Organic Letters

Letter

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N-Heterocyclic Carbene-Promoted Annulation Reaction of Allenals with Chalcones: Synthesis of Polysubstituted Pyranyl Aldehydes

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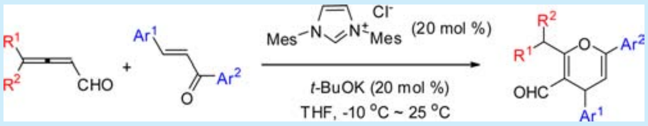
Ⓢ *Supporting Information*

ABSTRACT: A general *N*-heterocyclic carbene (NHC)-promoted annulation reaction of allenals with chalcones affording polysubstituted pyranyl aldehydes has been developed. Three mechanistic possible pathways have been proposed. The NHC attacks the center carbon of allenals or acts as a base for deprotonation and then undergoes a 1,4-addition with chalcones, followed by sequential reactions giving the final products.

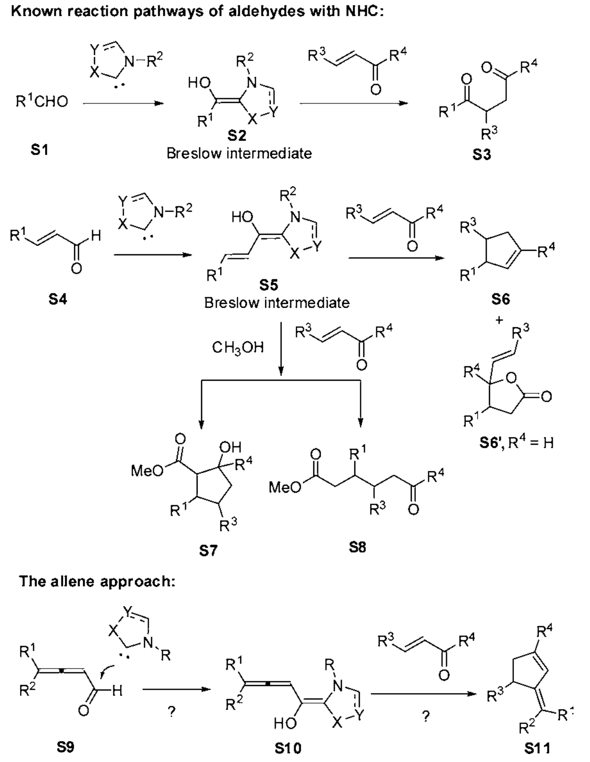


As one of the most important classes of small organic molecular catalysts, *N*-heterocyclic carbenes (NHC) have attracted increasing attention for the efficient construction of carbon−carbon and carbon−heteroatom bonds based on their reaction with the aldehyde functionality.[1] For example, simple aldehydes **S1** and enals **S4** would form Breslow intermediates **S2**[2] and **S5**[3] after the reaction with NHC, which would then nucleophilically react with chalcones, affording 1,4-diketones **S3**, cyclopentenes **S6**, cyclopentanols **S7**, or 1,6-diketones **S8** (Scheme 1).[4] We inferred that the aldehyde group of allenals **S9** may also react with NHC to afford a Breslow intermediate **S10**, in principle. Then it would react with chalcone by following a similar process to afford 3-alkylidene-subsitituted cyclopentene **S11**.

First, we attempted the reaction of allenal **1a** and chalcone **2a** with 13 mol % IMes·HCl and 27 mol % *t*-BuOK at room temperature in THF. Two new products were formed unexpectedly: liquid pyranyl aldehyde product **3aa** in 20% yield and a yet unidentified product **4aa** (Table 1, entry 1). The structure of **3aa** was confirmed by X-ray single crystal diffraction of **5**,[5] by its reaction with (2,4-dinitrophenyl)-hydrazine[6] (Figure 1); the expected five-membered compound **S11**-type product **P1** was not formed. The pyran ring constitutes many important natural products and alkaloids. The synthesis of these 3-pyrancarbaldehyde derivatives immensely enriches the pyran family, which provides more opportunities for easy and efficient synthesis of such natural products. However, the synthetic methods for pyranyl aldehydes are very limited. To the best of our knowledge, most 3-pyrancarbaldehydes were synthesized from pyrans utilizing trichlorophosphate and DMF to introduce the aldehyde group:[7] the substrates are limited, and diketones were also produced at the same time. Herein, we will report a general, easy, and efficient synthesis of 3-pyrancarbaldehydes in one pot.

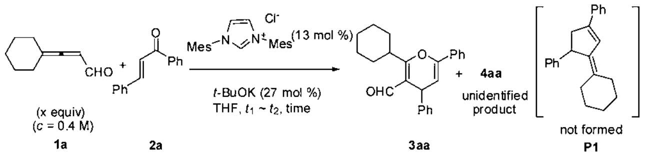
Based on the structure of product **3aa**, we proposed three possible pathways: (a) The *N*-heterocyclic carbene may attack the center carbon atom of allenal **1a**, instead of the aldehyde functionality in **1a**, to form intermediate **A**,[8] which is different from what has been reported for normal aldehydes or enals.[2,3] Then this intermediate would undergo 1,4-addition with chalcone **2a**, affording enolate anion intermediate **B**. Then

Scheme 1. Reported Reactions of Simple Aldehydes, Enals with NHC, and Hypothesized Reaction of Allenals with NHC



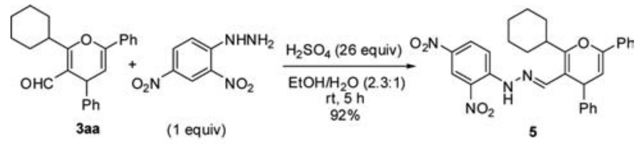
Received: July 22, 2014
Published: September 4, 2014

Table 1. Optimization of Reaction Conditions for the Synthesis of 3aa[a]



entry	x	t_1/t_2 (°C)	time (h)	yield of 3aa[b] (%)	recovery of 2a[b] (%)
1	1.33	rt/rt	10.75	20	55
2	1.33	rt/−10	35	10	22
3	1.33	−10/rt	22	19	9
4[c]	2	rt/rt	22	28	14
5[d]	2	−10/25	11.5	92	0

[a] Reaction conditions: A solution of IMes·HCl and *t*-BuOK in THF was stirred at rt for 20 min and then cooled to t_1. Then **1a**, 0.3 mmol of **2a** (0.2 mmol for entry 5), and THF were added at t_1 sequentially. The resulting mixture was then stirred at t_2 for the time indicated in the table (time). [b] Determined by NMR using dibromomethane as the internal standard. [c] With 20 mol % IMes·HCl and 40 mol % *t*-BuOK. [d] With 20 mol % IMes·HCl and 20 mol % *t*-BuOK stirring at 25 °C for 20 min.



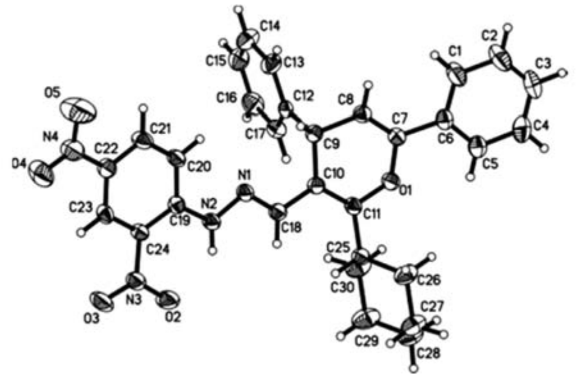
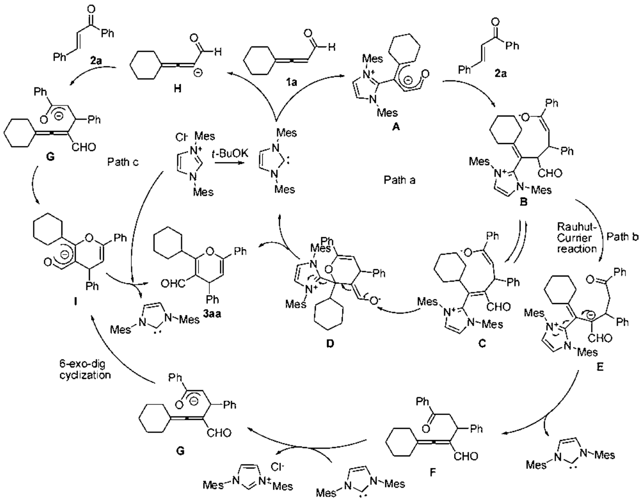


Figure 1. ORTEP representation of **5**.

Scheme 2. Possible Pathways for the Formation of Product 3aa

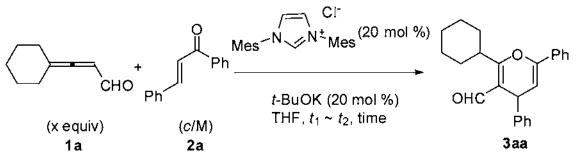


the double bond in intermediate **B** would isomerize into the conjugated position with the aldehyde followed by cyclic conjugate addition and elimination of the NHC catalyst, giving the final product **3aa**. (b) The intermediate **B** underwent a Rauhut–Currier-type reaction[9] to give product **F** with the regeneration of NHC. Then the regenerated NHC would act as a base[10] to give intermediate **G** by removing the α-hydrogen atom of product **F**. Enolic intermediate **G** would undergo an intramolecular 6-*exo-dig* cyclization to give intermediate **I**, which would be protonated with IMes·HCl to give product **3aa**. (c) The NHC would also react with allenal **1a** as a base[10] to deprotonate the α-olefinic proton giving anionic intermediate **H**. Then intermediate **H** would go through a 1,4-addition reaction with chalcone **2a**, affording intermediate **G**. The same process following path b would lead to product **3aa** (Scheme 2).

The conditions for this reaction were then optimized. The yield of **3aa** was 10% when the reaction was conducted at −10 °C (Table 1, entry 2) while it was slightly lower by adding **1a** at −10 °C (Table 1, entry 3); increasing the loading of **1a** to 2 equiv afforded **3aa** in 28% yield (Table 1, entry 4). Finally, we observed that increasing the loading of IMes·HCl to 20 mol % with 2 equiv of **1a** and running the reaction at a temperature from −10 to 25 °C led to a 92% yield of **3aa** (Table 1, entry 5).

While 1.75 equiv of **1a** proved to be the best with the complete consumption of **2a** (Table 2, entries 1–7), to our delight, running the reaction at a lower concentration led to further improved yields of **3aa** (Table 2, entries 9–11): the reaction of **2a** at 0.067 M brought the yield of **3aa** up to 97%

Table 2. Synthesis of 3aa: Effect of Concentration[a]



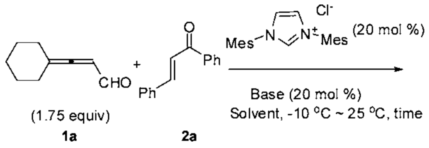
entry	x	c/M	t_1/t_2 (°C)	time (h)	yield of 3aa[b] (%)	recovery of 2a[b] (%)
1	2	0.2	−10/25	11.5	92	0
2	1	0.2	−10/25	17.5	46	36
3	1.5	0.2	−10/25	21.5	68	7
4	1.5	0.2	−30/25	21	81	2
5	1.5	0.2	−10/50	21.75	80	3
6	1.65	0.2	−10/25	8	74	2
7	1.75	0.2	−10/25	8.25	87	0
8	2	0.1	−10/25	17.3	90	0
9	1.75	0.1	−10/25	17.3	89	0
10	1.75	0.067	−10/25	8.5	97	0
11	1.75	0.05	−10/25	8.5	95	0
12[c]	1.75	0.067	−10/25	22	78	15
13[d]	1.75	0.067	−10/25	22	1	99
14	1.75	0.067	25/25	10.5	43	45

[a] Reaction conditions: A solution of IMes·HCl and *t*-BuOK in THF was stirred at 25 °C for 20 min and cooled to t_1. Then **1a** and 0.2 mmol of **2a** (0.4 mmol for entry 2) were added at t_1 sequentially. The resulting mixture was then stirred at t_2 for the time indicated in the table (time). [b] Determined by NMR using dibromomethane as the internal standard. [c] With 10 mol % IMes·HCl and *t*-BuOK. [d] With 5 mol % IMes·HCl and *t*-BuOK.

(Table 2, entry 10). However, the yields decreased with 10 or 5 mol % of the carbene catalyst (Table 2, entries 12 and 13).

The bases and solvents were also tested. *t*-BuOK proved to be the ideal base for this reaction (Table 3, entries 1–4). However, the reaction could not proceed in DCM (Table 3, entry 5); THF is still the best (Table 3, entries 1, 6, and 7). So we defined the standard conditions as follows: 1.75 equiv of **1a** with **2a** at 0.067 M in THF catalyzed by 20 mol % IMes·HCl and *t*-BuOK at a temperature ranging from −10 to 25 °C.

Table 3. Final Optimization of Reaction Conditions for the Synthesis of **3aa**[a]



entry	base	solvent	time (h)	yield of **3aa**[b] (%)	recovery[b] (%) **1a**/**2a**
1	***t*BuOK**	**THF**	**8.5**	**97**	**0/0**
2	Cs_2CO_3	THF	21.5	6	0/71
3	K_2CO_3	THF	21.5	1	0/81
4	DIPEA	THF	21.5	0	78/100
5	*t*BuOK	DCM	24	0	79/100
6	*t*BuOK	toluene	24	85	0/3
7	*t*BuOK	dioxane	24	62	0/28

[a] Reaction conditions: A solution of IMes·HCl and *t*-BuOK in THF (1.5 mL) was stirred at 25 °C for 20 min and cooled to −10 °C. Then 0.35 mmol of **1a**, 0.2 mmol of **2a**, and THF (1.5 mL) were added at −10 °C sequentially. The resulting mixture was then stirred at 25 °C for the time indicated in the table (time). [b] Determined by NMR using dibromomethane as the internal standard. DIPEA = *N*,*N*-Diisopropylethylamine.

With these optimized results in hand, different substrates were explored (Scheme 3). R^1 and R^2 could be the same: 4,4-pentamethylene (**3aa**–**3ag**), *n*-propyl (**3ba**, **3bh**, and **3bi**), and benzyl (**3cj**) or different: methyl and cyclohexyl or phenyl and ethyl with a diastereomeric ratio of 1:2.6 (**3da**) and 1:3.1 ((*R**,*R**)-**3ek**[11] and (*S**,*R**)-**3ek**),[12] respectively. For chalcones, Ar^1 and Ar^2 could be unsubstituted phenyl groups (**3aa**, **3ba**, and **3da**); Ar^1 may be substituted by an electron-withdrawing *p*-Br (**3ab**) or electron-donating *p*-CH_3 group (**3ac**). It was further observed that 1-naphthyl (**3ad**) and heterocyclic 2-thienyl (**3ae**) are also compatible. Ar^2 could also be 2-thienyl (**3af**) or 2-furyl (**3ag**). Finally, polysubstituted chalcones with *m*-BrC_6H_4, *p*-PhC_6H_4 (**3bh**), *m*-O_2N-*p*-ClC_6H_3 (**3bi**), *p*-ClC_6H_4 (**3cj**), and *p*-$NO_2C_6H_4$ (**3ek**) all performed well in this reaction process.

Then the mechanism was further investigated: 11% of **3aa** was obtained together with 42% recovery of **2a** under 20 mol % of *t*-BuOK without the NHC precursor (Table 4, entry 3). However, the reaction could not proceed in the absence of *t*-BuOK (Table 4, entry 4) or both the NHC precursor and *t*-BuOK (Table 4, entry 5). The reaction with 20 mol % of IMes·HCl afforded **3aa** in 92% yield (Table 4, entry 2). These results support the mechanistic pathways shown in Scheme 2.

Scheme 3. *N*-Heterocyclic Carbene Catalyzed Annulation Reaction of Allenals and Chalcones to Form Pyranyl Aldehydes

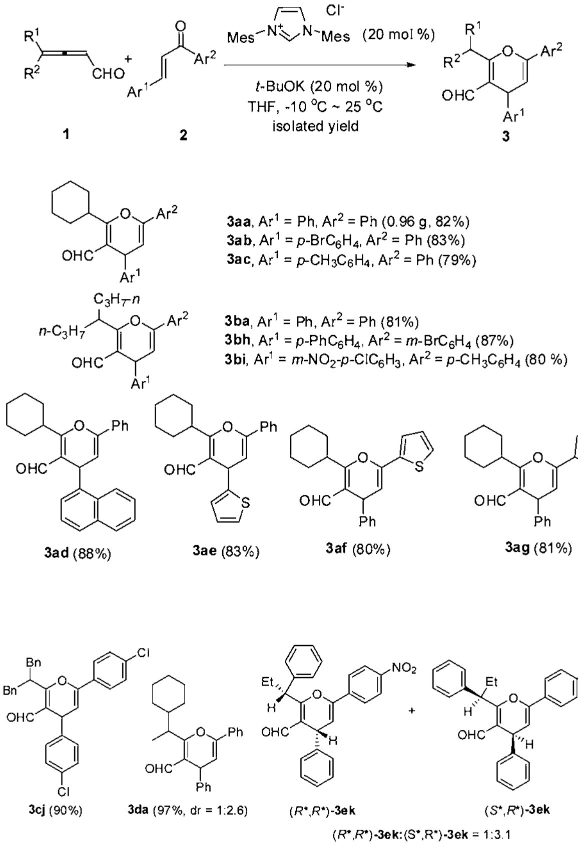
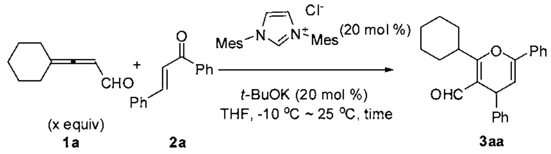


Table 4. Control Experiments for the Synthesis of **3aa**[a]



entry	*x*	time (h)	yield[b] (%)	recovery[b] (%) **1a/2a**
1	**1.75**	**8.5**	**97**	**0/0**
2	2	11.5	92	0/0
3[c]	2	11.5	11	0/42
4[d]	1.75	15.3	0	75/100
5[e]	1.75	15.5	0	79/100

[a] Reaction conditions: **1a** and 0.2 mmol of **2a** were added at −10 °C, then reacted at 25 °C in THF under N_2 after IMes·HCl and *t*-BuOK stirred at 25 °C for 20 min. [b] Determined by NMR using dibromomethane as the internal standard. [c] Without IMes·HCl. [d] Without *t*-BuOK. [e] Without IMes·HCl and *t*-BuOK.

In conclusion, a general NHC-promoted annulation reaction of allenals and chalcones to pyranyl aldehydes has been developed. This was the first report on the reaction of allenals with NHC: instead of forming the Breslow intermediate, its reaction with an allenal afforded the conjugate addition to the center carbon atom of the allene moiety. Further investigation involving the mechanistic pathways and new reactions under NHC catalysis with allenals are being carried out in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21232006) and the National Basic Research Program of China (2011CB808700) is greatly appreciated. S.M. is a Qiu Shi Adjunct professor at Zhejiang University. We thank Mr. B. Miao of this group for reproducing the preparation of **3ac**, **3ag**, and **3bh** in Scheme 3.

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(5) Crystal data for compound **5**: $C_{30}H_{28}N_4O_5$, MW = 524.56, monoclinic, space group $P21/c$, final R indices $[I > 2\sigma(I)]$, R1 = 0.0682, wR2 = 0.1992; Rindices (all data), R1 = 0.1166, wR2 = 0.2243; a = 13.1313(15) Å, b = 19.0446(14) Å, c = 12.9434(16) Å, α = 90.00°, β = 111.691(14)°, γ = 90.00°, V = 3007.7 (6) Å^3, T = 293(2) K, Z = 4, reflections collected/unique 11691/3123 (Rint = 0.0331), number of observations $[>2\sigma(I)]$ 5488, parameters: 352. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 1002355.

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(11) Crystal data for compound (R^*,R^*)-**3ek**: $C_{27}H_{23}NO_4$, MW = 425.46, monoclinic, space group $P121/n1$, final R indices $[I > 2\sigma(I)]$, R1 = 0.0723, wR2 = 0.1629; R indices (all data), R1 = 0.1724, wR2 = 0.2235; a = 28.281(2) Å, b = 6.5273(6) Å, c = 38.133(4) Å, α = 90.00°, β = 107.759(10)°, γ = 90.00°, V = 6703.9(10) Å^3, T = 293(2) K, Z = 12, reflections collected/unique 24600/4667 (Rint = 0.0995), number of observations $[>2\sigma(I)]$ 11779, parameters: 874. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 1014779.

(12) Crystal data for compound (S^*,R^*)-**3ek**: $C_{27}H_{23}NO_4$, MW = 425.46, monoclinic, space group $P21/c$, final R indices $[I > 2\sigma(I)]$, R1 = 0.0391, wR2 = 0.0996; Rindices (all data), R1 = 0.0498, wR2 = 0.1092; a = 10.6719(3) Å, b = 19.4897(5) Å, c = 10.9956(3) Å, α = 90.00°, β = 99.063(2)°, γ = 90.00°, V = 2258.44(10) Å^3, T = 293(2) K, Z = 4, reflections collected/unique 14856/3249 (Rint = 0.0367), number of observations $[>2\sigma(I)]$ 4007, parameters: 291. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 1014780.