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N-Heterocyclic Carbene Catalysis for Facile Access to Pentasubstituted 4*H*-Pyran Derivatives

Xiaolin Peng
Yulin Wang
Yixian Huang
Sheng Zhang
Zhichao Jin*
Shi-Chao Ren*

National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang, 550025, P. R. of China
zcjin@gzu.edu.cn
scren@gzu.edu.cn

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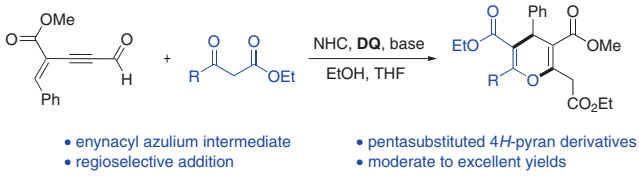

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Abstract The synthesis of polysubstituted 4*H*-pyran derivatives has attracted considerable attention due to its wide application in agrochemicals, pharmaceuticals, and other functional molecules. We report an N-heterocyclic carbene-catalyzed [3+3] annulation reaction of β-ketone esters with enynals for rapid access to pentasubstituted 4*H*-pyran derivatives through a regioselective activation of the ynal. A series of 4*H*-pyran derivatives bearing various substituents were obtained in moderate to excellent yields. This method could find further applications in the synthesis of structurally diverse 4*H*-pyran-derived functional molecules from readily available starting materials.

Key words N-heterocyclic carbene catalysis, organocatalysis, pyrans, regioselectivity, ketone esters, enynals

4*H*-Pyrans are privileged structures in agrochemicals, pharmaceuticals, and other functional molecules due to their unique properties and diverse bioactivities.[1] In particular, polysubstituted 4*H*-pyrans play important roles in these areas as a result of their greater numbers of sites for potential modifications.[2] For instance, examples of polysubstituted 4*H*-pyran derivatives display various interesting biological activities, including antifungal, antibacterial, anticancer, and specific IKCa channel blocker properties (Figure 1).[3] Therefore, the development of efficient methods to access polysubstituted 4*H*-pyran derivatives has attracted considerable scientific attention, and significant achievements have been made including metal- and nonmetal-catalyzed strategies.

Among the reported approaches, organocatalytic strategies are characterized by mild reaction conditions, environmental friendliness, and the ready availability of the catalysts.[4] As one of the most important organocatalytic reactions, N-heterocyclic carbene (NHC) catalysis has been developed as a powerful tool for the construction of structurally diverse molecules by symmetric or asymmetric pathways.[5] Indeed, NHC-catalyzed reactions have also been applied in the synthesis of 4*H*-pyran derivatives by the groups of Ma and Yao (Scheme 1a); in these reactions, the carbene catalyst acts as a Lewis base.[6] Although these seminal works provide straightforward access to 4*H*-pyran derivatives, these NHC-catalyzed methods are limited to accessing tetrasubstituted 4*H*-pyran derivatives. The synthesis of pentasubstituted 4*H*-pyran derivatives under NHC catalysis had not been realized. Here, we report an NHC-catalyzed [3+3] annulation reaction between a β-ketone esters and an ynal for rapid access to pentasubstituted 4*H*-pyran derivatives (Scheme 1b). The key steps involve the activation of the enynal by NHC catalysis in the presence of oxidant to form an NHC-bound acyl azolium intermediate as a three-atom synthon, and a subsequent regioselective annulation with the β-ketone ester as a second three-atom synthon. A series of pentasubstituted 4*H*-pyran derivatives bearing structurally diverse functional groups were obtained under mild conditions. Our reaction provides an al-

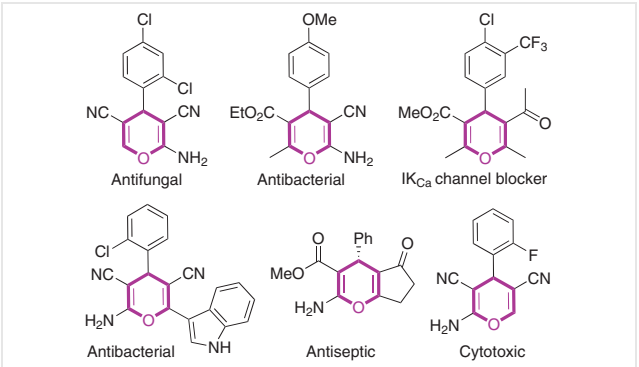

Figure 1 Bioactive molecules containing 4*H*-pyran fragments

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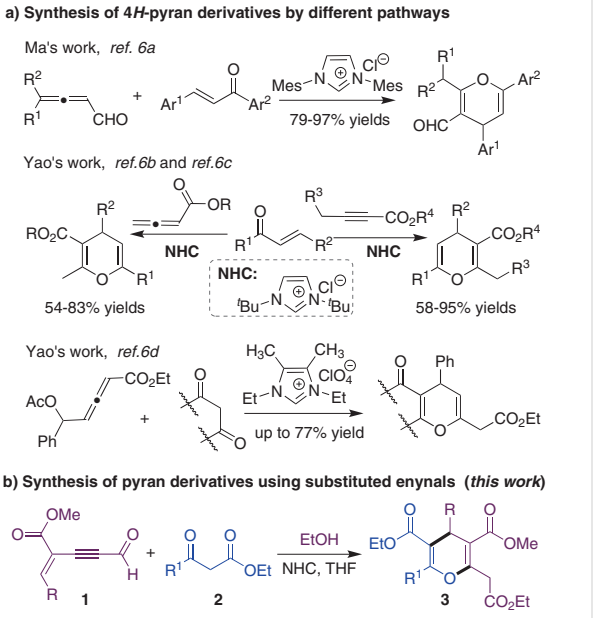
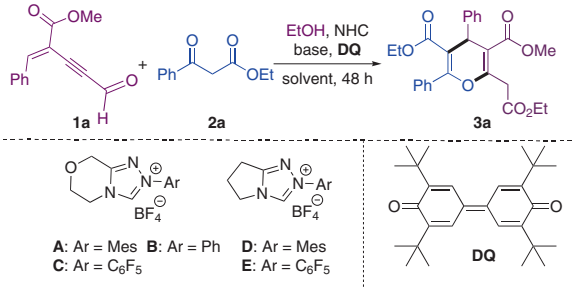
ternative and straightforward method for the synthesis of pentasubstituted 4*H*-pyran derivatives from readily available starting materials.



Scheme 1 Synthesis of 4*H*-pyran-containing molecules by NHC catalysis

We began our search for suitable reaction conditions for this [3+3] annulation reaction by using the phenyl enynal **1a** and the β-keto ethyl ester **2a** as model substrates. A typical reaction mixture contained **1a** (1.2 equiv), **2a** (1.0 equiv), NHC precatalyst **A** (20 mol%), the tetra-*tert*-butylated 4,4′-diphenylquinone **DQ** as an oxidant (1.5 equiv), ethanol (100 μL), and a base (1.5 equiv) in THF as the solvent (Table 1). To our delight, an initial study revealed that the target pentasubstituted 4*H*-pyran product **3a** was obtained in 23% yield (Table 1, entry 1). The yield increased to 45% when the base was changed to DABCO (entry 2). Whereas triethylamine did not promote the transformation (entry 30), inorganic bases such as K_3PO_4 (entry 4) and K_2CO_3 (entry 5) effectively promoted this transformation, with K_2CO_3 giving the best result (84% yield). Several NHC precatalysts were then examined to explore the influence of the NHC catalyst (entries 5–9). The results suggested that the electronic effect of the carbene catalyst has a significant effect on our reactions, as the yield of **3a** decreased dramatically when the electron-donating mesyl (Mes) group was replaced by an electron-neutral phenyl group (entry 6) or an electron-deficient perfluorophenyl group (entry 7). A similar trend was observed for a pyrrole-based NHC precatalyst (entries 8 and 9). Finally, the effect of the solvent was investigated. It appeared that the polarity of the solvent had a marked effect on the outcome. For example, the use of 1,4-dioxane as a solvent resulted in a slightly lower yield (75%; entry 11). In contrast, the use of the more-polar solvents acetonitrile and ethyl acetate resulted in a sharp decrease in the yield (entries 10 and 12); for more details, see the Supporting Information.

Table 1 Condition Optimization[a]



Entry	NHC	Base	Solvent	Yield[b] (%)
1	**A**	DBU	THF	23
2	**A**	DABCO	THF	45
3	**A**	Et_3N	THF	–
4	**A**	K_3PO_4	THF	78
5	**A**	K_2CO_3	THF	84
6	**B**	K_2CO_3	THF	35
7	**C**	K_2CO_3	THF	23
8	**D**	K_2CO_3	THF	60
9	**E**	K_2CO_3	THF	<5
10	**A**	K_2CO_3	MeCN	62
11	**A**	K_2CO_3	1,4-dioxane	75
12	**A**	K_2CO_3	EtOAc	61

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), NHC (20 mmol%), base (0.15 mmol), **DQ** (150 mmol%), EtOH (100 μL), solvent (1.0 mL), r.t., 48 h.
[b] Isolated yield after purification by silica gel column chromatography.

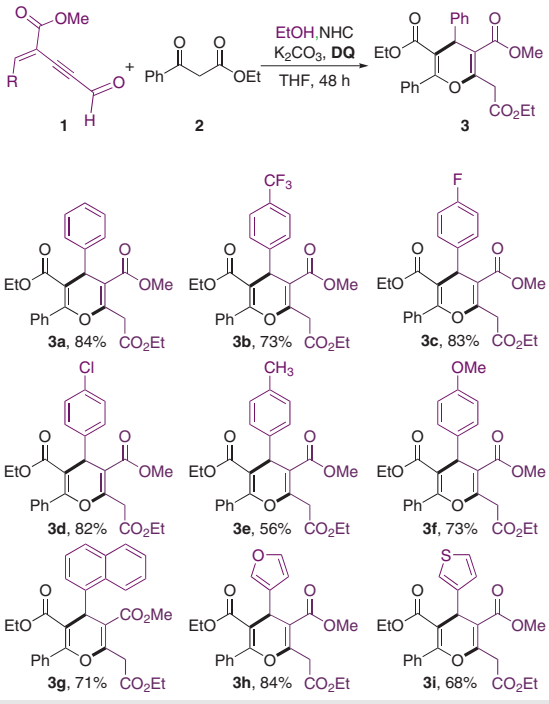
With the optimal reaction conditions in hand, we began to investigate the generality of this carbene-catalyzed [3+3] annulation for the preparation of pentasubstituted 4*H*-pyrans. We first evaluated the scope of the enynal by using **2a** as a model substrate (Scheme 2). Both electron-withdrawing groups, such as trifluoromethyl (**3b**), fluoro (**3c**), or chloro (**3d**), and electron-donating groups, such as methyl (**3e**) and methoxy (**3f**) on the phenyl ring of the enynal were tolerated, and the corresponding products were isolated in moderate to high yields. When the phenyl group of **1a** was replaced by a 2-naphthyl group, the desired product **3g** was isolated in 71% yield. Heterocyclic aromatic rings (3-furyl or 3-thienyl) were also tolerated in our reaction, and the corresponding heteroaromatic-ring-substituted 4*H*-pyrans **3h** and **3i** were isolated in yields of 84 and 68%, respectively.

We then explored the scope of the β-ketone ester by using enynal **1a** as a model substrate (Scheme 3). The electronic properties of the substituents on the benzene ring proved to have a significant effect on this transformation.

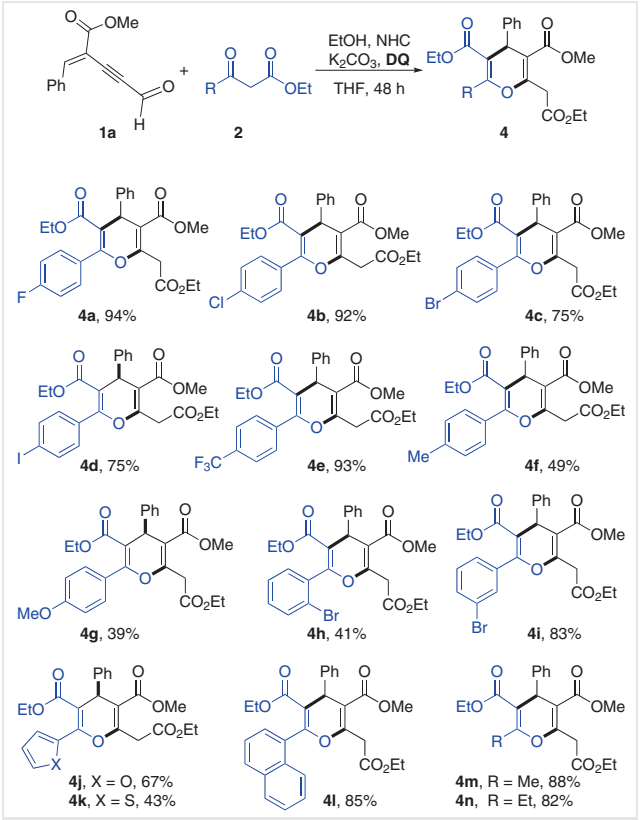
Specifically, substrates bearing electron-withdrawing groups such as halo (**4a–d**) or trifluoromethyl (**4e**) on the benzene ring reacted smoothly to give the corresponding products in good to excellent yield (75–94%). In sharp contrast, the reaction yields decreased dramatically when electron-donating groups such as methyl (**4f**; 49%) or methoxy (**4g**; 39%) were present on the benzene ring. This phenomenon might be attributable to the enhanced electrophilicity of the δ-carbon of the enynal-derived azolium intermediate. The steric nature of the benzene ring also had a significant effect on the transformation; for example, the *meta*-bromo-substituted enynal gave **4i** in 83% yield, whereas its *ortho*-substituted analogue gave **4h** in only 41% yield. It is noteworthy that the presence of halogen atoms such as bromine or iodine provides opportunities for further modification of the 4*H*-pyrans. Heterocyclic aromatic groups such as 2-furyl (**4j**) and 2-thienyl (**4k**) were tolerated, albeit with slightly lower yields. The aromatic rings of **2a** could also be replaced by an alkyl group without markedly affecting the reaction outcome; for instance, the methyl- and ethyl-substituted 4*H*-pyrans (**4m** and **4n**, respectively) were isolated in yields of 88 and 82%.

To test the potential utility of this NHC-catalyzed [3+3] annulation reaction, the model reaction was conducted on a 1 mmol scale, and the desired pentasubstituted 4*H*-pyran **3a** was obtained successfully without a reduction in the yield (Scheme 4a). The product **3a** could be reduced by Pd/C under a H_2 atmosphere to give the 3,4-dihydro-2*H*-pyran **5** in 79% yield. The structure of the product **5** was confirmed by X-ray analysis (Scheme 4b).[7]

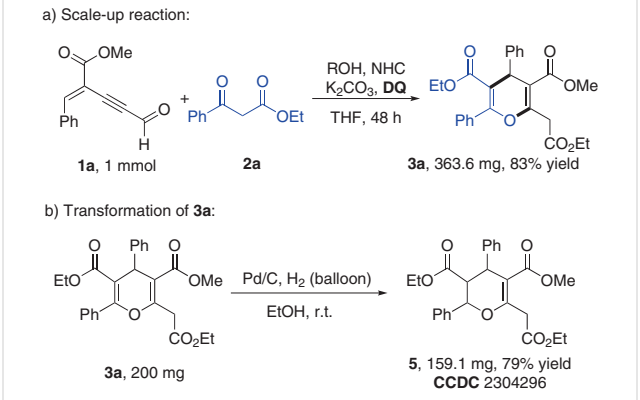
A plausible reaction mechanism is shown in Figure 2. The Breslow intermediate **I**, formed from the NHC catalyst and the enynic aldehyde **1a**, is oxidized to give the enynyl acylazolium intermediate **II**. Deprotonated **2a** attacks the



Scheme 2 Scope of the enynal **1**. *Reaction conditions*: **1** (0.12 mmol), **2a** (0.10 mmol), **D** (20 mol%), K_2CO_3 (0.15 mmol), **DQ** (150 mmol%), EtOH (100 μL), THF (1.0 mL), r.t., 48 h. The isolated yields are reported.



Scheme 3 Scope of the β-keto acetate **2**. *Reaction conditions*: **1a** (0.12 mmol), **2** (0.10 mmol), **D** (20 mol%), K_2CO_3 (0.15 mmol), **DQ** (150 mmol%), EtOH (100 μL), THF (1.0 mL), r.t., 48 h. The isolated yields are reported.



Scheme 4 Scaled-up reaction and a transformation of **3a**

electrophilic δ-position of intermediate **II** to give adduct **III**. This is esterified by EtOH to give intermediate **IV**, which undergoes an intramolecular cyclization to give the 4*H*-pyran product **3a**.

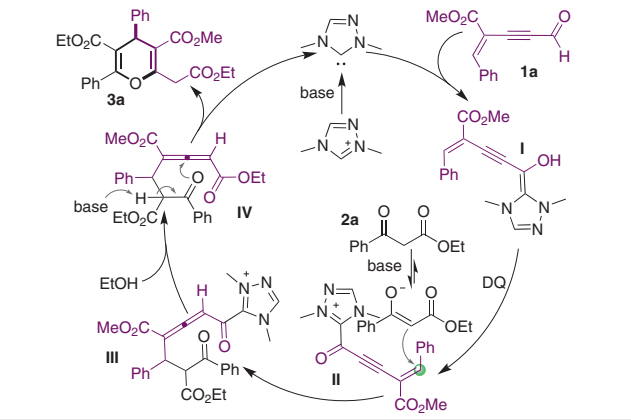


Figure 2 A plausible mechanism for the transformation of **3a**

In conclusion, we have demonstrated an NHC-catalyzed [3+3] annulation reaction for a concise access to pentasubstituted 4*H*-pyran derivatives.[8] The reaction proceeds under mild conditions with an enynal and a β-ketone ester as two three-atom synthons. The success of this transformation relies on the regioselective addition of the β-ketone ester to an enynal-derived acyl azolium intermediate. A series of pentasubstituted 4*H*-pyrans bearing various functional groups were obtained in good to excellent yields. Our method could find applications in preparing 4*H*-pyran-group-containing functional molecules. Further explorations, including an asymmetric version of this transformation and bioactivity investigation of the products, are in progress in our laboratory.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2253-4365.

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(7) CCDC 2304296 contains the supplementary crystallographic data for compound **5**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

(8) **4*H*-Pyrans 3a–i and 4a–n; General Procedure**

Under a N_2, the appropriate **1** (0.12 mmol) and **2** (0.10 mmol) together with NHC (0.02 mmol), K_2CO_3 (0.15 mmol), and **DQ** (0.15 mmol) were dissolved in anhyd THF (1.0 mL), and then EtOH (100 μL) was added. The mixture was stirred for 48 h at r.t. and then purified by column chromatography (silica gel).

5-Ethyl 3-Methyl 2-(2-ethoxy-2-oxoethyl)-4,6-diphenyl-4*H*-pyran-3,5-dicarboxylate (3a)

Yellow oil; yield: 36.8 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.34 (m, 7 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.24–7.19 (m, 1 H), 4.93 (s, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.00–3.82 (m, 4 H), 3.66 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.89 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl3): δ = 168.8, 166.4, 166.3, 156.9, 155.2, 144.5, 133.8, 129.8, 128.9 (2 C), 128.4 (2 C), 128.4 (2 C), 127.9 (2 C), 127.0, 110.4, 109.6, 61.3, 60.5, 51.8, 39.2, 38.3, 14.2, 13.6. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{26}NaO_7$: 473.1570; found: 473.1562.

3-Ethyl 5-Methyl 6-(2-ethoxy-2-oxoethyl)-2,4-diphenyl-3,4-dihydro-2*H*-pyran-3,5-dicarboxylate (5)

10% Pd/C (50 mg) was added to a solution of **3a** (443.96 μmol, 200 mg) in EtOH (20.0 mL) under a N_2 atmosphere. The suspension was degassed in vacuum and purged with H_2 (balloon) several times. The mixture was stirred at r.t. for 24 h and then filtered through Celite, which was washed with EtOH (3 × 10 mL). The combined organic solution was concentrated under reduced pressure to afford a crude product that was purified by flash chromatography (silica gel) to give a colorless solid; yield: 159.1 mg (79%); mp 117–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H), 7.24–7.11 (m, 5 H), 5.30 (d, *J* = 2.6 Hz, 1 H), 4.49 (d, *J* = 7.9 Hz, 1 H), 4.39 (d, *J* = 16.6 Hz, 1 H), 4.23–4.12 (m, 2 H), 3.60 (dd, *J* = 16.6, 0.8 Hz, 1 H), 3.48 (q, *J* = 7.1 Hz, 2 H), 3.42 (dd, *J* = 8.0, 2.7 Hz, 1 H), 3.37 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 0.65 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.4, 168.3, 167.7, 160.7, 140.6, 137.4, 128.4 (2 C), 128.1 (2 C), 128.1 (2 C), 127.3, 126.6, 125.6 (2 C), 106.7, 78.0, 60.9, 59.8, 52.2, 51.0, 42.2, 39.1, 14.2, 13.5. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{28}NaO_7$: 475.1727; found: 475.1732.