A New Green Approach to the Friedländer Synthesis of Quinolines

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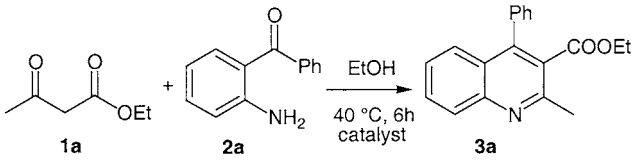
Abstract: A new approach to the Friedländer synthesis of quinolines is described. Polysubstituted quinolines are readily prepared under milder conditions than in other existing methods through a gold(III)-catalysed sequential condensation/annulation reaction of *o*-amino aromatic carbonyls and ketones containing active methylene groups.

Key words: quinolines, gold catalysis, annulations, *o*-amino aromatic carbonyls, domino reactions

The presence of the quinoline scaffold in the framework of various pharmacologically active compounds with antiasthmatic,[1] antiinflamatory[2] and tyrosine kinase PDGF-RTK inhibiting properties[3] continues to spur synthetic efforts regarding their acquisition.[4]

Most of the classical synthetic protocols for quinolines suffer from harsh conditions, poor yields and the use of hazardous acid or basic catalysts. In particular, since 1882 the synthesis of the quinoline nucleus by the Friedländer procedure has been extensively explored.[5] Hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, and polyphosphoric acid were widely employed as catalysts. In the cases in which acetic acid was used alone, it probably functioned as a convenient solvent and not as a catalyst. Uncatalysed Friedländer syntheses required more drastic reaction conditions, with temperatures in the range 150–220 °C. The reaction path suggested for the Friedländer procedure may involve sequential formation of N-(*o*-acylphenyl)-β-enaminones/cyclodehydration reaction.

During our studies towards the development of new environmentally friendly syntheses of heterocycles through transition metal catalysed domino reactions we observed the high efficiency of gold(III) catalysis[6] in sequential amination/annulation reaction of α-propargyl dicarbonyls with amine, aminoalcohols and α-aminoesters.[7] Moreover, we developed a simple and clean gold-catalysed synthesis of β-enaminones from 1,3-dicarbonyls and ammonia/amines that requires neither a corrosive acid catalyst nor azeotropic conditions using a large excess of aromatic solvents like benzene.[8] Consequently, since we were interested in the synthesis of functionalized quinolines,[9] we were driven to investigate the extension of the gold(III) catalysis to the development of a mild version of the Friedländer synthesis of quinolines. Indeed, by choosing as the model system the reaction of ethyl acetoacetate (**1a**) with 2-aminobenzophenone (**2a**) (Scheme 1), we failed to obtain the corresponding quinoline derivative **3a** without adding any catalyst; the starting 2-aminobenzophenone (**2a**) was recovered (90%) after reacting at 40 °C in ethanol for 6 hours. By contrast, in the presence of a catalytic amount of $NaAuCl_4 \cdot 2H_2O$ (Aldrich) the quinoline **3a** was isolated in 83% yield under the same reaction conditions. Furthermore, the reaction can be run very efficiently at room temperature (Table 1, entry 1).



Catalyst	**3a**(yield%)
/	/ [a]
$NaAuCl_4$	83
Na_2PdCl_4	/
CuI	/
$ZnCl_2$	43
$AgNO_3$	/

[a] 90% of **2a** recovered.

Scheme 1

A screening of the efficiency of other transition metal salts revealed that palladium(II)-, copper(I)-, and silver(I) salts were ineffective as catalysts; $ZnCl_2$ can lead to the formation of **3a** (43% yield), even if its efficiency is lower[10] than that of gold(III). Recently, Kobayashi and co-workers,[11] also, reported that $AuCl_3 \cdot 3H_2O$ exhibit higher catalytic activity compared to conventional Lewis acids. Thus, a further investigation of the gold-catalysed reaction of *o*-amino substituted aromatic ketones and carbonyl compounds containing a reactive methylene group promises to overcome some of the drawbacks caused by more vigorous reagents and drastic reaction conditions. To the best of our knowledge the gold-catalysed synthesis of quinolines has not been investigated.

Typically, *o*-amino substituted aromatic ketones **2** were taken along with a 1,3-dicarbonyl derivative and a catalytic quantity of $NaAuCl_4 \cdot 2H_2O$ (2.5 mol%) in ethanol at room temperature to give quinoline derivatives[12] **3**. When cyclic ketones[13] were used as reagents the reaction was carried out at 60 °C (Scheme 2 and Table 1).

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Table 1 Gold Catalysed Synthesis of Quinolines **3**[a,b]

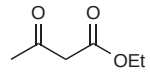
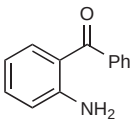
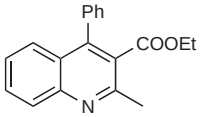
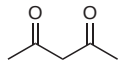
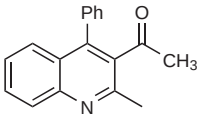
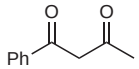
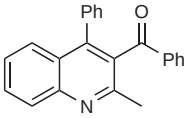
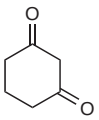
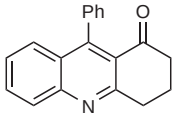
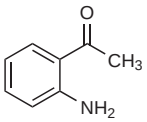
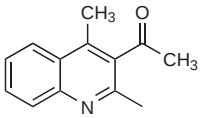
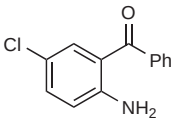
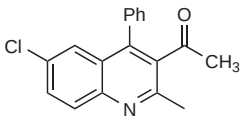
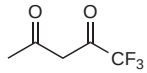
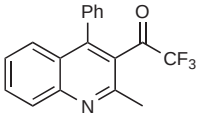
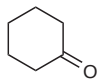
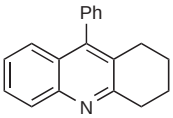
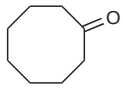
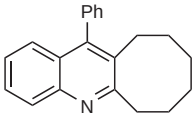
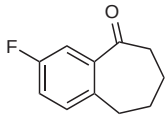
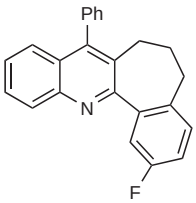
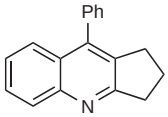
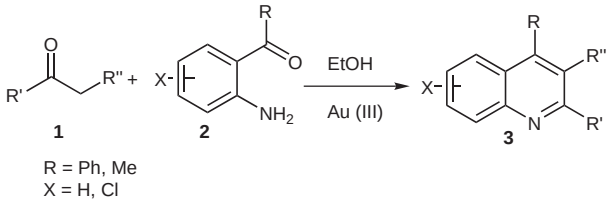
Entry	Compound **1**	Compound **2**	Product **3** Yield (%)	Previously reported results
1	 **1a**	 **2a**	 **3a** (93%)	H_2SO_4, HOAc reflux,[14] 2 h (Yield: 85%)
2	 **1b**	**2a**	 **3b** (87%)	150 °C,[15] 4 h (Yield: 70%)
3	 **1c**	**2a**	 **3c** (62%)	H_2SO_4, HOAc reflux,[15] 2 h (Yield: 86%).
4	 **1d**	**2a**	 **3d** (78%)	100–120 °C,[16] (Yield: 80%)[c]
5	**1b**	 **2b**	 **3e** (54%)	110 °C,[17] (Yield: 60%)[c]
6	**1b**	 **2c**	 **3f** (89%)	
7	 **1e**	**2a**	 **3g** (50%)[d]	
8	 **1f**	**2a**	 **3h** (62%)	HCl, 100–200 °C, 1 h[17] (Yield: 68%)
9	 **1g**	**2a**	 **3i** (60%)[d]	
10	 **1h**	**2a**	 **3j** (81%)[d]	

Table 1 Gold Catalysed Synthesis of Quinolines **3**[a,b] (continued)

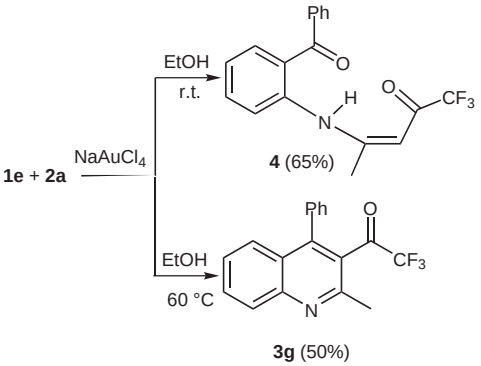
Entry	Compound **1**	Compound **2**	Product **3** Yield (%)	Previously reported results
11	 **1i**	**2a**	 **3k** (73%)[d,e]	HCl, 100–200 °C,[18] 2 h (Yield: 47%)

[a] Yields refer to single runs, are given for pure isolated product and are based on **2**.
[b] Unless otherwise stated reactions were carried out using the following molar ratios: **1**:**2**:$NaAuCl_4$ = 1.5:1:0.025, at r.t. in EtOH.
[c] The hydrochloride salts of *o*-aminobenzophenone and *o*-aminoacetophenone were used.
[d] Reactions were carried out at 60 °C.
[e] The catalyst used was $KAuCl_4$ (Strem Chemicals).

In the reaction of the aryl-alkyl dicarbonyl **1c** with **2a** we observed the regioselective formation of quinoline **3c** derived by the amination of the aliphatic carbonyl group (Table 1, entry 3). Surprisingly, when the 1,1,1-trifluoacetylacetone **1e** was allowed to react with **2a** under the usual reaction conditions a regioselective condensation reaction at the acetyl group led to β-enaminone **4** as the main reaction product[19] (65% yield) (Scheme 3). The sequential condensation/annulation reaction to form **3g** was accomplished by heating the reaction mixture at 60 °C for 12 hours (Scheme 3). Very likely, the strong electron-withdrawing trifluoroacetyl group hinders the annulation step.



Scheme 2



Scheme 3

It is clear from our results that the gold catalysed reaction of *o*-amino substituted aromatic carbonyls with ketones containing active methylene groups appears to provide an efficient new tool for the synthesis of quinolines under mild conditions. In conclusion, we have developed a 'green' approach to the Friedländer synthesis of quinolines that requires neither harsh conditions nor the use of hazardous acids or bases.

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(10) $ZnCl_2$ has been previously reported as catalyst in the Friedländer synthesis of quinolines: Walser, A.; Flynn, T.; Fryer, R. I. *J. Heterocycl. Chem.* **1975**, *12*, 737.
(11) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319.
(12) A typical procedure for quinoline **3** is as follows: to a solution of 2-amino-5-chlorobenzophenone **2c** (0.2 g, 0.86 mmol) and 2,4-pentanedione **1b** (0.13 g, 1.29 mmol) in

EtOH (3 mL) $NaAuCl_4 \cdot 2H_2O$ was added at r.t. under nitrogen atmosphere. The reaction mixture was stirred for 48 h. The solvent was then evaporated under reduced pressure. The residue, purified by flash chromatography (silica gel, 95/5 v/v *n*-hexane/ethyl acetate), afforded 1-(6-chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone **3f** (0.23 g, 89% yield); mp 153–155 °C. IR (KBr): 1715 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.00 (s, 3 H), 2.68 (s, 3 H), 7.33–7.96 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ = 23.8, 31.7, 124.8, 125.7, 128.9, 129.2, 129.8, 130.5, 130.8, 132.3, 134.4, 135.4, 142.9, 145.8, 153.8, 205.1. EI-MS: *m/z* (relative intensity) = 295 (39) [M^+], 281 (100), 252 (22).

(13) Selected data for **3g, 3i, 3j, 3g:** Mp 80–81 °C. IR (KBr): 1750 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.71 (s, 3 H), 7.34–7.67 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ = 23.8, 115,4 (q, *J* = 308 Hz), 126.3, 127.1, 127.6, 128.2, 129.1, 129.4, 130.3, 131.3, 131.6, 147.5, 148.3, 153.3, 189.4 (q, *J* = 38 Hz). EI-MS: *m/z* (relative intensity) = 315(68) [M^+], 247 (100), 218 (27). **3i:** Mp 118–120 °C. ^1H NMR ($CDCl_3$): δ = 1.33–1.47 (m, 6 H), 1.90–1.95 (m, 2 H), 2.73 (t, *J* = 5.6 Hz, 2 H), 3.21 (t, *J* = 6.1 Hz, 2 H), 7.18–7.26 (m, 4 H), 7.42–7.47 (m, 3 H), 7.52–7.60 (m, 1 H), 8.05–8.09 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 25.6, 26.5, 27.9, 31.0, 31.1, 36.2, 125.2, 125.9, 127.0, 127.4, 128.0, 128.1, 128.4, 129.1, 131.6, 137.4, 146.2, 146.3, 163.2. EI-MS: *m/z* (relative intensity) = 287 (100) [M^+], 258 (27). **3j:** Mp 194–196 °C. ^1H NMR ($CDCl_3$): δ = 2.02–2.06 (m, 2 H), 2.38 (t, *J* = 6.7 Hz, 2 H), 2.57 (t, *J* = 6.9 Hz, 2 H), 7.07–8.22 (m, 12 H). ^{13}C NMR ($CDCl_3$): δ = 25.1, 29.6, 31.9, 115.8 (d, *J* = 22.2 Hz), 126.2, 126.3, 127.2, 127.9, 128.4, 128.6, 129.4, 129.5, 129.7, 130.4, 161.9 (d, *J* = 244.2 Hz). EI-MS: *m/z* (relative intensity) = 339 (100) [M^+].

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(19) Selected data for **4**: IR(neat): 3460, 3350, 1720, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.05 (s, 3 H), 5.43 (s, 1 H), 7.27–7.66 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ = 20.3, 91.5, 114.4 (q, *J* = 218 Hz), 126.9, 127.3, 128.5, 129.4, 129.9, 130.7, 131.7, 133.5, 134.4, 137.6, 176.6 (q, *J* = 33 Hz), 195.3. EI-MS: *m/z* (relative intensity) = 324 (100) [M + 1^+], 265 (21), 220 (94), 105 (67).