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Multicomponent Cyanation of 2-Amino-3-cyano-4*H*-chromenes in Aqueous Media

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Chromenes represent a pivotal molecular structure found in a diverse range of biologically active compounds. Specifically, derivatives of 2-amino-3-cyano-4*H*-chromene have demonstrated pharmacological applications, displaying potential antioxidant and anticancer activities. This has heightened interest in the exploration of new and more efficient methods for their synthesis. In recent years, few examples have emerged, focusing on the organocatalytic and enantioselective synthesis of 2-amino-3-cyano-4*H*-chromene derivatives, although the overall number of works to date is limited. In this study, we present the results of the synthesis of 2-amino-4*H*-chromen-3,4-dicarbonitriles through a Michael addition of cyanide to 2-iminochromenes. To achieve this, we utilized a mild source of cyanide (acetone cyanohydrin), green solvents and catalytic conditions at room temperature, *via* a multicomponent approach. Furthermore, we initiated the enantioselective study of this process using chiral organocatalysts obtaining promising preliminary results.

Introduction

Chromenes constitute a privileged class of organic compounds for their significant presence in a wide array of biologically active substances.[1] These pharmacologically active compounds cover a broad spectrum of interesting biological properties, including antiproliferative, anticancer, antiviral, and antimicrobial effects, among others (Figure 1).[2–4] They are also utilized in the treatment of neurodegenerative diseases such as Alzheimer's and schizophrenia. Due to the high lipophilicity of chromenes, their derivatives can easily permeate the cell membrane, thereby enhancing their pharmacological activity.[5] Chromenes are also employed as food additives, cosmetic agents, and potential biodegradable agrochemicals, sparking the interest of numerous researchers over the last decade.[6,7]

Of particular interest within this category are the derivatives of 2-amino-3-cyano-4*H*-chromene (Figure 1, B and C), which have garnered attention in medicinal and pharmaceutical research due to its properties.[13] The exploration of efficient synthetic methods for the preparation of these compounds has become a main point, driven by the search for novel pharmacological agents. Advances in organocatalytic and enantioselective synthesis techniques have opened pathways to produce these derivatives as appealing candidates for drug discovery, particularly in diverse therapeutic areas like cancer treatment and neuroprotection. In this context, the synthesis of new 2-amino-3-cyano-4*H*-chromenes becomes pivotal, highlighting their role as key players in the pursuit of new and effective biologically active compounds.[14]

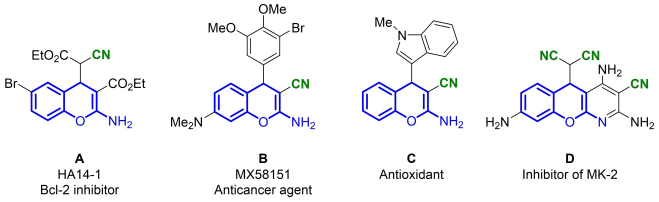

Figure 1. Interesting examples of 4*H*-chromenes with different biological properties: **A**,[8] **B**,[9,10] **C**,[11] and **D**.[12]

On the other hand, it is worth noting that, despite significant efforts made by the scientific community in the last three decades to develop efficient protocols for the enantioselective catalytic cyanation of diverse substrates,[15–17] this approach remains a highly active field with room for improvement. Enhancements could include increasing the process's intrinsic sustainability, improving atom economy, minimizing the toxicity of cyanation reagents, and using green solvents, among other aspects. The importance of these transformations lies in the versatility of the nitrile group[18] and its widespread presence in numerous compounds with biologically relevant properties.[19,20] In this regard, functionalizing with a CN group at C4 of 4*H*-chromenes could also be interesting in the pharmacological realm, although the literature on this is quite limited.[21] Therefore, in 2010, Bazgir and coworkers reported a conjugate addition of trimethylsilyl cyanide (TMSCN) to 2-iminochromenes, employing $LiClO_4$ (15 mol%) as a Lewis acid catalyst in ethanol (Scheme 1, a). This reaction yielded 2-amino-

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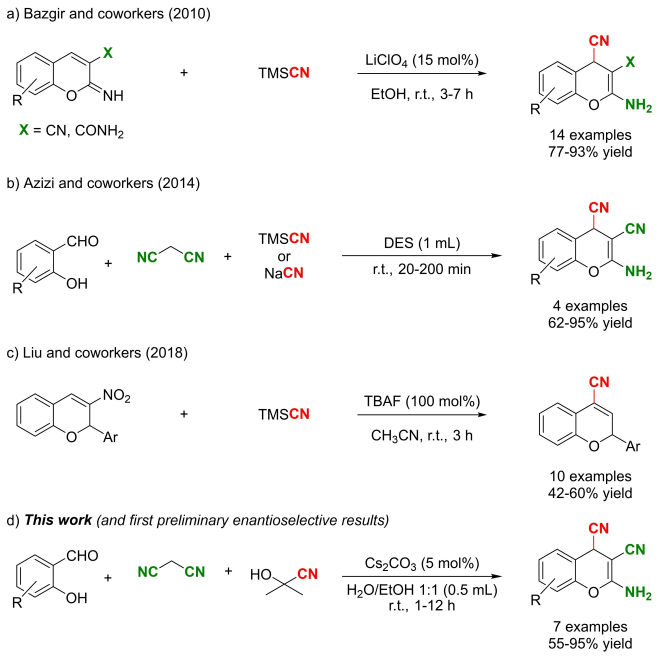


Scheme 1. Background and goal of the present study for the introduction of a CN group at the 4 position of chromenes.

4-cyano-4*H*-chromenes (X=CN) or 2-amino-4-amide-4*H*-chromenes (X=$CONH_2$) with good yields after 3–7 hours of reaction at room temperature.[21a] Azizi's group further developed the procedure using a deep eutectic solvent (DES) and presented only a few examples employing TMSCN and NaCN as cyanide sources, yielding very good results (Scheme 1, b).[21b] Additionally, Liu and coworkers described the use of TMSCN in acetonitrile with stoichiometric amount of tetrabutylammonium fluoride (TBAF) as a promoter, resulting in moderate yields (Scheme 1, c).[21c]

Therefore, the combination of chromene derivatives, cyanide chemistry, and green conditions presents a promising avenue of research that addresses intriguing challenges in organic chemical synthesis and may lead to noteworthy biological properties in the resulting products. Considering the background information and the growing interest in the development of new synthetic methodologies, we hereby report the successful synthesis of 2-amino-4*H*-chromen-3,4-dicarbonitriles (Scheme 1, d). This synthesis was achieved using a mild cyanide source (acetone cyanohydrin), environmentally friendly solvents, and a multicomponent reaction strategy under catalytic conditions at room temperature.

Results and Discussion

Cyanation of Chromenes in Aqueous Media using Acetone Cyanohydrin

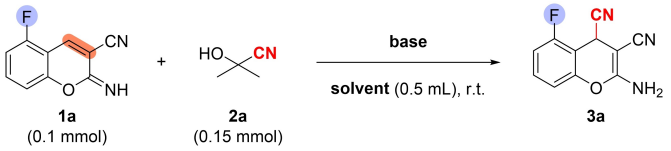
Based on our experience using cyanide species,[22] we envisioned that acetone cyanohydrin (**2a**) could represent an interesting and greener cyanide source for the cyanation of chromenes.[23] The advantages lie in its relative stability and ease of handling compared to other cyanide sources, rendering it a safer option for organic synthesis, since the utilization or generation of toxic HCN is minimized. As a milder alternative cyanide source, the use of cyanohydrin generates acetone as a byproduct. Therefore, focusing on this cyanide donor, we proceeded to study the influence of different parameters on the model reaction depicted in Table 1.

Firstly, several experiments starting with preformed 2-iminochromene **1a** were conducted using toluene as the solvent of the reaction (entries 1–5), to study the influence of different bases (both organic and inorganic), revealing that Cs_2CO_3 provided the highest yield of **3a** (94%, entry 2). In all cases, only a slight excess of cyanohydrin is used, and we did not consider increasing this amount to prevent waste generation. Interestingly, $LiClO_4$ did not catalyze the reaction with this source of cyanide, neither with toluene (entry 5) nor using ethanol, the same solvent previously used by Bazgir and coworkers (entry 6, Scheme 1, a).[21a] Next, maintaining a catalytic amount (20 mol%) of Cs_2CO_3, the effect of the solvent on the cyanation process was studied, using water (entry 7) or alternatives derived from renewable sources (entries 8–11). This interest in sustainable solvents is increasing both in the research community and the chemical industry due to growing awareness of the negative impact that many organic ones have on human health and the environment.[24] Among all these solvents, promising results were obtained using water as the reaction medium (entry 7). Although EtOH provided a fast process with only 15 minutes of reaction time, it did not result in better yields. This faster rate promoted the decomposition of the final product (entry 8). However, the use of other solvents derived from renewable sources led to poorer results (entries 9–11). In this regard, commonly used reaction media in organic synthesis such as MeOH or acetonitrile also yielded low values (entries 12 and 13) with dirtier reaction crudes more difficult to handle. When mixed water with EtOH (which provided a faster reaction) in a 1:1 ratio, a surprising synergistic effect was observed, achieving very good yields in a very short reaction time (entries 14–16). Moreover, we were able to decrease the amount of base to 5 mol%, also providing very good results (entry 16).

Therefore, it is concluded that the best reaction conditions to develop the study are 1.5 equivalents of cyanohydrin **2a** and 5 mol% of Cs_2CO_3 in H_2O/EtOH (1:1, 0.5 mL) at room temperature. Thus, once the optimal reaction conditions were obtained, the extension of this methodology using different substrates was carried out for other substrates (Figure 2).

There does not seem to be a direct correlation between the electronic characteristics of the final product and the yields obtained. Substitutions with F or Cl give very good results; in the former case, only 0.5 hours of reaction are needed to achieve a 94% yield (**3a**), while in the latest, 8 hours are required to reach a lower yield (77% yield, **3c**). In this sense, an electron-donating substituent such as naphthyl (**3b**) also provides a very good result (98% yield). A mixture of different substitution patterns on the aromatic ring seems to affect the

Table 1. Screening of the reaction conditions.[a]



1a (0.1 mmol) + **2a** (0.15 mmol) → **3a**

Entry	Solvent	Base (mol %)	Time (h or min)	Yield (%)[b]
1	toluene	K_2CO_3 (20)	17 h	73
2	toluene	Cs_2CO_3 (20)	17 h	94
3	toluene	DABCO (20)	17 h	35
4	toluene	$NaHCO_3$ (20)	17 h	traces
5	toluene	$LiClO_4$ (20)[21a]	17 h	traces
6	EtOH	$LiClO_4$ (20)[21a]	20 h	traces
7	H_2O	Cs_2CO_3 (20)	15 h	90
8	EtOH	Cs_2CO_3 (20)	15 min	64[c]
9	Me-THF	Cs_2CO_3 (20)	1 h	43[c]
10	L–Lactate	Cs_2CO_3 (20)	1 h	63[c]
11	CPME	Cs_2CO_3 (20)	2 h	18[c]
12	MeOH	Cs_2CO_3 (20)	1 h	50[c]
13	CH_3CN	Cs_2CO_3 (20)	2 h	18[c]
14	H_2O/EtOH 1 : 1	Cs_2CO_3 (20)	30 min	95
15	H_2O/EtOH 1 : 1	Cs_2CO_3 (10)	30 min	92
16	H_2O/EtOH 1 : 1	Cs_2CO_3 (5)	30 min	94

[a] The base is weighed in a reaction tube, and then iminochromene **1a** (0.1 mmol), the solvent (0.5 mL) and acetone cyanohydrin (**2a**) (0.15 mmol) are carefully added to it in this order. The mixture is stirred at room temperature for the time needed for total consumption of the starting reagent **1a** or no further progress is observed, monitoring the evolution by thin layer chromatography (TLC). [b] Isolated yield after purification by column chromatography. [c] Product not clean.

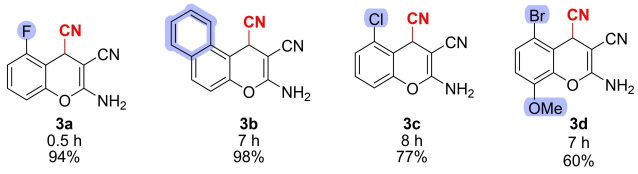


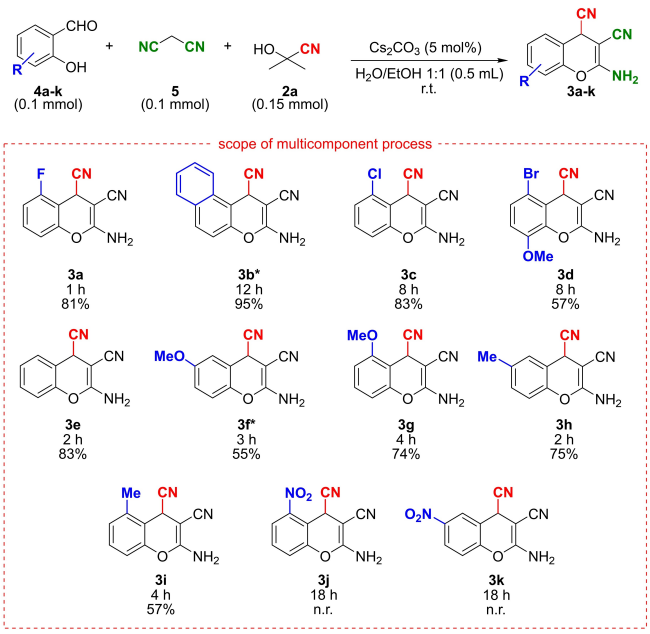
Figure 2. Scope of the reaction performed in H_2O/EtOH 1 : 1, starting from preformed iminochromenes.

yield, although maintaining a good result in just 7 hours (60 % yield, **3d**).

Furthermore, in the continuous search for more efficient protocols to synthesize complex structures, multicomponent reactions (MCRs) should be considered as an ideal strategy, as they generally represent a challenge in catalysis. In such multicomponent processes, the time-consuming isolation and purification of synthetic intermediates are eliminated. In general, energy, solvents, manipulation and, therefore costs are reduced, compared to classical stepwise methods.[25] The greatest advantages of these processes are their atom economy, convergent character, operational simplicity, structural diversity, and the molecular complexity that can be accessed. To this end, it was proposed to study this process following a multicomponent approach.

Although we also briefly explored other additional conditions for the multicomponent protocol (not reported), the previously optimized reaction conditions proved to be the best for this approach. Then, we proceeded to develop the scope of this methodology using aldehydes **4a-k**, malononitrile (**5**) – in order to *in situ* prepare the corresponding 2-amino-3-cyano-4*H*-chromene **1** – and cyanohydrin **2a** (Scheme 2). Our aim was to extend these conditions to a significant number of examples, thereby demonstrating the versatility and robustness of the methodology.

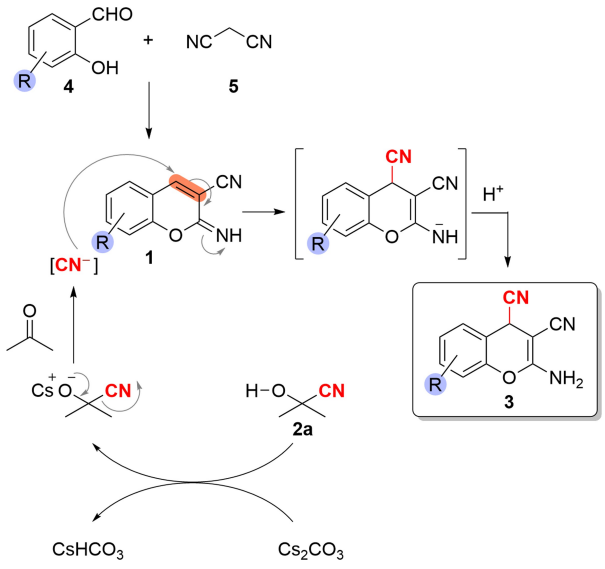
In this context, under these optimized conditions, we successfully synthesized a broader range of highly substituted compounds with moderate to very good yields (**3a-i**). Notably, these conditions allowed us to bypass the need for the synthesis and purification of the starting chromenes **1**, streamlining the process and enhancing overall efficiency. The elimination of intermediate purification steps further demonstrates the practicality of this methodology. The progress of the reactions was monitored by thin layer chromatography (TLC), continuing until no further advancement of the reaction was observed or until consumption of the starting material was detected. This allowed for careful control over the reaction



Scheme 2. Scope of the multicomponent cyanation performed in H_2O/EtOH 1:1. * 10 mol% of C_2CO_3. n.r. = no reaction.

time, ensuring optimal yield and minimizing the formation of undesired by-products. Unfortunately, a limitation of our work appears to be the presence of the NO_2 group in the starting aldehydes (**4j,k**), even when it is used in different positions (*ortho* and *meta*). The resonance effect of the NO_2 group in ring substitution may have implications for reactivity that we are not yet fully understand.

Although the mechanism involved in this reaction is still unknown, based on the experimental results obtained, our experience[22a] and on the nature of the species participating in the process, the following proposal is made (Scheme 3).



Scheme 3. Mechanism proposal.

After the *in situ* formation of the chromene **1**, the potassium carbonate would be solved in the medium and would deprotonate the cyanohydrin **2a** (Scheme 3). This would generate an anionic species, leading to acetone and releasing cyanide into the medium. The cyanide would add to the β-position of the Michael system of the iminochromene **1**, forming the corresponding 2-amino-4*H*-chromene-3,4-dicarbonitrile **3** after protonation of the generated intermediate.

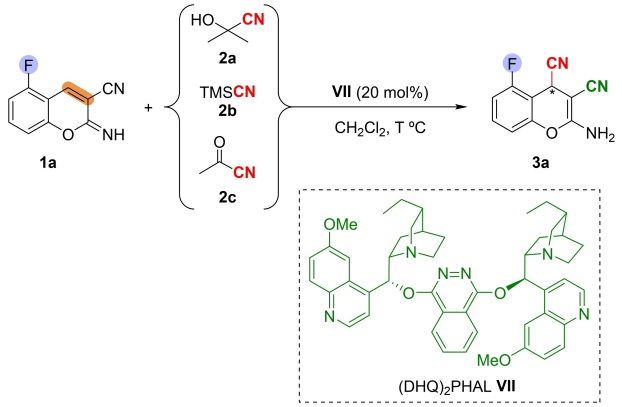
Asymmetric Organocatalytic Study of the Cyanation

Following the successful optimization of the racemic synthesis, which provided a proof of concept for the viability of this approach, we advanced to the enantioselective version of the study. Therefore, in the context of our research program focused on the development of new asymmetric catalytic processes, we centered our attention in the study of the asymmetric version of this reaction since to the best of our knowledge, the enantioselective synthesis of 2-amino-4*H*-chromene-3,4-dicarbonitriles has not been described so far in the literature. After an extensive study of the reactions conditions, catalysts and source of cyanides (see supporting information for all additional performed assays), in Table 2 we report the promising results obtained for product **3a**.

Among the family of catalysts studied **I–IX** (squaramide, phase transfer catalysts or cinchonas, see Figure S10 and Table S1), catalyst **VII** yielded the most promising results (Table 2). This study considered three different sources of cyanide: **2a-c**. By lowering the reaction temperature, better enantiomeric excess values were achieved, indicating a higher selectivity. However, this improvement in selectivity came at the cost of a slower reaction rate. The findings suggest encouraging results for this initial version of the process using pyruvonitrile (**2c**) at lower temperature (entry 6). However, despite achieving better selectivity, the methodology gives rise to low product quantities, indicating that further optimization is required to enhance both yield and efficiency. To address these challenges, we conducted additional experiments, particularly focusing on substrate **2c**. The results of these experiments are summarized in Table 3, where we systematically explored various reaction parameters to identify conditions that could further improve the overall performance of the methodology.

The results presented in Table 3 highlight the impact of varying the amount of substrate **2c**, the catalyst loading, and the solvent volume on the yield and enantioselectivity of the reaction. In entry 1, using 0.15 mmol of **2c** and 20 mol% catalyst **VII** in 0.25 mL of CH_2Cl_2, the reaction yielded 33% of the product with a promising enantiomeric excess of 50%. Increasing the amount of **2c** to 0.3 mmol (entry 2) rendered the same results (34% yield and 49% ee). Notably, when the catalyst loading was increased to 30 mol%, under the same conditions (entry 3), the yield decreased to 21%, but the ee improved significantly to 60%, indicating better selectivity under these conditions. Further adjustments to the solvent volume revealed that increasing it to 0.5 mL (entry 4) led to an improved yield of 45%, though with a reduced ee of 38%.

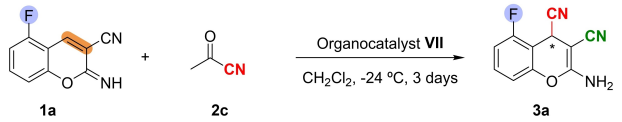
Table 2. Screening of the reaction conditions.[a]



Entry	2 (0.15 mmol)	T (°C)	Time (days)	Yield (%)[b]	ee (%)[c]
1	**2a**	0	1	99	16
2	**2a**	−24	7	30	26
3	**2b**	0	3	43	26
4	**2b**	−24	7	51	30
5	**2c**	0	3	31	36
6	**2c**	−24	3	33	50

[a] Organocatalyst **VII** (20 mol%, 0.02 mmol) is weighed in a reaction tube and the iminochromene **1a** (0.1 mmol) and CH_2Cl_2 (0.5 mL) are carefully added to it. The mixture is left to cool down to the desired temperature (0 °C or −24 °C). The cyanide source (**2a–c**) (0.15 mmol) is finally added over the reaction mixture, which is left to stir for the time needed for total consumption of the starting reagent or no further progress is observed, monitoring the evolution by thin layer chromatography (TLC). [b] Isolated yield after purification by column chromatography. [c] Enantiomeric excess (ee) determined by HPLC on a chiral stationary phase. Daicel Chiralpak column IC (*n*-hexane/^{i}PrOH = 80:20, flow rate 1 mL min^{-1}).

Table 3. Further exploration for the enantioselective cyanation of 2-iminochromene **1a** with pyruvonitrile **2c**.[a]



Entry	2c (mmol)	Catalyst (mol %)	CH_2Cl_2 (mL)	Yield (%)[b]	ee (%)[c]
1	0.15	20	0.25	33	50
2	0.3	20	0.25	34	49
3	0.3	30	0.25	21	60
4	0.3	30	0.5	45	38
5	0.3	30	0.125	51	52

[a] Organocatalyst **VII** is weighed in a reaction tube and the iminochromene **1a** (0.1 mmol) and CH_2Cl_2 are carefully added. The mixture is left to cool down to −24 °C. The cyanide source **2c** is finally added over the reaction mixture which is left to stir for 3 days. [b] Isolated yield after purification by column chromatography. [c] Enantiomeric excess (ee) determined by HPLC on a chiral stationary phase. Daicel Chiralpak column IC (*n*-hexane/^{i}PrOH = 80:20, flow rate 1 mL min^{-1}).

Conversely, reducing the solvent volume to 0.125 mL (entry 5) rendered the highest product quantity at 51%, with an ee of 52%. These results point out the delicate balance between reaction yield and enantioselectivity, with the highest selectivity (60% ee) achieved in entry 3 at the expense of yield. Further optimization is needed to improve both parameters simultaneously.

Conclusions

Considering the background provided and the growing interest in advancing synthetic methodologies, we have successfully synthesized 2-amino-4*H*-chromen-3,4-dicarbonitriles **3** through a Michael addition of cyanide to 2-iminochromenes with very good yields. The synthetic approach was designed employing a mild cyanide source, acetone cyanohydrin (**2a**), which allowed for safer and more controlled reactions. We further prioritized the use of green solvents to minimize environmental impact and adopted a multicomponent reaction strategy, which improved the synthetic process by reducing the number of steps and waste generated. The reactions were carried out under catalytic conditions at room temperature, ensuring that the process was both energy-efficient and favorable to maintaining the integrity of the sensitive molecular structures involved. The research aimed to explore innovative synthetic strategies that could efficiently construct more complex molecular architectures, thereby providing valuable tools for future chemical synthesis. We are currently working on converting the final products of this process into value-added compounds.

We also began exploring enantioselective processes using chiral organocatalysts, achieving a promising 60% of ee for product **3a**. The preliminary findings revel the difficulty of getting good enantioselectivity without punishing the yield of the process. Nevertheless, the groundwork for future research into the efficient and selective synthesis of these important chromene derivatives have been stablished.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetry · Chromene · Cyanohydrin · Michael addition · Multicomponent

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