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EXPERIMENTAL PAPER



Green Approach for Metal-free One-pot Synthesis of Tetrahydrobenzo[*b*]pyrans with Sodium Alginate as a Reusable Bifunctional Biopolymeric Catalyst


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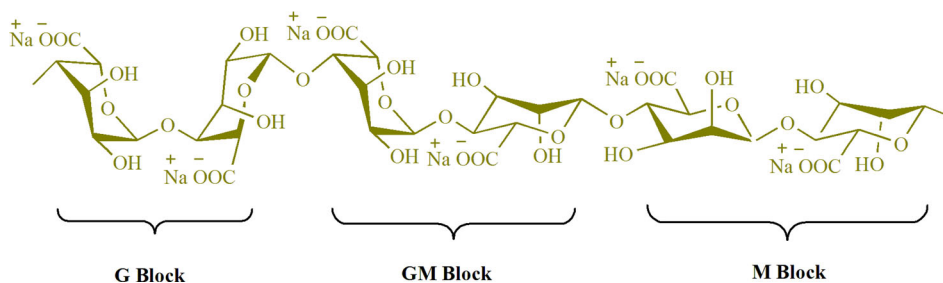
One of the most important factors in the greening of synthetic organic reactions is the use of green catalysts. In keeping with this, our laboratory's recent research efforts have focused on the development of green catalysts^{1,2} for organic synthesis. Naturally-occurring biodegradable and renewable feed stocks are the best substitutes for traditional chemical reagents. Biopolymers in heterogeneous catalytic systems have been gaining attention as substitutes for synthetic polymers. As natural polysaccharides, alginates are extensively distributed in the cell walls of such species of brown seaweed as *Laminaria spp*, *Ascophyllum nodosum*, *Lessonia nigrescens*, *Cystoseira barbata*, and *Sargassum turbinarioides* and may be readily isolated from them.^{3,4} Specific telluric bacteria, among those of the genus *Pseudomonas* and the genus *Azotobacter* excrete acetylated alginates.^{3,4} Sodium alginate (Scheme 1) is the sodium salt of alginic acid and an anionic biopolymer. It is considered to be a safe material that is notably used in the food industries as an emulsifying, gel-forming,⁵ and thickening ingredient. It is also used in the care of wounds and for encapsulating active ingredients in personal care goods.⁶ Sodium alginate possesses outstanding anti-oxidant features.⁷ It is a linear copolymer composed of 2 uronic acid monomers: (β -D-mannuronate (M); α -L-guluronate (G)) with a covalent link in a (1 \rightarrow 4) manner. There are homogeneous sequences established by G (G-blocks) and M units (M-blocks) alternating with mixed sequences (MG-blocks), all of varying lengths (Scheme 1). With its high availability of functional groups in the sodium alginate polymer (5.6 mmol g⁻¹ of carboxylate groups) and its stable status in many organic solvents, sodium alginate is a good catalyst option for organic synthesis.⁸ Since the monomeric units of sodium alginate include two hydroxyl groups and one carboxylate, the material can be a bifunctional organocatalyst, with the capability of activating both electrophilic and nucleophilic reaction sites. For those cases in which water is the reaction byproduct, it even has a more conspicuous catalytic activity, since sodium alginate can absorb 200-300 times its weight in water.⁵ This has led to some reports of its use in organic synthesis.^{9,10}

Pyrans have numerous significant pharmacological features (Figure 1), such as Chk1 kinase inhibitory,¹¹ analgesic,¹² anticancer,¹³ vasodilatory,¹⁴ antihypertensive, hepatoprotective, cardiotoxic,¹⁵ vasodilator,¹⁶ anti-leukemic,^{17,18} emetic,¹⁹ anti-anaphylactic,²⁰ diuretic²¹ and anti-Alzheimer²² properties (Figure 1).

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Scheme 1. Chemical structure of sodium alginate.

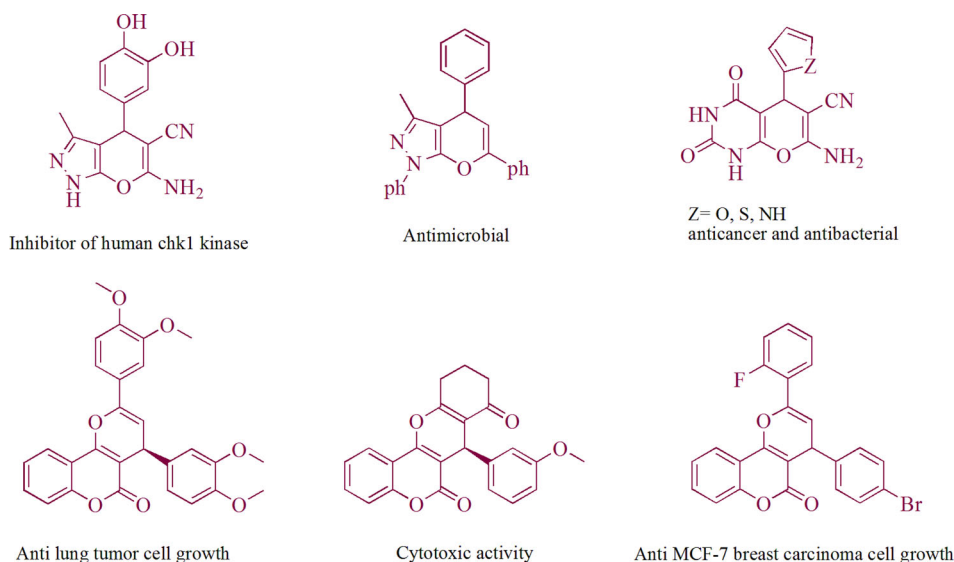
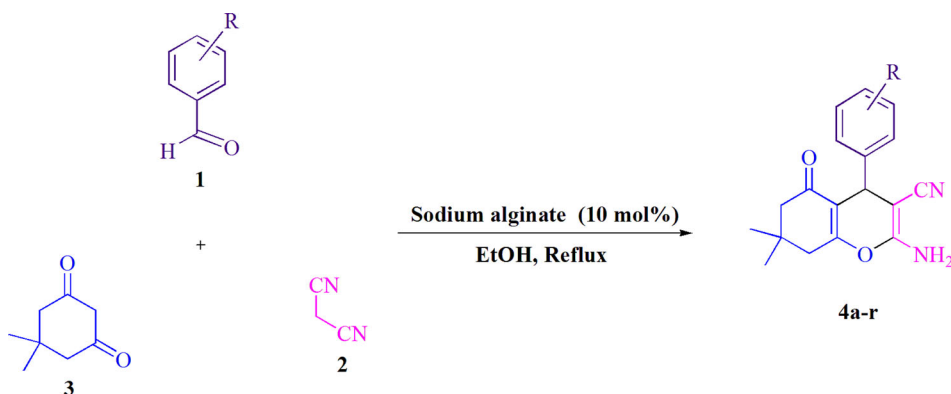


Figure 1. Some medicinally important compounds containing pyran motifs.

Several approaches for synthesizing these compounds use such catalysts as CaHPO_4 ,²³ SiO_2NPs ,²⁴ ethylenediamine diacetate,²⁵ SBPPSP,²⁶ DBSA,²⁷ $\text{NH}_4\text{Al}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$,²⁸ $\text{NH}_4\text{H}_2\text{PO}_4/\text{Al}_2\text{O}_3$,²⁹ ACoPc-MNPs,³⁰ ZnONPs,³¹ $\text{Fe}_3\text{O}_4@\text{SiO}_2$ -imid-PMA,³² $\text{NiFe}_2\text{O}_4@\text{SiO}_2$ -H₃PW₁₂O₄₀,³³ theophylline,³⁴ triethanolamine,³⁵ NaN_3 ,³⁶ $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{TiO}_2$,³⁷ MgFe_2O_4 nanoparticles³⁸ and trichloroisocyanuric acid.³⁹ As useful as they have been in moving the field forward, some of these catalysts have drawbacks, including the use of metals, costliness, or low yields, among others. With the present emphasis on environmentally benign protocols,^{40–42} the search continues for simple eco-safe strategies to produce tetrahydrobenzo[*b*]pyran scaffolds. Here, we provide data for the extension of sodium alginate catalysis to the preparation of tetrahydrobenzo[*b*]pyrans in a one-pot multi-component reaction procedure.

As a model for our reaction procedure, we studied the preparation of compound **4a** (Scheme 2 and Table 1). Without sodium alginate, very low yields were observed (Table 1, entries 1 and 2). The product was formed in MeOH, H₂O/EtOH (1:1), H₂O, CH₂Cl₂, THF, CH₃CN, CHCl₃, DMF, DMSO and under solvent-free conditions at different temperatures and with different catalyst loadings; but the best outcomes were found in the presence of sodium alginate (10 mol %) at reflux in EtOH (Table 1, entry 4). No important differences in reaction time and yield were observed by increasing the amount of catalyst to 15 mol %,



Scheme 2. Synthesis of tetrahydrobenzo[*b*]pyran scaffolds.

Table 1. Optimization table for the synthesis of **4a**.^a

Entry	Sodium alginate (mol %)	Solvent/Temperature (°C)	Time (min)	Yields ^b (%)
1	Catalyst free	EtOH/Reflux	180	18
2	Catalyst free	EtOH/rt	180	trace
3	5	EtOH/Reflux	40	71
4	10	EtOH/Reflux	30	93
5	10	EtOH/rt	85	54
6	10	EtOH/40 °C	60	68
7	10	EtOH/60 °C	45	80
8	10	Solvent free/100 °C	45	64
9	10	MeOH/Reflux	50	71
10	10	H ₂ O/EtOH (1:1)/Reflux	40	76
11	10	H ₂ O/Reflux	45	69
12	10	CH ₂ Cl ₂ /Reflux	60	34
13	10	THF/Reflux	55	47
14	10	CH ₃ CN/Reflux	45	69
15	10	CHCl ₃ /Reflux	60	31
16	10	DMF/Reflux	55	42
17	10	DMSO/Reflux	50	60
18	15	EtOH/Reflux	30	93

^aReaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol) with different temperatures, solvents and catalyst.

^bIsolated yield.

(Table 1, entry 18). Scheme 2 and Table 2 show that this technique can function well in a number of substrates, with yields ranging from very good to excellent (81-96%, mean yield 89%). No chromatographic purification was required. A plausible reaction mechanism is provided in the [Supplementary Materials](#). We found that the catalyst could be isolated from the reaction mixture upon completion and reused through five consecutive reaction runs without significant deterioration of reaction yields (see Experimental section).

Table 2. Sodium alginate promoted metal-free synthesis of tetrahydrobenzo[*b*]pyran scaffolds.

Entry	Compound	R	Time (min)	% Isolated Yield	mp (lit mp ^{reference}) °C
1	4a	H	30	93	228-30 (226-8 ²³)
2	4b	3,4-(OMe) ₂	35	88	226-8 (227-9 ³¹)
3	4c	4-F	25	96	199-201 (198-200 ²⁶)
4	4d	4-Br	40	83	206-8 (204-6 ²³)
5	4e	3-Me	25	92	200-2 (198-200 ²⁶)
6	4f	4-OMe	30	89	204-6 (202-5 ²³)
7	4g	2-Cl	30	84	215-7 (214-6 ²⁵)
8	4h	2-OMe	30	86	212-4 (211-2 ³³)
9	4i	3-NO ₂	30	94	208-10 (210-2 ³⁹)
10	4j	3-Br	40	85	227-9 (228-30 ²⁴)
11	4k	2,3-(OMe) ₂	35	90	215-7 (217-9 ²⁴)
12	4l	2-NO ₂	25	93	224-5 (223-6 ²³)
13	4m	3-OH	40	84	204-6 (226-8 ³⁰)
14	4n	3-F	25	95	211-3 (210-2 ³⁷)
15	4o	4-Me	25	93	220-2 (221-3 ²⁶)
16	4p	3-Cl	35	81	229-31 (228-30 ²³)
17	4q	4-OH	40	87	210-2 (210-2 ³⁰)
18	4r	4-NO ₂	30	91	181-3 (180-1 ²⁵)

Summing up, the present research demonstrates that sodium alginate, as a reusable and bifunctional biopolymeric heterogeneous catalyst, can be conveniently employed for the preparation of desirable tetrahydrobenzo[*b*]pyrans. The reaction is carried out in ethanol under reflux, and no chromatographic purification of products is required. We believe this is a significant advance in the greening of reaction procedures for the synthesis of pyrans. Future work in our laboratory may explore further uses of sodium alginate, including the synthesis of pyrans from heteroaromatic aldehydes.

Experimental section

Chemicals were purchased from Fluka, Merck and Acros and were used without further purification. Using a 9100 Electro-thermal device, the melting points of all compounds were found, and they are uncorrected. The nuclear magnetic resonance spectra (¹HNMR) were recorded on Bruker DRX-400 and DRX-300 instruments using CDCl₃ as solvent. Thin layer chromatography (TLC) was carried out with silica gel as the stationary phase and ethyl acetate–*n*-hexane (7:3) as the eluting solvent.

General procedure

The appropriate arylaldehyde (**1**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), dimedone (**3**, 1.0 mmol), and sodium alginate (10 mol %) in EtOH (5 mL) were refluxed for the necessary time (Table 2), as monitored by TLC. After completion of the reaction, the catalyst was removed by simple filtration from the hot mixture. The filtrate was kept at ambient temperature to afford the products. Recrystallization occurred in the reaction vessel from ethanol to yield the pure products (**4a-r**). Recovery and reuse of the catalyst to prepare **4a** was examined.

At the end of the reaction, the catalyst was removed by filtration and ethanol (2 × 3 mL) was used to wash the catalyst, which was then dried under vacuum. The sodium alginate was reused through five rounds of recycling, and the yields were 92%, 91%, 91%, 89% and 88%, in the respective rounds. All of the products of this study

were known compounds and were identified on the basis of matching their melting points with the literature values given in the references cited in Table 2. ¹HNMR spectra were also compatible with the product structures proposed. For the sake of completeness, several representative examples are given below.

2-Amino-4-(3-methylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e)

Yield: 92%; m.p. 200-202 °C; ¹HNMR (400MHz, CDCl₃) 1.06 (3H, s, CH₃), 1.13 (3H, s, CH₃), 2.23 (2H, d, *J* = 5.6 Hz, CH₂), 2.31 (3H, s, CH₃), 2.46 (2H, s, CH₂), 4.38 (1H, s, CHAr), 4.52 (2H, s, NH₂), 7.09-7.15 (3H, m, ArH), 7.28 (1H, s, ArH).

2-Amino-4-(2,3-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4k)

Yield: 90%; m.p. 215-217 °C; ¹HNMR (300MHz, CDCl₃) 1.10 (3H, s, CH₃), 1.14 (3H, s, CH₃), 2.25 (2H, s, CH₂), 2.47 (2H, s, CH₂), 3.77 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.47 (2H, s, NH₂), 4.73 (1H, s, CHAr), 6.68-6.84 (3H, m, ArH).

2-Amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4r)

Yield: 91%; m.p. 181-183 °C; ¹HNMR (300MHz, CDCl₃) 1.07 (3H, s, CH₃), 1.16 (3H, s, CH₃), 2.30 (2H, d, *J* = 14.0 Hz, CH₂), 2.52 (2H, s, CH₂), 4.55 (1H, s, CHAr), 4.68 (2H, s, NH₂), 7.45 (2H, d, *J* = 11.6 Hz, ArH), 8.20 (2H, d, *J* = 11.6 Hz, ArH).

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