

Article

Creatine-Functionalized Graphene Oxide Membrane Reactor for Efficient Synthesis of 2-Amino-4H-Chromene Derivatives

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Abstract

Derivatives of 2-amino-4H-chromene possess diverse pharmacological activities. However, traditional multicomponent synthesis suffers from toxic solvents, long reaction times, and difficulties in balancing catalytic activity and selectivity, which violates green chemistry requirements. Inspired by the nanoconfinement effect in enzymatic catalysis, this work uses graphene oxide (GO) as a two-dimensional scaffold to graft creatine (CR) and construct bifunctional catalytic sites. Thermal regulation of GO interlayer spacing yields an interlayer-confined flow membrane reactor for the three-component condensation of benzaldehyde, malononitrile and dimedone. A near-quantitative conversion of $99.0 \pm 1.7\%$ (mean $\pm$ SD, $n = 3$) was achieved within 18 s at room temperature. This nanoconfined membrane catalyst overcomes the defects of classic catalytic systems and provides a novel, practical route for continuous, green and high-yield synthesis of 2-amino-4H-chromene derivatives.

Keywords: creatine-functionalized graphene oxide (GO-CR) membrane reactor; 2-amino-4H-chromene derivatives; multicomponent reactions

1. Introduction

2-Amino-4H-chromene derivatives constitute a significant class of heterocyclic compounds that are extensively found in natural products and bioactive pharmaceutical agents. Pharmacological studies have demonstrated their diverse biological activities, including antibacterial [1], antiviral [2], anti-inflammatory [3], and antitumor [4] activities. Consequently, the development of efficient and environmentally friendly synthetic methodologies for constructing this core scaffold holds considerable importance in both medicinal chemistry and green synthesis. Multicomponent reactions (MCRs) have been widely recognized as an effective approach to this end, due to their high atom economy, operational simplicity, and ability to assemble complex molecular architectures in a single step [5]. In particular, the three-component reaction involving benzaldehyde, malononitrile, and dimedone has emerged as the predominant synthetic route for 2-amino-4H-chromene derivatives, benefiting from cheap starting materials, simple operation and convenient post-modification of products [6].

Traditional homogeneous and heterogeneous catalysts restrict the practical application of such MCRs, including complex reaction paths, undesired byproduct generation, and difficulty balancing catalytic activity and selectivity [7,8]. Although a variety of catalysts have been developed—such as GO-based functional materials [9,10], magnetic nanocomposites [11,12], and ionic liquids [13]—these approaches often depend on the use of toxic



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or costly organic solvents, suffer from prolonged reaction times, low product yields, and cumbersome post-treatment processes. These limitations not only impede the improvement of synthetic efficiency but also conflict with the fundamental principles of green chemistry [14]. Therefore, it is urgent to develop a novel green synthetic strategy to achieve efficient catalysis under mild conditions without hazardous solvents.

To address this unmet need, recent research has drawn inspiration from the confinement effect of natural enzymatic catalysis, focusing on reaction modulation within nanoscale confined spaces [15]. Spatial confinement can raise local reactant concentration, stabilize labile intermediates and reduce activation energy, thus inhibiting side reactions. This strategy simultaneously accelerates reaction kinetics and improves selectivity under mild conditions, offering a new avenue for constructing high-performance green MCR catalysts [16–21].

Inspired by this nanoconfinement strategy, GO was chosen as the two-dimensional confinement scaffold in this study. Its abundant surface functional groups and tunable interlayer spacing provide an ideal platform for engineering nanoconfined catalytic environments [22,23]. CR served as the catalytic moiety, with coexisting carboxyl and guanidyl groups enabling synergistic reactant activation. By grafting CR molecules onto the GO sheets and precisely regulating the interlayer dimensions via thermal treatment, an interlayer-confined flow membrane reactor was successfully fabricated. The membrane reactor was employed for the target three-component condensation, affording a near-quantitative conversion of $99.0 \pm 1.7\%$ (mean $\pm$ SD, $n = 3$) within 18 s at room temperature. Distinct from previously reported catalysts, the layered confined structure integrates substrate enrichment, intermediate stabilization and dual-site synergistic catalysis into one system. This work demonstrates excellent catalytic activity and promising potential for green synthesis, presenting an innovative strategy for eco-friendly, continuous, and highly efficient synthesis of 2-amino-4H-chromene derivatives.

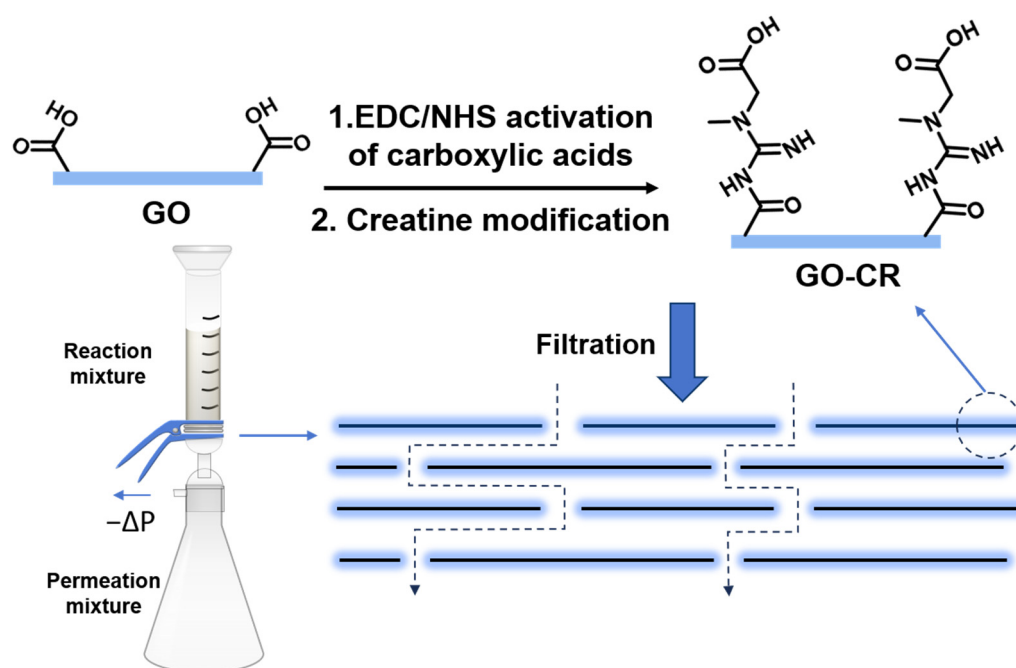
2. Materials and Methods

2.1. General

All chemicals were used as received without further purification. Single-layer graphene oxide (GO, lateral size > 500 nm) was purchased from XFNANO Materials Tech Co., Ltd., Nanjing, Jiangsu, China. Creatine (CR, 99%), benzaldehyde (99%) and 4-nitrobenzaldehyde (98%) were obtained from Sigma-Aldrich Trading Co., Ltd., Shanghai, China. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 98%) was supplied by TCI Shanghai Chemical Industry Development Co., Ltd., Shanghai, China. N-Hydroxysuccinimide (NHS, 98%) was purchased from Shanghai Aladdin Biochemical Technology Co., Ltd., Shanghai, China. Sodium hydroxide standard solution (0.05 mol/L) and hydrochloric acid standard solution (0.05 mol/L) were obtained from Hunan BKMAM Holding Co., Ltd., Changde, Hunan, China. 4-Methylbenzaldehyde (98%), 4-chlorobenzaldehyde (98%), malononitrile (99%) and dimedone (99%) were obtained from Beijing InnoChem Science & Technology Co., Ltd., Beijing, China.

2.2. Synthesis of GO-CR Nanosheets

The synthesis was carried out via a carbodiimide-mediated coupling reaction (Scheme 1). In this protocol, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and N-hydroxysuccinimide (NHS) were employed as carboxyl-activating agents to enable stable covalent grafting between the carboxyl groups of GO and the amino groups of CR.



Scheme 1. Scheme diagram of GO-CR Synthesis and Membrane Fabrication.

First, 50 mg of GO powder was dispersed in 25 mL of deionized water using a bath sonicator for 30 min. Subsequently, 400 μL (2.26 mmol) of EDC and 310 mg (2.7 mmol) of NHS were added to the GO suspension. The mixture was stirred at 400 rpm at room temperature for 1.5 h.

After activation, 289.3 mg of CR powder was divided into several portions and gradually added to the above activated GO mixture. The reaction was allowed to proceed under continuous stirring (400 rpm) at room temperature for 12 h.

The resulting mixture was transferred to a dialysis bag (MWCO: 8000 Da) and dialyzed against deionized water for 3 days, with the water being replaced every 6 h. After purification, the GO-CR dispersion was sonicated to ensure uniformity. This procedure yielded an aqueous stock dispersion with a concentration of approximately 0.75 mg mL^{-1} (based on the initial mass of GO). A portion of the dispersion was dried to obtain GO-CR powder, which was stored in a sealed vial for subsequent use in bulk reaction comparisons.

2.3. Preparation of GO-CR Membranes

The GO-CR membranes were fabricated via a vacuum-assisted filtration method. Specifically, an aqueous GO-CR dispersion was diluted with deionized water to a target concentration and subjected to ultrasonication to achieve a homogenized suspension. The resulting dispersion was then vacuum-filtered through a nylon membrane support (diameter: 47 mm, pore size: $0.22 \mu\text{m}$). The obtained wet film was air-dried at room temperature for 12 h, denoted as GO-CR-RT (diameter: $\sim 40 \text{ mm}$). The thickness of the membrane was precisely controlled by varying the volume of the filtered dispersion. In this study, two distinct membrane thicknesses were fabricated by adjusting the quantity of the GO-CR dispersion used, designated as 6-GO-CR-RT and 8-GO-CR-RT, respectively.

To investigate the effect of confinement size, the as-prepared GO-CR membranes were subjected to a thermal annealing process in an oven at 100°C for 12 h. The resulting thermally annealed membranes are correspondingly denoted as 6-GO-CR-100 and 8-GO-CR-100. Both types of membranes were subsequently used in the following reaction experiments.

2.4. GO-CR Powder for Conventional Bulk Reactions

GO-CR powder (4 mg; this amount exceeds that used in the corresponding membrane reaction) was added to a 20 mL glass vial containing a solution of malononitrile (0.13 mmol), dimedone (0.13 mmol), and benzaldehyde (0.13 mmol) in ethanol (2 mL). The mixture was stirred at room temperature for the prescribed time. After the reaction, the catalyst was separated by filtration. The filtrate was concentrated under reduced pressure, and the crude product was dissolved in DMSO- d_6 for proton nuclear magnetic resonance (^1H NMR) analysis for conversion determination. Reactions performed with different solvents or catalysts followed an analogous procedure.

2.5. GO-CR Membranes for Confinement Reactions

Prior to use, the membrane surface was purged with N_2 to remove any loosely adhered particulate contaminants. The GO-CR membrane (40 mm in diameter) was cut to an appropriate size and securely mounted in a microfiltration cell. The cell defined a central reaction zone with an inner diameter of 15 mm, corresponding to approximately one-eighth of the total membrane mass, and was sealed to form a filtration unit at room temperature. An ethanol solution containing malononitrile (0.13 mmol), dimedone (0.13 mmol), and benzaldehyde (0.13 mmol) was introduced into the upper measuring cylinder, which was then covered with aluminum foil. The reaction solution was driven through the two-dimensional nanochannels of the membrane under a constant pressure difference of 0.09 MPa (0.9 atm), enabling the reaction to proceed within the confined interlayer galleries. After the mixture had completely permeated the membrane, the cell was rinsed with fresh ethanol to recover any retained product. The combined permeate and rinse solution was collected, and ethanol was removed by rotary evaporation. The resulting residue was dissolved in DMSO- d_6 for ^1H NMR analysis to determine product composition and calculate conversion.

The ^1H NMR data of the product described in this study are consistent with the corresponding ^1H NMR spectrum previously reported in the literature [24] (Supporting Information, Figures S1–S11):

Dimedone: ^1H NMR (400 MHz, DMSO- d_6) δ 10.95 (s, 1H), 5.19 (s, 1H), 2.12 (s, 5H), 0.99 (s, 6H).

Benzaldehyde: ^1H NMR (400 MHz, DMSO- d_6) δ 10.01 (s, 1H), 7.98–7.87 (m, 2H), 7.74–7.65 (m, 1H), 7.58 (t, J = 7.5 Hz, 2H).

Malononitrile: ^1H NMR (400 MHz, DMSO- d_6) δ 4.44 (s, 2H).

2-Amino-4-(phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile: ^1H NMR (400 MHz, DMSO- d_6) δ 7.28 (t, J = 7.4 Hz, 2H), 7.22–7.10 (m, 3H), 6.98 (s, 2H), 4.17 (s, 1H), 2.52 (s, 2H), 2.25 (d, J = 16.1 Hz, 1H), 2.10 (d, J = 16.1 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 195.68, 162.51, 158.52, 144.74, 128.34, 127.16, 126.58, 119.72, 112.77, 58.38, 50.00, 38.35, 35.60, 31.80, 28.40, 26.82.

2-Amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile: ^1H NMR (400 MHz, DMSO- d_6) δ 8.17 (d, J = 8.5 Hz, 2H), 7.48–7.40 (m, 2H), 7.16 (s, 2H), 4.37 (s, 1H), 2.54 (s, 2H), 2.26 (d, J = 16.1 Hz, 1H), 2.11 (d, J = 16.1 Hz, 1H), 1.04 (d, J = 2.3 Hz, 3H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 195.64, 163.06, 158.57, 152.25, 146.25, 128.59, 123.63, 119.27, 111.72, 56.99, 49.85, 35.64, 31.79, 28.23, 26.92.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile: ^1H NMR (400 MHz, DMSO- d_6) δ 7.37–7.31 (m, 2H), 7.20–7.13 (m, 2H), 7.04 (s, 2H), 4.19 (s, 1H), 2.47 (s, 2H), 2.24 (d, J = 16.1 Hz, 1H), 2.10 (d, J = 16.1 Hz, 1H), 1.03 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 195.61, 162.57, 158.49, 143.71, 131.09, 129.09, 128.25, 119.50, 112.33, 57.79, 49.93, 39.66, 35.10, 31.76, 28.28, 26.84.

2-Amino-4-(p-tolyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile: ^1H NMR (400 MHz, DMSO-d_6) δ 7.15–6.98 (m, 4H), 6.95 (s, 2H), 4.12 (s, 1H), 2.43–2.38 (m, 2H), 2.23 (d, $J = 8.7$ Hz, 4H), 2.09 (d, $J = 16.1$ Hz, 1H), 1.03 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.59, 162.26, 158.43, 141.80, 135.60, 128.86, 127.06, 119.72, 112.89, 58.49, 50.00, 39.68, 35.18, 31.76, 28.40, 26.76, 20.57.

2.6. Calculation of the Reaction Time of the Confinement Reactions

The reaction time under confinement was estimated based on the permeation retention time of the solution through the GO-CR membrane, calculated according to the method reported by Pang et al. [16].

The retention time t_R was obtained using the formula:

$$t_R = \frac{V_M}{k} = \frac{(A \times h)}{k} \quad (1)$$

where V_M is the geometric volume of the membrane; k is the slope of the reactant flow volume versus time; A is the channel cross-sectional area of microfiltration devices ($A = \pi/4 \times 15^2 = 176.7 \text{ mm}^2$); h is the thickness of the membrane, which was determined by SEM. t_R represents the time required for the reaction solution to fill the geometric volume of the GO-CR membrane. Because the GO-CR nanosheets occupy a portion of this volume, the effective volume accessible to the reaction solution is smaller than V_M , and the actual reaction time within the confined space is shorter than the calculated retention time t_R . Because the exact accessible interlayer volume is difficult to determine precisely, and the reaction ceases once the solution exits the membrane, t_R serves as a practical approximation of the confined reaction time for comparison with the bulk reaction time.

2.7. Calculation of Conversions from Crude-Sample ^1H NMR Spectra

Conversions were determined by relative quantitative ^1H -NMR analysis of crude reaction mixtures. Ethanol was removed from the reaction solution by rotary evaporation, and the residue was dissolved in DMSO-d_6 for NMR measurement. Benzaldehyde, malononitrile, dimedone, and the target product each exhibit characteristic diagnostic proton signals (Figure 1). For both bulk and confined reactions, conversions were calculated from the integral ratio of the proton signals of the product versus unreacted dimedone. The conversion of dimedone was used as the standard to evaluate and compare all reactions.

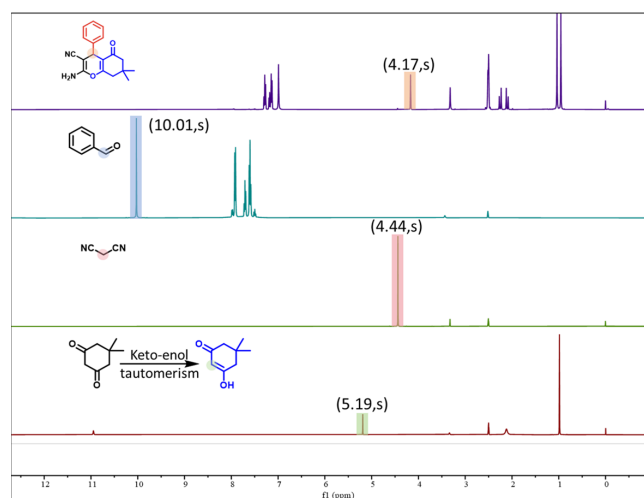


Figure 1. ^1H NMR spectra of the reactant and product, highlighting characteristic proton signals for structural verification.

2.8. Calculation of Turnover Number (TON) and Turnover Frequency (TOF)

The TON and TOF were calculated according to IUPAC definitions [25,26]. The number of active sites was determined based on the total basicity obtained from Boehm titration (Section 3.1.3), as the basic sites serve as the limiting component in the acid–base bifunctional catalysis (TB < TA).

For the bulk reaction:

$$TON = \frac{n_{product}}{n_{active\ site}} = \frac{n_{substrate} \times Conversion}{n_{active\ site}} \quad (2)$$

$$TOF = \frac{TON}{t} \quad (3)$$

where $n_{substrate}$ = 0.13 mmol. Conversion was determined by ^1H NMR spectroscopy, $n_{active\ site}$ = TB $\times$ catalyst mass, and t is the reaction time.

For the confined reaction, the retention time was calculated from the membrane volume and permeate flow rate (see Section 2.6), and the substrate amount within the membrane was calculated as $n = c \times V_{membrane}$, where c = 0.065 M. TON and TOF were obtained using the same equations as above.

3. Results

3.1. Characterization of GO-CR Membranes

X-ray photoelectron spectroscopy (XPS) measurements were performed on a Thermo ESCALAB 250Xi spectrometer equipped with a monochromatic Al K α radiation source under ultra-high vacuum. Data were processed with CasaXPS software. Fourier-transform infrared (FTIR) spectra were recorded on a Bruker INVENIO S spectrometer using the attenuated total reflection (ATR) mode. X-ray diffraction (XRD) was performed on a Bruker D8 Focus diffractometer using Cu K α radiation (λ = 1.5406 Å). Morphological analysis was conducted using a Hitachi S 4800 field emission scanning electron microscope (SEM). ^1H NMR spectra of all concentrated post-reaction samples were acquired on a Bruker Avance 400 MHz spectrometer using DMSO- d_6 as the solvent.

3.1.1. Spectral Analysis

XPS was employed to analyze the surface chemical compositions of pristine GO and GO-CR membranes. As illustrated in Figure 2, the atomic nitrogen content of the GO-CR membrane increased to 4.73% after CR modification, confirming the successful grafting of CR molecules onto GO. The high-resolution C 1s spectrum of pristine GO was deconvoluted into four characteristic peaks assigned to C–C (~284.8 eV), C–O (~286.7 eV), C=O (~287.6 eV), and O–C=O (~288.9 eV). After CR functionalization, the relative proportion of the C–C component rose from 39.8% to 42.7%. Furthermore, a new peak appeared at approximately 285.9 eV, which was attributed to C–N bonds with a relative area ratio of 4.5%. Concurrently, the relative intensity of the O–C=O component decreased significantly, demonstrating that surface carboxyl groups of GO were consumed during the amidation reaction. Additionally, the N 1s spectrum of GO-CR was deconvoluted into two peaks centered at 399.5 eV and 401.5 eV, assigned to guanidinium and amino nitrogen groups of CR (tertiary and primary amines, respectively). These findings are consistent with the molecular structure of CR [27], further verifying that CR molecules are covalently immobilized on the GO surface with intact chemical skeletons.

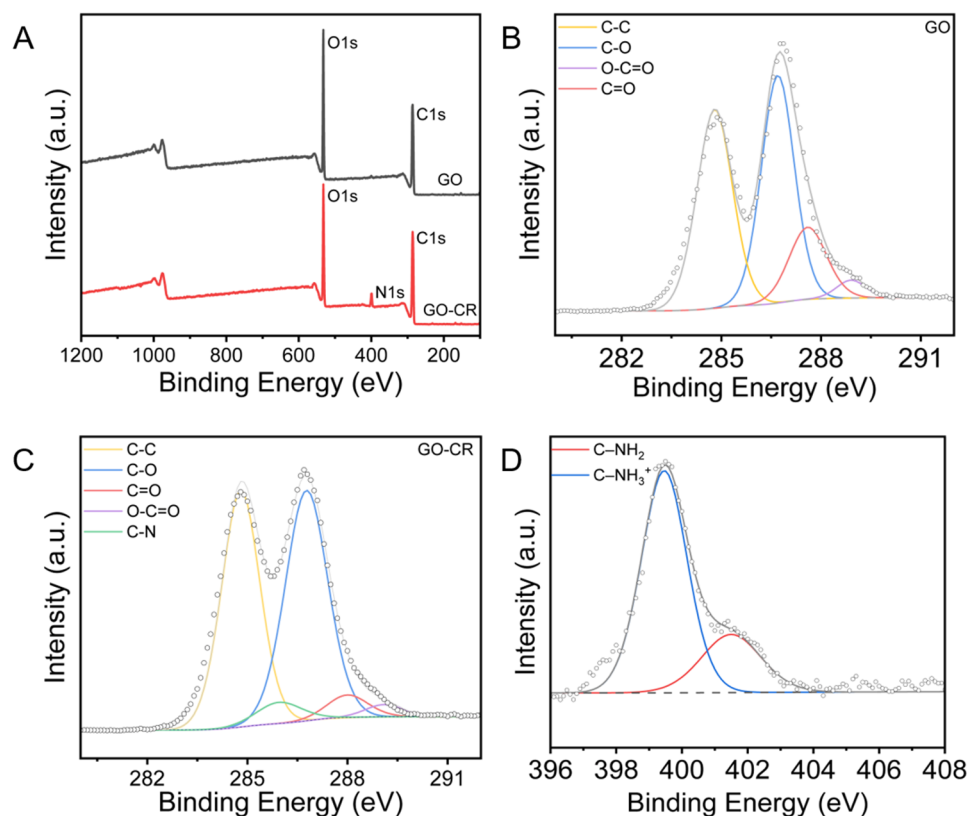


Figure 2. (A) XPS full spectra of GO (black line) and GO-CR (red line). High-resolution C 1s XPS spectra of (B) GO membrane and (C) GO-CR membrane. (D) High-resolution N 1s XPS spectrum of the GO-CR membrane.

The FTIR spectral analysis is presented in Figure 3. The pristine GO displays a prominent absorption peak at 1726 cm^{-1} , which is attributed to the stretching vibration of the carbonyl (C=O) group within the carboxyl (-COOH) functionalities [28]. Following modification with CR, a marked reduction in the intensity of this peak is observed, suggesting substantial consumption of the carboxyl groups on the GO surface via an amidation reaction with the amino groups of CR. Concurrently, the GO-CR composite film exhibits two novel characteristic absorption bands at 1630 cm^{-1} and 1537 cm^{-1} , corresponding respectively to the amide I band (C=O stretching vibration) and the amide II band (coupled N-H bending and C-N stretching vibrations) [29]. These spectral features serve as definitive evidence of amide bond formation, thereby confirming the covalent grafting of CR onto GO through amide linkages.

XRD patterns were used to determine the interlayer spacing (d-spacing) of the prepared membranes. The dry pristine GO membrane exhibited a d-spacing of 0.88 nm (Figure 4A). After CR modification, the d-spacing of the dry GO-CR-RT membrane increased to 1.17 nm (Figure 4A), and solvent swelling under wet conditions further expanded to 1.28 nm (Figure 4B). In contrast, for the GO-CR-100 membrane prepared by thermal treatment at $100\text{ }^{\circ}\text{C}$, the d-spacing of the dry state decreased to 1.13 nm (Figure 4A), while the wet state reached 1.22 nm due to the solvent swelling effect (Figure 4B). The effective interlayer catalytic space was calculated by subtracting the thickness of a single graphene layer (0.34 nm) from the measured d-spacing [30].

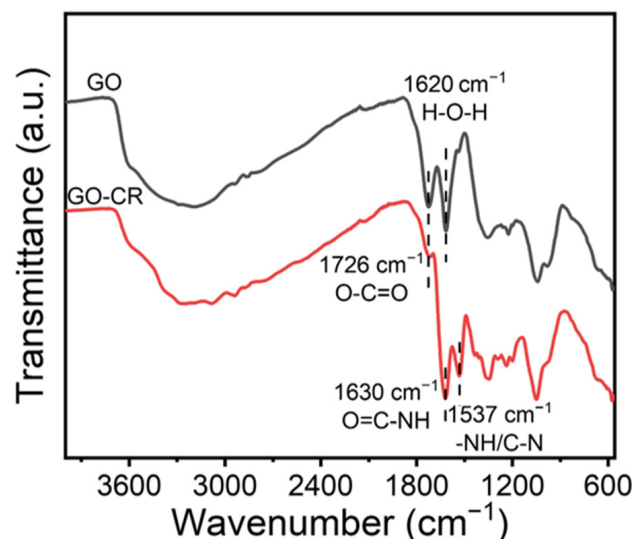


Figure 3. FTIR spectra of GO (black line) and GO-CR (red line).

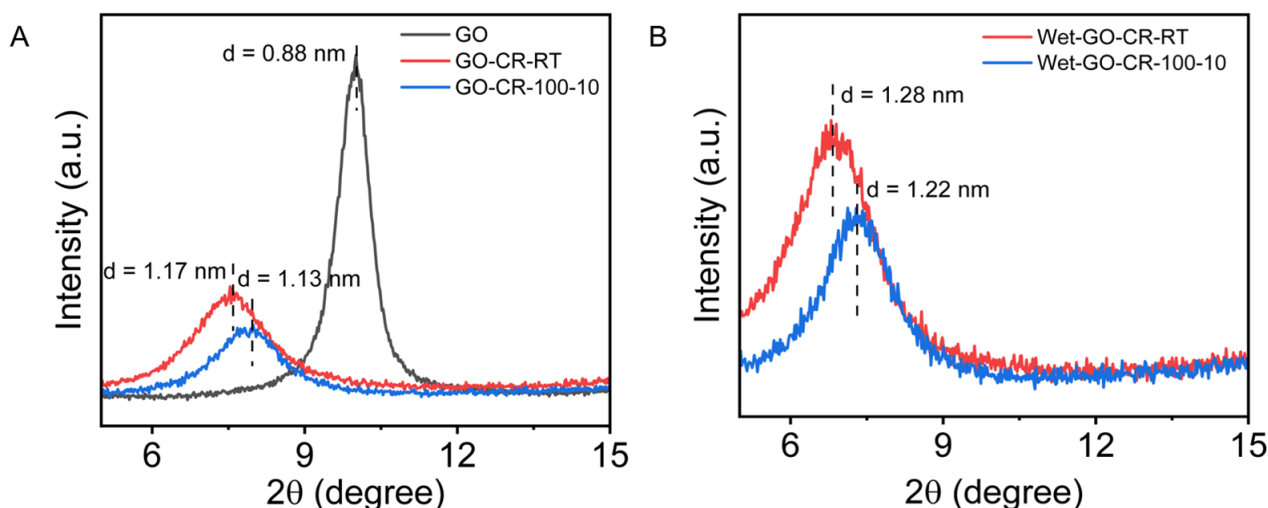


Figure 4. (A) XRD spectra of GO, GO-CR-RT and GO-CR-100 membranes. (B) XRD patterns measured for the GO-CR-RT and GO-CR-100 membranes in the wet state.

3.1.2. Morphological Characteristics of GO-CR Membranes

The cross-sectional observations obtained via SEM are presented in Figure 5. Following functionalization with CR, the GO-CR film preserves its intact two-dimensional layered morphology, suggesting that the amide grafting reaction does not compromise the fundamental microstructure. Notable variations in the thickness of GO-CR films were observed under different preparation conditions: the 6-GO-CR-RT and 8-GO-CR-RT films, dried at ambient temperature, exhibited thicknesses of 2.3 μm and 3.2 μm , respectively; conversely, the 6-GO-CR-100 and 8-GO-CR-100 films, subjected to thermal treatment at 100 $^{\circ}\text{C}$, showed a slight reduction in thickness to 2.1 μm and 3.0 μm , respectively. This thermal treatment induced a more compact interlayer arrangement. The measured film thicknesses serve as critical parameters for determining the residence time of reactants in subsequent confined flow reactions.

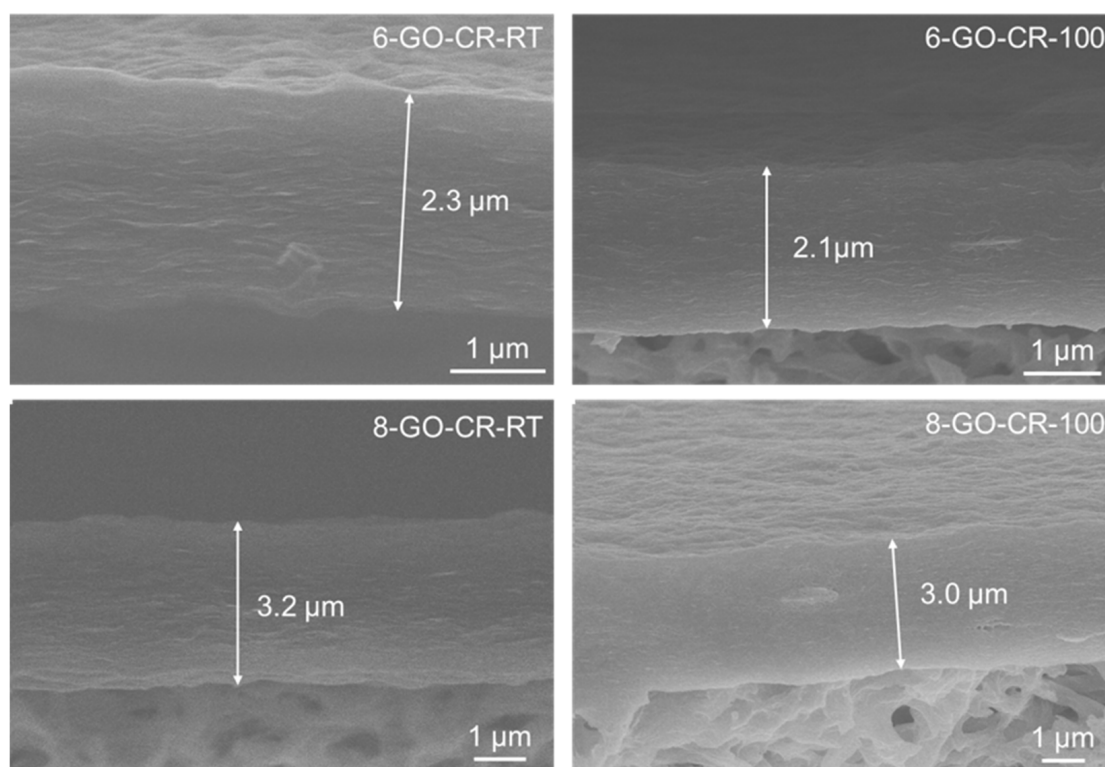


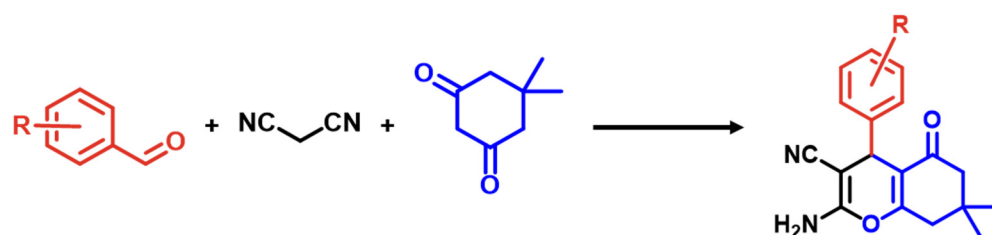
Figure 5. Cross-sectional SEM images of various GO-CR membranes, exhibiting a closely packed multilayer structure.

3.1.3. Surface Acidity and Basicity

The total acidity (TA) and total basicity (TB) of GO-CR were determined by the Boehm titration method [31]. For TA measurement, 100 mg of the sample was dispersed in 50 mL of 0.05 M NaOH solution and shaken at 25 °C for 48 h. After filtration, a 20 mL aliquot of the filtrate was treated with an excess of 0.05 M HCl and then back-titrated with 0.05 M NaOH. For TB measurement, 100 mg of the sample was dispersed in 50 mL of 0.05 M HCl solution and shaken at 25 °C for 48 h. After solid–liquid separation, a 20 mL aliquot of the filtrate was then mixed with an excess of 0.05 M NaOH, followed by back-titration with 0.05 M HCl. Parallel blank experiments were carried out under identical conditions without adding samples. The obtained TA and TB values of GO-CR were 4.01 mmol/g and 1.34 mmol/g, respectively.

3.2. Comparison of Confined Catalysis and Traditional Bulk Catalysis Effects

To evaluate catalyst performance and optimize reaction parameters, the three-component condensation of benzaldehyde, malononitrile, and dimedone was initially employed as a model reaction (Scheme 2). Under conventional bulk reaction conditions, the effects of catalyst type, solvent, and reaction time on the conversion of dimedone were systematically investigated, with the results summarized in Table 1. The data indicate that the GO-CR composite catalyst exhibits slightly higher activity than GO or CR alone under identical bulk conditions, achieving a maximum conversion of 87% in ethanol at room temperature within 24 h. Therefore, these conditions were established as the optimal parameters for the bulk reaction.



Scheme 2. Scheme diagram of the three-component reaction of benzaldehyde, malononitrile, and dimedone under the confined catalysis of GO-CR.

Table 1. Comparison of the synthetic conditions for the target 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile under various conditions via a three-component reaction of aldehydes, malononitrile, and dimedone in the bulk reaction.

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Conversion ¹ (%)
1	GO-CR	EtOH	r.t	24	87
2	GO-CR	MeCN	r.t	24	46
3	GO-CR	EA	r.t	24	20
4	GO-CR	EtOH	r.t	6	55
5	GO-CR	EtOH	r.t	12	76
6	GO	EtOH	r.t	24	Trace
7	CR	EtOH	r.t	24	85

¹ Reaction conditions: benzaldehyde (0.13 mmol), dimedone (0.13 mmol) and malononitrile (0.13 mmol), 4 mg Catalyst. The conversion of dimedone was confirmed by analyzing the ¹H NMR spectrum of the collected solution (Supporting Information, Figures S12–S18).

To optimize the conditions for confined-flow reactions, four types of GO-CR membranes (6-GO-CR-RT, 6-GO-CR-100, 8-GO-CR-RT, and 8-GO-CR-100) were fabricated by adjusting the amount of GO-CR dispersion and the drying method. Driven by a pressure difference, the reaction mixture permeates through the membrane and reacts within two-dimensional nanochannels. As shown in Figure 6A, the conversion of dimedone increased with extended residence time of the reactants within the membrane. When the residence time was less than 10 s, the conversion rate remained low, likely due to premature elution of reactants from the confined channels by solvent flow before the reaction could complete. When the residence time reached approximately 18 s, the conversion reached near-quantitative levels ($99.0 \pm 1.7\%$, mean $\pm$ SD, $n = 3$), attributed to sufficient contact time between the reactants and the catalytic sites within the channels. Based on these results, the optimal confined reaction conditions were determined to be ethanol as the solvent and the 8-GO-CR-100 membrane as the confined reactor. Under the optimized conditions described above, the volume of permeate shows a good linear relationship with time (Figure 6B), indicating that the reaction mixture can permeate steadily through the membrane.

To quantitatively compare the catalytic efficiency, TON and TOF were calculated based on the total basic sites (TB = $1.34 \mu\text{mol}/\text{mg}$) determined by Boehm titration. Since $\text{TB} < \text{TA}$, the basic sites serve as the limiting component in the acid–base bifunctional catalysis and were used as the basis for active site counting. For the bulk reaction ($n_{\text{active site}} = 5.36 \mu\text{mol}$), a TON of 21.1 and a TOF of 0.88 h^{-1} were obtained. For the confined reaction ($n_{\text{active site}} = 1.51 \mu\text{mol}$), the TON and TOF were determined to be 0.023 and 4.52 h^{-1} , respectively. Notably, the confined-flow membrane reactor exhibited a TOF approximately 5.1-fold higher than that of the bulk reaction, demonstrating the significantly enhanced catalytic efficiency under nanoconfinement. The key catalytic data are summarized in Table 2, with detailed calculation parameters provided in Table S2 in the Supporting Information.

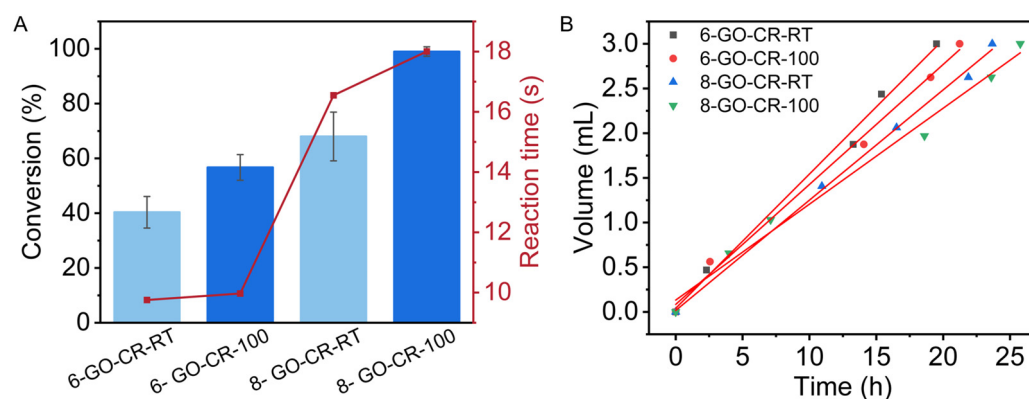


Figure 6. (A) Comparison of conversion–time profiles for the model three-component reaction catalyzed by different GO-CR confinement membranes. The corresponding raw experimental data are provided in the Supporting Information (Figures S19–S22, Table S1). (B) Flow curves of the reaction solution containing malononitrile, dimedone and benzaldehyde in ethanol.

Table 2. TON and TOF for Bulk and Confined reactions.

Reaction Mode	Catalyst (mg)/ $n_{\text{active site}}$ (μmol)	Time (h)	Conversion (%)	TON	TOF (h^{-1})
Bulk reaction	4/5.36	24	87	21.10	0.88
Confined reaction	1.125/1.51	0.005	99	0.023	4.52

Compared with previously reported conventional bulk reactions and the bulk reaction optimized in this study [9,11,32–34], the GO-CR membrane-confined reactor significantly reduced the reaction time under mild conditions while achieving excellent conversion (Figure 7). To further expand the substrate scope, malononitrile and dimedone were reacted with various substituted aromatic aldehydes. The results showed that the confined-flow reaction achieved conversions comparable to those of the corresponding bulk reactions within a significantly shorter time (Table 3). Furthermore, the permeation volume maintained a good linear relationship with time throughout the reactions of each substrate (Figure 8), further confirming the stability of this confined-flow system.

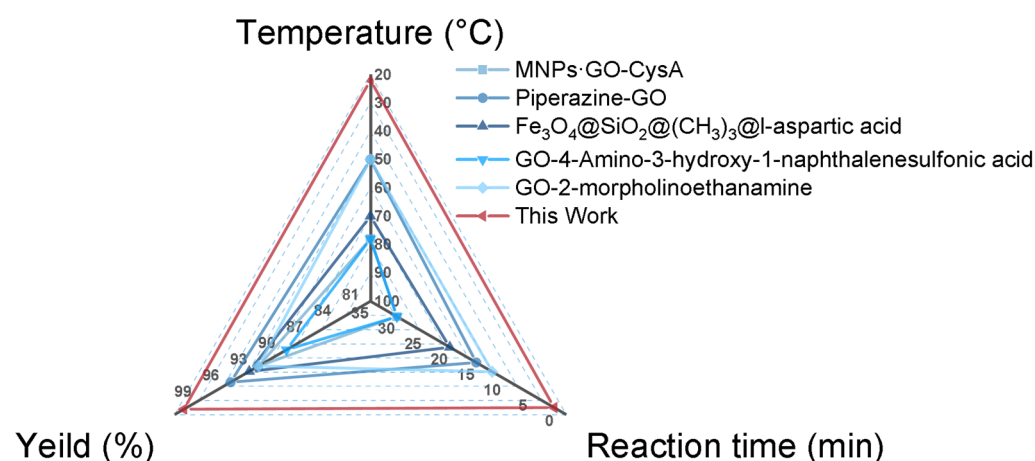
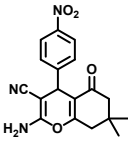
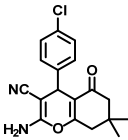
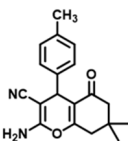
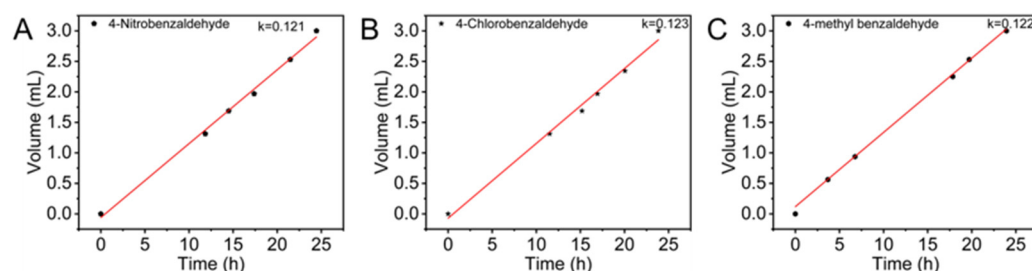


Figure 7. A comparison of the catalytic performance (temperature, time and conversion) of the 8-GO-CR-100 membrane with that of other reported catalytic systems.

Table 3. Comparison of confined and bulk reactions of malononitrile, dimedone and various substituted aromatic aldehydes.

Entry	Product	Bulk Reaction 24 h Conversion ¹ (%)	Confined Reaction 16 s Conversion ² (%)
1		89	95
2		83	80
3		80	73

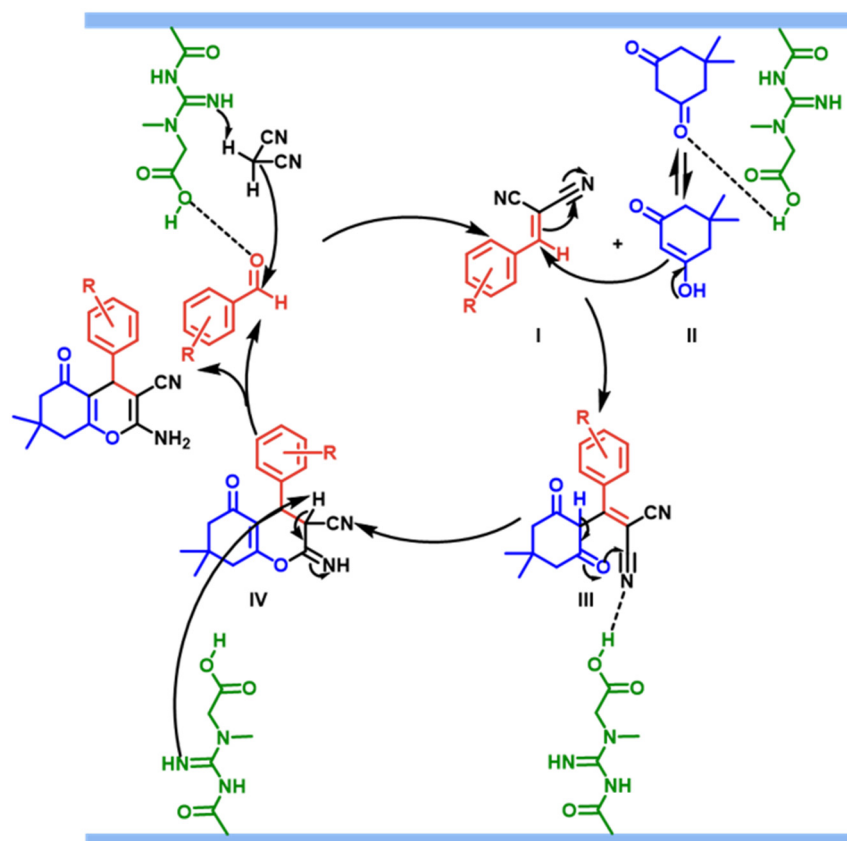
¹ Reaction conditions: aromatic aldehydes (0.13 mmol), dimedone (0.13 mmol) and malononitrile (0.13 mmol), 4 mg Catalyst. ² Reaction conditions: aromatic aldehydes (0.13 mmol), dimedone (0.13 mmol) and malononitrile (0.13 mmol), 8-GO-CR-100 membrane. Related NMR images are available in the Supporting Information (Figures S23–S28).

**Figure 8.** Flow curves for the reactions of dimedone and malononitrile with (A) 4-nitrobenzaldehyde, (B) 4-chlorobenzaldehyde, or (C) 4-methoxybenzaldehyde in ethanol.

4. Discussion

Based on the characterization results and catalytic performance data obtained in this study, combined with the previous literature reports [35], a plausible mechanism for the synthesis of 2-amino-4H-chromene derivatives is proposed as follows (Scheme 3). On the GO-CR catalyst, experimentally quantified acidic carboxyl sites are proposed to protonate the carbonyl oxygen of aromatic aldehydes, increasing the electrophilicity of the carbonyl carbon. Concurrently, guanidyl groups (basic sites) deprotonate the α -hydrogen of malononitrile to generate carbanions. These two intermediates undergo Knoevenagel condensation followed by dehydration to form Intermediate I. Subsequently, acidic sites promote the enolization of dimedone to form Intermediate II, which then attacks the β -carbon of Intermediate I via Michael addition to yield Intermediate III. Through hydrogen-bonding interactions, acidic sites enhance the electrophilicity of the cyano carbon in Intermediate III and induce intramolecular cyclization, leading to the formation of Intermediate IV bearing a tetrahydropyran ring. Finally, base-assisted deprotonation, followed by elimination and dehydrogenative aromatization, affords the target product. The two-dimensional confinement effect of the GO-CR membrane not only enriches reactants within the nanochannels but also stabilizes the conformations of key intermediates. It should be noted that the proposed pathway represents a reasonable hypothesis consistent with our experimental observations and literature precedents, rather than a rigorously proven kinetic model.

Further in situ spectroscopic investigations are warranted in future work to directly verify the transient intermediate species and the detailed stepwise conversion processes.



Scheme 3. Scheme illustration of the proposed reaction mechanism.

5. Conclusions

In summary, this work develops a flow reaction strategy based on GO-CR nanomembranes for efficient, continuous synthesis of 2-amino-4H-chromene derivatives. The GO-CR membrane offers a confined two-dimensional nano-reaction space and cooperative acid–base bifunctional sites, which effectively catalyze the tandem reaction. In contrast to conventional bulk reactions, this flow synthesis system operates efficiently at room temperature. Preorganization and confinement effects within the nanochannels remarkably enhance the frequency of effective molecular collisions, shortening the reaction time to approximately 18 s and affording a near-quantitative conversion ($99.0 \pm 1.7\%$, mean $\pm$ SD, $n = 3$). Moreover, products are eluted with the solvent, simplifying subsequent separation processes. While the current device is demonstrated at a proof-of-concept scale, its throughput can be scaled up by enlarging the membrane module or operating in recirculation mode. This work provides an efficient approach for the green and rapid synthesis of 2-amino-4H-chromene derivatives, and highlights the considerable application potential of functionalized nanomembrane reactors in fine organic synthesis.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/appliedchem6030066/s1>, Figures provided in the supporting information correspond to the ^1H NMR spectra displayed in the main manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

GO	Graphene oxide
CR	Creatine
GO-CR	Creatine-functionalized graphene oxide
MCRs	Multicomponent reactions
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
NHS	N-Hydroxysuccinimide
TON	Turnover number
TOF	Turnover frequency
XPS	X-ray photoelectron spectroscopy
FTIR	Fourier transform infrared
XRD	X-ray diffraction
SEM	Scanning electron microscope
NMR	Nuclear magnetic resonance
TA	Total acidity
TB	Total basicity

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