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An unexpected synthesis and application of ethyl 2,4-bis(chloromethyl)-6-iodoquinoline-3-carboxylate

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Abstract
An unexpected and direct synthesis of ethyl 2,4-bis(chloromethyl)-6-iodoquinoline-3-carboxylate (**3**) from the chlorotrimethylsilane (TMSCl)-promoted Friedländer reaction between 1-(2-amino-5-iodophenyl)ethanone (**2**) and ethyl 4-chloro-3-oxobutanoate has been disclosed. As a versatile and attractive building block, a synthetic application of the poly-functionalized quinoline **3** in the successive Williamson ether synthesis with various phenols and in situ ester hydrolysis reaction has been achieved and the corresponding 2,4-bis(aroxymethyl)quinoline-3-carboxylic acids (**5a-k**) were obtained in good yields of 71–86%.

Keywords Quinoline · Chlorotrimethylsilane · Friedländer reaction · Building block · Williamson reaction · Hydrolysis reaction

Introduction

Halomethyl-functionalized quinolines have been widely applied as fundamental building blocks to participate in a wide array of chemical transformations in organic chemistry [1], and considerable synthetic efforts directed toward the application of this class of compounds have been paid to reveal the synthetic potential of these platforms in accessing important drug-like small molecules or new quinoline luminescent materials [2–4]. For example, Muscia et al. [5] reported the synthesis and application of ethyl 6-chloro-2-(chloromethyl)-4-phenylquinoline-3-carboxylate as a

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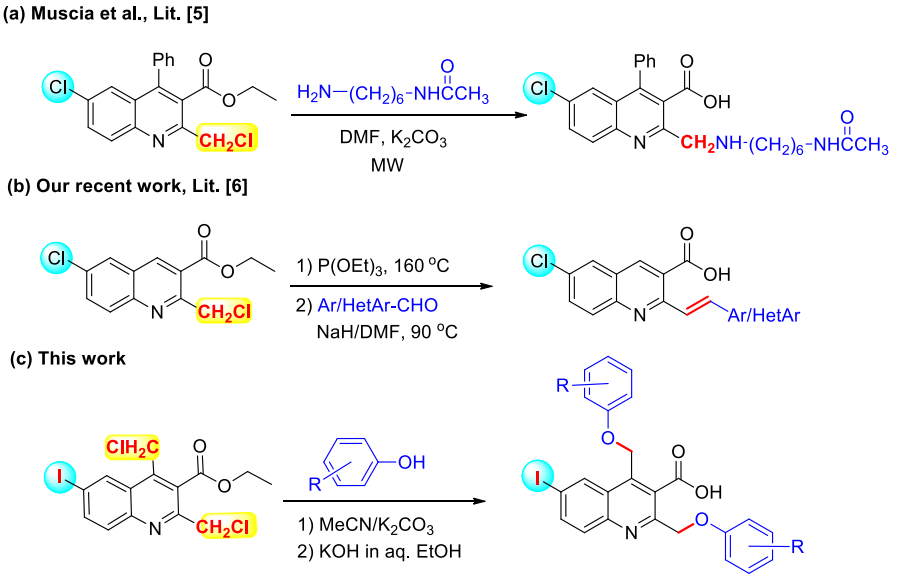
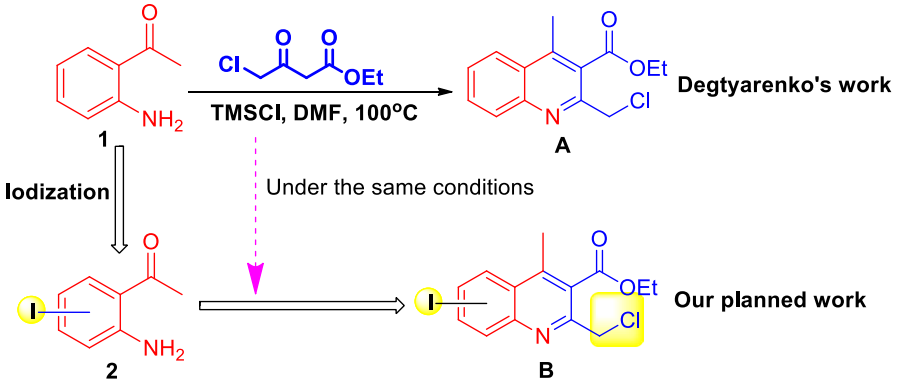


Scheme 1 Synthetic applications of 2-chloro- and 2,4-bis(chloromethyl)quinoline-3-carboxylates

versatile building block for furnishing new 2-alkylaminomethylquinoline derivatives as shown in Scheme 1a with potent and more selective antitrypanosomal activity. In this context, we have recently described the synthesis and application of ethyl 6-chloro-2-(chloromethyl) quinoline-3-carboxylate for the construction of 2-(aryl/hetarylvinyl)quinoline-3-carboxylic acids as shown in Scheme 1b [6].

On the other hand, Williamson reaction, which usually involves the reaction between alkyl halide and alkali metal salt of the hydroxy compounds [7], is a very useful transformation in organic synthesis since the products are of value in both industrial and academic applications [8, 9]. For example, 2-(aroxymethyl)quinolines derived from the Williamson reaction of 2-halomethylquinoline with phenols exist as substructures in numerous medicinally interesting compounds displaying potent biological and pharmacological activities [10, 11]. Additionally, among haloquinolines, iodoquinolines are well known to be a class of attractive and privileged synthetic targets [12, 13] and are widely used as drug-like chemical probes in pharmacological studies or as versatile intermediates for the development of more complex quinoline derivatives [14–16], for example, via cross-coupling reactions [17].

Taking these observations into account and in view of structural diversity playing a prominent role for the current medicinal chemistry needs, we felt that it would be a worthwhile endeavor to synthesize novel and intriguing iodo-substituted halomethyl-functionalized quinoline as a versatile intermediate for the flexible application in the Williamson reaction to obtain structurally diverse and promising iodoquinoline ether derivatives. Thus, in the context of our continuing interest in the design and synthesis of interesting types of quinoline-based compounds [18, 19], we would like to report herein an unexpected synthesis of ethyl 2,4-bis(chloromethyl)-6-iodoquinoline-3-carboxylate (**3**) and its application in Williamson reaction for the



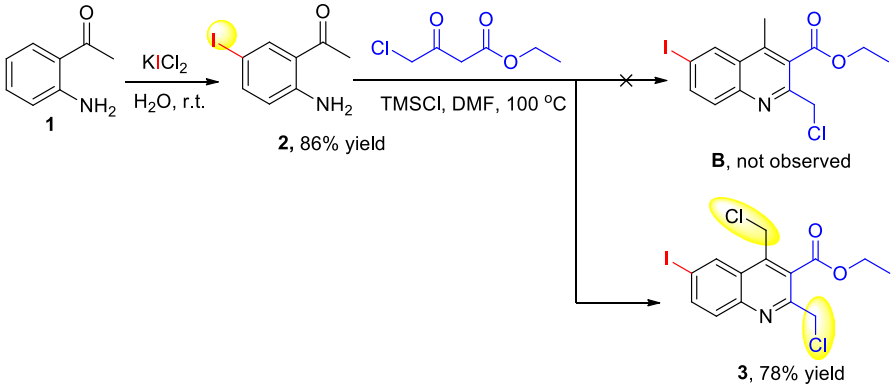
Scheme 2 Synthetic route designed for iodo-functionalized ethyl 2-chloromethylquinoline-3-carboxylate (**B**)

construction of a series of novel 6-iodo-2,4-bis(aroxymethyl)quinoline-3-carboxylic acids (**5**) as possible drug candidates for the current medicinal chemistry needs as shown in Scheme 1c, which, to our knowledge, have not yet been described in the literature.

Results and discussion

Previously, Degtyarenko et al. [20] reported an elegant and convenient chlorotrimethylsilane (TMSCl)-mediated Friedländer reaction of *o*-aminoacetophenone (**1**) with ethyl 4-chloro-3-oxobutanoate for the synthesis of ethyl 2-chloromethylquinoline-3-carboxylate (**A**) (Scheme 2). On the basis of this work, we conceived that if we could introduce an iodine atom into *o*-aminoacetophenone, the resulting iodo-substituted derivative **2** might be a feasible substrate to undergo the same Friedländer reaction to access the corresponding iodo-functionalized analogue **B** as shown in Scheme 2.

Accordingly, the first stage in our synthesis involved the preparation of the iodo-substituted *o*-aminoacetophenone. In fact, we initially used excess iodine as iodinating agent according to our previously reported method [21]. However, due to iodine being a weaker electrophile, the direct iodination of *o*-aminoacetophenone hardly proceeded without the formation of the expected product even in trace amounts. Subsequently, we investigated the iodination reaction by using potassium dichloroiodate ($KICl_2$) as an iodinating agent as outlined in Scheme 3, following the protocol of the literature [22]. Interestingly, this impressive method was found to be suitable for our transformation and the reaction proceeded very smoothly with one new compound being observed on TLC. After simple workup followed by purification by column chromatography over silica gel, the product obtained was identified as a known compound 1-(2-amino-5-iodophenyl)ethanone (**2**) in a good yield of 86%. Its melting points and spectral data are in good agreement with the reported literature [23], in which compound **2** was prepared



Scheme 3 Unexpected synthesis of ethyl 2,4-bis(chloromethyl)-6-iodoquinoline-3-carboxylate (**3**) from the TMSCl-promoted Friedländer reaction

through the iodination reaction of 2-aminoacetophenone with N-iodosuccinimide (NIC) using silver (I) triflimide as the catalyst. However, as far as we know, no related reports are available concerning the application of $KICl_2$ for the green synthesis of **2**. It is worth to mention that the order of addition of the reagents was crucial to the reaction: When an aqueous solution of $KICl_2$ was added dropwise to a stirred aqueous solution of *o*-aminoacetophenone at room temperature, the reaction is very clean and very small amounts of by-products were detected; however, if an aqueous solution or solid of *o*-aminoacetophenone was added to the aqueous $KICl_2$ solution, the resulting reaction mixture became very darkly colored with excess by-products, from which the corresponding product was isolated only in a very low yield of 23%.

Subsequently, our attention was turned to its Friedländer reaction for the synthesis of iodo-substituted halomethyl-functionalized quinoline. Thus, iodo-substituted **2** was subjected to the Friedländer reaction with ethyl 4-chloro-3-oxobutanoate, based on the method of literature [20] expecting to obtain the corresponding ethyl 2-(chloromethyl)-6-iodo-4-methylquinoline-3-carboxylate (**B**) (Scheme 3). The reaction was conducted in a sealed reaction kettle, and after heating at 100 °C for 10 h, TLC exhibited the complete consumption of the substrates and the appearance of a new dark product spot. However, we were surprised to find that the major product isolated from the reaction mixture was unexpectedly identified as 2,4-bis(chloromethyl)-substituted derivative **3** with 78% yield, rather than the expected product **B**. Our proposed Friedländer reaction of **2** under the reaction conditions displayed a different reactivity pattern compared with **1.** The structure of **3** could be easily deduced from its NMR spectroscopic data and HRMS. For example, the ^{1}H NMR spectrum (recorded using DMSO-d_6 as the solvent) as shown in Fig. 1 exhibited three quinoline proton signals at 7.87, 8.20 and 8.76 ppm, respectively, with the splitting pattern being in accordance with some 2-, 3-, 4-, 6-substituted quinolines [6, 24, 25]. Particularly, there were two characteristic singlets at 4.98 and 5.26 ppm in the ^{1}H NMR spectrum, readily recognizable as arising from the resonances of the two methylene protons CH_2 signals. Moreover, we could not observe

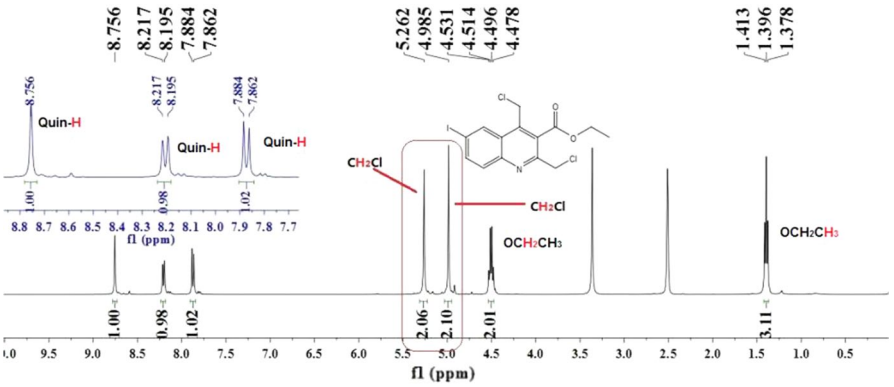


Fig. 1 ^{1}H NMR spectrum of compound **3**

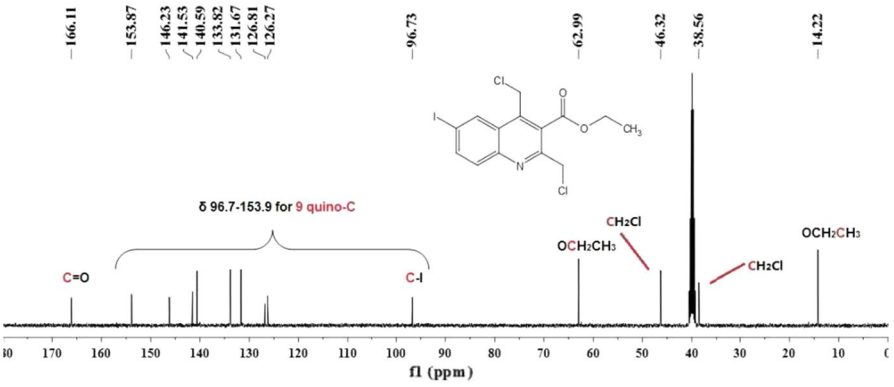


Fig. 2 ^{13}C NMR spectrum of compound **3**

in its ^{1}H NMR spectrum the existence of any signal that could be attributable to the 4-methyl protons.

Further, its ^{13}C NMR spectrum was also in good agreement with the assigned structure, which revealed the presence of two methylene carbons at 38.56 and 46.32 ppm, respectively. The characteristic signal corresponding to the 6-iodo-substituted carbon appeared at the upfield shift of 96.73 ppm due to the heavy atom effect of iodine (Fig. 2).

Finally, the molecular formula of compound **3** was deduced to be $C_{14}H_{12}Cl_2INO_2$ from its HRMS spectrum, which showed a *pseudo*-molecular ion peak at *m/z* 423.9380 ($[M+H]^+$, calc. for $C_{14}H_{13}I^{35}Cl_2NO_2^+$: 423.9363) in accordance with the suggested molecular structure as shown in Fig. 3.

To check whether the chlorination of methyl group happened only at higher temperature, we also carried out the reaction in a round-bottom flask with a condenser fully open to air with the conditions otherwise remaining unchanged.

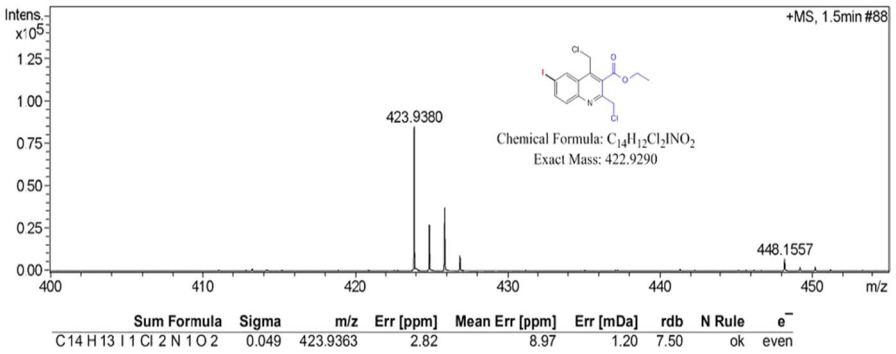


Fig. 3 HRMS spectrum of compound **3**

However, we found that the reaction did not proceed satisfactorily, giving a highly impure mixture of products from which the expected 2,4-bis(chloromethyl)-6-iodoquinoline (**3**) was not observed and instead the monochloromethylation product 2-(chloromethyl)-6-iodo-4-methylquinoline (**B**) was produced in a poor 27% yield together with some undefined by-products [26].[1] Further attempts by increasing the reaction temperature to refluxing condition were also to no avail, not leading to the occurrence of dichloromethylation reaction. As such, we presumed that the unexpected chlorination reaction might be closely related to the sealed condition and high reaction temperature. Additionally, to show the scope of substrate of this unexpected chlorination reaction, we also investigated the reactivity of 5-chloro- and 5-bromo-substituted 1-(2-aminophenyl)ethanones under the same reaction conditions. To our delight, both substrates were equally amenable to the reaction process, successfully furnishing the corresponding 2,4-bis(chloromethyl) quinoline derivatives in good yields [27].[2] To the best of our knowledge, the unexpected TMSCl-promoted Friedländer reaction for the direct and facile synthesis of 2,4-bis(chloromethyl)-functionalized 6-haloquinolines is unprecedented.

[1] The yields, physical properties and spectral data for ethyl 2-(chloromethyl)-6-iodo-4-methyl quinoline-3-carboxylate: White solid, yield 27%, m.p. 113–115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 1.54 (*t*, J=7.6 Hz, 3H, CH_2CH_3), 2.85 (s, 3H, CH_3), 4.63 (*q*, J=7.6 Hz, 2H, CH_2CH_3), 5.15 (*s*, 2H, CH_2Cl), 7.82 (dd, J=8.8, 2.0 Hz, 1H, Quino-H), 8.03 (d, J=2.0 Hz, 1H, Quino-H), 8.05 (d, J=8.8 Hz, 1H, Quino-H).

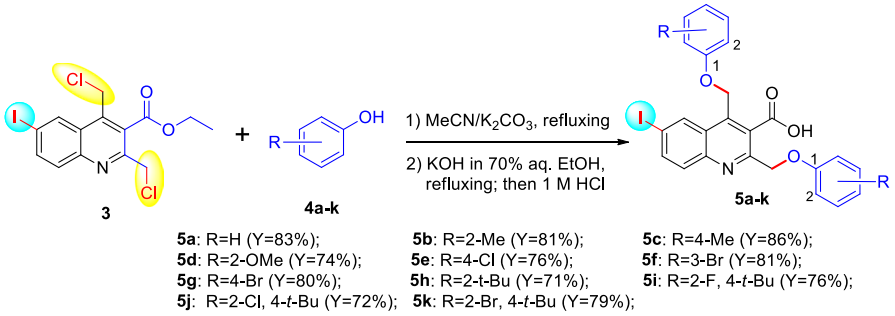
[2] The yields, physical properties and spectral data for ethyl 6-bromo-2,4-bis(chloromethyl)quinoline-3-carboxylate: Yellow solid, yield 67%, m.p. 144–145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 1.48 (*t*, J=7.6 Hz, 3H, CH_2CH_3), 4.50 (*q*, J=7.6 Hz, 2H, CH_2CH_3), 4.86 (*s*, 2H, CH_2Cl), 5.28 (*s*, 2H, CH_2Cl), 7.91 (dd, J=8.8, 1.6 Hz, 1H, Quino-H), 8.05 (*d*, J=8.8 Hz, 1H, Quino-H), 8.10 (d, J=1.6 Hz, 1H, Quino-H); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 15.17, 39.35, 48.24, 67.71, 129.69, 132.58, 132.86, 136.45, 138.56, 139.38, 145.48, 152.13, 161.51, 168.42; for ethyl 6-chloro-2,4-bis(chloromethyl)quinoline-3-carboxylate: Yellow, solid, yield 61%, m.p. 149–151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 1.50 (*t*, J=7.6 Hz, 3H, CH_2CH_3), 4.51 (*q*, J=7.6 Hz, 2H, CH_2CH_3), 4.94 (s, 2H, CH_2Cl), 5.27 (s, 2H, CH_2Cl), 7.78 (dd, J=8.8, 2.0 Hz, 1H, Quino-H), 7.91 (d, J=2.0 Hz, 1H, Quino-H), 8.08 (d, J=8.4 Hz, 1H, Quino-H); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 14.17, 37.81, 45.90, 62.18, 119.40, 122.11, 127.76, 130.38, 130.57, 135.71, 140.11, 146.29, 155.95, 165.06.

Currently, work is ongoing and more studies toward the scope of the cyclization reaction are being actively pursued in our laboratory. We believe this interesting reaction would have enough scope for further investigation and would likely render it a useful tool in the synthesis of this class of poly-functionalized quinoline derivatives, which have enormous potential as building blocks for the flexible construction of a large range of more novel, complex and promising quinoline-based compounds in organic synthesis.

Mechanistically, we have not yet established the rational mechanism at the current stage and the exact details of how the chlorination reaction proceeds still remain unclear and elusive. Taking into consideration the entire outcome, a tentative explanation is supposed that the unexpected chlorinating properties of the Me_3SiCl–DMF system are probably a consequence of the generation of chlorine from silicon–chlorine bonds of the much excess TMSCl [26] under the sealed and heating conditions during the Friedländer reaction course. In addition, it is worth to mention that there is a related report, wherein the methylene moiety could be chlorinated by the Me_3SiCl–$KBrO_3$–DMF system [27]. But the present explanation is still in its infancy, and the real reaction mechanism has not yet been elucidated. Our further research to explore its reaction mechanism by capturing the key intermediate or providing adequate prove-of-concept represents an intriguing goal that we are currently contemplating.

Having the newly synthesized ethyl 2,4-(dichloromethyl)quinoline-3-carboxylate (**3**) in hand and due to the importance of the 2-(aroxymethyl)quinolines, we became interested in investigating its Williamson reaction with phenols for building structurally novel and interesting iodo-substituted 2,4-bis(aroxymethyl)quinolines to expand the structure diversity for current medicinal chemistry needs. In our early work, we have reported the Williamson reaction of ethyl 2-(halomethyl)quinoline-3-carboxylates with 8-hydroxyquinolines or dihydroxy arenes for the synthesis of interesting bisquinoline systems [28, 29]. Accordingly, our investigation toward the Williamson reaction with phenols was conducted with a mole ratio of 1:2.2 according to our reliable reaction conditions using MeCN as the solvent with K_2CO_3 as the base as shown in Scheme 4.

Gratifyingly, the Williamson reaction proceeded very smoothly, and the TLC analysis did not indicate the formation of any distinct by-product after the substrates were completely consumed within 5 h. Upon completion of the Williamson reaction, we conceived that the newly formed quinoline ethers might not interfere with further ester hydrolysis reaction. Thus, the solvent MeCN was evaporated to dryness under reduced pressure and the in situ ester hydrolysis reaction was conducted by refluxing the residue in 70% aq. ethanolic KOH solution for 3 h. After the alkaline hydrolysis reaction was complete followed by acidification with 1 M HCl, the corresponding 2,4-bis(aroxymethyl)-6-iodo quinoline-3-carboxylic acids (**5a-k**) were obtained in overall good yields of 71–86% after recrystallization from ethanol (Scheme 4). It is worth to mention that the presence of 3-carboxyl functional group makes our synthesis particularly appealing, since quinolinecarboxylic acids are important substructures in a number of pharmacologically active molecules and could also be used as intermediates or building blocks for synthesis of valuable quinoline drugs [30–32].



Scheme 4 Synthesis of 2,4-bis(aroxymethyl)-6-iodoquinoline-3-carboxylic acids (**5a-k**)

The structures of compounds **5a-k** were confirmed by their spectral data, with the results being in good agreement with the assigned compounds. As an example, the ^{1}H NMR spectrum of **5d** exhibited the presence of two distinct three-proton singlets at 3.74 and 3.75 ppm due to the two methoxy protons, two two-proton singlets at 5.32 and 5.50 ppm attributable to the arising of two methylene protons and one broad singlet at 14.83 ppm for the carboxyl proton, along with the signals for 11 aromatic protons exactly matching their structures in the aromatic range of 6.75–8.65 ppm. Further, the ^{13}C NMR spectrum was also in good agreement with the assigned structure, which revealed the presence of two typical methylene carbons and carboxyl carbon at 66.32, 70.16 and 169.10 ppm, respectively, together with 21 quinoline and benzene ring carbon signals in the aromatic range of 93.66–154.68 ppm, which is consistent with the molecular structure suggested. The other synthesized compounds exhibited similar spectral characteristics, except the substituents, which exhibited characteristic signals with appropriate chemical shifts.

Conclusions

In summary, we have described an unexpected synthesis of ethyl 2,4-bis(chloromethyl)-6-iodoquinoline-3-carboxylate through TMSCl-promoted Friedländer reaction between 1-(2-amino-5-iodophenyl)ethanone and ethyl 4-chloro-3-oxobutanoate. The unexpected quinoline bearing iodo and two chloromethyl functional groups would be considered as a versatile building block, enabling the synthesis of a number of more complex and novel quinoline derivatives. A synthetic application in the successive Williamson ether synthesis and ester hydrolysis reaction with phenols has been attempted, and the corresponding 2,4-bis(aroxymethyl)-6-iodoquinoline-3-carboxylic acids were obtained in good yields. Currently, work is ongoing, mainly focusing on the detailed reaction mechanism and the scope of the unexpected reaction, which represent an intriguing goal that we are contemplating, and these results will be a part of future reports.

Experimental

The chemicals used in this work were obtained from Energy Chemical and were used without purification. Melting points were determined by use of a WRS-1B melting point apparatus and are uncorrected. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on an Agilent 400-MR spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent. The reported chemical shifts (δ values) are given in parts per million downfield from tetramethylsilane (TMS) as the internal standard (NMR abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, J = coupling constant). HRMS (ESI) data were acquired on a Bruker Customer micrOTOF-Q 125 high-resolution mass spectrometer with ESI. Elemental analyses were carried out on an EA 2400II elemental analyzer (PerkinElmer, Waltham, MA). The progress of reactions was monitored by TLC on silica gel GF254 using ethyl acetate/petroleum ether (1:8) as the eluent.

Procedure for the preparation of 1-(2-amino-5-iodophenyl)ethanone (2)

To a stirred aqueous solution of o-aminoacetophenone (50 mmol, 6.76 g) was added dropwise an aqueous solution of $KICl_2$ (25 mL, 2.0 M) at room temperature over a period of 1 h. During the addition, a yellow solid precipitated. After complete addition, the reaction mixture was maintained at room temperature overnight and then diluted with water (10 mL). The resulting precipitate was collected by filtration and purified by column chromatography over silica gel using ethyl acetate/petroleum ether mixture as eluent (1:8, v/v) to give 11.2 g of product **2** as yellow solid. Yield 86%, m.p. 94–96 °C (Lit [23]. mp 95 − 97 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 2.57 (s, 3H, Me), 6.33 (s, 2H, NH_2), 6.48 (d, J = 8.8 Hz, 1H, Ben-H), 7.49 (dd, J = 8.8, 2.0 Hz, 1H, Ben-H), 7.98 (d, J = 2.0 Hz, 1H, Ben-H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 27.87, 75.15, 119.39, 120.30, 140.25, 142.39, 149.49, 199.58. Anal. Calcd for C_8H_8INO: C, 36.81; H, 3.09; N, 5.37. Found: C, 36.96; H, 3.13; N, 5.21.

Procedure for the preparation of ethyl 2,4-bis(chloromethyl)-6-iodoquinoline-3-carboxylate (3)

To a stirred solution of 1-(2-amino-5-iodophenyl)ethanone (**2**) (10.44 g, 40 mmol) in 40 mL of DMF in a 100-mL reaction kettle was added ethyl 4-chloro-3-oxobutanoate (2) (6.60 g, 40 mmol). To the solution thus obtained, TMSCl (17.4 g, 160 mmol) was carefully added dropwise. The kettle was then sealed and heated at 100 °C for 10 h. After cooling, the kettle was opened and the mixture was poured into H_2O (100 mL) and the mixture thus obtained was allowed to stand at room temperature in ultrasonic bath for 1 h. The resulting precipitate was filtered off and purified by column chromatography on silica gel using ethyl acetate/petroleum ether (1:8, v/v) as eluent, affording the pure product **3** as a white solid. Yield 78%, m.p. 122–124 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 1.40 (t, J = 7.2 Hz, 3H, CH_2CH_3), 4.50

(q, J = 7.2 Hz, 2H, CH_2CH_3), 4.98 (s, 2H, CH_2Cl), 5.26 (s, 2H, CH_2Cl), 7.87 (d, J = 8.8 Hz, 1H, Quino-H), 8.21 (d, J = 8.8 Hz, 1H, Quino-H), 8.76 (s, 1H, Quino-H); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 14.22, 38.56, 46.32, 62.99, 96.73, 126.27, 126.81, 131.67, 133.82, 140.59, 141.53, 146.23, 153.87, 166.11. HRMS: Calcd. For: $C_{14}H_{13}ICl_2NO_2$ $[M+H]^+$: 423.9368. Found: 423.9380.

General Procedure for the preparation of 6-iodo-2,4-bis(aroxymethyl) quinoline-3-carboxylic acids (5a-k)

A mixture of ethyl 2,4-bis(chloromethyl)-6-iodoquinoline-3-carboxylate (**3**) (0.212 g, 0.5 mmol), different substituted phenol (**4a-k**, 1.1 mmol) and anhydrous K_2CO_3 (0.415 g, 3.0 mmol) was stirred in refluxing MeCN (15 mL) for 5 h (as monitored by TLC). After the reaction was complete, MeCN was evaporated to dryness, and then a solution of KOH (2.2 g, 40 mmol) in 70% aqueous ethanol (25 mL) was added directly to the residue and continued to heat under refluxing temperature for additional 3 h. Then, the reaction mixture was cooled, acidified to pH 4–5 with 1 mol/L HCl. The resulting crude product was collected by filtration, washed with water and recrystallized from ethanol to afford compounds **5a-k** in 71–86% yield.

6-Iodo-2,4-bis(phenoxymethyl)quinoline-3-carboxylic acid (5a)

White solid, yield 83%, m.p. 279–282 °C; IR (KBr, ν, cm^{-1}): 3429 (COOH), 1710 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 5.37 (s, 2H, $ArCH_2O$), 5.56 (s, 2H, $ArCH_2O$), 6.92 (t, J = 7.6 Hz, 1H, Ben-H), 6.95–6.99 (m, 3H, Ben-H), 7.05 (d, J = 8.0 Hz, 2H, Ben-H), 7.26 (t, J = 8.0 Hz, 2H, Ben-H), 7.31 (t, J = 8.0 Hz, 2H, Ben-H), 7.84 (d, J = 8.8 Hz, 1H, Quino-H), 8.10 (d, J = 8.8 Hz, 1H, Quino-H), 8.63 (s, 1H, Quino-H), 13.76 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 63.73, 71.02, 95.69, 115.17, 121.61, 121.81, 127.42, 129.15, 129.92, 130.02, 131.58, 133.96, 139.15, 139.63, 145.64, 154.35, 158.46, 158.49, 168.39. HRMS: Calcd. For: $C_{24}H_{19}INO_4$ $[M+H]^+$: 512.0353. Found: 512.0351.

6-Iodo-2,4-bis((*o*-tolyloxy)methyl)quinoline-3-carboxylic acid (5b)

White solid, yield 81%, m.p. 287–289 °C; IR (KBr, ν, cm^{-1}): 3439 (COOH), 1724 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 2.47 (s, 6H, 2 × Me), 5.40 (s, 2H, $ArCH_2O$), 5.63 (s, 2H, $ArCH_2O$), 6.84-6.92 (m, 2H, Ben-H), 6.99 (t, J = 8.4 Hz, 1H, Ben-H), 7.07 (t, J = 8.0 Hz, 1H, Ben-H), 7.13-7.23 (m, 3H, Ben-H), 7.59 (t, J = 8.8 Hz, 1H, Ben-H), 7.64 (d, J = 8.8 Hz, 1H, Quino-H), 7.85 (d, J = 8.8 Hz, 1H, Quino-H), 8.54 (s, 1H, Quino-H), 13.76 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 15.72, 15.85, 66.17, 70.09, 93.84, 115.69, 116.05, 116.22, 116.39, 121.22, 121.29, 121.65, 121.71, 125.05, 125.16, 128.61, 131.53, 134.05, 136.95, 146.21, 146.31, 146.90, 147.00, 150.91, 154.15, 168.58. Anal. Calcd for $C_{26}H_{22}INO_4$: C, 57.90; H, 4.11; N, 2.60. Found: C, 58.07; H, 3.97; N, 2.83.

6-Iodo-2,4-bis((*p*-tolyloxy)methyl)quinoline-3-carboxylic acid (5c)

White solid, yield 86%, m.p. 278–279 °C; IR (KBr, ν, cm^{-1}): 3432 (COOH), 1720 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 2.22 (s, 3H, Me), 2.25 (s, 3H, OMe), 5.36 (s, 2H, $ArCH_2O$), 5.55 (s, 2H, $ArCH_2O$), 6.90 (d, J = 7.6 Hz, 2H, Ben-H), 6.97 (d, J = 7.6 Hz, 2H, Ben-H), 7.08 (d, J = 7.6 Hz, 2H, Ben-H), 7.13 (d, J = 7.6 Hz, 2H, Ben-H), 7.87 (d, J = 8.8 Hz, 1H, Quino-H), 8.13 (d, J = 8.4 Hz, 1H, Quino-H), 8.64 (s, 1H, Quino-H), 13.79 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 20.53, 20.56, 63.86, 71.13, 95.58, 115.06, 127.41, 129.04, 130.21, 130.31, 130.56, 131.56, 134.00, 139.26, 139.58, 145.62, 154.51, 156.37, 156.41, 168.37. HRMS: Calcd. For: $C_{26}H_{23}INO_4$ $[M+H]^+$: 540.0672. Found: 540.0666.

6-Iodo-2,4-bis((2-methoxyphenoxy)methyl)quinoline-3-carboxylic acid (5d)

Yellow solid, yield 74%, m.p. 256–257 °C; IR (KBr, ν, cm^{-1}): 3445 (COOH), 1718 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 3.74 (s, 3H, OMe), 3.75 (s, 3H, OMe), 5.32 (s, 2H, $ArCH_2O$), 5.50 (s, 2H, $ArCH_2O$), 6.75 (t, J = 7.6 Hz, 1H, Ben-H), 6.80-6.95 (m, 5H, Ben-H), 7.02 (d, J = 7.6 Hz, 1H, Ben-H), 7.30 (d, J = 7.6 Hz, 1H, Ben-H), 7.66 (d, J = 8.8 Hz, 1H, Quino-H), 7.87 (d, J = 8.8 Hz, 1H, Quino-H), 8.65 (s, 1H, Quino-H), 14.83 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 55.95, 56.19, 66.32, 70.16, 93.66, 112.66, 112.69, 114.06, 114.96, 121.07, 121.15, 121.27, 121.94, 128.81, 131.43, 133.33, 134.46, 136.92, 138.64, 144.71, 147.95, 148.61, 149.37, 149.80, 154.68, 169.10. Anal. Calcd for $C_{26}H_{22}INO_6$: C, 54.66; H, 3.88; N, 2.45. Found: C, 54.37; H, 4.10; N, 2.24.

2,4-Bis((4-chlorophenoxy)methyl)-6-iodoquinoline-3-carboxylic acid (5e)

Yellow solid, yield 76%, m.p. 278–279 °C; IR (KBr, ν, cm^{-1}): 3457 (COOH), 1721 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 5.55 (s, 2H, $ArCH_2O$), 5.76 (s, 2H, $ArCH_2O$), 7.13 (d, J = 8.8 Hz, 2H, Ben-H), 7.22 (d, J = 8.8 Hz, 2H, Ben-H), 7.62 (d, J = 8.4 Hz, 2H, Ben-H), 7.67 (d, J = 8.4 Hz, 2H, Ben-H), 8.03 (d, J = 8.8 Hz, 1H, Quino-H), 8.30 (d, J = 8.8 Hz, 1H, Quino-H), 8.83 (s, 1H, Quino-H), 13.95 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 64.65, 71.28, 95.87, 113.14, 113.32, 117.56, 127.29, 131.14, 131.58, 132.58, 132.64, 133.49, 133.84, 139.15, 139.74, 145.61, 146.06, 153.94, 157.78, 168.33. Anal. Calcd for $C_{24}H_{16}Cl_2INO_4$: C, 49.68; H, 2.78; N, 2.41. Found: C, 49.40; H, 2.89; N, 2.12.

2,4-Bis((3-bromophenoxy)methyl)-6-iodoquinoline-3-carboxylic acid (5f)

Yellow solid, yield 81%, m.p. 227–228 °C; IR (KBr, ν, cm^{-1}): 3432 (COOH), 1716 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 5.36 (s, 2H, $ArCH_2O$),

5.51 (s, 2H, $ArCH_2O$), 7.00 (d, $J = 8.4$ Hz, 1H, Ben-H), 7.10–7.13 (m, 2H, Ben-H), 7.17–7.21 (m, 3H, Ben-H), 7.74 (d, $J = 8.4$ Hz, 1H, Ben-H), 7.83 (d, $J = 8.8$ Hz, 1H, Quino-H), 8.08 (d, $J = 8.8$ Hz, 1H, Quino-H), 8.44 (s, 1H, Ben-H), 8.57 (s, 1H, Quino-H), 14.06 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 64.54, 71.19, 95.25, 113.04, 123.54, 123.92, 124.04, 126.59, 127.66, 131.03, 131.58, 134.37, 134.65, 136.75, 137.24, 138.93, 139.49, 142.92, 142.99, 143.01, 145.92, 154.54, 155.44, 168.32. Anal. Calcd for $C_{24}H_{16}Br_2INO_4$: C, 43.08; H, 2.41; N, 2.09. Found: C,42.76; H, 2.33; N, 2.00.

2,4-Bis((4-bromophenoxy)methyl)-6-iodoquinoline-3-carboxylic acid (5 g)

Yellow solid, yield 80%, m.p. 262-264 °C; IR (KBr, ν, cm^{-1}): 3410 (COOH), 1710 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 5.36 (s, 2H, $ArCH_2O$), 5.57 (s, 2H, $ArCH_2O$), 6.99 (d, $J = 8.8$ Hz, 2H, Ben-H), 7.07 (d, $J = 8.4$ Hz, 2H, Ben-H), 7.30 (d, $J = 8.4$ Hz, 2H, Ben-H), 7.35 (d, $J = 8.8$ Hz, 2H, Ben-H), 7.83 (d, $J = 8.8$ Hz, 1H, Quino-H), 8.11 (d, $J = 8.4$ Hz, 1H, Quino-H), 8.63 (s, 1H, Quino-H), 13.79 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 64.13, 71.38, 95.89, 116.98, 117.04, 125.38, 125.56, 127.28, 128.96, 129.69, 129.75, 131.57, 133.84, 138.99, 139.75, 145.62, 153.96, 157.28, 157.33, 168.33. Anal. Calcd for $C_{24}H_{16}Br_2INO_4$: C, 43.08; H, 2.41; N, 2.09. Found: C, 42.94; H, 2.37; N, 2.27.

2,4-Bis((2-(*tert*-butyl)phenoxy)methyl)-6-iodoquinoline-3-carboxylic acid (5 h)

Yellow solid, yield 71%, m.p. 289–292 °C; IR (KBr, ν, cm^{-1}): 3423 (COOH), 1724 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 1.09 (s, 9H, *t*-Bu), 1.21 (s, 9H, *t*-Bu), 5.40 (s, 2H, $ArCH_2O$), 5.56 (s, 2H, $ArCH_2O$), 6.87–6.92 (m, 2H, Ben-H), 7.12–7.22 (m, 6H, Ben-H), 7.86 (d, $J = 8.4$ Hz, 1H, Quino-H), 8.11 (d, $J = 8.4$ Hz, 1H, Quino-H), 8.58 (s, 1H, Quino-H), 13.92 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 29.94, 30.23, 34.68, 34.81, 63.88, 71.29, 95.50, 112.83, 113.50, 121.32, 126.81, 127.60, 127.75, 129.16, 131.61, 134.68, 137.67, 138.12, 139.22, 139.72, 146.02, 154.27, 157.44, 157.72, 168.20. HRMS: Calcd. For: $C_{32}H_{35}INO_4$ $[M+H]^+$: 624.1611. Found: 624.1605.

2,4-Bis((4-(*tert*-butyl)-2-fluorophenoxy)methyl)-6-iodoquinoline-3-carboxylic acid (5i)

Yellow solid, yield 76%, m.p. 265–267 °C; IR (KBr, ν, cm^{-1}): 3428 (COOH), 1719 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 1.22 (s, 9H, *t*-Bu), 1.25 (s, 9H, *t*-Bu), 5.44 (s, 2H, $ArCH_2O$), 5.63 (s, 2H, $ArCH_2O$), 7.04 (d, $J = 8.0$ Hz, 1H, Ben-H), 7.11-7.15 (m, 2H, Ben-H), 7.20–7.29 (m, 3H, Ben-H), 7.86 (d, $J = 8.4$ Hz, 1H, Quino-H), 8.12 (d, $J = 8.4$ Hz, 1H, Quino-H), 8.70 (s, 1H, Quino-H), 13.55 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 31.47, 34.41, 34.49, 65.07, 71.63, 95.60, 113.72 ($J = 16.4$ Hz), 113.90 ($J = 16.0$ Hz), 115.10, 115.62, 117.52, 121.24 ($J = 10.8$ Hz), 121.43 ($J = 9.6$ Hz), 127.62, 131.59, 134.15, 138.20, 139.45, 143.72, 143.85 ($J = 16.0$ Hz), 143.98, 145.13 ($J = 20.0$ Hz), 145.62 ($J = 20.4$ Hz),

150.64 (J = 19.6 Hz), 153.06 (J = 18.0 Hz), 153.99, 168.38. Anal. Calcd for $C_{32}H_{32}F_2INO_4$: C, 58.28; H, 4.89; N, 2.12. Found: C, 58.49; H, 4.96; N, 4.83.

2,4-Bis((4-(*tert*-butyl)-2-chlorophenoxy)methyl)-6-iodoquinoline-3-carboxylic acid (5j)

Yellow solid, yield 72%, m.p. 278–281 °C; IR (KBr, ν, cm^{-1}): 3465 (COOH), 1712 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 1.82 (s, 9H, *t*-Bu), 1.20 (s, 9H, *t*-Bu), 5.41 (s, 2H, $ArCH_2O$), 5.63 (s, 2H, $ArCH_2O$), 7.11–7.19 (m, 2H, Ben-H), 7.27–7.35 (m, 4H, Ben-H), 7.80 (d, J = 7.6 Hz, 1H, Quino-H), 8.07 (d, J = 7.6 Hz, 1H, Quino-H), 8.71 (s, 1H, Quino-H), 13.93 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 31.47, 31.60, 34.37, 34.44, 65.09, 71.75, 95.60, 114.03, 114.59, 116.64, 121.56, 125.20, 125.37, 127.38, 127.60, 130.00, 131.53, 134.56, 138.29, 139.50, 142.92, 145.07, 145.55, 145.67, 151.37, 151.68, 153.85, 168.23. Anal. Calcd for $C_{32}H_{32}Cl_2INO_4$: C, 55.51; H, 4.66; N, 2.02. Found: C, 55.34; H, 4.70; N, 2.28.

2,4-Bis((2-bromo-4-(*tert*-butyl)phenoxy)methyl)-6-iodoquinoline-3-carboxylic acid (5 k)

Yellow solid, yield 79%, m.p. 276–277 °C; IR (KBr, ν, cm^{-1}): 3442 (COOH), 1718 (C = O); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 1.91 (s, 9H, *t*-Bu), 1.21 (s, 9H, *t*-Bu), 5.42 (s, 2H, $ArCH_2O$), 5.64 (s, 2H, $ArCH_2O$), 7.09 (d, J = 8.0 Hz, 1H, Ben-H), 7.25-7.33 (m, 3H, Ben-H), 7.49 (s, 1H, Ben-H), 7.50 (s, 1H, Ben-H), 7.82 (d, J = 8.4 Hz, 1H, Quino-H), 8.09 (d, J = 8.4 Hz, 1H, Quino-H), 8.72 (s, 1H, Quino-H), 14.01 (s br, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm): 31.49, 31.50, 34.35, 34.42, 65.15, 71.78, 95.66, 111.23, 111.27, 113.91, 114.35, 116.33, 125.96, 126.12, 127.60, 129.73, 130.31, 131.51, 134.75, 138.52, 139.61, 145.56, 145.72, 146.00, 152.32, 152.63, 153.83, 168.15. Anal. Calcd for $C_{32}H_{32}Br_2INO_4$: C, 49.19; H, 4.13; N, 1.79. Found: C, 48.94; H, 4.06; N, 2.07.

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