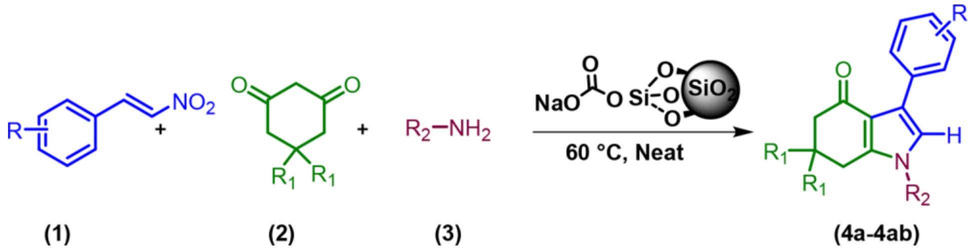
[a]Reaction of nitroolefins (**1**, 1 mmol), cyclic 1,3-dicarbonyl (**2**, 1 mmol) and amine (**3**, 1 mmo), catalyzed by SSC under ultrasonication at 60 °C.; [d]Yields of pure products isolated by column chromatography.

Table 3. Comparison of the results obtained for **4ac** using SSC versus the methods reported in the literature

Entry	Catalyst	Reaction condition	Time	Yield (%)[a]	Ref.
1	L-proline (10 mol%)	H_2O, 60 ℃	12 h	85	[20]
2	Carbonaceous materials(10 mg)	H_2O, 50 ℃	06 h	85	[39]
3	SSC	Neat, Ultracsonication, 60 ℃	25 min	92	This work

[a] Isolated yield

Scheme 1. Synthesis of tetrahydro-1H-indol-4(5H)-one derivative catalyzed by SSC.



Scheme 2. Scale-up Synthesis of tetrahydro-1H-indol-4(5H)-one (**4a**)

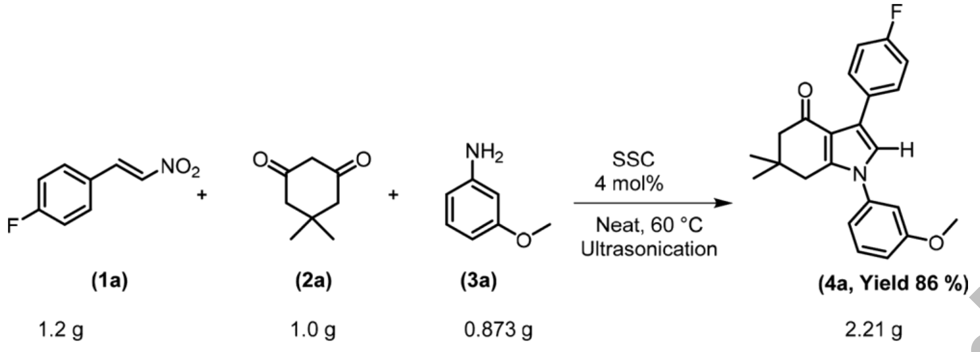


Figure 1. Silica sodium carbonate.

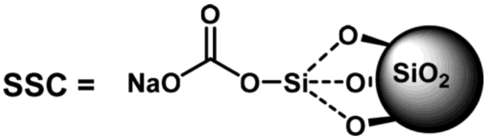


Figure 2 Plausible mechanism for the formation of tetrahydro-1H-indol-4(5H)-one derivatives.