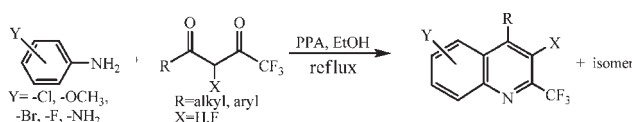# Quinoline formation via a modified Combes reaction: examination of kinetics, substituent effects, and mechanistic pathways

Joseph C. Sloop[a]*

A comprehensive product regioselectivity and kinetics study of the modified Combes quinoline synthesis shown below has been undertaken:

This is the first reported investigation of the Combes condensation employing 19F NMR spectroscopy to monitor intermediate consumption and product formation rates. The reaction was found to be first order in both the diketone and aniline. Product regioselectivity and reaction rates were found to be influenced by substituents on the diketones and anilines with rates varying as much as five fold. The consumption rate of key imine and enamine intermediates mirrored quinoline formation rates, in accord with rate determining annulation. A ρ of -0.32 was determined for this cyclization. While the sign of the reaction constant is consistent with rate limiting electrophilic aromatic substitution (EAS), the magnitude is likely a composite value, resulting from opposing substituent effects in the nucleophilic addition and EAS steps. Mechanistic details and reaction pathways supporting these findings are proposed. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Hammett correlation; steric effects; substituent effects; kinetics; Combes quinoline synthesis; trifluoromethyl-1,3-diketones

INTRODUCTION

Quinolines, which are important precursors to pharmaceuticals and agrochemicals,[1–4] have been studied extensively from a synthetic point of view.[5–14] The Combes quinoline synthesis depicted in Scheme 1 uses a β-diketone substrate, setting it apart from other quinoline preparations.[15] The reaction, which involves nucleophilic addition to the carbonyl, imine, and enamine intermediates and electrophilic aromatic annulation has been qualitatively investigated in terms of substituent effects on product regiochemistry and aniline reactivity, but a systematic kinetics investigation of this condensation is lacking.[16–19]

Reactant/catalyst composition and reaction conditions

The nucleophilic aniline reactant may contain a variety of substituents. Powerful electron-withdrawing groups (EWGs) have been found to inhibit the reaction while electron-donating groups (EDGs) can accelerate quinoline formation unless substituted *ortho* or *para* to the amino group.[5–8,17,18]

The β-diketone electrophile exists as a tautomeric mixture of two chelated, *cis*-enols and the diketo form in most solvent systems.[20–25] However, 2-fluoro-β-diketones are known to exist solely as the ketonic tautomers.[26] Both the enol and keto forms of β-diketones generally react rapidly with amines in acidic media.[27] These phenomena will be discussed in detail later.
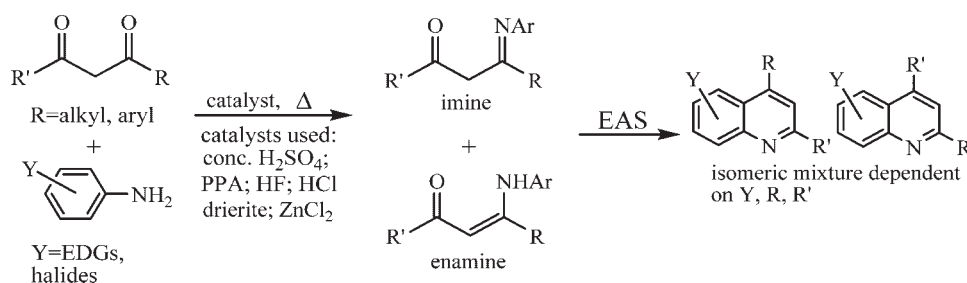
The problems attendant with early quinoline formation methods which used concentrated sulfuric acid as a dehydrating reagent at high temperatures[12–14,17] can be ameliorated by substituting mixtures of polyphosphoric acid (PPA) and selected alcohols.[28,29] The resulting polyphosphoric ester (PPE) catalysts are milder and more effective as dehydrating/cyclizing reagents than concentrated H_2SO_4 or neat PPA. This work[16,19,28] demonstrates that PPA in ethanol is an especially effective catalyst/solvent system, giving satisfactory yields of trifluoromethylquinolines at 70 °C.[29]

The role of intermediates in quinoline product distribution

Multiple modes of aniline addition to β-diketones lead to intermediates shown in Scheme 1, which have been isolated in several cases.[11,13,16–19] The 1,2-addition of anilines to the substrate keto group followed by a 1,2-elimination of water produce an imine,[11,16] whereas the enamine results from either

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Scheme 1. Combes quinoline synthesis

a 1,4-addition of the aniline to the enol species or 1,2-addition to the carbonyl followed by a 2,3-elimination of water.[18,19]

Substitution patterns on the aniline also influence quinoline regiochemistry and, in concert with intermediate topology, complicate product distribution. Figure 1 shows the various positions on the aniline ring at which cyclization could occur.

In earlier work, the syntheses of selectively fluorinated quinolines derived from a modified Combes' method were reported.[15] While preparing these heterocycles, variations in product formation rates and regioselectivity were noted, prompting a comprehensive kinetics and substituent effects study of this reaction.

With the exception of recent work by Clayton,[30] no other substituent effects studies on aromatic annulations have been conducted. The principal efforts in this work were directed at quantifying the influences that substituted trifluoro-methyl-β-diketones and substituted anilines exert on the rate of quinoline formation. Finally, mechanistic pathways for this condensation are proposed which are consistent with experimental observations.

QUINOLINE KINETICS STUDY FINDINGS AND DISCUSSION

Synthesis

Figure 2 shows the trifluoromethyl-β-diketones used in this work. Diketones **1a**–**f** are available commercially; **1g** was prepared by literature methods.[15,25]

Once the trifluoromethyl-β-diketones were in hand, their condensation with anilines in ethanol/PPA as solvent/catalyst system (Scheme 2) afforded the trifluoromethyl quinolines.[15]

Quinoline formation kinetic studies

Reaction progress was conveniently monitored over a 3 h period by 19F NMR using CFCl$_3$ as an internal reference. Consumption of the diketone tautomers ($\delta \approx -77$–78 ppm), imine, and enamine intermediates ($\delta \approx -75$–83 ppm) as well as formation of the two
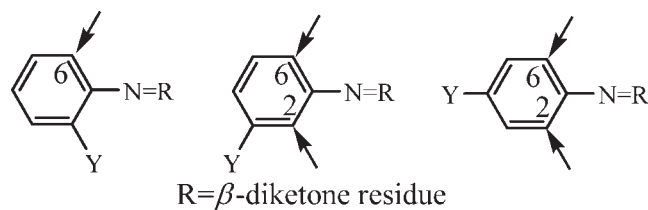

R = β-diketone residue

Figure 1. Cyclization positions for quinoline formation

possible quinoline regioisomers ($\delta \approx -62$–67 ppm)[15,31] were followed. The quinoline products are shown in Scheme 2.

Virtual quinoline formation rates were determined for the condensation of selected trifluoromethyl-β-diketones with anilines. The product distribution, initial rates of product formation, observed rate constants and relative rates are presented in Table 1. The initial rates were determined as the slope of the best fit line to a plot of (quinoline) *versus* time which consisted of 60 data points. All initial rates were obtained prior to $t_{1/2}$ for consumption of the imine and enamine intermediates observed, with $t_{1/2}$ ranging from ~40 min to > 3 h.
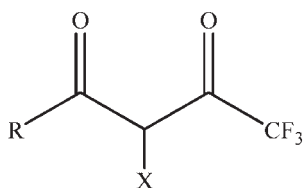
The reaction order for quinoline formation was determined by the isolation method. The results, recorded in Table 2, reflect first order dependence of quinoline formation on both diketone and aniline, where rate $= k$obs[diketone][aniline] and $k$obs is a second-order rate constant.

Effect of diketones and anilines on quinoline product distribution

The modulation of quinoline product distribution by diketone substituents is evident from the data in Table 1. Regioisomeric quinolines were formed in most cases, in agreement with prior investigations.[17,31] Exceptions to this trend include entries 6, 7, 12, 16, and 17, in which the 2-CF$_3$ quinoline was the sole product. Because 2-fluoro-1,3-diketones exist in ketonic form,[20,26] the initial nucleophilic addition of the aniline in the cases of entries 6 and 16 would preferentially occur at the carbonyl with the least electron density, for example, adjacent to the CF$_3$ substituent. For entry 17, the aniline preferentially attacks the carbonyl adjacent to the functional group with the smaller van der Waals volume (V_W); —CF$_3$ (20.49 cm^3/mol) *versus* —CH(CH$_3$)$_2$ (34.12 cm^3/mol).[32] At present, it is unclear why the 2-CF$_3$ quinoline was the only product for entries 7 and 12.

In most cases, increasing the bulk of the R group on the diketone led to formation of the 2-CF$_3$ quinoline product in larger proportion than the 4-CF$_3$ isomer. Exceptions to this tendency were entry 4 (R = *t*-Bu), in which the 4-CF$_3$ isomer formed to the exclusion of the 2-CF$_3$ quinoline product, and entry 5 (R = Ph) where the major product was the 4-CF$_3$ isomer. These cases seem to suggest that steric demands during the initial nucleophilic addition of aniline to the diketone may not be as great as those which must be overcome in the annulation (electrophilic aromatic substitution (EAS)) step in this reaction.

The effect of aniline substituents on quinoline product distribution in this work is in accord with that of previous investigators,[12,29] for example, *o*-substituted anilines give 8-quinolines, *m*-substituted anilines give predominately 7-quinolines, and *p*-substituted anilines give 6-quinolines. In only one case, Table 1 entry 18, was the 5-quinoline observed.

X=H: **1a**: R= CH$_3$, **1b**: R= CF$_3$, **1c**: R=C$_2$H$_5$,
1d: R=t-C$_4$H$_9$, **1e**: R=Ph, **1f**: R=i-C$_3$H$_7$;
X=F: **1g**: R= CH$_3$

Figure 2. Trifluoromethyl-β-diketones

With respect to —CF$_3$ substituent regiochemistry in the quinoline products, two patterns are discernible. Methoxy-substituted anilines (Table 1, entries 9, 10, 12, 18) gave predominantly the 2-CF$_3$ quinoline, whereas the chloro- and fluoroanilines (Table 1, entries 8, 11, 13–14) gave a majority of the 4-CF$_3$ regioisomer.

Effect of diketones and anilines on quinoline formation rates

Bulky R groups on the diketone were found to slow the reaction rate by as much as 80%. For the aliphatic examples, this is likely due to increased V_W of functional groups adjacent to the annulation site of the transition state in the rate-determining step.[32] Because of the similarities in electronic effect, log k values of Table 1, entries 1, 3, 4, and 15 correlate well with V_W to log $k = -0.0031V_W - 6.95$ ($R > 0.99$, $s = 2.00$).

However, log k for entry 5 (R = Ph) does not correlate with its van der Waals volume (45.84 cm^3/mol). While steric effects play a role in formation of the aromatic substituted quinolines, the predominant factor is electronic in nature. The extended conjugation exhibited by aromatic β-diketones lowers their ground state energy, decreasing their reactivity toward nucleophilic addition relative to alkyl β-diketones.[33]

The steric argument above failed for entries 2, 6, and 16 as well, where α-fluoro substituents on the diketones were found to accelerate the reaction by as much as 50%. This effect, while
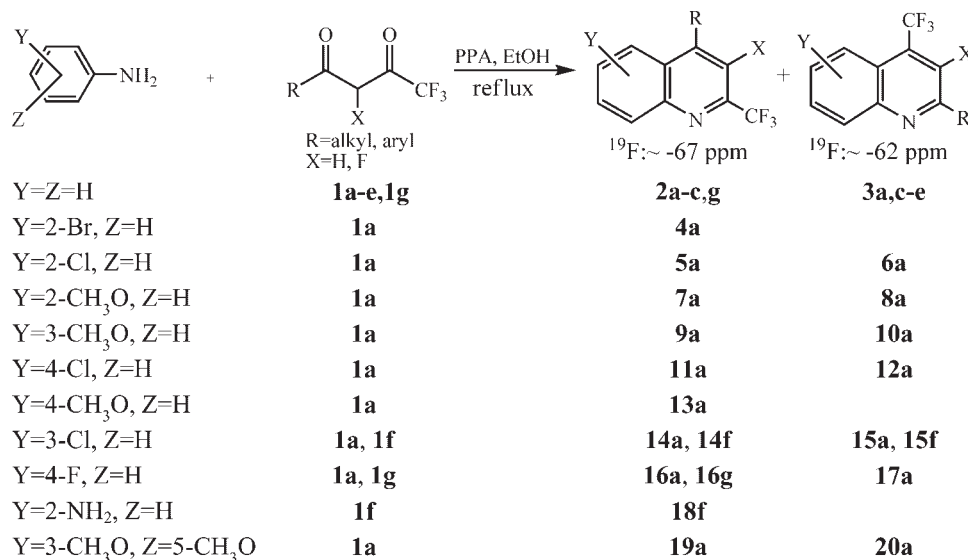
sizable for entry 2, is small for entries 6 and 16, indicating that EWGs enhance the electrophilic nature of the carbonyl undergoing condensation in the rate-determining step through induction for this series of reactions.

The complexity of the modified Combes condensation and the acidic reaction conditions employed in this study make analysis of the aniline substituent effect on quinoline formation rates challenging. Each step in this reaction is subject to substituent effects; these influences may oppose each other.[34,35] In the initial nucleophilic addition, protonation of approximately 80% of the aniline species undoubtedly slows this step. If this step were rate limiting, o,p-EDGs would accelerate the reaction while EWGs would have the opposite effect, with a correlation between log k and $\sigma_{o/m/p}$ anticipated. Such a correlation of the data for Table 1 entries 1, 7–14, and 18 was attempted, but the data fit unsatisfactorily to log $k = -0.12\sigma - 6.94$ ($R = 0.099$, $s = 0.176$).

For a rate-determining EAS step, through-resonance m-EDGs on the intermediate imine or enamine would accelerate the reaction, with a correlation between log k and σ_p^+ anticipated.[36,37] Inductive o,p-EWGs would slow the reaction and a correlation of log k with σ_m^+ would be expected.[38] Correlation of log k and $\sigma_{o/m/p}^+$ for Table 1 entries 1, 7–14, and 18 gave a least squares fit to the equation log $k = -0.31\sigma_{o/m/p}^+ - 6.98$ ($R = 0.95$, $s = 0.075$).

If, however, the observed substituent effect for this reaction system is a combination of the effects exerted in the two aforementioned steps, a more satisfactory correlation may be achieved using a dual parameter approach such as log $k = \rho\sigma_{o/m/p}^+ - \rho'\sigma_{o/m/p}$ or log $k = \rho(\sigma_{o/m/p}^+ - x\sigma_{o/m/p})$. Figure 3 depicts a plot of this type for the entries above.

The data were best fit to the equation log $k = -0.32$ $(\sigma_{o/m/p}^+ - 0.3\sigma_{o/m/p}) - 6.99$ ($R = 0.98$, $s = 0.036$).[39] This correlation shows that while EDGs on the imine intermediate such as m-OCH$_3$ increase the rate of product formation through resonance in the annulation step,[27] the dominance of inductive electron withdrawing effects over resonance donation contributions in the nucleophilic addition step offset this by 30%. This is one contributing factor to the small magnitude of ρ, -0.32, which is a composite of the reaction constants for the imine formation and EAS steps.

	R=alkyl, aryl X=H, F	1a–e,1g	2a–c,g	3a,c–e
Y=Z=H		1a–e,1g	2a–c,g	3a,c–e
Y=2-Br, Z=H		1a	4a	
Y=2-Cl, Z=H		1a	5a	6a
Y=2-CH$_3$O, Z=H		1a	7a	8a
Y=3-CH$_3$O, Z=H		1a	9a	10a
Y=4-Cl, Z=H		1a	11a	12a
Y=4-CH$_3$O, Z=H		1a	13a	
Y=3-Cl, Z=H		1a, 1f	14a, 14f	15a, 15f
Y=4-F, Z=H		1a, 1g	16a, 16g	17a
Y=2-NH$_2$, Z=H		1f	18f	
Y=3-CH$_3$O, Z=5-CH$_3$O		1a	19a	20a

Scheme 2. Condensation of trifluoromethyl-β-diketones with anilines

Table 1. Quinoline formation kinetic data[a]

Entry	Quinoline (%)[b]	R, X = H,F	dP_T/dt[c] (mM/s)	$k_{obs} \times 10^{-7}$[d] $(\text{mM s})^{-1}$
1	**2a**(28)/**3a**(72)	CH_3	0.083	1.02
2	**2b** (100)	CF_3	0.115	1.42
3	**2c**(90)/**3c**(10)	C_2H_5	0.075	0.926
4	**3d**(100)	$C(CH_3)_3$	0.066	0.815
5	**2e**(30)/**3e**(70)	Ph	0.040	0.494
6	**2g**(100)	CH_3, X = F	0.087	1.07
7	**4a**(100)	CH_3	0.066	0.815
8	**5a**(11)/**6a**(89)	CH_3	0.066	0.815
9	**7a**(56)/**8a**(44)	CH_3	0.076	0.938
10	**9a**(69)/**10a**(31)	CH_3	0.127	1.57
11	**11a**(23)/**12a**(77)	CH_3	0.066	0.815
12	**13a**(100)	CH_3	0.076	0.938
13	**14a**(46)/**15a**(54)	CH_3	0.073	0.901
14	**16a**(44)/**17a**(56)	CH_3	0.067	0.827
15	**14f**(50)/**15f**(50)	$CH(CH_3)_2$	0.072	0.889
16	**16g**(100)	CH_3, X = F	0.084	1.04
17	**18f**(100)	$CH(CH_3)_2$	0.076	0.938
18	**19a**(74)/**20a**(26)	CH_3	0.198	2.45

[a] (reactant) = 0.900 M (±0.001), 343 K.
[b] Product distributions are those obtained prior to distillation or other purification.
[c] $dP_T/dt = dP_2/dt + dP_3/dt$; accuracy ± 0.001 m M/s.
[d] k_{obs} determined from dP_T/dt; accuracy ± 0.001.

Other factors may also conspire to produce the small value for ρ observed here. Since temperature and dielectric constant are inversely proportional to log k_{obs}, reaction conditions used in this study would tend to drive down the value.[40,41] Additionally, the temperature at which this investigation was carried out for this reaction series may be near an isokinetic point and an attenuated substituent effect is being observed.[34,42] Additional studies would be needed to verify these effects.

The negative value of ρ, nonetheless, is in accord with rate-determining EAS. However, correlation of log k_{PT} with $(\sigma_p^+ - 0.3\sigma_m)$ and $((\sigma_p^+ + \sigma_o) - 0.3\,\sigma_m))$ for Table 1 entries 10 and 18, respectively, are suggestive of a multi-step process in which

the inductive substituent effects exerted during the nucleophilic addition step are significant and must be accounted for.

Proposed mechanisms of quinoline formation

These results enable us to provide some mechanistic detail of the modified Combes condensation leading to the 2-CF_3 quinoline. The following scheme summarizes reactions of the diketo form, enol 2, and Michael-fashion attack of enol 1 with aniline. An analogous mechanism involving the other carbonyl of the diketo form, enol 1, and Michael-fashion attack of enol 2 leads to the 4-CF_3 quinoline.

The first stage of the reaction likely commences with formation of a PPA ester (PPE), accompanied by some aniline protonation due to the acidity of the medium.[30] Approximately 200 mM of the free base is available for nucleophilic addition.

Stage 2 follows with a preassociative complex consisting of the aniline/anilinium, diketone, and PPE. The initial nucleophilic addition is assisted by the PPE. While the protonation of aniline likely slows the nucleophilic addition step, the diketone consumption rate for Table 1, entry 1 {−[d(**1a**)/dt]} was measured at 0.134 mM/s, and is not rate limiting. Both the diketo and enol tautomeric forms of the trifluoromethyl-β-diketones likely undergo nucleophilic attack by aniline[33] since its borderline hardness makes both 1,2- and 1,4-carbonyl additions possible.

Intermediates in this stage of the pathway are likely the initial amino-phosphate ester adduct, **I** and the amino-alcohol adduct,

Table 2. Initial rates for quinoline formation determined by the isolation method

[PhNH$_2$] (mM)	[**1a**] (mM)	dP_T/dt (Mm/s)	v_{Rel} (PhNH$_2$)	v_{Rel} (**1a**)
450	900	0.041	0.494	
900	900	0.083	1.00	1.00
900	450	0.041		0.494
1800	900	0.165	1.99	
900	1800	0.165		1.99

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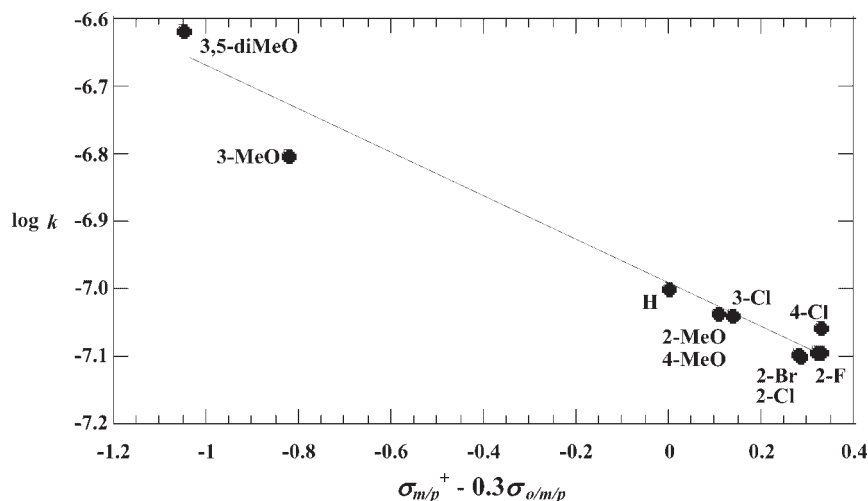
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Figure 3. Log(k_{PT}/k_0) *versus* σ_x for **1a** and substituted quinolines
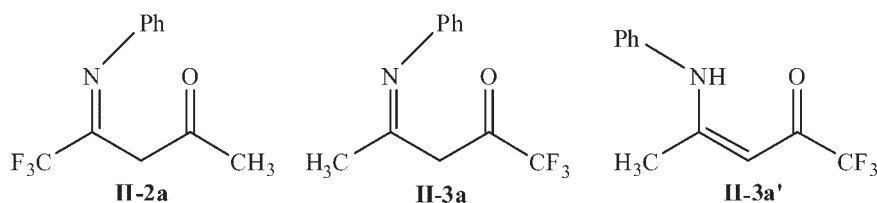

Figure 4. Phenylimine and phenylenamine intermediates

I′. Intermediate **I** undergoes dehydration to the imine intermediate **II** rapidly, while elimination of water from **I′** leads to the enamine intermediate **II′**. Tautomerization of **II′** Φ **II** takes place during this stage.

Imines **II-2a** and **II-3a** shown in Figure 4 leading to quinoline products **2a** and **3a** were isolated and characterized. The enamine intermediate **II-3a′** was identified by ^{19}F NMR and ^{1}H NMR, but constituted only 5% of the reaction mixture. Attempts to separate the intermediates led to tautomerization of **II-3a′** to **II-3a**. When the intermediates were resubjected to reaction conditions, the consumption rate ($-$d[**II**$_T$]/d$t = 0.083$ mM/s) was clearly comparable to the quinoline formation rate shown in Table 1, entry 1.

Rate-determining annulation occurs in the third stage and a rapid proton transfer leads to the dihydroquinoline phosphate ester intermediate **III**. Dihydroquinoline formation is consistent with the observation that EWGs on the diketones and *m*-substituted EDGs on aniline enhance the rate of intermediate **II** disappearance.

The final stage of the mechanism contains the dehydration of intermediate **III** to the heterocyclic products. At 70 °C and in the presence of PPA, this step is fast.

by an interplay of steric and electronic effects; these factors generally lead to a preference for 2-CF$_3$ quinolines.

The reaction follows 2nd order kinetics, 1st order in the diketone and 1st order in aniline. Diketones containing alkyl groups, multiple —CF$_3$ substituents or those with a 2-fluoro and a —CF$_3$ group react more rapidly than aryl diketones while anilines containing EDGs at the meta position accelerate quinoline formation.
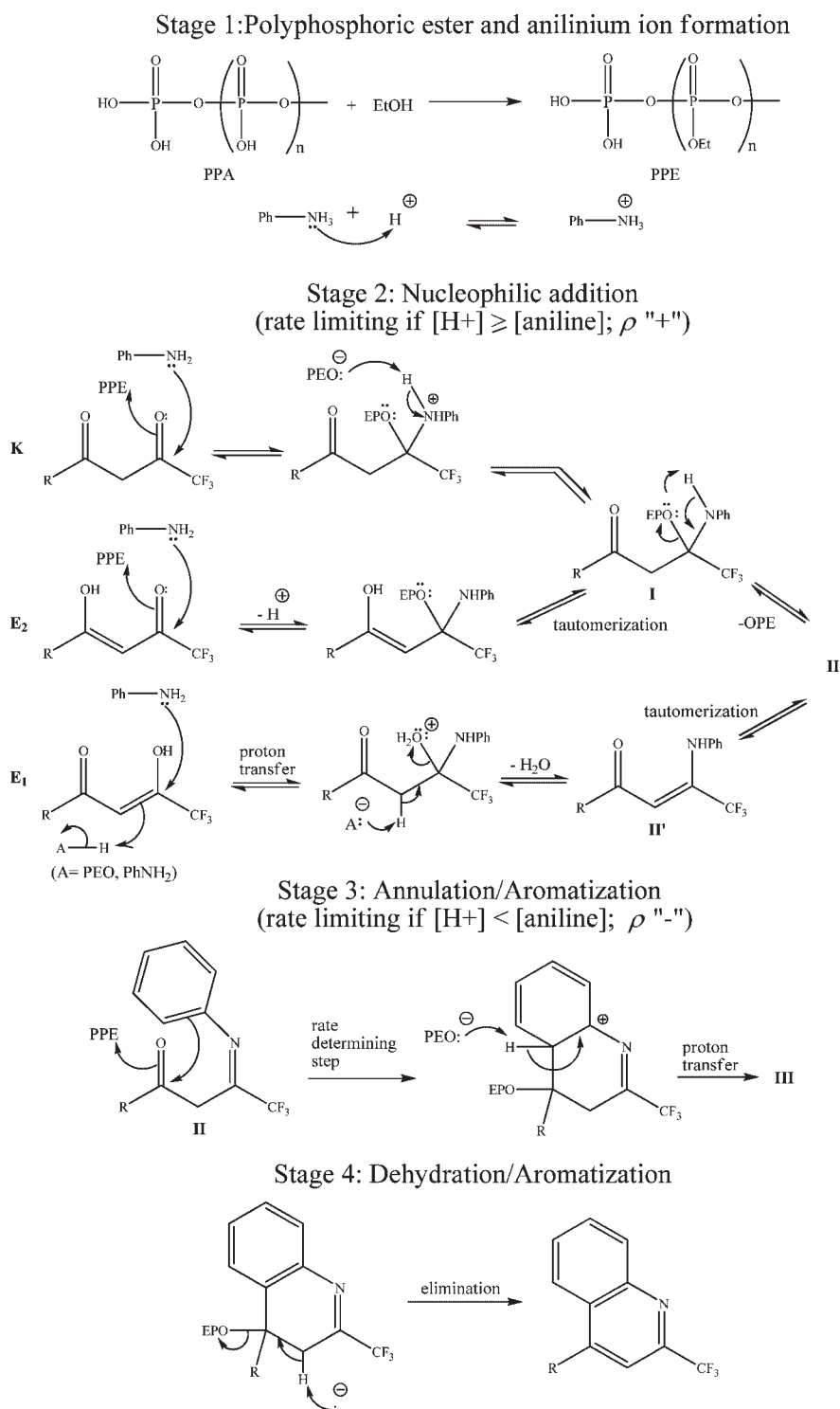
The modified-Combes condensation investigated under the specified experimental conditions and pH was not found to be as sensitive to substituent effects as expected. This can be attributed, at least in part, to the composite nature of ρ for this reaction. Otherwise the negative value of ρ, the isolation of imine and enamine intermediates, the consumption rate $-$d[int]/d$t < -$d[diketone]/dt, as well as the observation that $-$d[int]/d$t \approx$ d[quinoline]/dt are consistent with other rate-limiting EAS processes.

Scheme 3 provides a picture of quinoline formation from diketone and aniline that is consistent with the kinetics, observed substituent effects, and presence of identified intermediates.

EXPERIMENTAL

Chemicals and instrumentation

All chemicals used in the following procedures were obtained from the Aldrich Chemical Company. Solvents used were of spectrophotometric grade. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. NMR

CONCLUSIONS

This kinetics study of a modified Combes trifluoromethylquinoline synthesis has yielded information regarding how substituents influence product regioselectivity and reaction rate for this important condensation. Quinoline regioselectivity is influenced

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Stage 1: Polyphosphoric ester and anilinium ion formation

Stage 2: Nucleophilic addition
(rate limiting if [H+] ⩾ [aniline]; ρ "+")

Stage 3: Annulation/Aromatization
(rate limiting if [H+] < [aniline]; ρ "-")

Stage 4: Dehydration/Aromatization

Scheme 3. Proposed aniline formation mechanism

data were collected using a Varian VXR-200 spectrometer using $CDCl_3$ as an internal standard unless otherwise noted (^{19}F: 168 MHz in ethanol w/$CFCl_3$ as an external standard, ^{13}C: 50.2 MHz, ^{1}H: 200 MHz). Solution pH was determined using an Orion SA520 pH meter with a polymer body sealed combination reference electrode and calibrated using an HCl/NaCl buffer solution in ethanol at pH 1. Temperatures for the kinetic runs were thermostatically maintained by an Ace Glass

Type J temperature controller w/thermocouple. Combustion analysis was performed with a Perkin–Elmer CHN analyzer.

General procedures for the preparation of quinolines[15]

NMR kinetics studies

To a 100 ml volumetric flask equipped with a magnetic stirrer was added approximately 60.00 ml 95% ethanol via buret, followed by

addition of 15.00 g PPA. The mixture was stirred and warmed to 70 °C (±1 °C) to solubilize the PPA. The pH of the solution was measured at 0.15 (±0.01). Then, approximately 90.00 mmol of the 1,3-diketone and an equimolar amount of the aniline were added in rapid succession and the solution diluted with warm ethanol to 100.00 ml with a buret. The reaction mixture was transferred to a two-necked flask equipped with a reflux condenser and thermostatically heated at 70 °C (±1 °C) under a CaCl$_2$ drying tube. A 90.00 mmol solution of the 1,3-diketone in 95% ethanol was prepared, and a ^{19}F NMR taken to serve as a $t = 0$ s sample. Aliquots from the reaction flask were then extracted at 180.0 s intervals, transferred to an NMR tube, quenched in an ice bath, diluted with CDCl$_3$, and ^{19}F NMR data collected. Samples were drawn over a 3 h period. After 12 h, all reaction mixtures were neutralized with saturated NaHCO3, extracted with CH2Cl2, dried over MgSO4, the solvent removed under reduced pressure, and then distilled or recrystallized from EtOH.

4-Methyl-2-trifluoromethylquinoline (2a) and 2-methyl-4-trifluoromethylquinoline (3a)
These compounds were obtained as a yellow–brown liquid, a 28:72 mixture of **2a:3a**, bp 116–120 °C (20 mmHg), lit[15] 116–120 °C (20 mmHg).

2,4-Ditrifluoromethylquinoline (2b)
This compound was obtained as a yellow–green liquid, **2b**, bp 162–163 °C (20 mmHg), lit[15] bp 160–162 °C (20 mmHg).

4-Ethyl-2-trifluoromethylquinoline (2c) and 2-ethyl-4-trifluoromethylquinoline (3c)
These compounds were obtained as a yellow liquid, a 90:10 mixture of **2c:3c**, bp 159–162 °C (20 mmHg), lit[15] bp 160–162 °C (20 mmHg).

2-t-Butyl-4-trifluoromethylquinoline (3d)
This compound was obtained as a tan solid (EtOH), **3c**, mp 142–144 °C, lit[15] mp 142–143 °C.

4-Phenyl-2-trifluoromethylquinoline (2e) and 2-phenyl-4-trifluoromethylquinoline (3e)
These compounds were obtained as a yellow–brown liquid, a 30:70 mixture of **2e:3e**, bp 192–193 °C (20 mmHg), lit[15] bp 193 °C (20 mmHg).

3-Fluoro-4-methyl-2-trifluoromethylquinoline (2g)
This compound was obtained as a yellowish–brown liquid, **2g**, bp 157–159 °C, lit[15] bp 158–160 °C.

8-Bromo-4-methyl-2-trifluoromethylquinoline (4a)
This compound was obtained as a brown solid (EtOH), **4a**, mp 75–77 °C, lit[15] mp 75–77 °C.

8-Chloro-4-methyl-2-trifluoromethylquinoline (5a) and 8-chloro-2-methyl-4-triftuoromethylquinoline (6a)
These compounds were obtained as a brown solid (EtOH), a 11:89 mixture of **5a:6a**, mp 122–125 °C, lit[15] mp 122–124 °C.

8-Methoxy-4-methyl-2-trifluoromethylquinoline (7a) and 8-methoxy-2-methyl-4-trifluoromethylquinoline (8a)
These compounds were obtained as a yellowish solid (EtOH), a 56:44 mixture of **7a:8a**, mp 75–77 °C, lit[15] mp 75–77 °C.

7-Methoxy-4-methyl-2-trifluoromethylquinoline (9a) and 7-methoxy-2-methyl-4-trifluoromethylquinoline (10a)
These compounds were obtained as a tan solid (EtOH), a 69:31 mixture of **9a:10a**, mp 65–68 °C. NMR:**9a**: ^{1}H: δ 2.7 (3H, s), 6.5 (d, $J = 6.6$ Hz, 1H), 6.7 (1H, s), 6.9 (1H, d, $J = 6.7$ Hz), 7.2 (1H, d, $J = 6.9$ Hz). ^{13}C: δ 24, 114, 121 (CF$_3$, q, $^2J_{C—F} = 270$ Hz), 143 (C—CF$_3$, q, $^2J_{C—F} = 31$ Hz, C—CF$_3$). ^{19}F: δ −67.2 (3F, s). **10a**: ^{1}H: δ 2.6 (3H, s), 6.4 (1H, d, $J = 6.8$ Hz), 6.6 (1H, s), 6.8 (1H, d, $J = 6.9$ Hz), 7.1 (1H, d, $J = 6.7$ Hz). ^{13}C: 6 24, 114, 124 (CF$_3$, q, $^1J_{C—F} = 272$ Hz), 133 (C—CF$_3$, q, $^2J_{C—F} = 33$ Hz). ^{19}F:δ −62.3 (3F, s). Analysis: calculated for C$_{13}$H$_{12}$F$_3$NO: C, 59.76, H, 4.18, N, 5.81. Found: C, 59.80, H, 4.15, N, 5.82.

6-Chloro-4-methyl-2-trifluoromethylquinoline (11a) and 6-chloro-2-methyl-4-trifluoromethylquinoline (12a)
These compounds were obtained as a brown solid (EtOH), a 23:77 mixture of **11a:12a**, mp 106–109 °C, lit[15] mp 105–108 °C.

6-Methoxy-4-methyl-2-trifluoromethylquinoline (13a)
This compound was obtained as a yellowish-brown solid (EtOH), **13a**, mp 84–86 °C, lit[15] mp 83–87 °C.

7-Ch1oro-4-methyl-2-trifluoromethy1quinoline (14a) and 7-ch1oro-2-methyl-4-trifluoromethy1quino1ine (15a)
These compounds were obtained as a yellowish-brown liquid, a 46:54 mixture of **14a:15a**, bp 151–155 °C (4 mmHg), lit[15] bp 151–154 °C (4 mmHg).

7-Ch1oro-4-isopropyl-2-trifluoromethylquinoline (14f) and 7-chloro-2-isopropyl-4-trifluoromethylquinoline (15f)
These compounds were obtained as a yellow–brown liquid, a 1:1 mixture of **14f:15f**, bp 163–165 °C (25 mmHg), lit[15] bp 165 °C (25 mmHg).

6-Fluoro-4-methyl-2-trifluoromethy1quinoline (16a) and 6-fluoro-2-methyl-4-trifluoromethylquinoline (17a)
These compounds were obtained as a yellowish-brown solid (EtOH), a 44:56 mixture of **16a:17a**, mp 95–97 °C, lit[15] mp 95–97 °C.

3,6-Difluoro-4-methyl-2-trifluoromethylquinoline (16g)
This compound was obtained as a yellowish-brown liquid, **16g**, bp 152–155 °C, lit[15] bp 152–155 °C.

8-Amino-4-isopropyl-2-trifluoromethylquinoline (18f)
This compound was obtained as a brownish-black solid (EtOH), **18f**, mp 161–163 °C, lit[15] mp 160–162 °C.

5,7-Dimethoxy-4-methyl-2-trifluoromethylquinoline (19a) and 5,7-dimethoxy-2-methyl-4-trifluoromethylquinoline (20a)
These compounds were obtained as a yellowish-brown solid (EtOH), a 74:26 mixture of **19a:20a**, mp 95–97 °C. NMR:**19a**: ^{1}H: δ 2.7 (3H, s), 6.5 (d, $J = 6.6$ Hz, 1H), 6.7 (1H, s), 6.9 (1H, d, $J = 6.7$ Hz), 7.2 (1H, d, $J = 6.9$ Hz). ^{13}C: δ 24, 114, 121 (CF$_3$, q, $^2J_{C—F} = 270$ Hz), 143 (C—CF$_3$, q, $^2J_{C—F} = 31$ Hz, C—CF$_3$). ^{19}F: δ −67.2 (3F, s). **20a**: ^{1}H: δ 2.6 (3H, s), 6.4 (1H, d, $J = 6.8$ Hz), 6.6 (1H, s), 6.8 (1H, d, $J = 6.9$ Hz), 7.1 (1H, d, $J = 6.7$ Hz). ^{13}C: δ 24, 114, 124 (CF$_3$, q, $^1J_{C—F} = 272$ Hz), 133 (C—CF$_3$, q, $^2J_{C—F} = 33$ Hz). ^{19}F:δ −62.3 (3F, s). Analysis: calculated for C$_{13}$H$_{12}$F$_3$NO: C, 57.57, H, 4.46, N, 5.16. Found: C, 57.60, H, 4.42, N, 5.15.

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Preparation of intermediates

4-Phenylimino-5,5,5-trifluoro-2-pentanone (II-2a),
4-phenylimino-1,1,1-trifluoro-2-pentanone (II-3a),
4-anilino-1,1,1-trifluoro-3-penten-2-one (II-3a′)

To a solution of 3.08 g (20.0 mmol) **1a** in 100 ml absolute ethanol is added 1.86 g (20.0 mmol) aniline and heated to 70 °C with stirring for 4 h. The solvent was removed under reduced pressure giving 4.03 g (88%) of a 30:65:5 mixture (determined by integration of ^{19}F NMR resonances) of **II-2a:II-3a:II-3a′** as a brownish oil. Chromatography of the crude reaction mixture (20% EtOAC/hexane) resulted in isomerization of **II-3a′** to **II-3a**. NMR: **II-2a**: 1H: δ 2.22 (s, 3H), 2.99 (s, 2H), 7.00–7.12 (m, 3H), 7.46 (t, $J = 7.42$ Hz, 2H). 13C: δ 22.0, 30.6, 118.3 (—CF3, q, 1JC—F = 275.1 Hz), 123.5, 128.6, 130.2, 152.1, 166.2 (C—CF3, q, 2JC—F = 34.2 Hz), 208.1. 19F: δ: −81.5 (—CF3, s, 3F). **II-3a**: 1H: δ 2.01 (s, 3H), 2.86 (s, 2H), 7.00–7.12 (m, 3H), 7.41 (t, $J = 7.40$ Hz, 2H). 13C: δ 22.2, 27.9, 117.8 (−CF3, q, 1JC—F = 269.2 Hz), 120.7, 126.9, 128.7, 150.1, 162.1 (C—CF3, q, 2JC—F = 35.4 Hz), 208.1. 19F: δ: −83.1 (—CF3, s, 3F). **II-3a′** (crude reaction mixture): 1H: δ 5.7 (s, 1H), 11.4, (—NH, bs, 1H). 19F: δ: −75.2 (—CF3, s, 3F). Analysis: calulated for C11H10F3NO: C: 57.64%, H: 4.40%, N: 6.11%. Found: C: 57.69%, H: 4.42%, N: 6.16%.

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