Chlorotrimethylsilane-Mediated Friedländer Synthesis of Polysubstituted Quinolines

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Abstract: New convenient conditions for the Friedländer synthesis of quinolines are described. Polysubstituted quinolines were readily prepared using chlorotrimethylsilane as a promoter and water-acceptor agent.

Key words: quinolines, annulation, *o*-amino aromatic carbonyls, chlorotrimethylsilane, parallel synthesis

The quinoline scaffold plays an important role as a component of antimalarial, antibacterial, anti-asthmatic, antihypertensive, and anti-inflammatory agents.[1–3] Aryl-substituted quinolines exhibit 5-lipoxygenase[4] and tyrosine kinase PDGF-RTK[5] inhibiting properties, leucotriene[6] and LTD_4[7] antagonistical properties, and others. Furthermore, polyquinolines derived from quinolines undergo hierarchical self-assembly into a variety of nanostructures with electronic and photonic functions.[8]

Although various methods have been developed for quinoline synthesis,[9] such as the Skraup, Dobner von Miller, Friedländer, and Combes syntheses, novel methods are still desired.[10] Of the available methods, the Friedländer annulation is one of the most simple and straightforward approaches to polysubstituted quinolines.[11] Generally the reaction is carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of a base or by heating the reactants at high temperatures in the absence of catalyst. Subsequent work has shown that acidic catalysts are more effective than basic catalysts for the reaction.[11b,12] However, many of these classical methods require drastic conditions that result in lower yields due to side reactions. In recent times, iodine,[13] Lewis acids[14] [e.g., $NaAuCl_4$, $Bi(OTf)_3$, $Nd(NO_3)_3 \cdot 6H_2O$], a combination of acidic catalysts and microwave irradiation,[15] and ionic liquids[16] have all been found to be effective for this conversion; effective methods based on the generation of aminocarbonyl compounds in situ have also been elaborated.[17] Nevertheless, the majority of efficient reaction procedures requires the use of expensive catalysts or special equipment, thus limiting their wider use.

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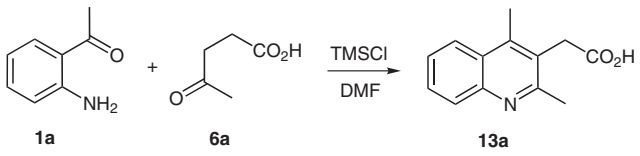
We now show that chlorotrimethylsilane in *N*,*N*-dimethylformamide can be used as a condensation agent in the Friedländer annulation.[18]

Initially we sought a convenient preparative method for the synthesis of derivatives of quinolin-3-ylacetic acid[19] without additional functional groups in the pyridine ring.[20] Several approaches have earlier been described for this acid using 3-acetyl-[21a] (Willgerodt reaction) or 3-haloquinolines as starting compounds.[21b–d] For this purpose we decided to use a Friedländer annulation based on 4-oxo acids. 1-(2-Aminophenyl)ethanone (**1a**) and 4-oxopentanoic acid (**6**) were chosen as model substrates for the optimization of the reaction conditions (Scheme 1). The best results were obtained when heating equivalent quantities of 1-(2-aminophenyl)ethanone (**1a**) and 4-oxopentanoic acid (**6**) in *N*,*N*-dimethylformamide in the presence of chlorotrimethylsilane (5 equiv) at 95 °C (water bath) for eight hours in an Ace pressure tube to keep the volatile chlorotrimethylsilane and formed hydrogen chloride in the reaction mixture.[18g] In this case using starting compounds (2 mmol), *N*,*N*-dimethylformamide (2 mL) in an 8-mL Ace pressure tube, after simple dilution with three volumes of water, filtration, and, if necessary, triturating with water in an ultrasonic bath for several hours and then washing with isopropyl alcohol, gave the desired product **13a** as its hydrochloride salt in 91% yield with 97% purity. The reaction was scaled up to 0.25 mol of compound **1a** using a 0.5-L autoclave and, in this case, the yield of **13a** was 95%.



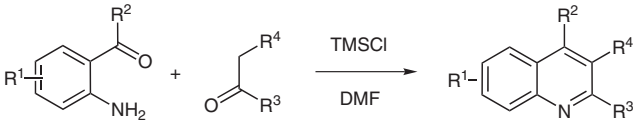
1a **6a** **13a**

Scheme 1

To demonstrate the generality of this method we investigated the scope of this reaction under the optimized conditions [DMF (5 equiv), TMSCl, 95 °C, Ace pressure tube). The results are summarized in Table 1. As shown in Table 1 this method is equally effective for both cyclic and acyclic ketones. In particular, we draw attention to 4-chloroacetoacetic ester (**2c**), ethyl pyruvate (**5**), deriva-

tives of piperidin-4-one **7c**,**i**, and sterically hindered ketones **4g**,**h**. It is worthwhile to note that, to our knowledge, sterically hindered ketones of type **4g**,**h** have not previously been used in the Friedländer annulation. Thus, in the literature only the *tert*-butyl analogue of **11g** has been described, which was obtained by cyclocondensation of 1-isocyano-2-(2-methoxy-1-phenylvinyl)benzene with *tert*-butyllithium.[10h]

Table 1 Chlorotrimethylsilane-Promoted Synthesis of Quinolines **9**–**18**[d,e]



1 **2–8** **9–18**

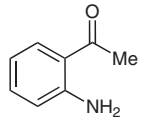
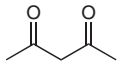
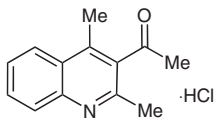
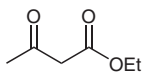
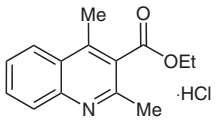
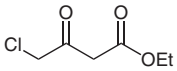
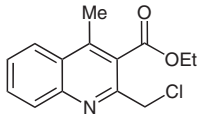
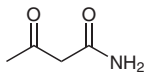
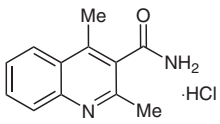
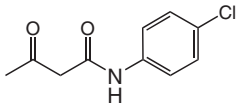
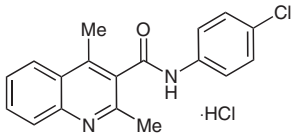
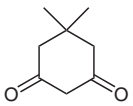
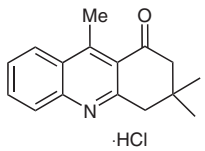
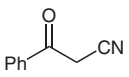
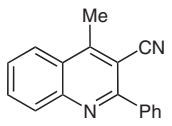
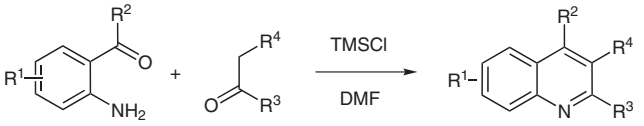
Entry	Amino ketone	Carbonyl compound	Product	Yield (%)[a]	Mp (°C)[b] [lit.][c]	Previously reported results
1	 **1a**	 **2a**	 **9a**	84	199–200 [oil][22a]	110 °C (60%);[22a] $NaAuCl_4$ (2.5 mol%), 40 °C (54%);[14a] $Bi(OTf)_3$ (5 mol%), r.t. (82%);[14b] I_2 (1 mol%), r.t. (53%);[13] PTSA (1 equiv), MW (300 W) (92%)[15b]
2	**1a**	 **2b**	 **9b**	90	205–206 [oil][15b]	I_2 (1 mol%), r.t. (68%);[13] PTSA (1 equiv), MW (300 W) (91%)[15b]
3	**1a**	 **2c**	 **9c**	87	107–108	Friedländer condensation using 4-chloroacetoacetic ester[23]
4	**1a**	 **2d**	 **9d**	89	243–244 [198][22b]	Friedländer condensation using β-ketoamides[24]
5	**1a**	 **2e**	 **9e**	81	268–269	
6	**1a**	 **2f**	 **9f**	86	175–176 [105–106][15b]	PTSA (1 equiv), MW (300 W) (95%)[15b]
7	**1a**	 **3**	 **10**	84	156–157 [166–167][22b]	related cyclization[25] using oxonitriles in EtOAc–piperidine system or in 18 M H_2SO_4

Table 1 Chlorotrimethylsilane-Promoted Synthesis of Quinolines **9–18**[d,e] (continued)



1 **2–8** **9–18**

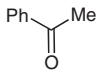
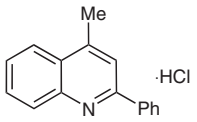
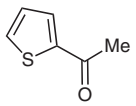
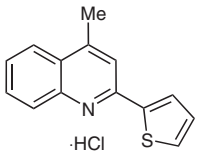
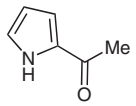
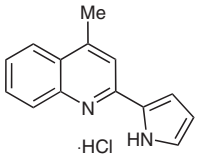
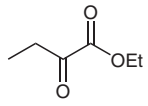
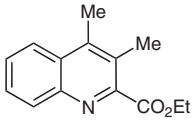
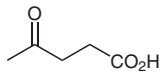
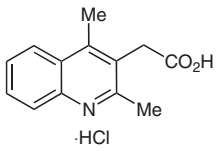
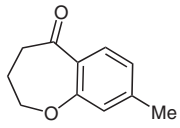
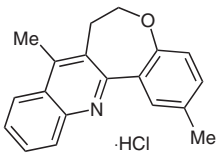
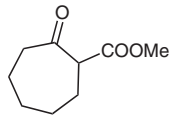
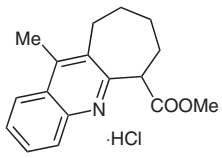
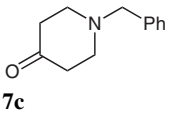
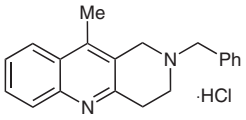
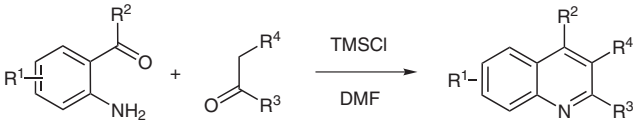
Entry	Amino ketone	Carbonyl compound	Product	Yield (%)[a]	Mp (°C)[b] [lit.][c]	Previously reported results
8	**1a**	 **4a**	 **11a**	86	167–168 [108–110][15a]	DPP (0.5 equiv), 108 °C, MW (76%)[15a]
9	**1a**	 **4b**	 **11b**	83	184–185 [120–121][22c]	
10	**1a**	 **4c**	 **11c**	79	195–196	
11	**1a**	 **5**	 **12a**	87	187–188	Friedländer condensation using derivatives of pyruvic acid[25a,26]
12	**1a**	 **6**	 **13a**	91	237–238	
13	**1a**	 **7a**	 **14a**	82	183–184	
14	**1a**	 **7b**	 **14b**	84	71–72	
15	**1a**	 **7c**	 **14c**	76	211–212 [104–105][22d]	HCl, 140 °C (55%)[22d]

Table 1 Chlorotrimethylsilane-Promoted Synthesis of Quinolines **9–18**[d,e] (continued)



1 **2–8** **9–18**

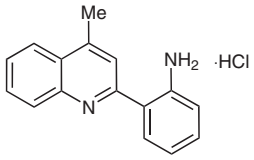
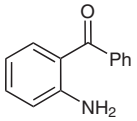
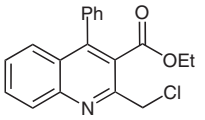
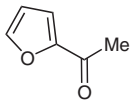
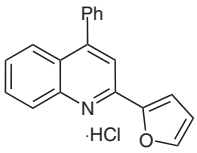
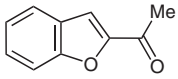
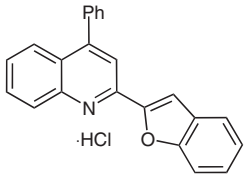
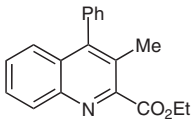
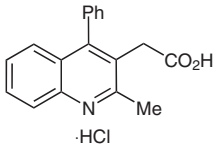
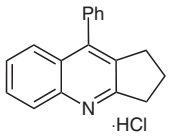
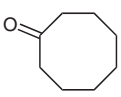
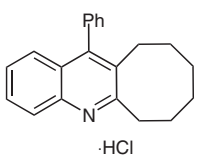
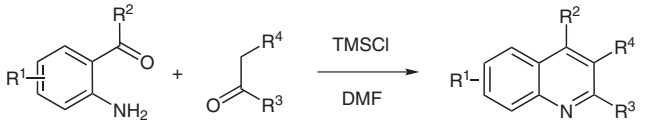
Entry	Amino ketone	Carbonyl compound	Product	Yield (%)[a]	Mp (°C)[b] [lit.][c]	Previously reported results
16	**1a**	**1a**	 **15**	96	158–159 [58–60][27a] [79][27b]	70% H_2SO_4, heat, 30 min (92%);[27a] HCl, 160 °C (66%)[27b]
17	 **1b**	**2c**	 **9g**	94	111–112 [75–76][23]	AcOH–benzene, reflux (62%)[23]
18	**1b**	 **4d**	 **11d**	85	140–141 [109–111][10h].	
19	**1b**	 **4e**	 **11e**	96	191–192 [202.5][22f]	HCl, 130 °C (41%)[22f]
20	**1b**	**5**	 **12b**	88	90–91 [114–115][26]	
21	**1b**	**6**	 **13b**	97		
22	**1b**	 **7d**	 **14d**	92	186–187 [128–130][22e]	HCl, 100–200 °C, 2 h (47%);[22e] $NaAuCl_4$ (2.5 mol%), 40 °C (73%);[14a] $Bi(OTf)_3$ (5 mol%), r.t. (90%)[14b]
23	**1b**	 **7e**	 **14e**	89	215–216 [118–120][14a]	$NaAuCl_4$ (2.5 mol%), 40 °C (60%)[14a]

Table 1 Chlorotrimethylsilane-Promoted Synthesis of Quinolines **9–18**[d,e] (continued)



1 **2–8** **9–18**

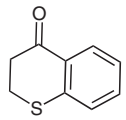
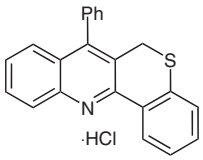
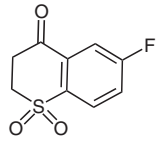
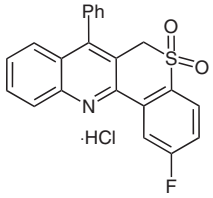
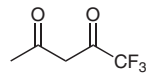
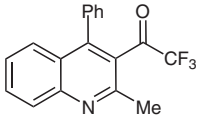
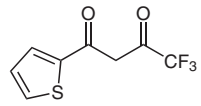
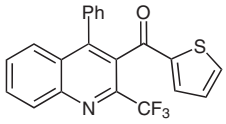
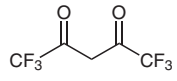
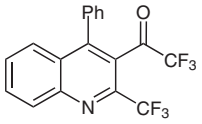
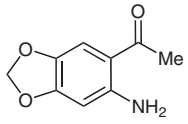
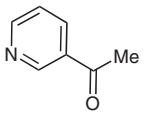
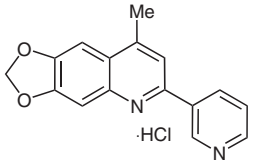
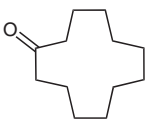
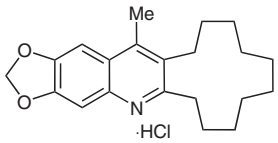
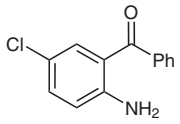
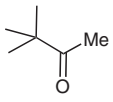
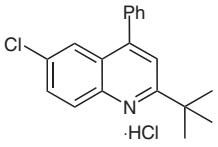
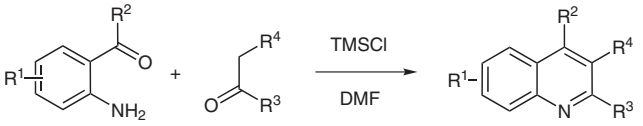
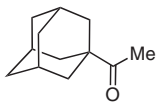
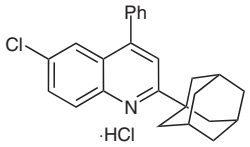
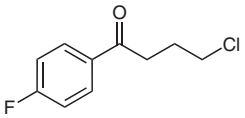
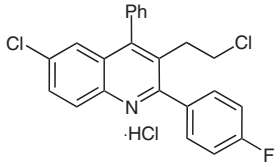
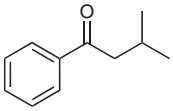
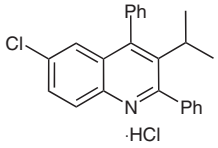
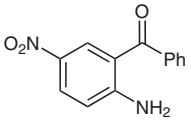
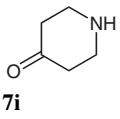
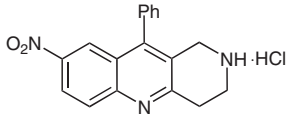
Entry	Amino ketone	Carbonyl compound	Product	Yield (%)[a]	Mp (°C)[b] [lit.][c]	Previously reported results
24	**1b**	 **7f**	 **14f**	83	123–124 [137–139][22g]	
25	**1b**	 **7g**	 **14g**	85	212–213	
26	**1b**	 **8a**	 **16**	87	89–90 [80–81][14a]	$NaAuCl_4$ (2.5 mol%), 60 °C (50%);[14a] bmimCl·$ZnCl_2$, 80 °C (55%)[16c]
27	**1b**	 **8b**	 **17**	92	147–148	
28	**1b**	 **8c**	 **18**	76	79–80	
29	 **1c**	 **4f**	 **11f**	81	204–205	
30	**1c**	 **7h**	 **14h**	86	223–224	
31	 **1c**	 **4g**	 **11g**	93	82–83 [oil][10h]	

Table 1 Chlorotrimethylsilane-Promoted Synthesis of Quinolines **9–18**[d,e] (continued)



1 **2–8** **9–18**

Entry	Amino ketone	Carbonyl compound	Product	Yield (%)[a]	Mp (°C)[b] [lit.][c]	Previously reported results
32	**1c**	 **4h**	 **11h**	89	141–142	
33	**1c**	 **4i**	 **11i**	85	177–178	
34	**1c**	 **4j**	 **11j**	94	185–186	
35	 **1c**	 **7i**	 **14i**	84	254–255	

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] Literature melting points refer to corresponding free base.
[d] Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25.
[e] The HCl content in compounds **9–18** was determined by elemental analysis and by titration using Mettler Toledo DL31 KF Titrator.

Table 2 ^{1}H NMR[a] and APCI MS Data of Quinolines **9–18**

	^{1}H NMR δ (DMSO-d_6), J (Hz)	MS m/z $[M + H]^+$
9a	2.68 (s, 3 H, $COCH_3$), 2.76 (s, 3 H, CH_3), 2.81 (s, 3 H, CH_3), 7.86 (t, ^3J = 8.0, 1 H, 7-Qn), 8.11 (t, ^3J = 8.0, 1 H, 6-Qn), 8.38 (d, ^3J = 8.0, 2 H, 5,8-Qn)	200
9b	1.37 (t, ^3J = 6.8, 3 H, CH_2CH_3), 2.75 (s, 6 H, 2 CH_3), 4.47 (q, ^3J = 6.8, 2 H, CH_2CH_3), 7.80 (t, ^3J = 8.4, 1 H, 7-Qn), 7.95 (t, ^3J = 8.4, 1 H, 6-Qn), 8.19 (d, ^3J = 8.4, 1 H, 5-Qn), 8.28 (d, ^3J = 8.4, 1 H, 8-Qn)	230
9c	1.37 (t, ^3J = 6.9, 3 H, CH_2CH_3), 2.71 (s, 3 H, CH_3), 4.46 (q, ^3J = 6.9, 2 H, CH_2CH_3), 4.96 (s, 2 H, CH_2Cl), 7.74 (td, ^3J = 8.4, ^4J = 0.9, 1 H, 7-Qn), 7.88 (td, ^3J = 8.4, ^4J = 0.9, 1 H, 6-Qn), 8.06 (d, ^3J = 8.4, 1 H, 5-Qn), 8.22 (d, ^3J = 8.4, 1 H, 8-Qn)	264
9d	2.82 (s, 3 H, CH_3), 2.90 (s, 3 H, CH_3), 7.89 (t, ^3J = 8.4, 1 H, 6-Qn), 8.07(t, ^3J = 8.4, 1 H, 7-Qn), 8.19 (br s, 1 H, NH), 8.29 (br s, 1 H, NH), 8.39 (d, ^3J = 8.4, 1 H, 8-Qn), 8.44 (d, ^3J = 8.4, 1 H, 5-Qn)	201
9e	2.85 (s, 3 H, CH_3), 2.90 (s, 3 H, CH_3), 7.47 (d, ^3J = 8.7, 2 H, 2,6-Ar), 7.79 (d, ^3J = 8.7, 2 H, 3,5-Ar), 7.92 (t, ^3J = 8.4, 1 H, 7-Qn), 8.09 (t, ^3J = 8.4, 1 H, 6-Qn), 8.42 (d, ^3J = 8.4, 2 H, 5,8-Qn), 11.20 (s, 1 H, NH)	311
9f	1.11 [s, 6 H, $C(CH_3)_2$], 2.75 (s, 2 H, $COCH_2$), 3.18 (s, 3 H, CH_3), 3.49 (s, 2 H, CH_2), 7.91 (t, ^3J = 8.4, 1 H, 7-Qn), 8.15 (t, ^3J = 8.4, 1 H, 6-Qn), 8.47 (d, ^3J = 8.4, 1 H, 5-Qn), 8.59 (d, ^3J = 8.4, 1 H, 8-Qn)	240

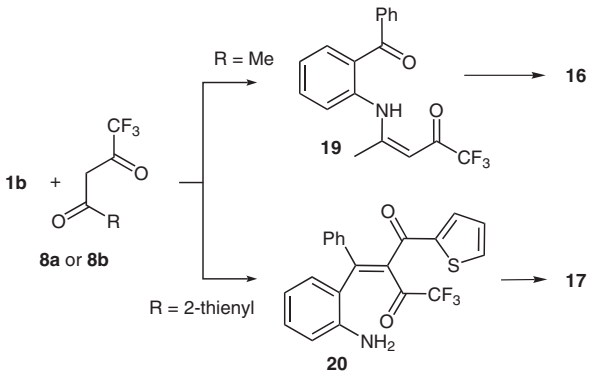
Table 2 ^{1}H NMR[a] and APCI MS Data of Quinolines **9**–**18** (continued)

	^{1}H NMR δ (DMSO-d_6), J (Hz)	MS m/z $[M + H]^+$
9g	0.82 (t, ^3J = 6.8, 3 H, CH_2CH_3), 3.97 (q, ^3J = 6.8, 2 H, CH_2CH_3), 5.01 (s, 2 H, CH_2Cl), 7.35 (m, 2 H, Ph), 7.52 (m, 4 H, Ph, 5-Qn), 7.66 (t, ^3J = 8.4, 1 H, 7-Qn), 7.90 (t, ^3J = 8.4, 1 H, 6-Qn), 8.14 (d, ^3J = 8.4, 1 H, 8-Qn)	326
10	2.99 (s, 3 H, CH_3), 7.58 (m, 3 H, Ph), 7.77 (m, 1 H, 7-Qn), 7.87 (m, 2 H, Ph), 7.97 (m, 1 H, 6-Qn), 8.12 (d, ^3J = 8.4, 1 H, 5-Qn), 8.30 (d, ^3J = 8.4, 1 H, 8-Qn)	245
11a	2.95 (s, 3 H, CH_3), 7.68 (m, 3 H, 3,4,5-Ph), 7.85 (t, ^3J = 8.0, 1 H, 7-Qn), 8.05 (s, 1 H, 3-Qn), 8.30 (m, 4 H, 2,6-Ph, 5,6-Qn), 8.48 (m, 1 H, 8-Qn)	220
11b	2.80 (s, 3 H, CH_3), 7.30 (m, 1 H, 4-Th), 7.67 (m, 1 H, 7-Qn), 7.83–7.91 (m, 2 H, 6-Qn, 3-Th), 8.07 (s, 1 H, 3-Qn), 8.14 (dd, ^3J = 8.4, ^4J = 0.9, 1 H, 5-Qn), 8.26–8.30 (m, 2 H, 8-Qn, 5-Th)	226
11c	2.82 (s, 3 H, CH_3), 6.43 (dd, $^3J_1$ = 4.2, $^3J_2$ = 2.1, 1 H, 4-pyr), 7.45 (d, ^3J = 2.1, 1 H, 3-pyr), 7.64 (d, ^3J = 4.2, 1 H, 5-pyr), 7.72 (t, ^3J = 8.4, 1 H, 7-Qn), 7.94 (t, ^3J = 8.4, 1 H, 6-Qn), 8.14 (d, ^3J = 8.4, 1 H, 5-Qn), 8.24 (s, 1 H, 3-Qn), 8.63 (d, ^3J = 8.4, 1 H, 8-Qn), 13.40 (br s, 1 H, NH)	209
11d	6.82 (dd, ^3J = 3.6, ^4J = 2.0, 1 H, 4-fur), 7.58–7.70 (m, 6 H), 7.94 (t, ^3J = 8.0, 2 H), 8.04 (d, ^3J = 6.8, 2 H), 8.18 (m, 1 H), 8.65 (m, 1 H, 8-Qn)	272
11e	7.28 (t, ^3J = 8.1, 1 H), 7.42 (t, ^3J = 8.1, 1 H), 7.55–7.65 (m, 7 H,), 7.76 (d, ^3J = 8.1, 1 H), 7.84 (t, ^3J = 8.1, 1 H), 7.92 (d, ^3J = 8.1, 1 H), 8.10 (m, 2 H), 8.39 (m, 1 H, 8-Qn)	322
11f	2.69 (s, 3 H, CH_3), 6.27 (s, 2 H, CH_2), 7.48 (s, 1 H, 5-Qn), 7.52 (s, 1 H, 8-Qn), 7.87 (dd, $^3J_1$ = 8.0, $^3J_2$ = 5.2, 1 H, 5-py), 8.05 (s, 1 H, 3-Qn), 8.82 (dd, ^3J = 5.2, ^4J = 1.2, 1 H, 6-py), 8.91 (dd, ^3J = 8.0, ^4J = 1.2, 1 H, 4-py), 9.47 (d, ^4J = 1.2, 1 H, 2-py)	265
11g	1.50 (s, 9 H, CH_3), 7.60 (m, 5 H), 7.71 (s, 1 H, 3-Qn), 7.77 (d, ^4J = 2.4, 1 H, 5-Qn), 7.85 (dd, ^3J = 8.6, ^4J = 2.4, 1 H, 7-Qn), 8.36 (d, ^3J = 8.6, 1 H, 8-Qn)	297
11h	1.73 (s, 6 H), 2.05 (s, 9 H), 7.52 (m, 6 H), 7.71 (s, 1 H), 7.74 (d, ^3J = 9.1, 1 H), 8.09 (m, 1 H)	375
11i	3.04 (t, ^3J = 7.85, 2 H), 3.25 (t, ^3J = 7.85, 2 H), 7.17 (m, 1 H), 7.37 (t, ^3J = 8.8, 2 H), 7.43 (d, ^3J = 6.6, 2 H), 7.59 (m, 1 H), 7.63 (m, 2 H), 7.69 (m, 2 H), 7.77 (dd, ^3J = 9.1, ^4J = 2.5, 1 H), 8.08 (d, ^3J = 9.1, 1 H)	397
11j	0.86 (d, ^3J = 7.1, 6 H), 3.16 (m, 1 H), 6.98 (s, 1 H), 7.35 (d, ^3J = 6.6, 2 H), 7.47 (m, 5 H), 7.55 (m, 3 H), 7.68 (d, ^3J = 9.0, 1 H), 8.00 (d, ^3J = 9.0, 1 H)	359
12a	1.38 (t, ^3J = 6.9, 3 H, CH_2CH_3), 2.81 (s, 3 H, CH_3), 2.85 (s, 3 H, CH_3), 4.50 (q, ^3J = 6.9, 2 H, CH_2CH_3), 7.86 (t, ^3J = 8.7, 1 H, 7-Qn), 8.05 (t, ^3J = 8.7, 1 H, 6-Qn), 8.36 (d, ^3J = 8.7, 1 H, 5-Qn), 8.58 (d, ^3J = 8.7, 1 H, 8-Qn)	230
12b	0.88 (t, ^3J = 7.2, 3 H, CH_2CH_3), 2.68 (s, 3 H, CH_3), 4.02 (q, ^3J = 7.2, 2 H, CH_2CH_3), 7.34 (m, 2 H, Ph), 7.54 (m, 5 H, Ph, 5,6-Qn), 7.81 (t, ^3J = 8.3, 1 H, 7-Qn), 8.04 (d, ^3J = 8.3, 1 H, 8-Qn)	292
13a	2.74 (s, 3 H, CH_3), 3.03 (s, 3 H, CH_3), 3.98 (s, 2 H, CH_2), 7.82 (t, ^3J = 8.4, 1 H, 7-Qn), 7.98 (t, ^3J = 8.4, 1 H, 6-Qn), 8.34 (d, ^3J = 8.4, 1 H, 5-Qn), 8.66 (d, ^3J = 8.4, 1 H, 8-Qn)	216
13b	3.00 (s, 3 H, CH_3), 3.71 (s, 2 H, CH_2), 7.31 (m, 2 H, Ph), 7.45 (d, ^3J = 8.4, 1 H, 5-Qn), 7.64 (m, 3 H, Ph), 7.77 (t, ^3J = 8.4, 1 H, 7-Qn), 8.06 (t, ^3J = 8.4, 1 H, 6-Qn), 8.49 (d, ^3J = 8.4, 1 H, 8-Qn)	278
14a	2.49 (s, 3 H, CH_3), 2.96 (s, 3 H, CH_3), 3.15 (t, ^3J = 6.9, 2 H, CH_2), 4.55 (t, ^3J = 6.9, 2 H, OCH_2), 7.11 (d, ^3J = 8.1, 1 H, 6-Ar), 7.41 (d, ^3J = 8.1, 1 H, 5-Ar), 7.83 (t, ^3J = 8.4, 1 H, 7-Qn), 7.89 (s, 1 H, 3-Ar), 7.94 (t, ^3J = 8.4, 1 H, 6-Qn), 8.35 (d, ^3J = 8.4, 1 H, 5-Qn), 8.76 (d, ^3J = 8.4, 1 H, 8-Qn)	276
14b	1.73 (m, 4 H, $CH_2CH_2CH_2CH_2CH$), 1.89 (m, 2 H, $CH_2CH_2CH_2CH_2CH$), 2.62 (s, 3 H, CH_3), 3.00 (m, 2 H, $CH_2CH_2CH_2CH_2CH$), 3.07 (s, 3 H, OCH_3), 3.15 (m, 1 H, $CH_2CH_2CH_2CH_2CH$), 7.44 (t, ^3J = 8.4, 1 H, 7-Qn), 7.55 (t, ^3J = 8.4, 1 H, 6-Qn), 7.81 (d, ^3J = 8.4, 1 H, 5-Qn), 7.94 (d, ^3J = 8.4, 1 H, 8-Qn)	270
14c	2.72 (s, 3 H, CH_3), 2.94 (m, 2 H, CH_2CH_2N), 3.55 (m, 2 H, CH_2CH_2N), 3.72 (s, 2 H, CH_2N), 4.56 (m, 2 H, NCH_2Ph), 7.45 (m, 3 H, Ph), 7.81 (m, 3 H, Ph, 7-Qn), 7.91 (t, ^3J = 8.1, 1 H, 6-Qn), 8.29 (d, ^3J = 8.1, 1 H, 5-Qn), 8.36 (d, ^3J = 8.1, 1 H)	289
14d	2.17 (qt, ^3J = 6.9, 2 H, $CH_2CH_2CH_2$), 2.89 (t, ^3J = 6.9, 2 H, CH_2), 3.17 (t, ^3J = 6.9, 2 H, CH_2), 7.64 (d, ^3J = 8.4, 2 H, Ph), 7.40–7.54 (m, 6 H, Ph, 5,6,7-Qn), 7.93 (d, ^3J = 8.4, 1 H, 8-Qn)	246
14e	1.35 (m, 2 H), 1.48 (m, 4 H), 1.95 (m, 2 H), 2.80 (t, ^3J = 6.0, 2 H), 3.49 (t, ^3J = 6.0, 2 H), 7.32 (d, ^3J = 8.4, 1 H, 5-Qn), 7.37 (d, ^3J = 8.0, 2 H, Ph), 7.82 (m, 3 H, Ph), 7.86 (t, ^3J = 8.4, 1 H, 7-Qn), 8.05 (t, ^3J = 8.4, 1 H, 6-Qn), 8.51 (d, ^3J = 8.4, 1 H, 8-Qn)	288

Table 2 ^{1}H NMR[a] and APCI MS Data of Quinolines **9**–**18** (continued)

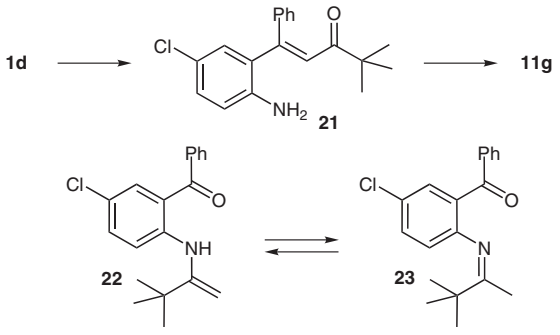
	^{1}H NMR δ (DMSO-d_6), J (Hz)	MS m/z $[M + H]^+$
14f	3.90 (s, 2 H, CH_2S), 7.41 (m, 6 H), 7.52 (t, J = 8.2, 1 H), 7.61 (m, 3 H), 7.76 (t, ^3J = 8.2, 1 H), 8.14 (d, ^3J = 8.2, 1 H), 8.58 (m, 1 H)	326
14g	4.68 (s, 2 H, CH_2), 7.39 (d, ^3J = 6.6, 2 H), 7.46 (d, ^3J = 8.3, 1 H), 7.68 (m, 5 H), 7.91 (t, ^3J = 8.3, 1 H), 8.11 (dd, $^3J_1$ = 6.6, $^3J_2$ = 5.3, 1 H), 8.26 (d, ^3J = 8, 1 H), 8.45 (dd, ^3J = 9.7, ^4J = 2.7, 1 H)	376
14h	1.40–1.70 (m, 12 H), 1.91 (m, 2 H), 2.77 (s, 3 H, CH_3), 2.92 (m, 2 H), 3.24 (m, 4 H), 6.33 (s, 2 H, OCH_2O), 7.68 (s, 1 H, 5-Qn), 7.92 (s, 1 H, 8-Qn)	326
14i	3.52 (m, 4 H, CH_2CH_2N), 4.15 (s, 2 H, CH_2N), 7.42 (m, 2 H, Ph), 7.67 (m, 3 H, Ph), 8.23 (m, 2 H), 8.43 (d, ^3J = 8.8, 1 H), 10.31 (br s, 1 H, NH)	306
15	2.89 (s, 3 H, CH_3), 5.10 (br s, 2 H, NH_2), 7.19 (t, ^3J = 7.8, 1 H, 5-Ar), 7.33 (d, ^3J = 7.8, 1 H, 3-Ar), 7.50 (td, ^3J = 7.8, ^4J = 1.5, 1 H, 4-Ar), 7.77 (dd, ^3J = 7.8, ^4J = 1.5, 1 H, 6-Ar), 7.86 (t, ^3J = 8.4, 1 H, 7-Qn), 8.02 (t, ^3J = 8.4, 1 H, 6-Qn), 8.15 (s, 1 H, 3-Qn), 8.32 (d, ^3J = 8.4, 1 H, 5-Qn), 8.40 (d, ^3J = 8.4, 1 H, 8-Qn)	235
16	2.62 (s, 3 H, CH_3), 7.38 (m, 2 H, Ph), 7.56–7.67 (m, 5 H, Ph, 5,7-Qn), 7.92 (m, 1 H, 6-Qn), 8.11 (d, ^3J = 8.4, 1 H, 8-Qn)	316
17	7.03 (dd, ^3J = 4.8, ^4J = 3.2, 1 H, 4-Th), 7.24 (d, ^3J = 8.4, 1 H), 7.28–7.47 (m, 4 H), 7.56 (d, ^3J = 4.8, 1 H, 3-Th), 7.59 (d, ^3J = 8.4, 1 H, 5-Qn), 7.82 (t, ^3J = 8.4, 1 H, 7-Qn), 7.98 (d, ^3J = 3.2, 1 H, 5-Th), 8.03 (t, ^3J = 8.4, 1 H, 6-Qn), 8.33 (d, ^3J = 8.4, 1 H, 8-Qn)	384
18	7.37–7.48 (m, 2 H, 3,5-Ph), 7.57–7.64 (m, 3 H, 2,4,6-Ph), 7.68 (d, $^3J_{HH}$ = 8.3, 1 H, 8-Qn), 7.88 (t, $^3J_{HH}$ = 8.3, 1 H, 7-Qn), 8.10 (t, $^3J_{HH}$ = 8.3, 1 H, 6-Qn), 8.35 (d, $^3J_{HH}$ = 8.3, 1 H, 5-Qn)	370

Unexpected results were obtained in the Friedländer annulation with trifluoromethyl-containing diketones **8a**–**c**. Thus, 1,1,1-trifluoropentane-2,4-dione (**8a**) gave 3-(trifluoroacetyl)quinoline **16**, the same results as previously reported in the literature ($NaAuCl_4$ or bmimCl·$ZnCl_2$ as a catalyst). Meanwhile, 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione (**8b**) afforded 2-(trifluoromethyl)quinoline **17** in high yield as the sole product of the reaction. The structure of these compounds was confirmed by ^{13}C and ^{19}F NMR spectroscopy as well as by comparison with model compound **18** obtained from symmetrical 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**8c**). It is thought that the differing regioselectivity is due to different reaction mechanisms. In the case of 1,1,1-trifluoropentane-2,4-dione (**8a**) the reaction proceeds via the corresponding enaminone **19**,[14a] which was detected by ^{19}F NMR spectroscopy in the reaction mixture. In the case of 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione (**8b**) no intermediates were detected by ^{19}F NMR spectroscopy. The first step of the reaction is considered to be a crotonic condensation between a ketone fragment and a CH-acidic group of the diketone affording intermediate **20**, followed by cyclization with participation of the more active trifluoroacetyl group, with the stage of formation of the intermediate **20** being limiting (Scheme 2).



Scheme 2

With sterically hindered ketones of type **4g**,**h** the reaction can occur via an intermediate of type **21** that cyclizes intermolecularly to give the corresponding quinolines.[28] In this case an alternative reaction is almost impossible, so that formation of intermediates of type **22** is hampered by steric hindrance (Scheme 3).



Scheme 3

The general procedure for the synthesis of compounds **9**–**18** was used. In all the cases except **9c**, **9g**, **10**, **12a**, **12b**, **16**, **17**, **18**, which contain acceptor substituents such as ethoxycarbonyl, cyano, and trifluoroacetyl in the quinoline ring, these precipitates were obtained as the monohydrochloride of the corresponding quinolines **3** with 80–

95% purity. The purification of these compounds can be achieved by simple washing with acetonitrile. Compounds **9c**, **9g**, **10**, **12a**, **12b**, **16**, **17**, **18** precipitate as the free base and can be purified by recrystallization from methanol. ^{1}H NMR and mass spectra data are given in Table 2.

Nevertheless, some limitations were found in the course of this work. In the case of sterically hindered ketones **4g**,**h**,**j**, 1-(2-aminophenyl)ethanone (**1a**) undergoes self-condensation affording compound **15** as the major product.

In conclusion, we described an efficient route for the synthesis of quinolines and polycyclic quinolines using chlorotrimethylsilane as a promoter and water scavenger via Friedländer annulation. The methodology is applicable to a wide variety of α-methylene ketones and delivers the target products in good yields, excellent homogeneity and often in analytically pure form. The procedure is very simple and could be easily adapted to semi-automated solution-phase parallel synthesis of quinoline libraries. Over 1000 analogues have been synthesized in our laboratories[29] by parallel synthesis methods. This procedure can be easily scaled up as illustrated by two examples (see experimental) and can be used for the synthesis of building blocks based on functionalized quinolines.

All chemicals were obtained from commercially available sources (Aldrich, Fluka, Enamine Ltd) and used without further purification. DMF was freshly distilled and dried by standard methods, monitoring of water concentration in solvents (the solvent contained <0.05%, usually 0.02% of H_2O) were performed using Mettler Toledo DL31 KF Titrator. All solvents for the crystallization were used without additional purification.

Melting points were measured with a Buchi melting points apparatus and are uncorrected. The ^{1}H, ^{13}C and ^{19}F NMR spectra (500 MHz, 125 MHz and 470 MHz, respectively) were recorded on a Bruker Avance DRX 500 with DMSO-d_6 as a solvent, TMS (^{1}H and ^{13}C) and $CFCl_3$ (^{19}F) were used as internal standards. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of HPLC Agilent 1100 Series equipped with diode-matrix and mass-selective detector Agilent LC\MSD SL. According to HPLC MS data all the synthesized compounds have purity >95%. BRANSON 2510E-MT ultrasonic bath and autoclave BERGHOF HR-500 were used.

Quinolines 9–18; General Procedure

An appropriate *o*-aminocarbonyl compound **1a–e** (1 mmol) and an appropriate carbonyl component **2–8** (1 mmol) were placed in an 8-mL Ace pressure tube and dissolved in DMF (2 mL). TMSCl (4 mmol) was added dropwise to the soln. The tube was thoroughly sealed and heated on a water bath for 4–10 h. After cooling, the flask was opened (*CAUTION:* excessive pressure inside) and the mixture was poured into H_2O (5 mL) and allowed to stand at 20 °C in an ultrasonic bath for 1 h. The thus-formed precipitate was filtered and washed with small amount of MeOH (or MeCN). Recrystallization from an appropriate solvent yielded the target compound.

9d

^{13}C NMR (125 MHz): δ = 16.8, 20.11, 122.9, 126.0, 126.6, 128.9, 133.2, 133.3, 139.4, 148.7, 154.0, 167.6.

11c

^{13}C NMR (125 MHz): δ = 19.8, 113.0, 119.2, 119.9, 120.1, 123.7, 125.7, 125.9, 128.1, 129.6, 133.9, 137.5, 144.7, 154.8.

11g

^{13}C NMR (125 MHz): δ = 30.1, 38.4, 120.4, 124.5, 126.0, 128.9, 129.5, 129.8, 130.0, 131.6, 132.1, 136.9, 143.8, 150.5, 168.9.

11h

^{13}C NMR (125 MHz): δ = 28.6, 36.6, 40.0, 41.5, 119.5, 124.2, 125.8, 129.3, 129.4, 129.9, 130.0, 130.5, 131.3, 131.5, 137.5, 148.0, 169.0.

11i

^{13}C NMR (125 MHz): δ = 33.7, 42.8, 115.8 (d, ^2J = 25.2 Hz), 124.8, 127.9, 128.4, 129.2, 129.4, 129.7, 130.6, 131.3, 131.4, 131.8, 132.0, 135.8, 137.3, 144.9, 160.3, 162.6 (d, ^1J = 245.7 Hz).

11j

^{13}C NMR (125 MHz): δ = 23.1, 31.0, 124.6, 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 129.1, 130.0, 130.3, 131.5, 136.9, 137.6, 142.2, 143.5, 146.7, 162.1.

14a

^{13}C NMR (125 MHz): δ = 16.0, 20.9, 28.0, 76.9, 122.8, 123.7, 126.0, 127.4, 128.2, 129.0, 130.9, 132.0, 132.7, 134.3, 134.7, 139.5, 151.0, 153.1, 154.6.

14g

^{13}C NMR (125 MHz): δ = 52.5, 115.3 (d, ^2J = 25.2 Hz), 118.9 (d, ^2J = 25.2 Hz), 121.1, 126.6, 126.7, 127.0, 129.0, 129.6, 129.7, 129.9, 131.2, 133.8, 134.4, 138.6, 138.7, 147.2, 147.3, 148.9, 165.5 (d, ^1J = 251.7 Hz).

14i

^{13}C NMR (125 MHz): δ = 30.1, 40.0, 43.2, 122.7, 123.7, 123.9, 125.2, 129.4, 129.9, 130.0, 130.9, 133.4, 145.5, 147.9, 148.6, 158.3.

16

^{13}C NMR (125 MHz): δ = 23.8, 115.0 (q, ^1J = 293.3 Hz), 124.1, 126.4, 127.0, 128.2, 129.25, 129.27, 130.2, 130.7, 132.4, 133.6, 147.8, 148.3, 153.1, 189.3 (q, ^2J = 37.3 Hz).

^{19}F NMR: δ = –75.3.

17

^{13}C NMR (125 MHz): δ = 121.8 (q, ^1J = 276.5 Hz), 126.9, 127.8, 128.3, 128.9, 129.1, 129.3, 129.4, 130.3, 130.4, 130.5, 130.7, 132.5, 133.8, 137.6, 137.9, 142.8 (q, ^3J = 33.9 Hz), 144.1, 146.5, 149.0, 186.0.

^{19}F NMR: δ = –62.9.

18

^{13}C NMR (125 MHz): δ = 111.4 (^3J = 19.2 Hz), 114.7 (^1J = 292.3 Hz), 121.2 (^1J = 275.9 Hz), 123.5, 127.0, 128.6, 129.0, 129.3, 130.3, 130.6, 130.7, 131.6, 132.3, 134.0, 142.0 (^2J = 34.1 Hz), 147.0, 150.7, 186.3 (^2J = 38.8 Hz).

^{19}F NMR: δ = –64.2 (3 F), –76.8 (3 F).

Ethyl 2-(Chloromethyl)-4-methylquinoline-3-carboxylate (9c)

1-(2-Aminophenyl)ethanone (**1a**, 25.6 g, 0.19 mol) was dissolved in DMF (150 mL). To the soln thus obtained, ethyl 4-chloro-3-oxobutanoate (**2c**, 31.2 g, 0.19 mol) was added and TMSCl (82.4 g, 0.76 mol) was carefully added dropwise. The autoclave was sealed and heated at 100 °C for 8 h. After cooling the autoclave was opened and the mixture was poured into H_2O (1 L) and the mixture thus obtained was allowed to stand at r.t. in ultrasonic bath for 1 h. The pre-

cipitate formed was filtered and washed with *i*-PrOH (3 × 10 mL). The mother liquor was evaporated in vacuo and the residue was washed with *i*-PrOH (10 mL). The two portions were combined and recrystallized (EtOH), affording the target compound; yield: 46.4 g (93%).

^{13}C NMR: δ = 14.4, 16.4, 46.0, 62.6, 125.6, 126.8, 126.9, 128.8, 129.0, 129.1, 132.1, 145.6, 152.6, 167.4.

(2,4-Dimethylquinolin-3-yl)acetic Acid (13a)

1-(2-Aminophenyl)ethanone (**1a**, 31.4 g, 0.232 mol) was dissolved in DMF (150 mL). To the soln thus obtained 4-oxopentanoic acid (**6**, 29.7 g, 0.256 mol) was added and TMSCl (126.2 g, 1.161 mol) was carefully added dropwise. The autoclave was sealed and heated at 100 °C for 8 h. After cooling the autoclave was opened and the mixture was poured into H_2O (1 L) and the mixture thus obtained was allowed to stand at r.t. in ultrasonic bath for 1 h. The precipitate formed was filtered and washed with *i*-PrOH (3 × 10 mL). The mother liquor was evaporated in vacuo and the residue was washed with *i*-PrOH (10 mL). The two portions were combined and recrystallized (EtOH) affording the target compound **13a** as the hydrochloride salt; yield: 55.5 g (95%).

^{13}C NMR: δ = 16.5, 20.1, 34.9, 121.5, 126.1, 127.0, 128.8, 129.2, 133.5, 137.2, 157.1, 171.5.

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