Organic Base-Mediated Condensation of Pyridinecarboxaldehydes to Azachalcones

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Abstract: A DBU-mediated aldol condensation-dehydration sequence has been used to prepare a series of synthetically important substituted 2- and 3-azachalcones. Michael products that typically accompany this sequence with inorganic bases were *not* observed in this protocol of high practical value.

Keywords: aldol reaction; azachalcones; chemoselectivity; organic catalysis; pyridinecarboxaldehydes

Azachalcones are valuable intermediates for Diels–Alder and Michael reactions as well as many other conversions.[1] Although there are many ways to prepare azachalcones (Scheme 1),[2–4] none appear universally applicable to synthesize a wide variety of azachalcones using a common synthetic protocol. All current approaches suffer from subsequent Michael addition to the desired azachalcone to varying degrees. In one case, the precipitate isolated from the condensation of **2** and acetophenone was actually an oily mixture of the Michael adduct **13** or **14** and the desired azachalcone (**9** or **10**).[2] In condensations of **1** and several substituted benzaldehydes, cyclic products (e.g., **15**) were reportedly isolated regardless of the stoichiometry used.[5] These compounds form in high yields under conditions identical to those suggested for the synthesis of the azachalcones, and their structures were confirmed using X-ray crystallography. Aryl-substituted oligopyridines (**17**) are isolated in 40% yield *via* the Kröhnke methodology by using Michael adduct **16**, generated under conditions identical to those used to prepare the azachalcones.[6] A reliable preparation of azachalcones therefore necessitates the prevention of the Michael pathway.

A recent study by Wachter-Jursczak and co-workers proposed that the Michael pathway is favored by coordination of the metal ion to the azachalcone through an interaction with the nitrogen.[7] The cation withdraws electron density from the conjugated system, making the enone a better Michael acceptor (Scheme 2). Only the Michael adducts (e.g., **13** and **14**) were isolated from condensations using **2** and 2-quinolinecarboxaldehyde. The study showed that the reaction of 2-quinolinecarboxaldehyde could be stopped at the dehydration product by applying stoichiometric amounts of pyridine to bind the metal ion. The same approach, however, did not prevent Michael addition in reactions involving **2**.

In order to circumvent all of the problems noted above, we considered application of an organic base to eliminate the metal ion from the reaction mixture. We chose 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base because it is readily available, highly basic, and of low nucleophilicity.[8] In our continuing interest with organocatalysis and specifically the use of thioureas to catalyze Diels–Alder reactions, we sought a series of substituted azachalcones that would elucidate the binding mechanism of thiourea catalysts.[9] Since these catalysts are believed to activate dienophiles through hydrogen bonding, azachalcones present the potential for activation by bidentate chelation.

For comparison with literature data, we first prepared **4**–**8** using published protocols,[3] but we favored a chromatography step over crystallization. We have been unable to prepare **9**–**12** and **18**–**23** similarly although the condensation products of 2-acetylpyridine (**1**) and 2- and 3-pyridinecarboxaldehyde (**2** and **3**, respectively) have been prepared under almost identical conditions (Scheme 1). As in the study by Wachter-Jurcsak, we isolated the Michael adduct as the major product in condensations of pyridinecarboxaldehydes **2** and **3**.[7] Condensations of **2** using pyridine as an ion scavenger still yielded only the Michael product. Condensations of **3** and pyridine gave inseparable mixtures of the azachalcone and its Michael adduct.

The DBU-mediated condensation of **2** with acetophenone was optimized using quantitative GC analyses (Table 1 and Supporting Information). The optimized protocol was extended to all azachalcone targets. The DBU protocol reliably effects condensations of **2** and **3** in yields comparable to or better than those reported

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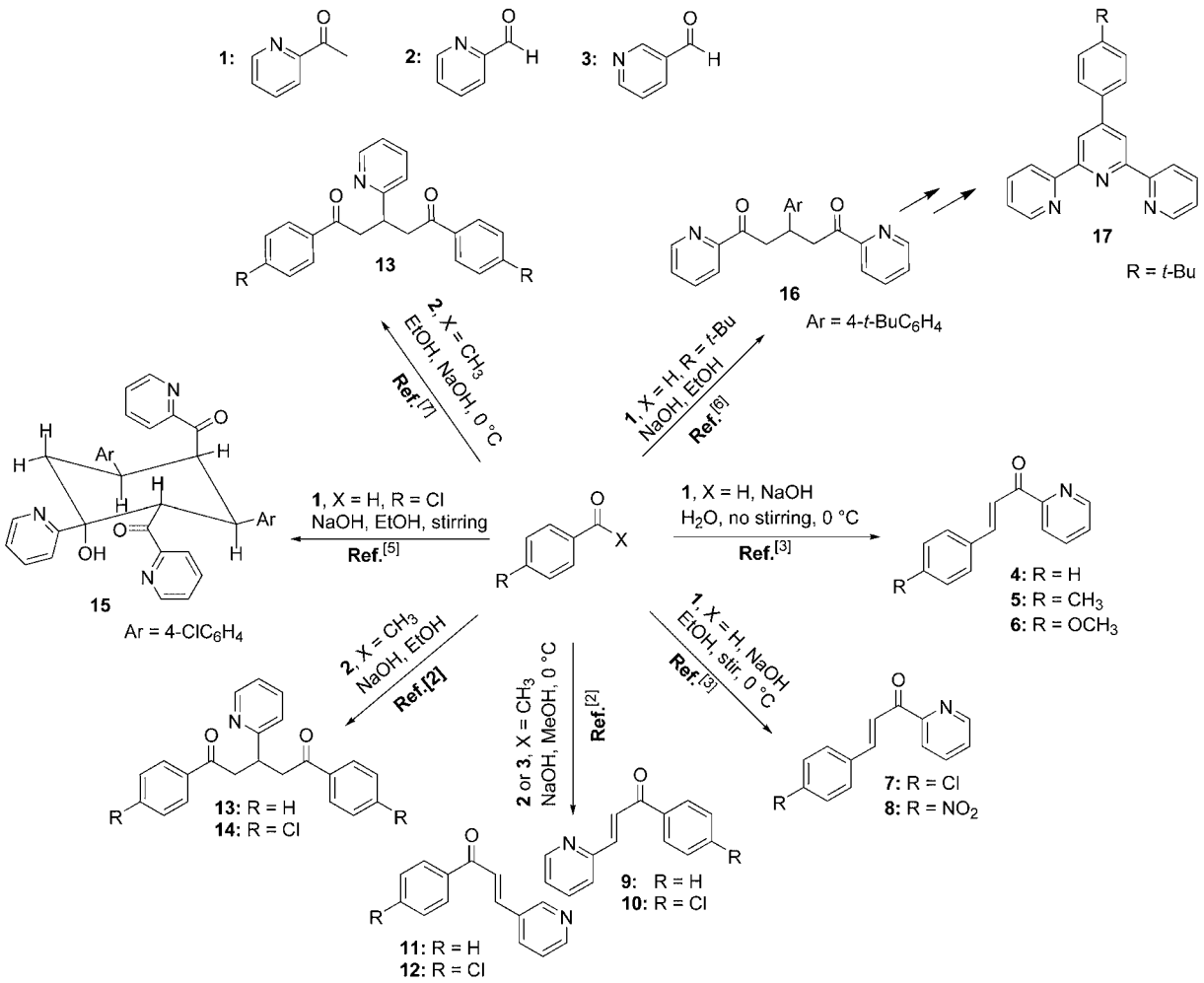
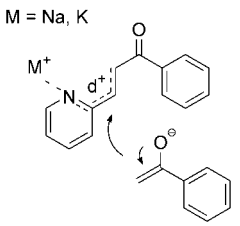


Scheme 1. Condensation products of reactions using 2-acetylpyridine (**1**) and 2- and 3-pyridinecarboxaldehyde (**2** and **3**).



Scheme 2. Metal ion coordination activating the Michael acceptor.

for the aqueous protocols (Table 2). However, we reiterate that the synthesis of 2- and 3- azachalcones is ***only*** possible with the DBU protocol (Scheme 3). The current limitation of this protocol is that it fails to effect condensations of the less reactive ketone **1**.

Our mechanistic proposal (Scheme 4) suggests that these reactions could in principle be catalytic in DBU although an uncharacterized side product suggests that DBU is consumed in a separate side reaction. Indeed, the reaction using 0.1 mol equivalents of DBU produced the azachalcone in only 7% yield, and a dark red layer separated from all mixtures left longer than 32 hours. These data indicate that DBU cannot be used in catalytic amounts. Reactions employing a two-fold excess in **2** or a five-fold excess in DBU each showed a large amount of side product formation indicated by GC, leading us to believe that the side product incorporates the aldehyde and DBU, but we were unable to obtain this side product in pure form. Upon heating, the side reaction overtook the desired transformation, and the impurity appeared in significant amounts after only ten minutes. Attempts to accelerate the DBU reaction by heating were abandoned.

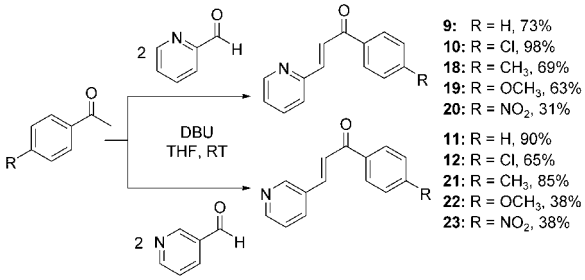
The present DBU-mediated condensation succeeds with both electron-donating and electron-withdrawing substituents for the aldehydes studied and shows no formation of the Michael addition product that is common when metal-containing inorganic bases are used for these condensations. This finding reinforces and supercedes the conclusions of Wachter-Jurcsak and co-workers that the metal cation promotes the Michael pathway in the condensations towards azachalcones. The utility of the organobase-mediated approach makes it an at-

Table 1. Parameters and yields for optimizing the DBU protocol.

2 [mol]	Acetophenone [mol]	DBU [mol]	GC Yield [%]	Time [h]	Temperature [°C]
1	1	1	40	50	25
1	2	1	53	27.5	25
2	1	1	90	32	25
1	1	0.1	7	24	25
1	1	5	36	7.5	25
2	1	1	54	3	Reflux

Table 2. Yield comparison for DBU protocol *versus* reported syntheses.

Compound	Yield [%]		
	DBU Protocol	Ref.[2]	Ref.[5]
9	73	42	35
10	98	–	85
11	90	40	40
12	65	–	63
18	69	–	86
19	63	–	–
20	31	–	–
21	85	–	63
22	38	–	–
23	38	–	–



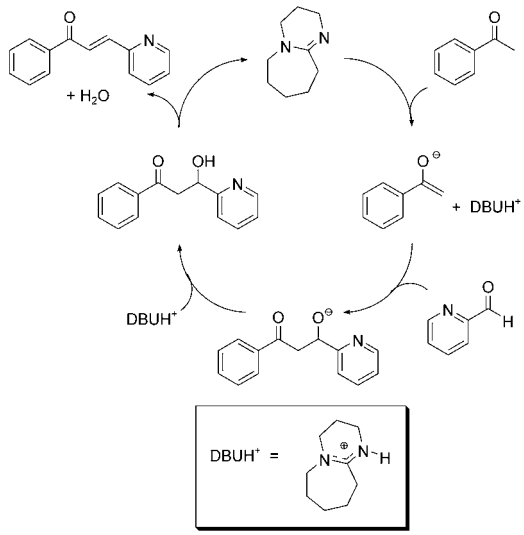
Scheme 3. Base-mediated protocol for condensations of 2- and 3- pyridinecarboxaldehydes.

tractive alternative to aqueous protocols that suffer from accompanying Michael additions. We are currently investigating ways to increase yields of the nitro-substituted azachalcones and the application of the DBU protocol to condensations using 2-acetylpyridine and *N*-acetyloxazolidinone.

Experimental Section

Compounds 9–12, 18, 19, 21, 22

These compounds were synthesized using the optimized DBU-catalyzed aldol condensation/dehydration procedure (see Supporting Information for the optimization protocol): 32 mmol of the acetophenone, 32 mmol of DBU, and 64 mmol of 2-pyridinecarboxaldehyde were dissolved in 80 mL of dry THF. This mixture was stirred at room temperature for 36 hours. The THF was then removed, and the residual oil was purified by flash column chromatography with 2:1 petroleum ether:ether as the mobile phase. These solids were then crystallized from *n*-heptane. Yields of isolated pure products are given below; all compounds are known and gave NMR spectral data identical to literature data (see cited references):



Scheme 4. Proposed mechanistic pathway for DBU catalysis in the present aldol/dehydration sequence.

9: 73%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, 1H), 8.13 (m, 3H), 7.82 (d, 1H), 7.77 (dd, 1H), 7.63 (t, 1H), 7.54 (M, 3H), 7.34 (dd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.45, 125.43, 125.50, 128.66, 128.73, 133.09, 136.90, 137.80, 142.80, 150.18, 153.17, 190.45.

10: 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, 1H), 8.06 (m, 3H), 7.74 (m, 3H), 7.48, (d, 2H), 7.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.62, 124.89, 125.67, 128.98, 130.14, 136.12, 136.96, 139.55, 143.19, 150.22, 152.94, 189.09.

11: 90%; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.67 (d, 1H), 8.64 (dd, 1H), 8.03 (dd, 2H), 7.96 (dt, 1H), 7.80 (d, 1H), 7.56 (m, 4H), 7.36 (q, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 123.74, 124.16, 128.59, 130.82, 133.06, 134.55, 137.96, 140.90, 150.02, 121.15, 189.86.

12: 65%; ^{1}H NMR (400 MHz $CDCl_3$): δ = 7.38 (m, 1H), 7.55 (m, 3H), 7.80 (d, 1H), 7.98 (m, 3H), 8.63 (d, 1H), 8.88 (s, 1H).

18: 69%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, 1H), 8.16 (d, 1H), 8.05 (d, 2H), 7.79 (m, 2H), 7.51 (d, 1H), 7.33 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.72, 124.35,

125.41, 125.55, 128.90, 129.36, 135.29, 136.89, 142.37, 144.00, 150.15, 153.31, 189.91.

19: 63%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (d, 1H), 8.16 (m, 3H), 7.78 (m, 2H), 7.50 (d, 1H), 7.32 (m, 1H), 7.01 (d, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.52$, 113.86, 124.30, 125.43, 127.92, 130.82, 131.12, 136.92, 141.96, 150.12, 153.363, 163.65, 188.67.

20: 31%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (d, 1H), 8.36 (d, 2H), 8.24 (d, 2H), 8.11 (d, 1H), 7.80 (m, 2H), 7.51 (d, 1H) 7.36 (m, 1H).

21: 85%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.43$ (s, 3H), 7.32 (m, 3H), 7.58 (d, 1H), 7.77 (d, 1H), 7.93 (d, 3H), 8.62 (d, 1H), 8.85 (d, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.66$, 123.73, 124.26, 128.76, 129.49, 130.96, 134.53, 135.44, 140.463, 144.00, 149.98, 151.05, 189.34.

Compounds 20 and 23

The nitro-substituted compounds showed some evidence of polymerization as the reaction mixture turned from an orange to a deep purple after thirty minutes. For **20**, the THF was removed after 30 min and the residue chromatographed as above. For **23**, the product precipitated from the reaction mixture and was recrystallized from dry acetonitrile. The short reaction time explains the lower isolated yields; all compounds are known and gave NMR spectral data identical to literature data (see cited references):

22: 38%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.90$ (s, 3H), 7.00 (d, 2H), 7.36 (t, 1H), 7.61 (d, 1H), 7.78 (d, 1H), 7.94 (d, 1H), 8.05 (d, 2H), 8.62 (d, 1H), 8.86 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.55$, 114.02, 123.74, 123.83, 130.93, 134.55, 140.09, 149.91, 150.96, 163.74, 188.04.

23: 38%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ (m, 1H), 7.58 (d, 1H), 7.85 (d, 1H), 8.02 (d, 1H), 8.19 (d, 2H), 8.39 (d, 2H), 8.69 (d, 1H), 8.92 (s, 1H).

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