Superacid-promoted synthesis of quinoline derivatives.

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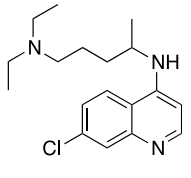
Abstract: A series of vinylogous imines have been prepared from anilines and cinnamaldehydes. These substrates react in superacidic media to provide quinolines and related compounds. A mechanism for the conversion is proposed which involves the cyclization of dicationic superelectrophilic intermediates. Aromatization of the quinoline ring is thought to occur by superacid-promoted elimination of benzene.

Keywords: Heterocycle; Quinoline; Superacid; Superelectrophile

Introduction

Quinolines are an important class of heterocycles.[1] This ring system is commonly found in natural products and biologically active substances.[2] This includes medicinal agents such as quinine and the anti-malaria drug (**1**). Quinolines are also common structural elements in material science applications, polymers, and in dyes/pigments. For example, a well-known



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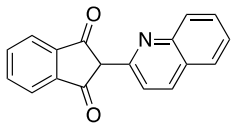

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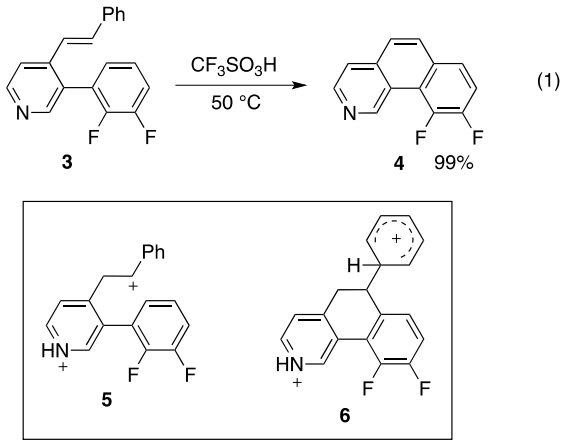
pigment is quinolone yellow (**2**). While a number of synthetic methods have been developed leading to the quinolone ring system,[1,3] there continues to exist the need for new synthetic methods – especially those utilizing inexpensive reagents or catalysts.

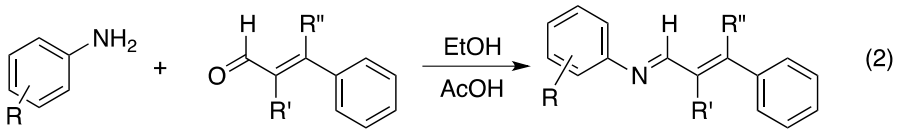
Recently, we described a series of reactions in superacid that provided access to aza-polycyclic aromatic compounds.[4-6] The superacid-promoted chemistry allowed for the synthesis of a wide-variety of ring systems and substituent patterns. For example, the pyridine derivative **3** reacts in triflic acid to provide the benzo[h]isoquinoline **4** in nearly quantitative yield (eq 1).[5] This chemistry is thought to involve double protonation of substrate **3** to generate the dicationic intermediate **5**. Cyclization is then followed by *ipso* protonation of the phenyl group (**6**) followed by elimination of benzene and aromatization of the aza-polycyclic aromatic



compound. As an extension of this methodology leading to condensed arenes, we describe herein an efficient synthetic route to quinolone derivatives. The methodology formally derives the quinolone ring system from anilines and cinnamaldehydes.

Results and Discussion

It was hypothesized that vinylogous imines should undergo double protonation and the resulting superelectrophilic intermediates should provide the condensed aromatic ring system – in this case the quinoline ring system. The required substrates (**7**) are prepared readily by reacting anilines with cinnamaldehydes in ethanol with catalytic acetic acid (eq 2).[7] Initial



(2)

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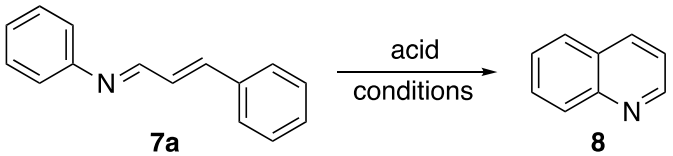
experiments sought to explore the conditions necessary to promote the cyclization (eq 3). Using excess trifluoroacetic acid or methanesulfonic acid at 80°C gave no product even with a 24 hr reaction period. Sulfuric acid does give a trace amount of quinoline product using similar reaction conditions. Using the Brønsted superacid, triflic acid (CF_3SO_3H), quinoline (**8**) can be isolated in 95% yield. This conversion required 34 equivalents of acid and a reaction temperature of 80°C. Using a lower reaction temperature (25°C) or less triflic acid leads to a markedly lower product yield.

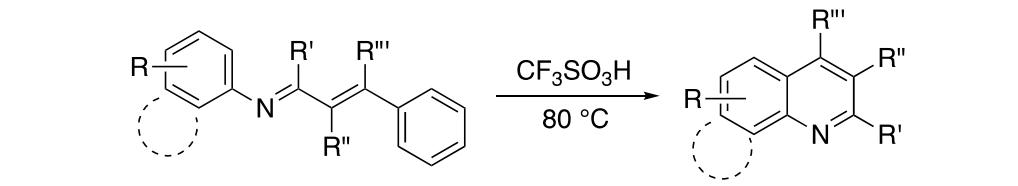


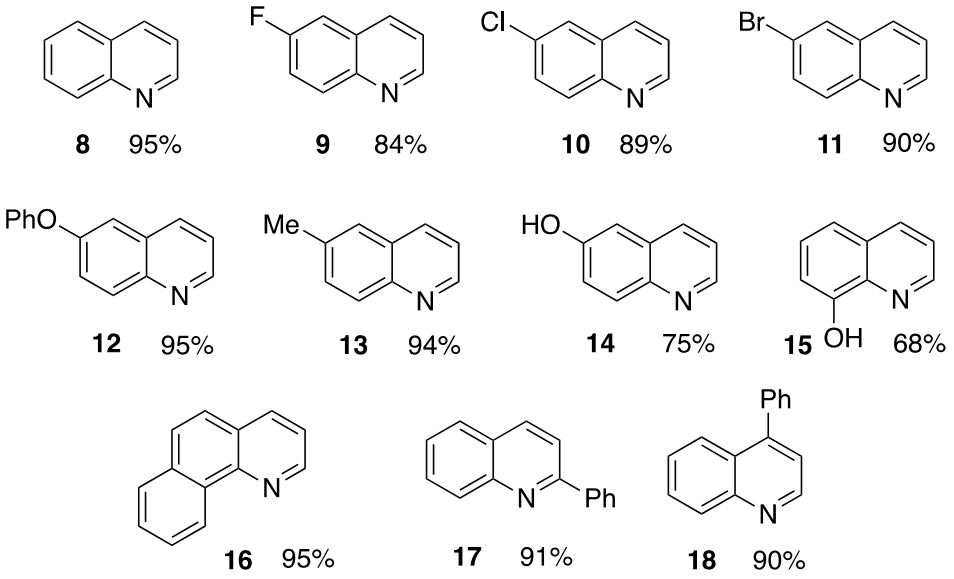
(3)

7a **8**

Using excess triflic acid to promote the condensation reactions, a series of vinylogous imines were converted to quinoline derivatives (Table 1).[8] The quinoline derivatives are prepared in generally good yields (70-95%) from this chemistry. By varying the aniline component, substituents are readily incorporated into the quinoline product. This includes quinolines with halogen (**9-11**), ether (**12**), alkyl (**13**), and phenolic substituents (**14-15**). Likewise, ring-fused products are readily prepared. Thus, 1-aminonaphthalene and

Table 1. Products and yields from the superacid-promoted condensations of vinylogous imines.



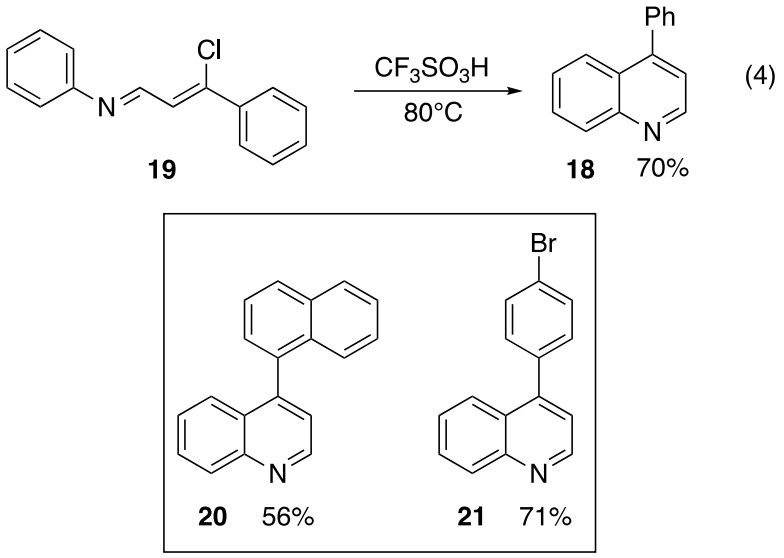


8 95% **9** 84% **10** 89% **11** 90%

12 95% **13** 94% **14** 75% **15** 68%

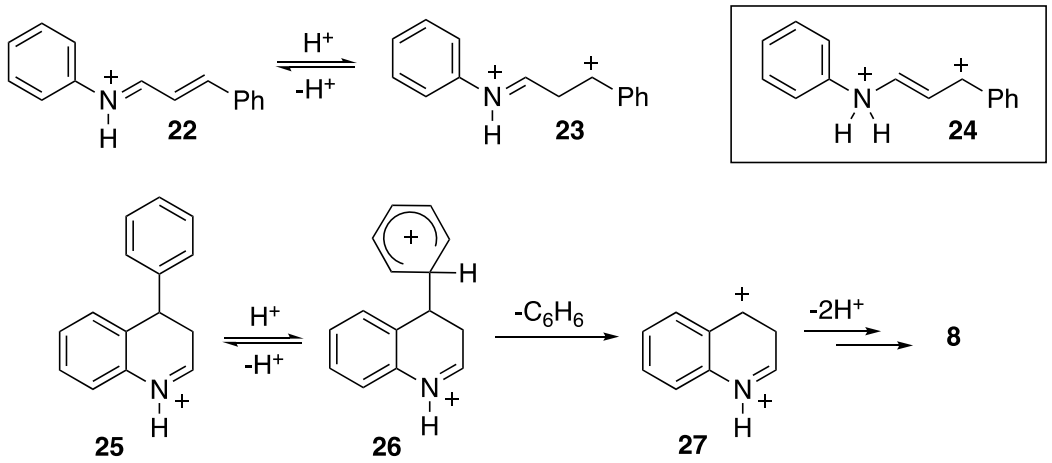
16 95% **17** 91% **18** 90%

cinnamaldehyde provide the vinylogous imine, which upon reaction in superacid, provides benzo[*h*]quinoline (**16**) in excellent yield. With chalcone and aniline, 2-phenylquinoline (**17**) is obtained, while aniline and β-phenylcinnamaldehyde provides 4-phenylquinoline (**18**). In an effort to prepare a halogen-functionalized product, imine **19** was prepared. Upon reaction with superacid however, 4-chloroquinoline was not formed but instead only the phenyl-substituted product (**18**) was obtained (eq 4). The chlorinated substrate (**19**) was prepared from a published



procedure,[9] utilizing the Vilsmeier-Haack reaction ($POCl_3$-DMF) with acetophenone -providing β-chlorocinnamaldehyde – followed by condensation with aniline. Using a similar approach, the naphthyl- and bromophenyl- derivatives (**20** and **21**) were obtained in fair yields. These products were prepared, respectively, from 1-acetylnaphthalene and 4-bromoacetophenone with aniline.

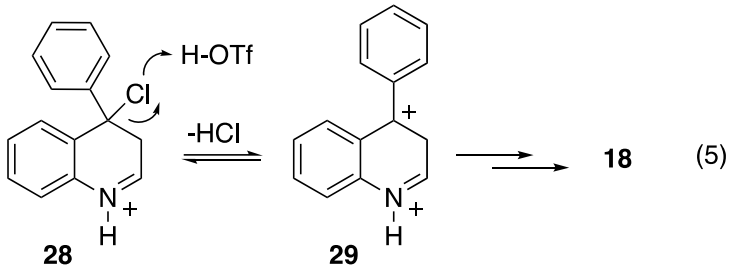
As with our previous studies, a mechanism is suggested involving dicationic, electrophilic cyclizations and benzene elimination leading to the condensed aromatic (Scheme 1). Initial protonation of imine **7a** provides the monocationic iminium ion **22**. In the excess superacid, ion **22** is likely in equilibrium with the the dicationic, superelectrophilic species **23**.[10-12] An isomeric dication (**24**) is conceivable, however DFT calculations (see Supporting Information) indicate that ion **23** is about 6 kcal/mol more stable than ion **24**.[13] There may be several factors that contribute to the greater stability of dication **23**. One factor may be the separation of the two cationic charge centers by the sp^3 carbon in structure **23**.[14] With



Scheme 1.

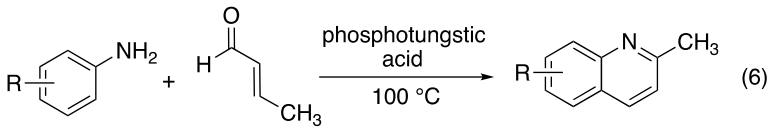
formation of the reactive carbocationic center, cyclization provides intermediate **25**. *Ipso*-protonation leads to ion **26** and loss of benzene, gives the dicationic secies **27** as the precursor to the quinoline aromatic system. Deprotonation provides quinoline (**8**).

In the case of the chlorinated systems, a similar mechanism is proposed (eq 5). Superacid-promoted cyclization leads to intermediate **28**, however instead of ionization at the phenyl group, the chloride is evidently the source of ionization. It is suggested that the superacid protosolvates the chloride, and with loss of HCl, the carbocation species (**29**) is formed. This leads to product **19** from deprotonation steps.



(5)

Interestingly, the Doebner-von Miller reaction is a classic synthetic method leading to quinolines.[15] One example of this transformation involves the reactions of anilines with crotonaldehyde and condensation with heteropolyacids (eq 6).[16] The mechanism for this



(6)

conversion is thought to involve an initial conjugate addition step followed by subsequent dehydrative cyclization (S_EAr step). In our chemistry, the initial step involves condensation of the aniline at the carbonyl group of cinnamaldehyde, followed by a Friedel-Crafts cyclization. This type of reaction sequence has been previously described as a reverse Doebner-von Miller reaction.[15,17] Our chemistry is a unique extension of the reverse Doebner-von Miller reaction, in that the aromatization occurs by superacid-promoted benzene elimination (or in some cases, HCl elimination).

In summary, we have found that vinylogous imines provide good access to functionalized quinolines by reaction in superacid. The proposed mechanism involves formation of iminium-carbenium dications. Cycilzation of this superelectrophilic species leads to formation of the new heterocycles, and with protolytic elimination of benzene, the quinoline product in generated. The chemistry represents a convenient synthetic route to the quinoline ring system from readily available precursors and it is promoted by a Brønsted acid which may be quantitatively recycled.[18]

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8. Typical procedure: Imine (0.25 mmol) is placed in a flask and the vessel is flushed with inert gas. Triflic acid (0.75 mL, 8.5 mmol) is then added to the flask and the solution is stirred at 80 °C for 24 hours. The resulting solution is cooled and then is poured over several grams of ice. Following the addition of chloroform (ca. 20 mL), the aqueous phase is made basic with the addition of saturated $NaHCO_3$. Following extraction of the organic products, the organic extracts are washed with water and then (2x) with brine solution. The organic solution is then dried with sodium sulfate, filtered, and concentrated under vacuum. The product may be further refined by passage through a silica gel plug.

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Graphical Abstract: