Letter

Magnetic Graphitic Carbon Nitride-Catalyzed Highly Efficient Construction of Functionalized 4H-Pyrans

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Abstract A high-yielding, practical, efficient, and environmentally benign one-pot multicomponent synthesis of functionalized 2-amino-4*H*-pyrans from β -dicarbonyl compounds, malononitrile, and aldehydes is presented. Good to excellent yields were obtained under mild reaction condition and with short reaction times by using magnetite-supported graphitic carbon nitride as a truly recyclable catalyst. This efficient and simple technique avoids the use of solvent extraction and column chromatography. In addition, the catalyst can be easily and effectively recovered and reused several times without significant loss of its catalytic activity.

Key words pyrans, multicomponent reactions, graphitic carbon nitride, ferrite, catalyst support, green chemistry

Multicomponent reactions (MCRs), used for the construction of complex molecules by performing multiple steps in a single operation, have emerged as a group of useful strategies in organic synthesis, and are receiving considerable attention.¹ Ongoing development of novel synthetic methods and catalysts in MCR chemistry have opened up ways of rendering such transformations green.² Increasingly, severe economic and environmental constraints are forcing the synthetic community to develop novel procedures and synthetic concepts to optimize the efficiency of known MCRs. Indeed, the green performance of multicomponent chemistry involving a combination of MCRs and recoverable catalysts in green solvents justifies its central position in the toolbox of sustainable synthetic methodologies.³

Since the discovery of cromakalim (Figure 1) as a typical ATP-sensitive potassium-channel opener, used to treat hypertension by relaxing vascular smooth muscle, the syn-

thesis of benzopyrans and their derivatives has attracted much attention.⁴ Polyfunctional 4*H*-pyrans demonstrate a broad spectrum of biological and pharmaceutical properties, such as antiagenesis, antiallergy, and antitumor activities.⁵ In addition, amino- and cyano-functionalized 4*H*pyrans have been used as synthetic intermediates in organic synthesis.⁶ Because of the broad spectrum of biological activities of benzopyrans, many methods for the synthesis of benzopyran derivatives, including two-step and one-pot three-component reactions have been reported.⁷ However, most of these give moderate yields, even after prolonged reaction times, and they require subsequent workup and product purification. Consequently, there is still scope to develop a method involving exclusively green solvents and a recoverable catalyst.



Figure 1 Selected bioactive compounds containing a 4H-pyran core



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In a continuation of our interest in green chemistry-oriented organic synthesis in novel solvents,⁸ we describe a simple method for the construction of structurally diverse fused pyran derivatives under extremely mild conditions.

Carbon-based nanomaterials possess unique physical, chemical, and mechanical properties, and extensive research efforts are being made to utilize these materials for a wide variety of applications as catalysts, optoelectronic materials, and electrodes in fuel cells, as well as in the biomedical field.⁹ Among such carbon materials, graphitic carbon nitride (g-C₃N₄) exhibits distinctly different properties, such as excellent thermal conductivity, high electrical mobility, and great mechanical strength.¹⁰ Furthermore, g-C₃N₄ can be easily synthesized by a hydrothermal method, without any organic solvents, from melamine or urea derivatives, and it is insoluble in most solvents.¹¹ Because of these characteristics, g-C₃N₄ has attracted attention, as it provides potential means for clean energy production and environmental remediation.¹² However, g-C₃N₄ has been relatively less explored as a catalyst in organic synthesis.

Here, we report a simple and efficient three-component reaction of a 1,3-dicarbonyl compound, an aldehyde, and malononitrile to give a highly functionalized benzopyran or pyran derivative with magnetic nanoparticle-supported $g-C_3N_4$ (Fe₃O₄@g-C₃N₄) as a catalyst under mild conditions. In addition to being an excellent nanocomposite in permitting the magnetic separation of the catalyst, Fe₃O₄@g-C₃N₄ also provides the basic environment required to accomplish the reaction without the need for an external base.

Fe₃O₄@g-C₃N₄ composites were synthesized by a calcination method. The g-C₃N₄ was synthesized by calcination of melamine at 500 °C for five hours, as reported in the literature,^{10a} and then dispersed in aqueous ethanol (50%) under sonication. An aqueous solution of iron salts was added to the dispersion of g-C₃N₄ in the presence of ammonia, and the mixture was stirred for 30 minutes at 80 °C under N₂. The product was then separated magnetically, washed with water and ethanol, and dried under vacuum at 60 °C to afford Fe₃O₄@g-C₃N₄, as a dark-brown solid (Scheme 1).

The catalytic activity of Fe₃O₄@g-C₃N₄ was evaluated in a one-pot synthesis of the 4*H*-chromene **4a** through the condensation of benzaldehyde (**1**; 1 mmol), malononitrile (**2**; 1 mmol) and dimedone (**3**; 1 mmol) as model substrates in a series of experiments designed to optimize the reaction conditions (Table 1). To our satisfaction, the reaction proceeded smoothly in ethanol at ambient temperature within two hours in the presence of Fe₃O₄@g-C₃N₄ (20 mg). Simple separation of the catalyst with an external magnet, followed by crystallization of the product from ethanol gave the desired 4*H*-chromene **4a** in 72% isolated yield. (Table 1, entry 1). To determine the optimum temperature, the reaction was carried out at 40, 60, and 80 °C, which afforded 80, 97, and 97% yields of **4a**, respectively (entries 2–4). Raising

 Table 1
 Optimization of the Reaction Conditions for the Synthesis of benzopyran 4a



Entry	Solvent	Temp (°C)	Yieldª (%)	
1	EtOH	25	72	
2	EtOH	40	80	
3	EtOH	60	97	
4	EtOH	80	97	
5	H ₂ O	60	80	
6	PEG	60	78	
7	DMF	60	72	
8	MeCN	60	60	
9	EtOAc	60	65	
10	toluene	60	50	
11	no solvent	60	76	
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the temperature not only affected the yield of the product, but also reduced the reaction time to one hour. Little change in the yield or reaction time was observed when the loading of $Fe_3O_4@g-C_3N_4$, was lowered to 10 mg or increased to 40 mg. Various solvents such as DMF, PEG, EtOAc, MeCN, toluene, and H_2O or neat conditions were tested in the presence of $Fe_3O_4@g-C_3N_4$, but all resulted in lower yields than that obtained in ethanol (entries 5–11).

With the optimal conditions established, we proceeded to examine the scope of this transformation with various aromatic aldehydes, 1,3-dicarbonyl compounds, and malononitrile for the construction of a range of pyran derivatives (Table 2). In general, the reaction proceeded smoothly under mild conditions to afford the desired products in good to excellent yields. For the reaction of malononitrile and dimedone with aromatic aldehydes bearing electron-withdrawing or electron-donating groups on the aromatic ring, a wide range of substituted benzopyrans were obtained in high yields within a short reaction time. Functionalities on the aromatic ring such as Cl, Br, F, NO₂, OH, and OMe were compatible with the reaction conditions. The aliphatic aldehyde octanal was also a good substrate for the reaction, and gave the corresponding product **4k** in 71% yield. More importantly, a series of 4*H*-pyran derivatives were readily obtained when the conditions were extended to threecomponent domino reactions of aromatic aldehydes, malononitrile, and 1,3-dicarbonyl compounds such as acetylacetone, ethyl acetoacetate, or methyl acetoacetate. The results summarized in Table 2 show that all reactions proceeded well to afford the corresponding pyran derivatives in good to excellent yields.

Table 2 Fe₃O₄@g-C₃N₄-Catalyzed Synthesis of 4H-Pyran Derivatives



Entry	R	1,3-Dione	Product	Yieldª (%)	Physical state	Ref.
1	Ph	dimedone	4a	97	colorless crystals	7i
2	4-CIC ₆ H ₄	dimedone	4b	95	colorless crystals	7c
3	3-O ₂ NC ₆ H ₄	dimedone	4c	92	yellow powder	7a
4	$3-BrC_6H_4$	dimedone	4d	95	colorless crystals	7m
5	Tol	dimedone	4e	97	colorless crystals	7d
6	4-HOC ₆ H ₄	dimedone	4f	78	colorless crystals	7a
7	$4-BrC_6H_4$	dimedone	4g	90	colorless crystals	7a
8	4-MeOC ₆ H ₄	dimedone	4h	82	colorless crystals	7d
9	$4-FC_6H_4$	dimedone	4i	84	white powder	7h
10	4-MeO ₂ CC ₆ H ₄	dimedone	4j	86	white powder	7i
11	Me(CH ₂) ₇	dimedone	4k	72	white powder	7i
12	2-thienyl	dimedone	41	80	yellow powder	7n
13	2-furyl	dimedone	4m	81	yellow powder	7n
14	4-pyridyl	dimedone	4n	85	yellow powder	7n
15	Tol	ethyl acetoacetate	40	82	white powder	7b
16	Ph	ethyl acetoacetate	4р	80	colorless crystals	7b
17	4-MeOC ₆ H ₄	ethyl acetoacetate	4q	78	white powder	7с
18	Ph	methyl acetoacetate	4r	84	colorless crystals	7j
19	$4-BrC_6H_4$	methyl acetoacetate	4s	80	colorless crystals	7b
20	Ph	acetylacetone	4t	82	white powder	70
21	Tol	acetylacetone	4u	78	white powder	70

^a Isolated yield.

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The recovery and reuse of the magnetic catalyst were studied for the preparation of **4a** as a model (Figure 2). Because of the low solubility of $Fe_3O_4@g-C_3N_4$ in organic solvents, its stable nanostructure, and good magnetization, it is easily separated by an external magnet. After the initial reaction was complete, ethanol was added and the catalyst was separated and reused directly in a subsequent reaction without any pretreatment such as drying or washing. As shown in Figure 2, the catalyst could be recycled at least ten times without any marked decrease in the yield, which ranged from 97% to 92%.



In summary, by using $Fe_3O_4@g-C_3N_4$ as a recyclable catalyst, we have developed a mild and green one-pot synthesis of 4*H*-pyran derivatives in good to excellent yields (72– 97%) within a short reaction time (30–190 min), and the products can be purified by simple crystallization. The magnetically recoverable and inexpensive catalyst and simple experimental procedure with no column purification or hazardous organic solvent are advantages of this process.^{13,14}

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(13) **4H-Pyrans; General Procedure**

A mixture of the appropriate aldehyde **1** (1.0 mmol), malononitrile (**2**; 1.0 mmol), 1,3-dicarbonyl compound **3** (1.0 mmol), and Fe₃O₄@g-C₃N₄ (20 mg) in EtOH (1 mL) was stirred at 60 °C for 60 min until the reaction was complete (TLC). EtOH (10 mL) was added, and the Fe₃O₄@g-C₃N₄ was separated with an external magnet. The crude product was then crystallized from EtOH. **2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-**

4H-chromene-3-carbonitrile (4a)

Colorless crystals; yield: 143 mg (97%); mp 228–230 °C. ¹H NMR (CDCl₃, 500 MHz): δ = 7.38–7.00 (m, 7 H, PhH and NH₂), 4.30 (s, 1 H), 5.23 (s, 2 H), 2.39 (m, 2 H), 2.13–2.15 (m, 2 H), 1.03 (s, 3 H),

0.98~(s, 3~H). ^{13}C NMR (CDCl_3, 125 MHz): δ = 196.8, 162.8, 157.9, 144.3, 129.5, 128.8, 127.9, 118.8, 114.7, 61.9, 51.6, 35.9, 33.0, 29.6, 28.1.

(14) Preparation of the magnetic $g-C_3N_4$ catalyst

A $g-C_3N_4$ nanosheet was prepared by directly calcining melamine in air. An alumina crucible with a loose cover containing melamine (2.0 g) was placed in a muffle furnace, and the temperature was programmed to 550 °C for 5 h at an initial ramp rate of 5 °C/min. After heat treatment, bulk $g-C_3N_4$ was obtained as a pale-yellow powder (see Ref. 10a). This bulk $g-C_3N_4$ (1.0 g) was added to a second alumina crucible, which was

heated at 550 °C for 2 h, with initial heating at a rate of 10 °C/min, to obtain white g-C₃N₄ nanosheets. In the final step, Fe₃O₄@g-C₃N₄ was prepared by the reported method (Ref. 10). The g-C₃N₄ (500 mg) was dispersed in 1:1 EtOH-H₂O by sonication at r.t. FeCl₃·6H₂O (1.838 g, 0.0216 mol) and FeCl₂·4H₂O (0.703 g, 0.0108 mol) were dissolved in the dispersion by sonication for 30 min, and then 28% aq NH₃ (10 mL) was rapidly added to the stirred solution. The mixture was stirred under N₂ for 30 min at 80 °C, then cooled to r.t. The solid was separated magnetically, washed with H₂O and EtOH, and dried overnight at 60 °C under vacuum.