Novel Synthesis of Fully-Substituted Pyridine Derivatives via Self-Condensation of Cyclic Ketones in Aqueous Ammonium Chloride under Hydrothermal Conditions[1]

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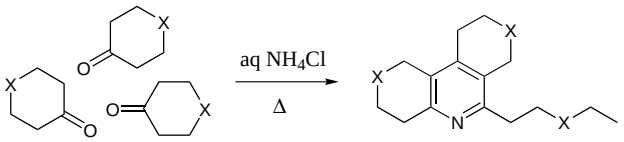
Abstract: A new method for synthesizing fully-substituted pyridine derivatives was developed using the self-condensation of cyclic ketones in aqueous ammonium chloride under hydrothermal conditions.

Key words: self-condensation, cyclic ketones, fully-substituted pyridines, aqueous ammonium chloride, hydrothermal reaction

Pyridine ring systems are an important class of compounds in heterocyclic chemistry because of their occurrence in nature as biologically active substances and their applications in both pharmaceutical and agricultural chemistry. As a consequence, for the past century, several methods for the formation of pyridines have been reported.[2] However, while these are of great value, there is still a need for a new method which would allow us to obtain pyridine derivatives in an environment-friendly manner.

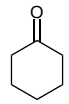
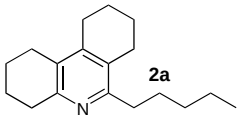
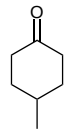
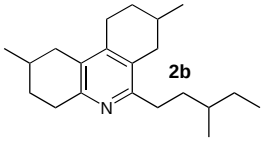
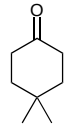
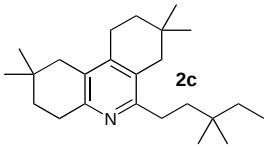
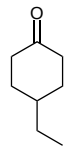
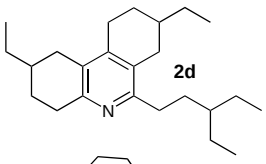
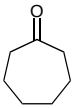
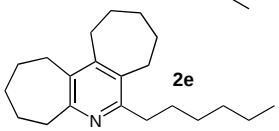
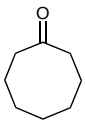
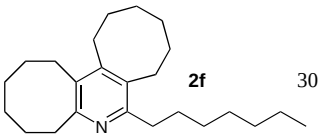
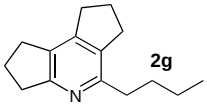
As one approach toward this end, we were particularly interested in the use of aqueous reaction media under hydrothermal conditions. Although there have been several investigations of the use of near-supercritical water (T_c water = 374 °C) for organic reactions,[3] these are mostly limited to the degradative combustion of organic materials, and only a few studies directed toward an application to organic synthesis have been reported.[4] In the course of our own efforts in this field, we found that the self-condensation of cyclic ketones in hot aqueous ammonium chloride provided a novel entry to fully-substituted pyridine derivatives (Scheme 1). Although there is a report of a similar type of transformation using cyclohexanone and ammonia, this work only deals with the pyridine formation as a side reaction and its general utility is unclear.[5] The purpose of this paper is to describe the great value of hydrothermal reactions in the above field of pyridine synthesis via the self-condensation of cyclic ketones. The results are summarized in the Table.



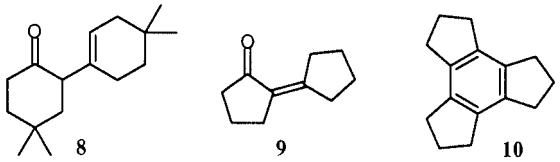
X = CH_2, $(CH_2)_2$, $(CH_2)_3$, CHR, CR_2

Scheme 1

Table Preparation of Pyridine Derivatives via Self-condensation of Cyclic Ketones in aq NH_4Cl[a]

Entry	Ketone (**1**)	Temp. (°C) Time (h)	Product(s) (**2**)	Yield (%)[b]
1	 **1a**	250 48	 **2a**	74
2	 **1b**	250 48	 **2b**	70[c, d]
3	 **1c**	250 48	 **2c**	66[d, e]
4	 **1d**	250 48	 **2d**	64[c, d]
5	 **1e**	300 96	 **2e**	39[d]
6	 **1f**	300 96	 **2f**	30[d]
7	 **1g**	250 24	 **2g**	trace[f]

[a]All reactions were conducted in 30M aq NH_4Cl.
[b]Isolated yield.
[c]Isolated as a diastereomeric mixture.
[d]Unreacted starting ketone was recovered.
[e]1: 1 dimer **8** was also obtained in 4% yield.
[f]Aldol products **9** and **10** were obtained in 11% and 23% yields, respectively.



To establish the optimum conditions, we first examined the reaction of cyclohexanone (**1a**) with aqueous ammonium chloride at 250 °C. The best results were obtained in the presence of 30 M aqueous ammonium chloride,[6] which after 48 h gave 6-pentyl-1,2,3,4,7,8,9,10-octahydrophenanthridine (**2a**) in an isolated yield of 74% (entry 1).[7] The hydrothermal reaction is undoubtedly quite effective as a new tool for promoting the desired pyridine formation through the simple trimerization of cyclic ketones, and is an efficient contribution to "green chemistry".[8] A plausible mechanism for the formation of **2a** is outlined in Scheme 2.[5] It can be easily understood that the reaction should be initiated by the self-aldol condensation of **1a** to give dimer **3**. The crucial step in this sequence might be the Pictet-Spengler-type cyclization[9] of the imino-intermediate **6** followed by fragmentation of **7** through irreversible aromatization toward **2a**.

Under similar conditions, several cyclohexanone derivatives **1b**-**1d** gave **2b**-**2d** in good yields (entries 2-4).[10] Cycloheptanone (**1e**) and cyclooctanone (**1f**) gave the desired pyridine derivatives **2e** and **2f** in moderate yields at higher temperatures (entries 5 and 6).[10] Apparently, increasing the hydrophobicity of the substrates causes a significant decrease in the product yield, probably due to their reduced solubility in the hot water system. Despite our extensive efforts, only a trace amount of pyridine **2g** was formed from cyclopentanone (**1g**) (entry 7), which implies that the initial aldol condensation product **9** is quite insensitive toward ammonium chloride.[11]

In conclusion, we have found a novel method for preparing a variety of fully-substituted pyridine derivatives via the self-condensation of cyclic ketones in aqueous ammonium chloride under hydrothermal conditions.[12] The results illustrate the potential utility of this method as an environment-friendly process, and further studies to elaborate a new effective way to derive a variety of heterocyclic compounds are now in progress.

References and Notes

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(6) Under the similar conditions (250 °C, 24 h), the reactions of **1a** with 10 M and 20 M aqueous NH_4Cl gave **2a** in yields of 21% and 37%, respectively. The use of NH_4OAc or $(NH_4)_2CO_3$ in place of NH_4Cl gave only a trace amount of **2a**.
(7) All reactions were conducted in a Hasteloy-C autoclave reaction vessel with cone and thread fittings and an internal volume of 20 mL, designed to withstand temperatures up to 400 °C.
Typical experimental procedure: Preparation of **2a** (entry 1). A mixture of cyclohexanone (**1a**; 440 mg, 4.5 mmol), NH_4Cl (8.0 g, 0.15 mol), and water (5 mL) was placed in a reaction vessel, and reacted at 250 °C for 48 h. After quenching with water, the mixture was extracted with AcOEt. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 9: 1) to afford **2a** (286 mg, 74%) as a thick colorless oil: R_f 0.30 (hexane/AcOEt = 4: 1); FTIR (neat) ν 1568, 1433, 1414 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.1 Hz), 1.30-1.42 (4H, m), 1.57-1.65 (2H, m), 1.76-1.82 (8H, m), 2.52 (4H, brs), 2.67 (4H, t, *J* = 8.0 Hz), 2.85 (2H, t, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.03, 22.34, 22.57, 22.60, 22.91 (×2), 25.24, 25.77, 26.17, 29.21, 32.20, 32.80, 35.22, 127.02, 127.56, 144.40, 152.33, 157.12; MS *m/e* 257 (M^+).
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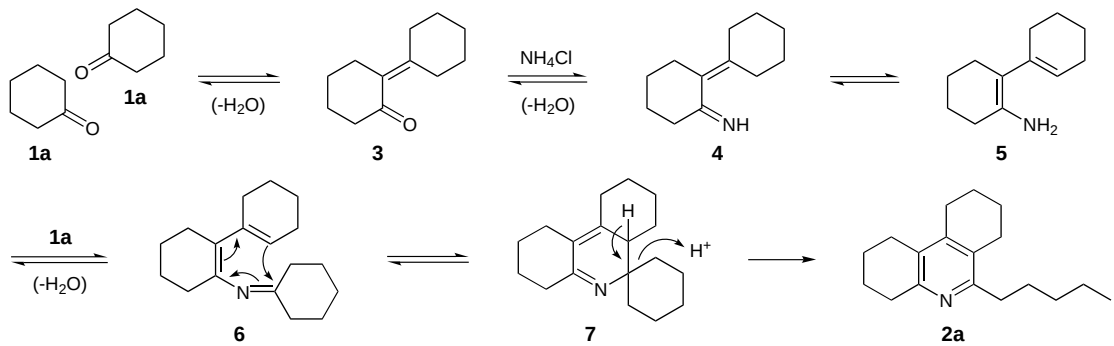

Scheme 2

(10) Data for **2b** (mixture of diastereomers): thick colorless oil; R_f 0.40 (hexane/AcOEt = 4: 1); FTIR (neat) ν 1568, 1456, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.6 Hz), 0.95 (3H, d, *J* = 6.1 Hz), 1.08 (3H, d, *J* = 6.6 Hz), 1.09 (3H, d, *J* = 6.3 Hz), 1.13-1.50 (5H, m), 1.54-2.26 (8H, m), 2.38-2.91 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.39, 19.10, 21.80 and 21.94, 22.10 and 22.17, 25.85 and 26.56, 28.42 and 28.65, 28.97 and 29.11, 29.36 and 29.41 and 29.44, 30.38 and 30.54, 31.07 and 31.22, 32.44 and 32.66, 33.08 and 33.10, 33.83 and 34.25, 34.29 and 34.41, 35.03, 36.21, 126.72 and 126.77, 127.00 and 127.14, 143.91 and 143.98, 152.10 and 152.13, 157.29 and 157.32; MS *m/e* 299 (M^+). Data for **2c**: thick colorless oil; R_f 0.41 (hexane/AcOEt = 4: 1); FTIR (neat) ν 1570, 1458, 1431 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, *J* = 7.6 Hz), 0.93, 0.98, 1.00 (each 6H, s), 1.32 (2H, q, *J* = 7.6 Hz), 1.43-1.47 (4H, m), 1.55 (2H, t, *J* = 6.8 Hz), 1.61 (2H, t, *J* = 6.8 Hz), 2.31, 2.43 (each 2H, s), 2.53 (2H, t, *J* = 6.8 Hz), 2.61-2.66 (2H, m), 2.89 (2H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.50, 23.83, 26.38 (×2), 28.10 (×2), 28.54 (×2), 28.72, 29.20, 29.62, 30.19, 33.11, 34.24, 34.85, 35.53, 39.37, 39.61, 40.92, 126.33, 126.50, 143.49, 151.12, 157.85; MS *m/e* 341 (M^+). Data for **2d** (mixture of diastereomers): thick colorless oil; R_f 0.42 (hexane/AcOEt = 4: 1); FTIR (neat) ν 1570, 1460, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, t, *J* = 7.3 Hz), 0.99 (6H, t, *J* = 7.3 Hz), 1.20-1.65 (15H, m), 1.92-2.95 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.88 (×2), 11.43 and 11.49, 11.55 and 11.59, 25.28 (×2), 25.80 and 26.50, 28.07 and 28.23, 28.61 and 28.74, 28.86 and 29.12, 29.24 and 29.39, 31.67 and 32.06, 32.13 and 32.24, 32.44 and 32.55, 32.59 and 32.66, 32.99 and 33.02, 35.16 and 35.36, 37.70 and 35.82, 40.97, 126.74 and 126.79, 127.00 and 127.11, 144.31 and 144.39, 152.39 and 152.43, 157.46 and 157.51; MS *m/e* 341 (M^+). Data for **2e**: thick colorless oil; R_f 0.40 (hexane/AcOEt = 4: 1); FTIR (neat) ν 1564, 1453, 1418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.1 Hz), 1.26-1.43 (6H, m), 1.53-1.70 (10H, m), 1.76-1.85 (4H, m), 2.73-2.84 (8H, m), 2.98-3.02 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.11, 22.64, 26.61, 26.70, 27.45, 27.49, 28.36, 28.91 (×2), 29.63, 30.55, 31.54, 31.81, 32.10, 36.67, 38.89, 132.57, 133.46, 149.41, 154.66, 159.94; MS *m/e* 299 (M^+). Data for **2f**: thick colorless oil; R_f 0.47 (hexane/AcOEt = 4: 1); FTIR (neat) ν 1562, 1453, 1416 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.1 Hz), 1.23-1.45 (16H, m), 1.59-1.71 (8H, m), 1.73-1.79 (2H, m), 2.71-2.82 (8H, m), 2.91-2.94 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.12, 22.66, 25.96, 26.24, 26.41, 26.52, 26.76, 26.96, 27.13, 29.34, 29.99, 30.47, 30.61, 30.78, 30.84, 31.05, 31.86, 35.64, 35.81, 129.98, 131.40, 147.58, 156.77, 157.90; MS *m/e* 341 (M^+).

(11) We cannot exclude the possibilities that **1g** is less reactive toward aldol condensation and also the tautomerization step like **4** → **5** is fairly slow.

(12) Similar reactions using acyclic ketones such as 3-pentanone gave only a complex mixture of products.

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