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ORIGINAL PAPER

Synthesis of 6-chloroquinolines using benzyltrimethylammonium tetrachloroiodate as a selective chlorinating agent and an efficient generator of HCl

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Abstract A simple and efficient one-pot synthesis of 6-chloroquinolines was achieved in good yields via the three-component reaction of 2-aminoaryl ketones, α-methylene carbonyl compounds, and BTMA ICl_4 in AcOH.

Keywords Benzyltrimethylammonium tetrachloroiodate · 6-Chloroquinolines · Catalysts · Chlorination · Aldol reactions

Introduction

The synthesis of 6-chloroquinoline derivatives has been considered of great interest to organic chemists owing to their wide range of biological and pharmaceutical properties [1–7], such as antiparasitic, antitubercular, antibacterial, antifilarial, HIV inhibiting, HMG-CoA reductase inhibiting, cell adhesion inhibiting, cytokine formation inhibiting agents, and allosteric enhancers of the GABAB receptors. Friedlander quinoline synthesis is one of the most straightforward approaches for the synthesis of 6-chloroquinolines. This method involves the acid or base catalyzed or thermal condensation between a 2-aminoaryl ketone and another carbonyl compound possessing an α-reactive methylene group followed by cyclodehydration. Recently, Lewis acids [8–15], such as $Ag_3PW_{12}O_{40}$, $SnCl_2$, $FeCl_3$, $Mg(ClO_4)_2$, $Nd(NO_3)_3$, $Y(OTf)_3$, $NiCl_2$, I_2/CAN, and heterogeneous solid acid catalysts [16–18], including $NaHSO_4$–SiO_2, Amberlyst 15, dodecyl phosphoric acid, ionic liquids [19], microwave [20], urea [21], poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) [22], and KO*t*Bu [23] have been shown to be effective for the synthesis of quinolines.

In this work, we report a modification of the Friedlander reaction for the synthesis of 6-chloroquinolines, which involves the formation in situ of the chloroaminoaryl ketone using benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4) as chlorinating agent. This latter reagent also serves as an in situ generator of HCl, which acts as a catalyst for the subsequent Friedlander condensation.

Results and discussion

A range of 6-chloroquinolines was synthesized from a combination of 2-aminoaryl ketones (**1**), α-methylene carbonyl compounds (**2**) and BTMA ICl_4 (**3**) in a 1:1:1 ratio in AcOH, and the reaction was completed in 10–14 h at room temperature (Table 1).

Previously, BTMA ICl_4 was used as a chlorinating agent [24]. This solid reagent is considerably safe and convenient, and has a fine selectivity. It is well known that the chlorination of amines having electron withdrawing groups in the aromatic ring with a calculated amount of BTMA ICl_4 can give the desired *p*-chloro-substituted products [25]. Thus, it is conceivable that the reaction involves the following two steps: (1) the chloroaminoaryl ketone is initially formed in situ using BTMA ICl_4 as chlorinating agent; (2) BTMA ICl_4 serves as an in situ generator of HCl, which acts as a catalyst for the subsequent Friedlander condensation in the second step (see Scheme 1).

It is well known that the reaction of acetophenone with 2 equiv of BTMA ICl_4 in AcOH at 70 °C can give α,α-dichloroacetyl derivatives [26], which can result in the formation of the product **5**. However, as shown in entries

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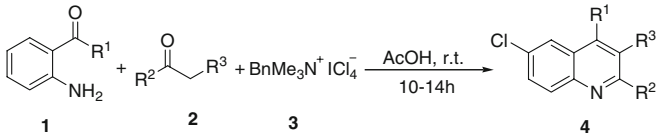
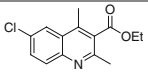
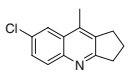
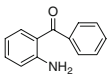
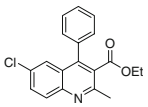
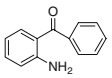
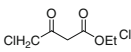
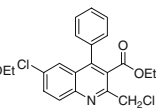
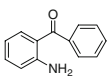
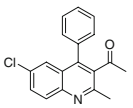
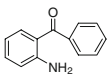
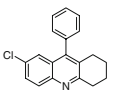
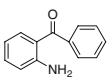
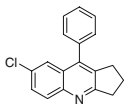
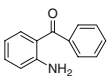
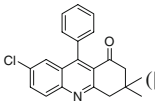
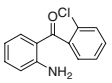
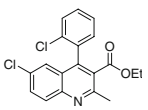
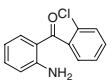
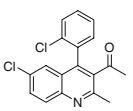
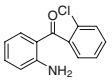
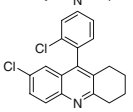
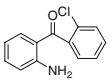
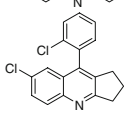
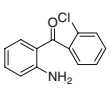
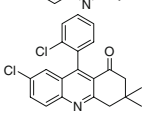
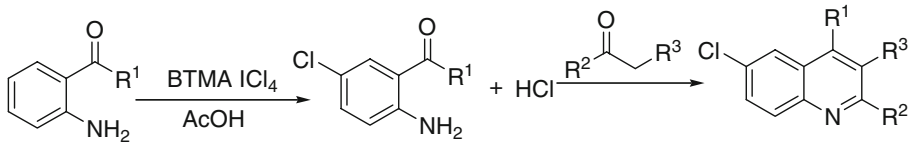
Table 1 Synthesis of 6-chloroquinolines



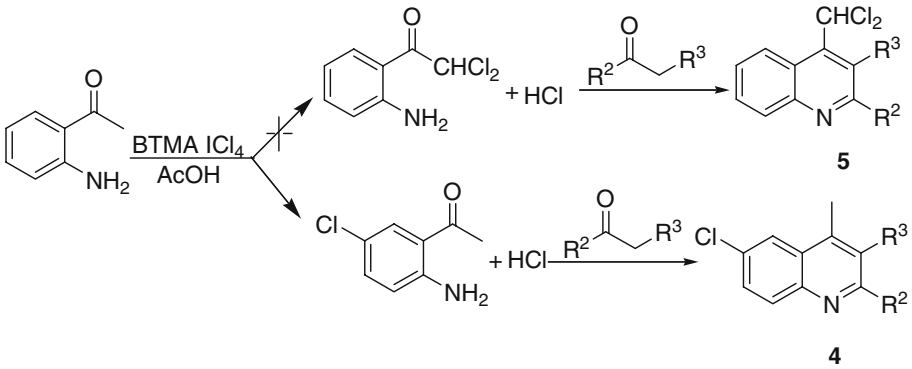
Entry	Substrate **1**	Substrate **2**	Product **4**	Mp/°C found (Reported)	Yield/% (Time/h)
a				oil	92 (10)
b				oil	87 (12)
c				105–106 ([19] 108)	76 (10)
d				107–108 ([1] 106–108)	93 (10)
e				147–148 ([l9] 151)	86 (12)
f				161–162 ([19] 163)	84 (12)
g				103–104 ([19] 105)	86 (12)
h				206–207 ([13] 208–209)	82 (14)
i				113–114 ([8] 110)	90 (10)
j				137–138 ([11] 138–140)	92 (10)
k				150–151 ([8] 153)	86 (12)
l				141–142 ([8] 141)	87 (12)
m				213	86 (14)

2-Aminoaryl ketones:α-methylene carbonyl compounds:BTMA ICl_4 = 1:1:1; reactions executed in a sealed vessel at room temperature

Scheme 1



Scheme 2



a–**b**, only product **4** was formed under the reaction conditions. This means that chlorination of the aromatic ring is faster than side-chain chlorination (Scheme 2).

In summary, we have developed a simple and efficient methodology to synthesize 6-chloroquinolines using BTMA ICl_4 as a selective chlorinating agent and an efficient generator of HCl in Friedlander reaction. We believe that this methodology will be a valuable addition to the existing methods in the field of 6-chloroquinolines [27, 28].

Experimental

NMR spectra were taken on a Bruker AV-300 spectrometer with TMS as internal standard. Coupling constants (*J*) were measured in Hz. Elemental analyses were recorded on a PEA-1110 elemental analyzer and agreed favorably with calculated values. Melting points were determined on a Mel-Temp capillary tube apparatus. BTMA ICl_4 was prepared according to the literature [26]. Commercially available reagents were used without further purification unless otherwise stated.

General procedure for the preparation of ***4***

To a stirred solution of the 2-aminoaryl ketone (1 mmol) and the α-methylene carbonyl compound (1 mmol) in 4 cm^3 AcOH at room temperature in a 20 cm^3 vessel, BTMA ICl_4 (1 mmol) was added in a single portion. The vessel was sealed immediately and stirred at room temperature for 10–14 h. After completion of the reaction (TLC), the mixture was filtered and then poured into 50 cm^3 saturated $NaHCO_3$ solution, extracted with 50 cm^3 diethyl ether, and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography over silica gel using EtOAc (8%) in hexane to obtain pure quinoline **4**.

Ethyl 6-chloro-2,4-dimethylquinoline-3-carboxylate (**4a**, $C_{14}H_{14}Cl_2NO_2$)
Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.02$ (d, $J = 8.9$ Hz, 1H), 7.68 (d, $J = 2.5$ Hz, 1H), 7.55 (dd, $J = 8.9$, 2.5 Hz, 1H), 4.82 (q, $J = 7.0$ Hz, 2H), 2.92 (s, 3H), 2.76 (s, 3H), 1.74 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.4$, 153.6, 146.5, 140.8, 128.9, 128.7, 127.2, 125.8, 124.9, 123.1, 60.5, 23.0, 15.9, 14.9 ppm; IR (KBr): $\bar{\nu} = 3{,}072$, 2,942, 2,863, 1,730, 1,615, 1,582, 1,200, 1,080, 620 cm^{-1}.

7-Chloro-9-methyl-2,3-dihydro-1H-cyclopenta[b]quinoline (**4b**, $C_{13}H_{12}ClNO$)
Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.04$ (d, $J = 8.7$ Hz, 1H), 7.65 (d, $J = 2.3$ Hz, 1H), 7.52 (dd, $J = 8.7$, 2.3 Hz, 1H), 3.22 (t, $J = 7.0$ Hz, 2H), 3.22 (t, $J = 7.2$ Hz, 2H), 2.42 (s, 3H), 2.08–2.01 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.2$, 145.3, 136.2, 132.2, 127.5, 127.1, 126.3, 124.8, 122.3, 33.6, 28.9, 21.9, 15.8 ppm; IR (KBr): $\bar{\nu} = 3{,}068$, 2,954, 1,609, 921, 756 cm^{-1}.

7-Chloro-3,3-dimethyl-9-phenyl-3,4-dihydroacridin-1(2H)-one (**4m**, $C_{21}H_{18}ClNO$)
Yellow solid. M.p.: 212 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.01$ (d, $J = 8.79$ Hz, 1H), 7.67–7.45 (m, 5H), 7.35–7.30 (m, 2H), 2.96 (s, 2H), 2.42 (s, 2H), 1.10 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 198.4$, 156.2, 146.3, 142.8, 136.7, 135.6, 133.1, 130.2, 129.3, 129.2, 129.0, 128.2, 127.9, 126.3, 125.0, 123.3, 55.3, 49.2, 32.0, 28.3 (2C) ppm; IR (KBr) $\bar{\nu} = 3{,}043$, 2,980, 1,710, 1,605, 1,540, 1,220, 745 cm^{-1}.

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