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Unprecedented Hydrothermal Reaction of *O*-Phenylaniline and Related Derivatives with Cyclic Ketones. A Novel Approach to the Construction of Phenanthridine and Quinoline Ring Systems†

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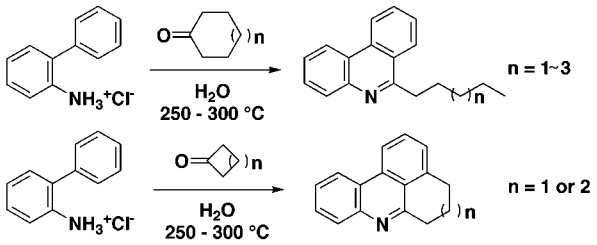
ABSTRACT



A new method for synthesizing phenanthridine and its related compounds was developed using the condensation of *o*-phenylaniline and its homologues with cyclic ketones under hydrothermal conditions.

There is a growing requirement for the development of "green" process reactions that avoid the use of potentially harmful organic solvents.[1] Hence, over the past decade, considerable effort has been directed toward developing a method for extending synthetic organic reactions to an aqueous environment. As part of our study of organic synthesis in hydrothermal reaction media, we recently reported a novel synthesis of fully substituted pyridines via the self-condensation of cyclic ketones in hot aqueous ammonium chloride.[2] The mechanism proposed for this transformation involves aza-triene-type electrocyclization,[3] followed by irreversible cycloalkane ring-fission, as crucial steps (Scheme 1). As an extension of this work, we became aware that incorporation of an aza-triene moiety into an aromatic ring would provide a novel entry to 6-substituted phenanthridine derivatives (Scheme 1).[4] In this paper, we report a realization of this expectation.

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(1) *Green Chemistry. Designing Chemistry for the Environment*; Anastas, P. T., Williamson, T. C., Eds.; American Chemical Society: Washington, DC, 1996. *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: New York, 1999.

(2) Kotsuki, H.; Mehta, B. K.; Yanagisawa, K. *Synlett* **2001**, 1323.

(3) *Thermal Electrocyclic Reactions*; Marvell, E. N.; Academic Press: New York, 1980.

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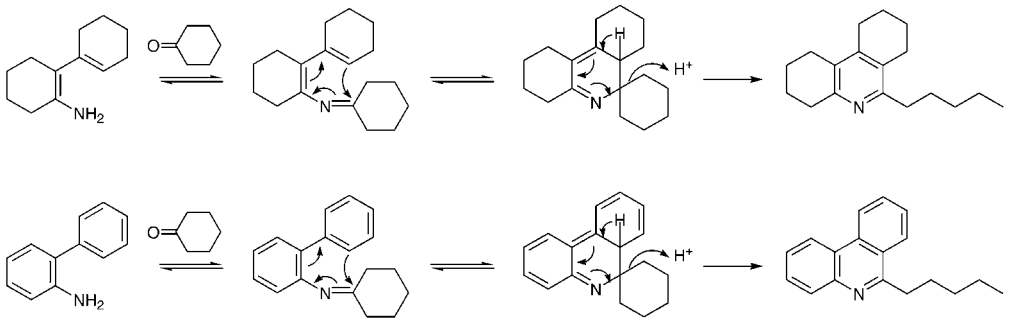
Scheme 1



Phenanthridines are an important class of heterocyclic compounds in materials science and in medicinal chemistry due to their significant biological activities.[5] Although there have been several studies on the synthesis of these molecules, most of them require multistep syntheses or strictly anhydrous conditions.[6] Thus, there is a need for more versatile and simpler methods that can serve as safe and environmentally friendly processes. As one promising approach, we were particularly interested in reactions in hot water, since it has been shown that the solvent properties of water at higher temperatures are roughly equivalent to those of acetone at 25 °C.[7]

First, we examined the reaction of *o*-phenylaniline·HCl (**1a**) with various cyclic ketones (see Table 1).[8] When a mixture of **1a** and 2.2 equiv of cyclohexanone (**2a**) in water (0.04 M solution) was heated at 250 °C for 24 h, 6-pentylphenanthridine (**3a**) was obtained in 72% yield along with a small amount (12%) of byproduct **3b** (entry 1).[9] The latter compound may be formed by a quite unusual cyclohexylation[10] of **1a** at the *para*-position, followed by annulation with **2a**.[11] Under similar conditions, cycloheptanone (**2b**) and cyclooctanone (**2c**) gave the desired 6-substituted phenanthridine derivatives **3c** and **3e** in moderate yields (entries 2 and 3). In these examples, **3d** and **3f** could be detected as only very minor byproducts.[12] Again, as in our previous observation,[2] increasing the hydrophobicity of the substrates tends to retard the reaction progress, probably due to their reduced solubility in the hot water system.

Unexpectedly, when cyclobutanone (**2d**) and cyclopentanone (**2e**) were used as ketone components, completely different types of ring-fused compounds **3g** and **3i**, respectively, were obtained as the major product (entries 4 and 5).[13] The structures of these products were unequivocally determined by their X-ray crystallographic analyses.[14] Our proposed

(4) For a related work on the synthesis of phenanthridines from *o*-phenylanilines via radical cyclization, see: Leardini, R.; Tundo, A.; Zanardi, G. *Synthesis* **1985**, 107.

(5) Keene, B. R. T.; Tissington, P. *Adv. Heterocycl. Chem.* **1971**, *13*, 315. Troll, T. In *Houben-Weyl-Methods of Organic Chemistry*; Georg Thieme Verlag: Stuttgart, 1992; Vol. E7b, pp 157−204.

(6) Lysén, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2002**, *4*, 257. Pawlas, J.; Begtrup, M. *Org. Lett.* **2002**, *4*, 2687 and references therein.

(7) For reviews see: Siskin, M.; Katritzky, A. R. *Science* **1991**, *254*, 231. Katritzky, A. R.; Allin, S. M.; Siskin, M. *Acc. Chem. Res.* **1996**, *29*, 399. Bröll, D.; Kaul, C.; Krämer, A.; Krammer, P.; Richter, T.; Jung, M.; Vogel, H.; Zehner, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2998. Savage, P. E. *Chem. Rev.* **1999**, *99*, 603. Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725.

(8) All reactions were conducted in a Teflon autoclave reaction vessel (for higher temperature reactions, a Hasteloy-C reaction vessel was used) with cone and thread fittings and an internal volume of 20 mL, designed to withstand temperatures up to 250 °C. **Typical Experimental Procedure for the Reaction of 1a with 2a (entry 1).** A mixture of *o*-phenylaniline·HCl (**1a**, 144 mg, 0.7 mmol) and cyclohexanone (**2a**; 151 mg, 1.54 mmol) in 15 mL of H_2O was placed in an autoclave reaction vessel and allowed to react at 250 °C for 24 h. After basification with saturated $NaHCO_3$, the mixture was extracted with AcOEt. The crude product was purified by preparative TLC (hexane/AcOEt = 9:1) to afford **3a** (126 mg, 72%) and **3b** (28 mg, 12%). Compound **3a**: colorless oil; UV (C_6H_6) λ_{max} (ϵ) 344.0 (680), 329.0 (810), 293.0 (1780); FTIR (neat) ν 1613, 1586, 1487, 1462, 758, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.43 (2H, sextet, J = 7.3 Hz), 1.47−1.56 (2H, m), 1.88−1.96 (2H, m), 3.36 (2H, dd, J = 8.1, 6.0 Hz), 7.61 (1H, ddd, J = 8.3, 7.1, 1.5 Hz), 7.68 (1H, ddd, J = 8.1, 7.1, 1.2 Hz), 7.70 (1H, ddd, J = 8.1, 7.1, 1.5 Hz), 7.82 (1H, ddd, J = 8.3, 7.1, 1.2 Hz), 8.13 (1H, dd, J = 8.1, 1.5 Hz), 8.25 (1H, dd, J = 8.2, 1.2 Hz), 8.53 (1H, dd, J = 8.3, 1.5 Hz), 8.63 (1H, dt, J = 8.3, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05, 22.60, 29.35, 32.18, 36.41, 121.88, 122.46, 123.62, 125.22, 126.23, 126.35, 127.19, 128.54, 129.51, 130.25, 132.94, 143.71, 162.50. Compound **3b**: colorless oil; FTIR (neat) ν 1613, 1584, 1495, 1449, 831, 787, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.2 Hz), 1.26−1.67 (9H, m), 1.79−2.02 (7H, m), 2.76 (1H, tt, J = 11.7, 3.4 Hz), 3.33 (1H, dd, J = 8.1, 7.8 Hz), 7.58 (1H, dd, J = 8.3, 1.7 Hz), 7.65 (1H, ddd, J = 8.0, 7.8, 1.2 Hz), 7.79 (dt, J = 7.8, 1.2 Hz), 8.05 (1H, d, J = 8.3 Hz), 8.22 (1H, dd, J = 8.0, 1.2 Hz), 8.34 (1H, d, J = 1.7 Hz), 8.65 (1H, dd, J = 7.8, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.03, 22.58, 26.16, 26.91 (×2), 29.48, 32.13, 34.67 (×2), 36.20, 44.94, 119.23, 122.41, 123.40, 125.15, 126.35, 126.98, 128.13, 129.10, 130.09, 132.99, 142.04, 146.21, 161.54.

(9) We found that the product ratio was highly dependent upon the molar concentration of **1a**: at 0.04 M, **3a** (72%) and **3b** (12%) (Table 1, entry 1); at 0.07 M, **3a** (54%) and **3b** (16%); at 0.1 M, **3a** (46%) and **3b** (23%); at 0.2 M, **3a** (40%) and **3b** (40%); and at 0.4 M, **3a** (32%) and **3b** (42%).

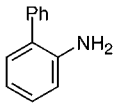
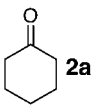
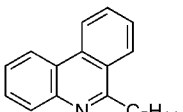
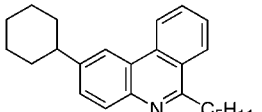
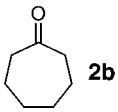
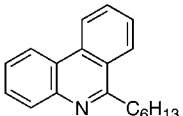
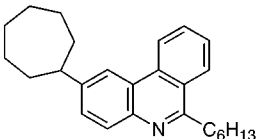
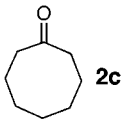
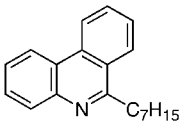
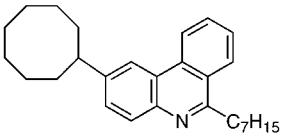
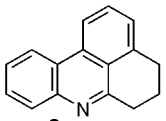
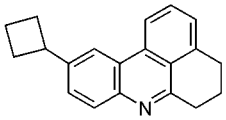
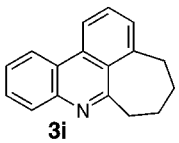
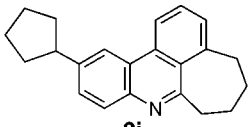
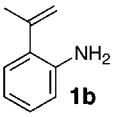
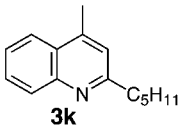
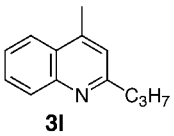
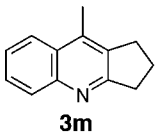
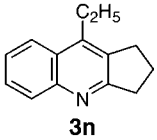
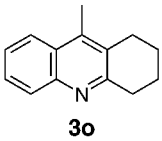
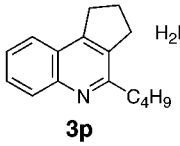
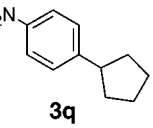
(10) There is only one precedent for this type of cycloalkylation of anilines: Gataullin, R. R.; Kazhanova, T. V.; Fatykhov, A. A.; Spirikhin, L. V.; Abdrakhmanov, I. B. *Russ. Chem. Bull.* **2000**, *49*, 174. Mechanistic studies on this unusual reaction are currently in progress and will be reported in the future.

(11) In a separate reaction, we confirmed that no detectable amount of **3b** was formed by the treatment of **3a** with **2a** under the same conditions.

(12) Compound **3f** could only be detected by GCMS analysis of the crude sample.

(13) Compound **3g**: oil; FTIR (neat) ν 1597, 1574, 1478, 1458, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (2H, quint, J = 6.1 Hz), 3.15 (2H, t, J = 6.1 Hz), 3.30 (2H, t, J = 6.1 Hz), 7.41 (1H, dd, J = 7.1, 1.0 Hz), 7.56 (1H, dd, J = 8.0, 1.2 Hz), 7.66−7.70 (2H, m), 8.08 (1H, d, J = 8.0 Hz), 8.39 (1H, d, J = 8.3, 1.0 Hz), 8.47 (1H, d, J = 8.1, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.26, 30.84, 35.31, 119.74, 122.18, 123.17, 123.85, 125.95, 126.31, 128.54, 129.06, 130.28, 132.80, 139.64, 143.48, 160.15. Compound **3i**: mp 92.0−94.0 °C; FTIR (KBr) ν 2943, 1572, 1460, 1313, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00−2.13 (4H, m), 3.30 (2H, dd, J = 6.4, 5.1 Hz), 3.49 (2H, dd, J = 6.8, 4.9 Hz), 7.45 (1H, d, J = 7.3 Hz), 7.58 (1H, ddd, J = 8.3, 7.3, 1.2 Hz), 7.65−7.70 (2H, m), 8.04 (1H, d, J = 8.3 Hz), 8.49 (2H, dd, J = 8.3, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.90, 25.95, 34.42, 38.33, 120.42, 122.16, 123.81, 126.16, 126.59, 128.52, 128.97, 129.23, 129.95, 134.38, 143.07, 143.18, 163.69.

Table 1. Reaction of Aniline·HCl Salts with Cyclic Ketones under Hydrothermal Conditions[a]

Entry	Aniline•HCl (**1**)	Ketone (**2**)	Conditions	Products	Yield (%)
1	 **1a**	 **2a**	250°C, 24 h	 **3a**  **3b**	84 (86 : 14)
2	**1a**	 **2b**	250°C, 48 h	 **3c**  **3d**	61 (98 : 2)
3	**1a**	 **2c**	300°C, 24 h	 **3e**  **3f**	44 (>99 : 1)
4[b]	**1a**	 **2d**	200°C, 24 h	 **3g**  **3h**	50 (88 : 12)
5[b]	**1a**	 **2e**	250°C, 14 h	 **3i**  **3j**	67 (87 : 13)
6[b]	 **1b**	**2a**	200°C, 24 h	 **3k**	64
7[b]			200°C, 24 h		28 (64 : 13 : 23)[c]
8[b]	**1b**	**2d**	150°C, 24 h	 **3l**  **3m**  **3n**	26 (69 : 15 : 16)
9[b]			100°C, 24 h		27 (100 : 0 : 0)
10[b]			250°C, 14 h		33 (52 : 22 : 26)
11[b]	**1b**	**2e**	200°C, 24 h	 **3o**  **3p**  **3q**	32 (77 : 11 : 12)[d]
12[b]			150°C, 24 h		36 (100 : 0 : 0)

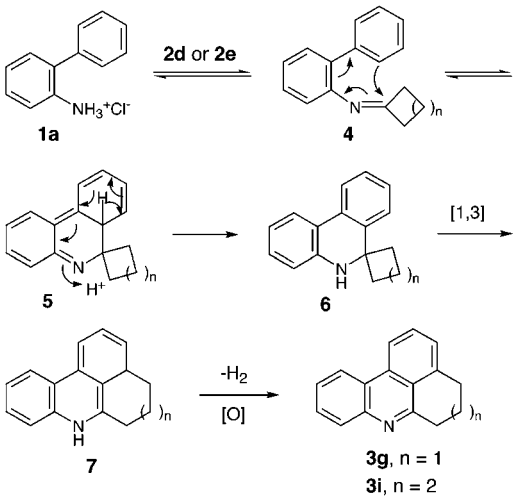
[a] Unless otherwise noted, all reactions were performed with **1** (0.7 mmol) and **2** (1.54 mmol) in water (15 mL). [b] Used 3.0 equiv of **2**. [c] 2,4-Dimethylquinoline was also isolated in 5% yield. [d] Trace amount of 2-butyl-4-methylquinoline was detected.

mechanism for the formation of these compounds is outlined in Scheme 2. At the initial stage, **1a** should condense with **2d** or **2e** to provide imine **4**, which is further converted to the spiro-compound **5** via thermal 6-π electrocyclization. This compound is then aromatized to afford cyclobutylamine **6**, which undergoes spontaneous [1,3]-migrative ring expansion[15] followed by aromatization in the air, thus giving the corresponding ring-fused phenanthridines **3g** and **3i**. In contrast to the case with **2a**−**c**, the remarkably different mode of reactivity for **2d** and **2e** can be understood by invoking their inherent ring strain at the stage from **6** to **7**.

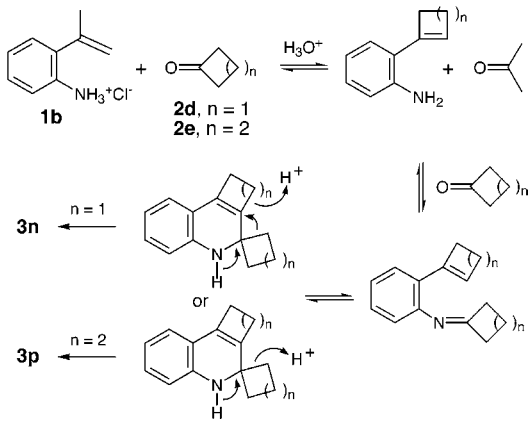
(14) See Supporting Information.

(15) Berson, J. A. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 311−390. Wong, H. N. C.; Lau, K.-L.; Tam, K.-F. In *Small Ring Compounds in Organic Synthesis I*; de Meijere, A., Ed.; Springer-Verlag: Berlin, 1986; pp 138−141.

Scheme 2



Scheme 3



We extended this methodology to the reaction of 2-isopropenylaniline·HCl (**1b**) to obtain quinoline derivatives. As expected, the reaction with **2a** proceeded quite smoothly through a normal pathway to afford quinoline **3k** in 64% yield (entry 6). Although the yields were not always so high, the reactions with **2d** and **2e** again gave an unpredictable mixture of products, and we found that their product distributions were strongly dependent upon the reaction temperature. Thus, heating **1b** and **2d** at 200 °C for 24 h resulted in **3l**, **3m**, and **3n** in a combined yield of 28% and in a ratio of 64:13:23 (entry 7),[16] while the same reaction at 100 °C gave mostly **3l** (27% yield) (entry 9). On the other hand, the use of **2e** led to a different mixture, from which **3o**, **3p**, and *p*-cyclopentylaniline (**3q**) could be isolated (entries 10−12). Among these products, **3o** was always a major product and **3p** and **3q** were isolated as minor components. The formation of tricyclic compounds, **3n** and **3p**, implies the possibility of equilibration like that shown in Scheme 3 under these conditions.

In conclusion, we have described for the first time a novel and simple method for preparing a variety of phenanthridines and related compounds via the condensation of *o*-phenylaniline or 2-isopropenylaniline with cyclic ketones under hydrothermal conditions.[17] The results illustrate the potential utility of this method as an environment-friendly process, and further studies to elucidate the reaction mechanism and extend the scope of this reaction are now in progress.

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Supporting Information Available: Experimental procedures and spectral data for compound **3** as well as X-ray data for the picrate salt of compound **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In this case 2,4-dimethylquinoline was also detected as a minor byproduct (5% yield). This might be formed by condensation of **1b** with acetone, formed by decomposition of **1b** (see Scheme 3), followed by electrocyclization and aromatization.

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