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An efficient methodology for the synthesis of 4-hydroxy-8-tosyloxyquinoline-3-carboxylates

Walaa A. E. Omar*

Department of Science and Mathematics, Faculty of Petroleum and Mining Engineering, Suez University, Suez 43721, Egypt

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ABSTRACT

The transesterification reaction between ethyl 4-hydroxy-8-tosyloxyquinoline-3-carboxylate **3** and a series of alcohols has been investigated. Among the different examined catalysts, indium triiodide could affect the transesterification of **3** with alcohols of different structures giving the products smoothly in high yields. A high reactivity for compound **3** towards the transesterification reaction has been observed under the employed conditions.

Introduction

Quinoline derivatives are well known for their pharmaceutical properties [1-7]. Among the important quinoline classes are those which have an ester group at position-3. For example, alkyl 6,7-dialkoxy-4-hydroxy-3-quinolinecarboxylates possessed anticoccidial activity [1]. 4-Amino-3-quinolinecarboxylic acids and esters are antisecretory antiulcer compounds [8]. One of the original methods for the preparation of ethyl quionoline-3-carboxylic esters is Gould-Jacobs approach [3,9]. The method involves the reaction between a suitably substituted aniline and substituted ethylenemalonate in an addition-elimination followed by cyclization of the product.

The production of different quinolinecarboxylates other than methyl and ethyl ester is usually performed by heating the methyl or ethyl quinolinecarboxylate with the appropriate alcohol at high temperature in the presence of a protic acid or base catalyst [1,4,10-13]. Such procedure is time consuming as it may take several days besides its limited success with branched and olefinic alcohols. Moreover, transesterification in multifunctional quinolinecarboxylates is problematic to happen selectively on the ester group. Recently, many research groups devoted their efforts to develop more efficient and versatile catalysts for the transesterification reaction to avoid the traditional protic acid and base catalyst complications. In this context, 4-(*N,N*-dimethylamino)pyridine (4-DMAP) [13], cobalt complexes [14], zeolites [15], amberlyst-15 [16], palladium catalysts [17], titanium alkoxides [18], boric acid [19], and

lewis acids [20,21] have been successfully employed. Ranu *et al.* [21] reported indium triiodide as an effective lewis acid to catalyze the transesterification of a variety of aliphatic and aromatic esters with alcohols. The advantages of this method are the non-toxicity of the reagent, very clean and the mild reaction conditions. Although the importance of quinoline-3-carboxylic acid esters, to our knowledge, transesterification catalyzed with non protic acids has not been yet investigated in this class of quinolines.

In this paper the authors developed an efficient synthetic route for the preparation of different ester derivatives of 4-hydroxy-8-tosyloxyquinolin-3-caroxylates. The starting ester, ethyl 4-hydroxy-8-tosyloxyquinoline-3-carboxylate **3**, was prepared via Gould-Jacobs approach after protecting the hydroxyl group at C-8 with a tosyl group. Different ester derivatives were prepared from **3** by clean and efficient transesterification reaction using indium triiodide as a catalyst.

Materials and Methods

General

Melting points were determined using METTLER TOLEDO DSC 821 thermo analyzer. NMR (^{1}H and ^{13}C) analysis were performed on bruker DPX 200 (200 M*Hz*) spectrometer using DMSO-d_6 solution referenced internally to Me$_4$Si, *J* values are given in *Hz*. TLC were performed on dry silica gel plates and developed by using chloroform/ methanol mixture as eluent. The starting material diethyl 2-[(2-hydroxyanilino) methylene]propanedioate **1** has been prepared according to the earlier reported procedures [22,23].

* Corresponding author.
  E-mail address: *walaa.abbas.omar@gmail.com*

Synthesis of diethyl 2-[[2-(p-tolylsulphonyloxy) anilino]methylene]propanedioate (2)

Diethyl 2-[(2-hydroxyanilino)methylene]propanedioate **1** (7 g, 25 mmol) was stirred with 1M NaOH (aq) (25 mL) for 30 min. Then *p*-toluenesulphonyl chloride (4.8 g, 25 mmol) dissolved in ethanol (12 mL) was added and the mixture was stirred for 30 min. More water was added (13 mL) to the mixture and stirring was continued for more 10 min. The precipitate formed was collected by filtration and washed with distilled water to give the title compound in a pure form as yellowish powder of mp 103-104 °C, yield 10.7 g, 99%. ^{1}H NMR (200 M*Hz*, DMSO-d_6) δ 1.22 (t, *J* = 7.1 *Hz*, 3H), 1.28 (t, *J* = 7.1 *Hz*, 3H), 2.32 (s, 3H), 4.04-4.15 (q, *J* = 7.2 *Hz*, 2H), 4.18-4.29 (q, *J* = 7.2 *Hz*, 2H), 7.19-7.65 (m, 8H), 7.98-8.05 (d, *J* = 13.3 *Hz*, 1H), 10.64-10.71 (d, *J* = 13.3 *Hz*, 1H); ^{13}C NMR (50 M*Hz*, DMSO-d_6) δ 14.7 (2C), 21.6, 60.1, 60.5, 95.1, 118.3, 124.2, 125.7, 128.7 (2C), 129.3, 130.5 (2C), 131.1, 132.8, 138.9, 146.9, 151.2, 164.9, 167.9. HRMS (M+Na)$^+$ calc for $C_{21}H_{23}NO_7NaS$: 456.1093, found: 456.1086.

Synthesis of ethyl 4-hydroxy-8-(p-tolylsulphonyloxy) quinolone-3-carboxylate (3)

Diethyl 2-[[2-(p-tolylsulphonyloxy)anilino]methylene] propanedioate **2** (9.2 g, 21 mmol) and diphenylether (75 mL) were stirred and heated in a dry round bottom flask at 240-250°C for 1 h. The reaction mixture was then cooled to room temperature and gradually poured over 200 mL petroleum ether with stirring. The precipitate formed was collected by filtration, washed with petroleum ether and recrystallized from ethanol affording the title compound as colorless needles (mp 191-192 °C, yield 7.8 g, 95%). ^{1}H NMR (200 M*Hz*, DMSO-d_6) δ 1.21-1.28 (t, *J* = 7.4 *Hz*, 3H), 2.34 (s, 3H), 4.14-4.24 (q, *J* = 6.9 *Hz*, 2H), 7.36-7.43 (m, 4H), 7.74-7.78 (d, *J* = 8.3 *Hz*, 2H), 8.04-8.06 (d, *J* = 7.9 *Hz*, 1H), 8.22-8.25 (d, *J* = 6.9 *Hz*, 1H), 12.01-12.04 (d, *J* = 7.06 *Hz*, 1H); ^{13}C NMR (50 M*Hz*, DMSO-d_6) δ 14.7, 21.6, 60.3, 110.9, 124.8, 125.0, 125.2, 129.2 (3C),130.6 (2C), 130.7, 132.4, 138.7, 145.2, 147.0, 164.7, 172.9. HRMS (M+H)$^+$ calc for $C_{19}H_{18}NO_6S$: 388.0855, found: 388.0855.

General procedures for the transesterification reaction

Ethyl 4-hydroxy-8-(*p*-tolylsulphonyloxy)quinolone-3-carboxylate **3** (200 mg, 0.52 mmol) was refluxed for ½ - 7 h in a dry alcoholic solution of indium triiodide, prepared in situ by stirring indium metal slices (89 mg, 0.78 mmol) and iodine (295 mg, 1.17 mmol) in excess of the proper alcohol (15 mL) overnight. Molecular sieves 4Å were added to the reaction mixture to ensure dryness and absorb the formed ethanol. The reaction mixture was filtered and the excess alcohol was evaporated under vacuum. The residue formed was washed with water and purified either by recrystallization or flash chromatography.

Synthesis of butyl 4-hydroxy-8-(p-tolylsulphonyloxy) quinoline-3-carboxylate (4a)

The title compound was prepared according to the general procedures for the transesterification reaction. The alcohol used was *n*-butanol and the reaction time was 30 min. The resulting product was purified by flash chromatography using acetone/ *n*-hexane (1:1). Compound **4a** was obtained as colorless crystals of mp 89-90 °C, yield 200 mg, 94%. ^{1}H NMR (200 M*Hz*, DMSO-d_6) δ 0.83-0.90 (t, *J* = 7.3 *Hz*, 3H), 1.28-1.41 (m, 2H), 1.52-1.62 (m, 2H), 2.32 (s, 3H), 4.08-4.14 (t, *J* = 4.1 *Hz*, 2H), 7.37-7.41 (m, 4H)), 7.71-7.75 (m, 2H), 8.0-8.04 (d, *J* = 8.2 *Hz*, 1H), 8.27 (s, 1H), 12.03 (br.s, 1H, OH exchangeable); ^{13}C NMR (50 M*Hz*, DMSO-d_6) δ 14.1, 19.2, 21.7, 30.7, 64.2, 110.4, 125.0, 125.1, 125.4, 129.1, 129.2 (2C), 130.6 (3C), 132.3, 138.6, 145.5, 147.1, 164.8, 173.4. HRMS (M+H)$^+$ calc for $C_{21}H_{22}NO_6S$: 416.1168, found: 416.1167.

Synthesis of isopropyl 4-hydroxy-8-(p-tolylsulfonyloxy) quinoline-3-carboxylate (4b)

The title compound was prepared according to the general procedure for transesterification reaction. The alcohol used was *iso*propyl alcohol and the reaction time was 7 h. The resulting product was recrystallized from aqueous ethanol affording **4b** as yellowish crystals of mp 88-9 °C, yield 184 mg, 89%. ^{1}H NMR (200 M*Hz*, DMSO-d_6) δ 1.24-1.27 (d, *J* = 6.1 *Hz*, 6H), 2.36 (s, 3H), 4.96-5.10 (m, 1H), 7.33-7.47 (m, 4H), 7.75-7.79 (d, *J* = 8.2 *Hz*, 2H), 8.02-8.06 (d, *J* = 7.4 *Hz*, 1H), 8.20-8.24 (d, *J* = 5.9 *Hz*, 1H), 11.96-12.00 (d, *J* = 6.5 *Hz*, 1H, NH); ^{13}C NMR (50 M*Hz*, DMSO-d_6) δ 21.6, 22.2 (2C), 67.6, 111.2, 124.8, 125.0, 125.2, 129.2 (3C), 130.6, 130.7 (2C), 132.4, 138.6, 145.1, 147.1, 164.1, 173.0. HRMS (M+H)$^+$ calc for $C_{20}H_{20}NO_6S$: 402.1011, found: 402.1020.

Synthesis of sec-butyl 4-hydroxy-8-(p-tolylsulfonyloxy) quinoline-3-carboxylate (4c)

The title compound was prepared according to the general procedure for transesterification reaction. The alcohol used was *sec*butyl alcohol and the reaction time was 7 h. The resulting product was purified by flash chromatography using acetone/ *n*-hexane (1:1) as eluent affording **4c** as yellowish crystals of mp 92-93°C, yield 193 mg, 90%. ^{1}H NMR (200 M*Hz*, DMSO-d_6) δ 0.86 (t, *J* = 7.6 *Hz*, 3H), 1.1.(d, *J* = 6.72 *Hz*, 3H), 1.57 (quintet, *J* = 7.2 *Hz*, *J* = 7.2 *Hz*, 2H), 2.32 (s, 3H), 4.84 (sextet, *J* = 6.2 *Hz*, 1H), 7.32 (m, 4H), 7.72 (d, *J* = 7.4 *Hz*, 2H), 8.01 (d, *J* = 7.39 *Hz*, 1H), 8.25 (s, 1H), 12.0 (br.s, 1H, OH exchangeable); ^{13}C NMR (50 M*Hz*, DMSO-d_6) δ 10.0, 19.9, 21.7, 28.7, 72.1, 110.8, 119.0, 125.0 (2C), 125.3, 129.1 (2C), 130.6 (3C), 132.4, 138.6, 145.2, 147.0, 164.3, 173.3. HRMS (M+H)$^+$ calc for $C_{21}H_{22}NO_6S$: 416.1168, found: 416.1175.

Synthesis of allyl 4-hydroxy-8-(p-tolylsulfonyloxy) quinolone-3-carboxylate (4d)

The title compound was prepared according to the general procedures for the transesterification reaction.

The alcohol used was allyl alcohol and the reaction time was 30 min. The resulting product was recrystallized from ethanol giving **4d** as white needles of mp 178-179°C, yield 186 mg, 90%. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.35 (s, 3H), 4.68 (d, J = 5.2 Hz, 2H), 5.21-5.48 (m, 2H), 5.89-6.05 (m, 1H), 7.37-7.48 (m, 4H), 7.75 (d, J = 7.9 Hz, 2H), 8.03 (d, J = 7.9 Hz, 1H), 8.26 (s, 1H), 12.04 (br.s, 1H, OH exchangeable); ^{13}C NMR (50 MHz, DMSO-d_6) δ 21.6, 64.7, 110.6, 117.8, 124.8, 125.0, 125.3, 129.2 (3C), 130.6 (3C), 132.4, 133.3, 138.7, 145.5, 147.1, 164.4, 172.8. HRMS (M+H)[+] calc for $C_{20}H_{18}NO_6S$: 400.0855, found: 400.0855.
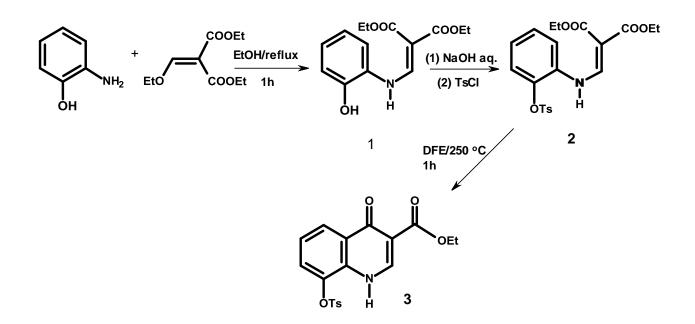
Synthesis of benzyl 4-hydroxy-8-(p-tolylsulfonyloxy) quinoline-3-carboxylate (4e)

The title compound was prepared according to the general procedure for the transesterification reaction. The In/I_2 mixture was stirred in benzyl alcohol overnight at 90-100 °C then compound **3** and MS 4Å were added and the mixture was stirred at 120 °C for 1 h. The reaction mixture was then allowed to cool to room temperature and filtered. The filtrate was charged in a silica gel column and eluated by $CHCl_3$ followed by a second eluation with $CHCl_3$/MeOH (10: 1) to afford the title compound as white powder of mp 195-196°C, yield 181 mg, 78%. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (s, 3H), 5.25 (s, 2H), 7.29-7.49 (m, 9H), 7.74 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.6 Hz, 1H), 8.28 (s, 1H), 12.05 (br.s, 1H, OH exchangeable); ^{13}C NMR (50 MHz, DMSO-d_6) δ 21.6, 65.8, 110.5, 124.9, 125.0, 125.3, 126.8, 128 (2C), 128.9 (2C), 129.2 (3C), 130.6 (3C), 132.4, 137.0, 138.7, 145.6, 147.0, 164.7, 172.9. HRMS (M+H)[+] calc for $C_{24}H_{20}NO_6S$: 450.1011, found: 450.1018
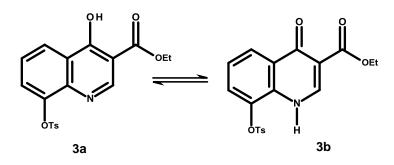
Results and discussion

The starting material, diethyl 2-[(2-hydroxyanilino)methylene]propanedioate **1**, was prepared by refluxing 2-aminophenol and diethyl ethoxymethylene malonate in ethanol for 1 h. The reaction could be performed in large scale (12 g of 2-aminophenol) affording **1** in high yield (95%). Before cyclization reaction of **1**, the phenolic hydroxyl group was protected with a tosyl group. The protection is a prerequisite to avoid the participation of the phenolic hydroxyl in any consequent reactions [24]. The tosyl group has been chosen as a protecting group because it can tolerate the acidic medium employed in the transesterification reaction [25-27]. In addition, it has been reported that the tosyl group can be removed selectively after completion of the desired reactions by a suitable alkoxide. The protection of the hydroxyl group in **1** took place smoothly using TsCl and the reaction was successfully scaled up at room temperature affording diethyl 2-[[2-(p-tolylsulphonyloxy)anilino]methylene] propanedioate **2** in excellent yield (99%). The cyclization of **2** was carried out at 250°C by applying Gould Jacobs type cyclization reaction affording ethyl 4-hydroxy-8-(p-tolylsulfonyloxy)quinolone-3-carboxylate **3** in high yield (95%). The overall synthetic route for compound **3** is illustrated in **Scheme 1**.

Theoretically, compound **3** can exist in two forms **3a** and **3b**, **Scheme 2**. ^{1}H NMR analysis for compound **3** showed a clear coupling between N-H and C-2 protons which indicates the existence of **3** as 4-quinolone derivative (**3b**) only, **Fig 1**. Similar coupling between the N-H and C-2 protons in 4-hydroxy-8-tosyloxyquinoline was observed by Heiskanen *et al* [28].

Scheme 1: The synthetic route for ester **3**

Scheme 2: Compound **3** can exist in two forms, **3a** and **3b**.
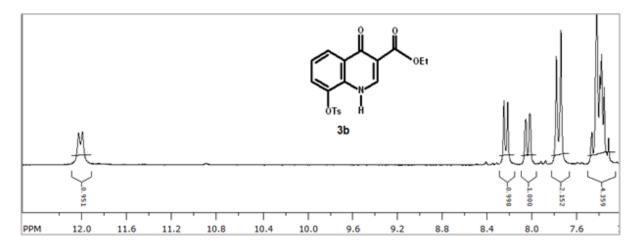

Fig. 1: The ^{1}H NMR spectrum for compound **3** shows coupling between N-H and C-2 proton.

Preliminary tests for the transesterification reaction by heating **3** with *n*-butanol in the presence of a protic acid catalyst resulted in hydrolysis of the ester group forming the corresponding acid after long reaction time (24 h). Transesterification of **3** with *n*-butanol in the presence of catalytic amount of boric acid or 4-(*N,N*-dimethylamino)pyridine (DMAP) failed and the starting material was recovered even after prolonged reaction time (24 h).
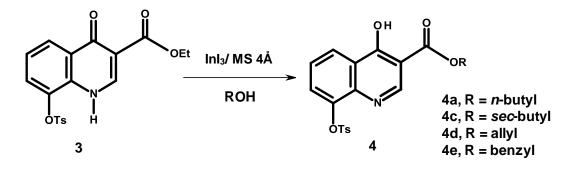
A successful transesterification reaction for the ethyl ester in compound **3** with *n*-butanol could be achieved by using Indium triiodide as the catalyst. The transesterification reaction is an equilibrium process, therefore molecular sieves 4 Å were used to absorb the liberated ethanol from the reaction media and shifting the equilibrium towards the formation of the product **4a**. Although the reaction could proceed using 0.75 equivalent of InI$_3$, the use of 1.5 equivalent shortened the reaction time dramatically. After optimization of the reaction conditions, the desired transesterification reaction with different alcohols such as *iso*-propyl, *sec*-butyl, allyl and benzyl alcohol went smoothly affording the desired products **4b-e** in high yields (**Scheme 3**).

Ranu *et al*. [21] reported that the use of 1.5 equivalent of InI$_3$ reduces the transesterification reaction time to be 5-6 h in case of aliphatic esters and 25-30 h in case of aromatic esters. In this work, although our starting ester was aromatic (compound **3**), the use of 1.5 equivalent of InI$_3$ shortened the reaction time to be only ½ - 7 h depending on the structure of the alcohol used in the transesterification (**Table 1**). Aliphatic primary alcohol such as *n*-butanol has replaced the ethoxy group of **3** in 30 minutes (entry 1, **Table 1**) while transesterification by *iso*-propanol and *sec*-butanol took 7 h (entry 2, 3, **Table 1**).

Transesterification with allyl alcohol is known to be difficult as it may undergo the Carroll rearrangement [9,29-31]. However the reaction of **3** with allyl alcohol (entry 4, **Table 1**) proceeded smoothly giving the corresponding ester product **4d** within 30 min.

Goswami *et al*. [32] reported that, long chain aliphatic alcohols and benzylic alcohols reacted easily with methyl acetoacetate in the presence of a catalytic amount of Al(H$_2$PO$_4$)$_3$, while the tertiary alcohols failed to undergo the transesterification. On the other hand, a successful catalytic transesterification between *β*-ketoesters and *tert*-alcolohs has been carried out using ceria-yttria based lewis acid and ZnO as catalysts [33,34]. During this work, although InI$_3$ transesterification of **3** with primary, secondary, allyl and benzyl alcohols was feasible, the reaction with *tert*-alcohols such as *tert*-butyl and *tert*-amyl alcohol was problematic as no transesterification product was formed under the applied conditions even after prolonged reaction time (24 h) (entry 5, 6, **Table 1**).

Scheme 3: The synthetic route for compounds **4a-e**. ^{1}HNMR spectra revealed that compounds **4a** and **4c-e** exist mainly as 4-hydroxyquinoline derivatives, while compound **4b** (where R = *iso*propyl) exists mainly as 4-quinolone derivative.

Table 1: Transesterification of **3** with different alcohols.

Entry	Alcohol	Reaction time (h)[a]	Product (%)[b]
1	$CH_3(CH_2)_3OH$	1/2	**4a** (94)
2	$(CH_3)_2CHOH$	7	**4b** (89)
3	$CH_3CH_2CH(OH)CH_3$	7	**4c** (90)
4	$CH_2=CHCH_2OH$	1/2	**4d** (90)
5	$(CH_3)_3COH$	24	No reaction
6	$CH_3CH_2C(OH)(CH_3)_2$	24	No reaction
7	$PhCH_2OH$	1	**4e** (78)

[a] reaction time in hours, [b] isolated yield between brackets.

In general, this noticeable short transesterification reaction time might be attributed to two factors. First is the use of molecular sieves[13] during the reactions, which shift the equilibrium towards the formation of the product by absorbing the liberated ethanol. Second is the reactivity of **3**, which is attributed to the *β*-keto ester structure of **3**. Many research groups have reported that *β*-keto esters are specifically active towards transesterification reaction more than other types of ester [32-36]. Balaji *et al.* [36] referred that to the enol form that enables it to undergo facile and efficient transesterification reactions with different types of alcohol. Similar reactivity was also observed during the non-catalyzed aminolysis of the quinoline derivative, methyl 5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carboxylate **5**, **Fig. 2** [37].
A suggested mechanism for the InI₃ catalyzed transesterification of **3** with different alcohols involves the formation of a cyclic intermediate in which the two carbonyl oxygen atoms interacted with InI₃ (lewis acid). Then the formed cyclic intermediate probably reacts with the alcohol affording products **4a-e** with the elimination of the ethanol and the lewis acid (**Scheme 4**). The proposed mechanism of the InI₃ catalyzed trans-

esterification of **3** is in a good agreement with the reported efforts of Pasini *et al.* [38,39] and Krishnaiah *et al.* [40].

During the transesterification, the alcohol involved in the reaction was used in excess. The purification of the ester products **4a-e** was performed either by recrystalization or flash chromatography. The highly boiling point benzyl alcohol was also used in excess during the transesterification reaction. Therefore purification of the product **4e** took place through two subsequent eluations in the same column. In the first eluation, benzyl alcohol was removed using CHCl₃ leaving the product **4e** behind in the column. Subsequent eluation with CHCl₃/MeOH (10:1) released the product as a pure white powder in 78% yield.
^{1}HNMR spectra reveal that compounds **4a** and **4c-e** exist as 4-hydroxyquinoline derivatives rather than 4-quinolone derivatives. This finding can be attributed to the formation of hydrogen bond between the hydroxyl hydrogen and carbonyl oxygen of the ester group of compounds **4a** and **4c-e,** which favors their existence as 4-hydroxyquinoline derivatives. On the other hand ^{1}HNMR spectrum for the isopropyl ester **4b** showed coupling between NH and C-2 protons, which suggests the existence of **4b** as 4-quinolone derivative.
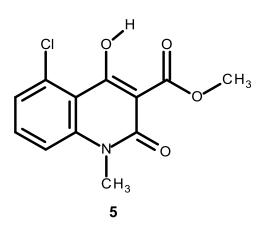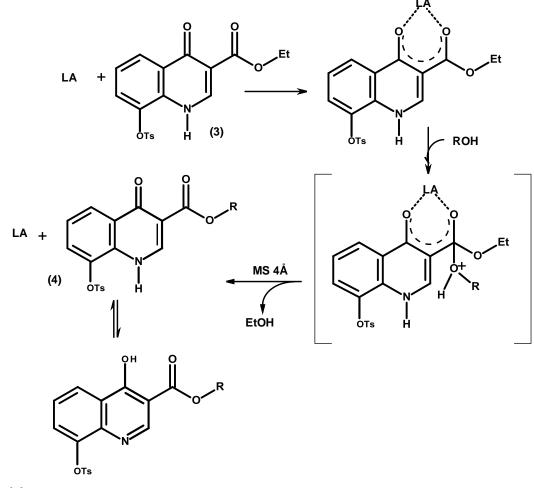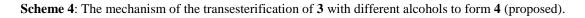
Fig. 2: Methyl(5-Chloro-1,2-dihydro-4-hydroxy-1-methy-2-oxo)quinoline-3-carboxylate **5.**

Scheme 4: The mechanism of the transesterification of **3** with different alcohols to form **4** (proposed).

Conclusion

Different 4-hydroxy-8-tosyloxyquinoline-3-carboxylates have been prepared by transesterification reaction using InI$_3$ as a catalyst. The tosyloxy group showed high stability during the transesterification with different alcohols. The reaction was efficient and relatively fast affording the transformed products in high yields. The efficiency of the transesterification reaction of **3** is attributed to the structure of the starting material, which is likely to behave as a β-keto ester derivative in addition to the use of molecular sieves during the reaction. Transesterification by allyl alcohol was successful under the applied conditions. In general during the transesterification, the branching of the alcohol decreases its reactivity and subsequently elongate the reaction time.

Acknowledgement

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