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A novel aromatic alkylation of anilines with cyclic and acyclic ketones under hydrothermal conditions

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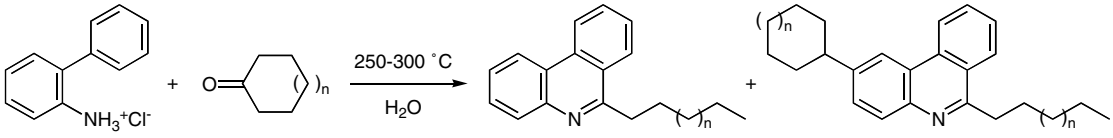
Abstract—A novel aromatic ring-alkylation was achieved by condensation between aniline·HCl salts and cyclic or acyclic ketones under hydrothermal conditions.

Over the past decade, a great deal of attention has been focused on the development of new synthetic reactions in aqueous media, mainly due to the increasing importance of 'green chemical processes' in modern organic synthesis.[1] In our own efforts in this field, we recently reported a novel synthesis of phenanthridine derivatives that involves the efficient condensation of *o*-phenylaniline·HCl with cyclic ketones under hydrothermal conditions (Scheme 1).[2] In this work, in addition to the targeted 6-alkyl-substituted phenanthridine derivatives, we noted that unexpected byproducts with a cycloalkyl functionality at the 2-position were formed in the reaction mixture. We considered that the latter compounds might be accessed through aromatic ring-alkylation followed by phenanthridine core-construction.[3]

A survey of the literature revealed that there are no precedents for this type of alkylation, except for the related work on the alkylation of pyrrole with ketones in a hot-water system.[4] The purpose of this study was to clarify the general features of the above mentioned aromatic ring-alkylation and to demonstrate the power of the hydrothermal technique in the development of environment-friendly chemical transformations. The results are summarized in Table 1.[5]

When a mixture of aniline·HCl (**1a**, 2 mmol)[6] and cyclohexanone (**2a**, 7 mmol) in 10 mL of H_2O was reacted at 250 °C for 24 h, *p*-cyclohexylaniline (**3**) was isolated in 29% yield along with tetrahydrophenanthridine derivatives **4** (36%) and **5** (17%) (entry 1).[7] It is conceivable that **1a** was first condensed with **2a** at both the *ortho*- (product **A**) and *para*-positions (product **D**), and, because of its favorable 6π-electronic system (**B**→**C**), the intermediate *ortho*-adduct **A** was converted immediately to **4** by condensation with another equivalent of **2a** (Scheme 2). Following an identical process, **5** should be derived from **3**. Accordingly, the only problematic pathway in this reaction sequence is the formation of **3** from **D**. One possible explanation for this step is that ionic hydrogenation of the benzylic carbocation intermediate **E** occurs,[8,9] since under hydrothermal conditions the acidic reaction



Scheme 1.

Keywords: Hydrothermal reactions; Anilines; Aromatic ring-alkylation; Ketones.
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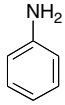
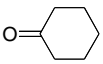
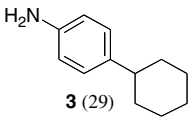
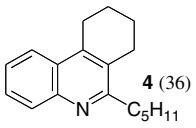
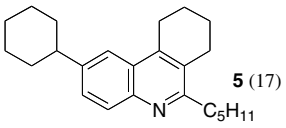
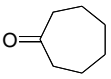
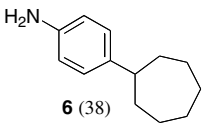
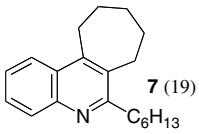
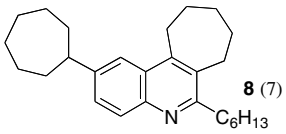
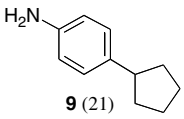
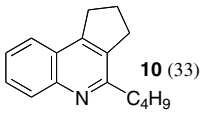
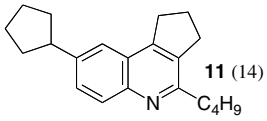
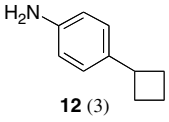
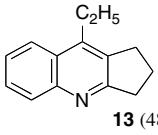
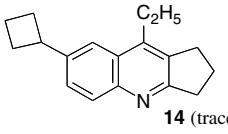
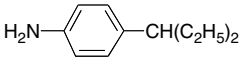
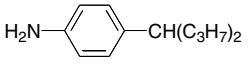
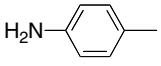
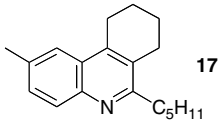
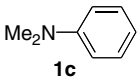
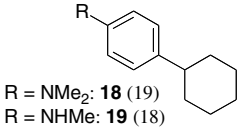
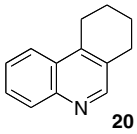
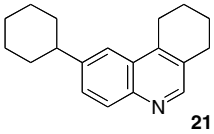
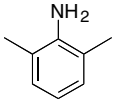
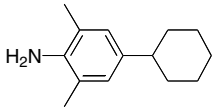
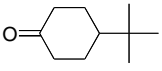
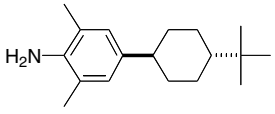
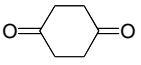
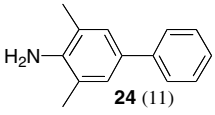
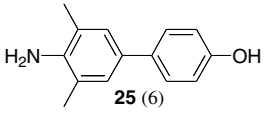
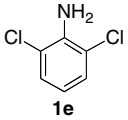
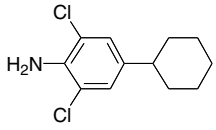
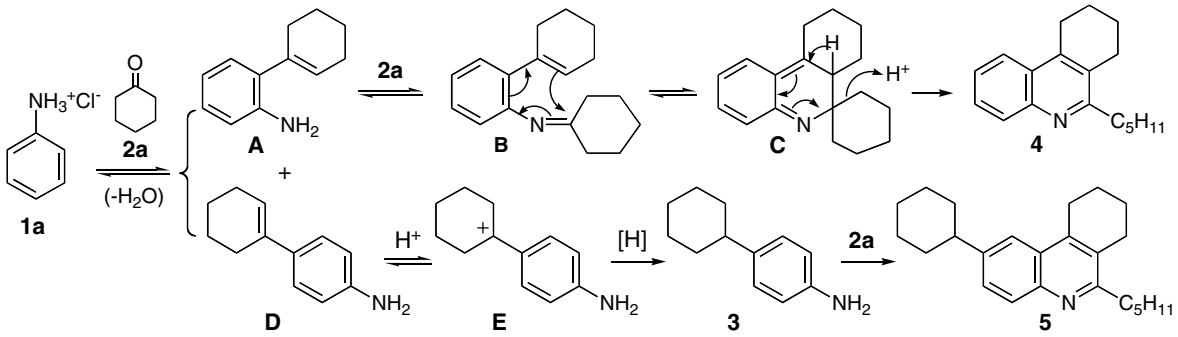
Table 1. Reaction of aniline·HCl salts (**1**) with ketones (**2**) under hydrothermal conditions (250 °C, 24 h)[a]

Entry	Aniline·HCl (**1**)	Ketone (**2**)	Product(s) (yield, %)[b]
1	 **1a**	 **2a**	 **3** (29)  **4** (36)  **5** (17)
2	**1a**	 **2b**	 **6** (38)  **7** (19)  **8** (7)
3[c]	**1a**	 **2c**	 **9** (21)  **10** (33)  **11** (14)
4	**1a**	 **2d**	 **12** (3)  **13** (48)  **14** (trace)
5	**1a**	3-Pentanone (**2e**)	 **15** (27)
6	**1a**	3-Heptanone (**2f**)	 **16** (31)
7	 **1b**	**2a**	 **17** (71)
8	 **1c**	**2a**	 R = NMe_2: **18** (19) R = NHMe: **19** (18)  **20** (9)  **21** (10)
9	 **1d**	**2a**	 **22** (67)
10	**1d**	 **2g**	 **23** (48)
11	**1d**	 **2h**	 **24** (11)  **25** (6)
12	 **1e**	**2a**	 **26** (47)

[a] All reactions were performed with **1** (2.0 mmol) and **2** (7.0 mmol) in water (10 mL).
[b] Isolated yields after silica gel column chromatography.
[c] 2-Cyclopentylidenecyclopentan-1-one was also isolated in 7% yield.

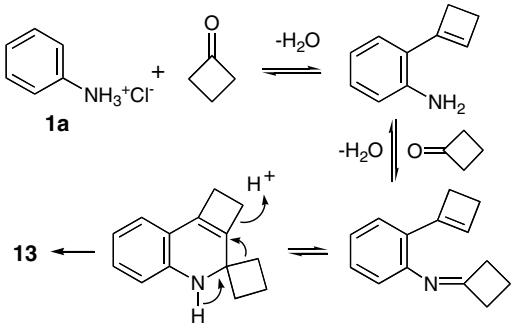
media might be considerably altered, leading to a superacidic-like environment.[10]

Under similar conditions, cycloheptanone (**2b**), cyclopentanone (**2c**), and cyclobutanone (**2d**) reacted with



Scheme 2.

1a to give adducts **6**–**14**, following the same reaction course as above (entries 2–4). By analogy with our previous observations,[2] the formation of quinolines **13** and **14** can be interpreted as the result of a sequential mechanistic relay of (i) 6π-electrocyclic ring closure, (ii) spontaneous [1,2]-migrative ring-expansion, and (iii) cyclobutane ring-opening (Scheme 3). The present method was also effective for reactions using acyclic ketones such as 3-pentanone (**2e**) and 4-heptanone (**2f**), and *para*-alkylated compounds **15** and **16** were obtained in respective yields of 27% and 31% (entries 5 and 6).



Scheme 3.

The use of 4-methylaniline·HCl (**1b**) as the substrate proceeded cleanly to provide tetrahydrophenanthridine **17** in reasonably good yield (71%) (entry 7). On the other hand, *N*,*N*-dimethylaniline (**1c**) was less reactive than aniline itself: compounds **18**–**21** were obtained in a combined yield of 56% and in a ratio of 34:32:16:18 (entry 8). These results imply that the presence of a free NH function is essential for the desired aromatic ring-alkylation.[11]

We also examined the reactions using 2,6-disubstituted anilines such as **1d** and **1e** to protect against concomitant *ortho*-alkenylation. As expected, the reaction between **1d** and **2a** gave **22** as a single product in 67% yield (entry 9). Interestingly, when 4-*tert*-butylcyclohexanone (**2g**) was used as a ketone component, the thermodynamically stable *trans*-isomer **23** was only isolated in moderate yield (48%) (entry 10). The use of diketone **2h** caused no dialkylation, and instead arylated compounds **24** and **25** were obtained in low yields (entry 11), suggesting that the alkylation–aromatization process is much faster than the double alkylation–hydrogenation process. Finally, the reaction between 2,6-dichloroaniline (**1e**) and **2a** also proceeded effectively to afford the desired adduct **26** in 47% yield without loss of the chlorine atoms (entry 12).

In conclusion, we have described a novel pathway for the aromatic ring-alkylation of anilines with a variety of cyclic and acyclic ketones under hydrothermal conditions.[12] Although the yields are not always so high, we believe that the method provides a potential utility of hydrothermal chemistry in organic synthesis. Further studies to explore the feasibility of hydrothermal reactions in other types of transformation are now in progress.

Acknowledgments

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References and notes

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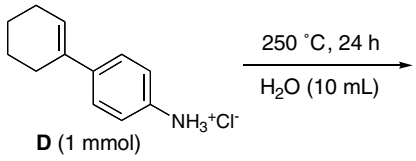
2. Mehta, B. K.; Yanagisawa, K.; Shiro, M.; Kotsuki, H. *Org. Lett.* **2003**, *6*, 1605–1608.
3. In a separate experiment, we confirmed that cyclohexanone did not react with 6-pentyl-phenanthridine under the similar conditions.

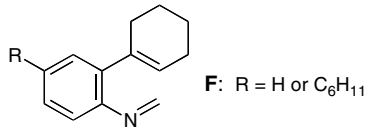
4. Sobral, A. J. F. N.; Rebanda, N. G. C. L.; da Silva, M.; Lampreia, S. H.; Silva, M. R.; Beja, A. M.; Paixao, J. A.; Rocha Gonsalves, A. M. d'A. *Tetrahedron Lett.* **2003**, *44*, 3971–3973.
5. All reactions were conducted in a Teflon autoclave reaction vessel (for higher temperature reactions a Hasteloy-C 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 aniline·HCl (**1a**; 260 mg, 2 mmol) and cyclohexanone (**2a**; 687 mg, 7 mmol) in 10 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 crude mixture was extracted with ethyl acetate. Purification by silica gel column chromatography gave **3** (102 mg, 29%), **4** (182 mg, 36%), and **5** (112 mg, 17%).
Compound **3**: $R_f = 0.15$ (hexane/AcOEt = 9:1); FTIR (neat) ν 3353, 1620, 1516, 1449, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15–1.26 (1H, m), 1.30–1.40 (4H, m), 1.68–1.75 (1H, m), 1.77–1.84 (4H, m), 2.35–2.42 (1H, m), 3.53 (2H, br), 6.63, 7.00 (each 2H, dm, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.22, 27.01 (×2), 34.75 (×2), 43.69, 115.21 (×2), 127.52 (×2), 138.55, 144.14; MS *m/z* 175 (M^+).
Compound **4**: $R_f = 0.41$ (hexane/AcOEt = 9:1); FTIR (neat) ν 1589, 1499, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, $J = 7.2$ Hz), 1.34–1.49 (4H, m), 1.72–1.80 (2H, m), 1.87–1.96 (4H, m), 2.85 (2H, br t, $J = 5.6$ Hz), 2.91 (2H, m), 3.12 (2H, br t, $J = 5.6$ Hz), 7.45, 7.59 (each 1H, ddd, $J = 8.3$, 6.8, 1.0 Hz), 7.89, 7.99 (each 1H, dd, $J = 8.3$, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.10, 22.12, 22.66, 22.69, 25.64, 26.37, 28.75, 32.24, 36.14, 122.36, 125.32, 126.59, 127.83, 128.38, 129.20, 141.10, 145.59, 162.21; HRMS *m/z* 253.1854, calcd for $C_{18}H_{23}N$: 253.1831.
Compound **5**: $R_f = 0.46$ (hexane/AcOEt = 9:1); FTIR (neat) ν 1588, 1499, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, $J = 7.3$ Hz), 1.24–1.57 (8H, m), 1.69–1.81 (4H, m), 1.86–1.96 (8H, m), 2.68 (1H, tt, $J = 11.5$, 3.2 Hz), 2.84 (2H, t, $J = 5.8$ Hz), 2.89 (2H, m), 3.12 (2H, t, $J = 5.8$ Hz), 7.49 (1H, dd, $J = 8.6$, 2.0 Hz), 7.66 (1H, d, $J = 2.0$ Hz), 7.92 (1H, d, $J = 8.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.10, 22.19, 22.67, 22.76, 25.71, 26.22, 26.41, 26.96 (×2), 28.91, 32.23, 34.64 (×2), 36.08, 44.96, 119.15, 126.45, 127.83, 128.18, 128.95, 140.77, 144.41, 145.11, 161.29; HRMS *m/z* 335.2606, calcd for $C_{24}H_{33}N$: 335.2613.
6. All anilines were used as their hydrochloric salts. The use of free anilines under neutral conditions resulted in no product formation.
7. The use of a large excess of **2a** gave only a complex mixture of products.
8. For reviews on hot-water reactions see: Siskin, M.; Katritzky, A. R. *Science* **1991**, *254*, 231–237; Katritzky, A. R.; Allin, S. M.; Siskin, M. *Acc. Chem. Res.* **1996**, *29*, 399–406; Bröll, D.; Kaul, C.; Krämer, A.; Krammer, P.; Richter, T.; Jung, M.; Vogel, H.; Zehner, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2998–3014; Savage, P. E. *Chem. Rev.* **1999**, *99*, 603–621; Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725–2750.
9. For a similar work on the transformation of *o*-cyclopentenylanilines to *p*-cyclopentylanilines in hot aniline, see: Gataullin, R. R.; Kazhanova, T. V.; Fatykhov, A. A.; Spirikhin, L. V.; Abdrakhmanov, I. B. *Russ. Chem. Bull.* **2000**, *49*, 174–176.
To confirm the proposed mechanism, compound **D** was prepared independently by Suzuki-Miyaura cross-coupling of cyclohexenyl triflate with *p*-$NH(Boc)C_6H_4B(OH)_2$ followed by deprotection of the Boc group. When this substrate, as its HCl salt, in H_2O was reacted at 250 °C for 24 h, the formation of **3** and **4** was observed in addition to a significant amount of aniline (**1a**).



D (1 mmol)

1a (68%) + **3** (14%) + **4** (5%) + **5** (trace)

10. For similar reactions using cycloalkanes in the presence of superacids, see: Koltunov, K. Yu.; Surya Prakash, G. K.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 4330–4336; Koltunov, K. Yu.; Surya Prakash, G. K.; Rasul, G.; Olah, G. A. *Tetrahedron* **2002**, *58*, 5423–5426, and references cited therein. In accordance with this postulation no reaction was observed when aromatic ketones such as benzophenone was used.
11. The formation of 6-unsubstituted products **20** and **21** indicates that the reaction may proceed via the methylene imine intermediate **F** formed by a loss of methane from initial adducts.



F: R = H or C_6H_{11}

12. We briefly examined the applicability of this method to phenols, anisole, and pyridine under acidic conditions, but the reactions completely failed. Although further studies are necessary, at present we can conclude that this method is limited to aniline·HCl salts. See also Ref. 3.