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PII: S0040-4039(16)30076-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.01.077
Reference: TETL 47241

To appear in: *Tetrahedron Letters*

Received Date: 17 December 2015
Revised Date: 11 January 2016
Accepted Date: 20 January 2016

Please cite this article as: Shmidt, M.S., Perillo, I.A., Camelli, A., Fernández, M.A., Blanco, M.M., Polyfunctional 4-quinolinones. Synthesis of 2-substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.01.077

## Graphical Abstract

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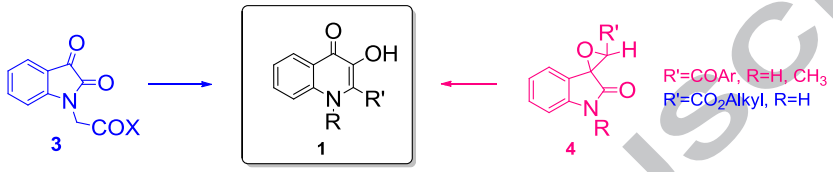

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# Polyfunctional 4-quinolinones. Synthesis of 2-substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Rearrangement
Ring expansion
Spiro compounds
Heterocycles
Epoxidation

ABSTRACT

We present here two new methods based on rearrangement reactions to obtain novel 2-substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines, an important family of heterocycles with potential applications. Alkyl 3-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylates were obtained by alkoxide promoted rearrangement of alkyl isatinacetates. A second synthetic route involves the alkoxide promoted reaction of both isatin and *N*-methylisatin, with alkylating agents having acidic methylenes. This reaction leads to the formation of spiroepoxyoxindoles *via* Darzens' condensation. When phenacyl bromides are used, the initially obtained benzoyl substituted spiroepoxyoxindoles were smoothly transformed into the corresponding 2-benzoyl-3-hydroxy-4-quinolinones with good to excellent yields.



## 1. Introduction

Hydroxypyridonecarboxylic acid derivatives containing an aromatic or heteroaromatic fused ring (**A**, **B**) represent a type of compounds which has been the subject of interest of many researchers (Figure 1). This group includes hydroxy derivatives of quinolinone (**A**, Ar= $C_6H_4$),[1] isoquinolinone (**B**, Ar= $C_6H_4$)[2] and different type of naphthyridinones (**A** and **B,** Ar= $C_5H_3N$).[3] Some of these compounds display interesting biological activities such as immunomodulating and antiangiogenic,[1a-d,3d] antiinflamatory,[2c,d,3d] gastric antisecretory[3b,c] and PAI-1 inhibitory[1f] among others. These compounds have also been used as synthetic intermediaries,[2d,4] models to study tautomerism,[5] analytical and spectroscopic applications.[6]

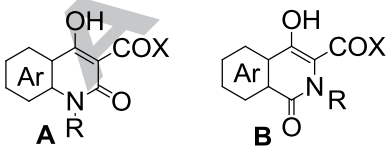
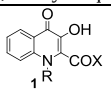



**Figure 1.** Hydroxypyridonecarboxylic acid derivatives

Following our ongoing research on the synthesis of polyfunctional compounds containing the hydroxypyridone moiety[2b,e,3a,g-k] we were interested in the synthesis of 3-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid derivatives (**1**, Table 1), a family of scarcely explored 4-quinolinones.[7] This type of compounds has interesting structural features which would result in possible applications. Bearing the chromophore 4-quinolinone, they are an important class of biologically active compounds that have enormous potential in medicine. 1-Alkyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acids, appropriately substituted on the benzene nucleus (such as Norfloxacin and Ciprofloxacin[8]) belong to a synthetic broad spectrum antibiotics family, including also second-line drugs for treatment of tuberculosis[9] and antimycobacterial agents.[10] Also hypoglycemic[11] and citotoxic[12] biological activities have been reported.

**Table 1.**
2-Substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines **1** synthesized




| Compound | X | R |
|---|---|---|
| **1a** | OH | H |
| **1b** | $OCH_3$ | H |
| **1c** | $OC_2H_5$ | H |
| **1d** | $OCH(CH_3)_2$ | H |
| **1e** | $OC(CH_3)_3$ | H |
| **1f** | $C_6H_5$ | H |
| **1g** | [a] | H |
| **1h** | 4-$ClC_6H_4$ | H |
| **1i** | $C_6H_5$ | $CH_3$ |
| **1j** | 4-$ClC_6H_4$ | $CH_3$ |
| **1k** | 4-$CH_3C_6H_4$ | $CH_3$ |

[a] COX = 4-$NO_2C_6H_4$

Moreover, these compounds should have good chelating properties due to their polyfunctionality and therefore can also find applications in analytical chemistry, *i.e.* in metal ion analysis

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by complexation. Metal ion interactions play an important role in the solubility, pharmacokinetic, and bioavailability of compounds and, in many cases, they are involved in the drug's mechanism of action.[6b-d]

We present herein the synthesis of a series of 2-substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines **1** most of which are new compounds (Table 1). We have used three different synthetic approaches to determine their scope and limitations. The precursors used were 4-oxo-1,4-dihydroquinoline-2-carboxylic acid (**2a**, kynurenic acid), *N*-substituted isatins **3** and spiroepoxyoxindoles **4** (Figure 2).

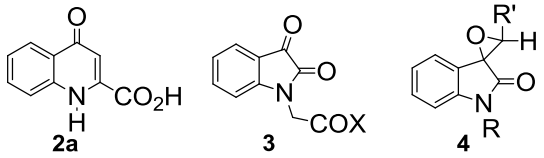


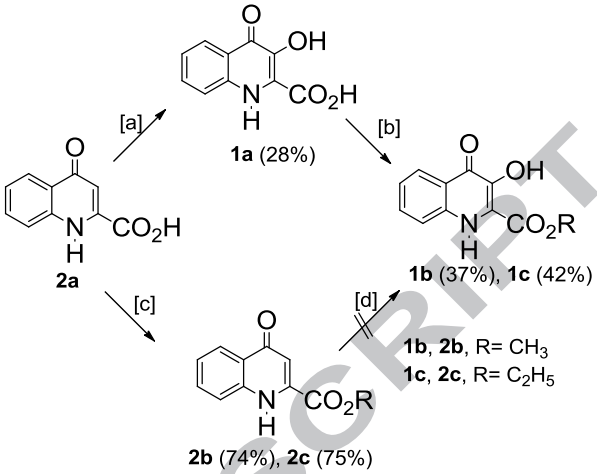

**Figure 2.** Precursors for the synthesis of hydroxyquinolinones **1**

## 2. Results and discussion

We were initially interested in the synthesis of alkyl 3-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylates **1** (X= OR), which are potentially valuable synthetic intermediaries. The first option was to employ a precursor with the 4-quinolinone nucleus preformed. Thus, we used the commercially available kynurenic acid **2a** as starting material, which through C-3 hydroxylation and esterification would lead to the desired compounds (Scheme 1). Oxidation using peroxydisulfate in basic medium (Elbs´ reaction)[13] afforded poor yields of the 3-hydroxy derivative **1a** (28%). Furthermore, esterification of the acid **1a** proved to be difficult due to its insolubility and low reactivity. The best results were obtained using methanesulfonic acid/alumina as catalyst (**1b**, 37%, **1c**, 42%). Alkylating reactions in neutral or basic media yielded mixtures of *N*- and *O*-alkylated derivatives.[14] Inverting the sequence of reactions, esters **2b,c** were easily obtained with good yields (Scheme 1). Nevertheless C-3 hydroxylation, employing Elbs´ oxidation or the sequence halogenation-hydrolysis[15], failed.

Given the poor results achieved by the methods described above, we explored other approaches based on rearrangement reactions. In 2007 we described the synthesis of novel 3-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxamides (**1**, X= $NR^1R^2$) by alkoxide promoted rearrangement of isatinacetamides (**3**, X= $NR^1R^2$).[7b] However, to the best of our knowledge, the sole attempts of rearrangement of alkyl isatinacetates (**3**, X= OR) with hot sodium ethoxide date from the first half of the past century. In 1934, Ainley and Robinson unsuccessfully attempted to obtain ethyl 3-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (**1c**) from ethyl isatinacetate (**3c**).[16] By the same time and exploring the same reaction, Putokhin obtained isatinacetic acid (**3a**) and the hydroxyacid **1a** identified as silver salt and as the *O,O*-diethyl derivative.[7a]

With the focus on the synthesis of alkyl 3-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylates (**1**, X= OR), we studied the reaction of alkyl isatinacetates with alkoxides. Starting products **3b-e** were obtained with excellent yields by *N*-alkylation of isatin employing the corresponding haloester, $Cs_2CO_3$ as base and a few drops of DMF as solvent under MW irradiation (Scheme 2).



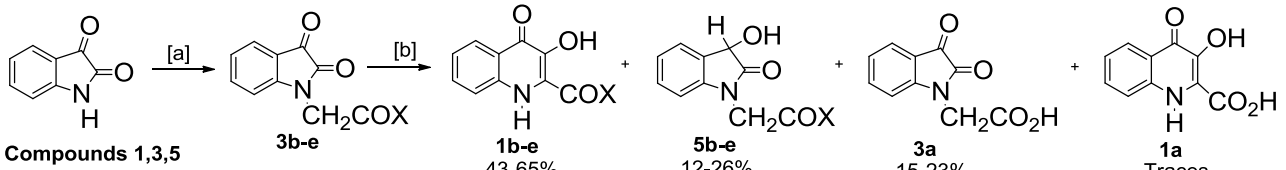

**Scheme 1.** Synthesis of esters**1b,c** from kynurenic acid **2a**
[a] 1) $K_2S_2O_8$, NaOH, $H_2O$, r.t., 12 h, 2)HCl, 100 °C, 1 h. [b] MeOH or EtOH/MsOH/alumina, 60 °C, 12 h. [c] MeOH or EtOH/HCl(g). [d] 1) $K_2S_2O_8$, NaOH, $H_2O$, r.t., 12 h, 2)AcOH, 100 °C, 1 h, or 1) NBS/$H_2O$, -10 °C, 3 h, 2) NaOH reflux or MW.

Reactions of alkyl isatinacetates **3b-e** with 4 equivalents of alkoxide in the corresponding anhydrous alcohol followed a common behavior. At room temperature only isatinacetic acid **3a** was obtained. At 100-120 °C a reddish-black syrup was formed and, by acidification with HCl-ice, mixtures of alkyl 3-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylates **1b-e** (43-65%) were isolated together with variable amounts of acid **3a**, the corresponding 3-hydroxy-2-oxindoles **5b-e** and traces of 3-hydroxykynurenic acid **1a** (Scheme 2).

3-Hydroxy-2-oxindoles **5b-e**, (3-hydroxy-2-oxo-2,3-dihydroindol-1-yl)acetic acid alkyl esters, result from reduction of the 3-carbonyl of the isatin nucleus. The formation of compounds **5** can be explained by the carbonyl reductive ability of alkoxides derived from metals with low ionization potentials (Meerwein-Ponndorf-Verley type reductions) and which probably proceeds through radical intermediates.[7b]

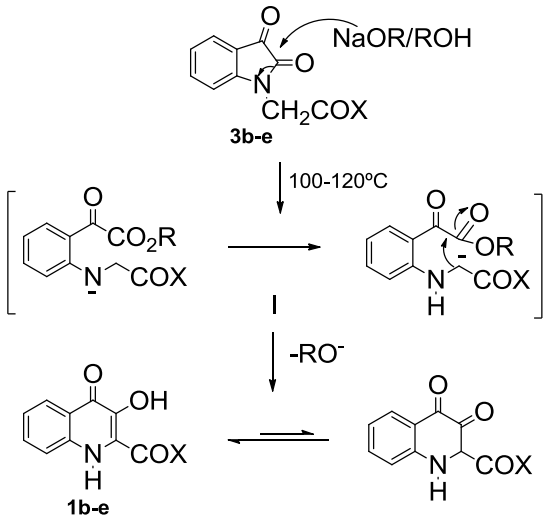
Many attempts to increase yield of esters **1b-e** under various conditions were poor due to the hydrolysis of the ester. However, even though yields were low, the results for the transformation isatin → **1b-e** can be considered satisfactory, taking into account the polyfunctionality of the 4-quinolinones **1** obtained, and that precursors **3** were obtained with excellent yields.

Unlike other families of compounds with enolic OH (isoquinolinones,[2] naphthyridinones[3]), hydroxyquinolinones **1b-e** do not give positive reaction with $FeCl_3$. Structures were confirmed by spectral analysis ($^1$H- and $^{13}$C-NMR, IR and MS).




**Scheme 2.** Reaction of *N*-substituted isatins **3b-e** with alkoxides.
[a] $ClCH_2COX/Cs_2CO_3$/DMF, MW.[20] [b] NaOR/ROH, 100-120 °C, 5-10 min

By analogy with the proposed mechanism for rearrangement of isatinacetamides[7b] the rearrangement **3** → **1** should involve nucleophilic attack of the alkoxide with opening of the isatin ring, isomerization of the resultant anion (**I**) and subsequent Dieckmann cyclization (Scheme 3).



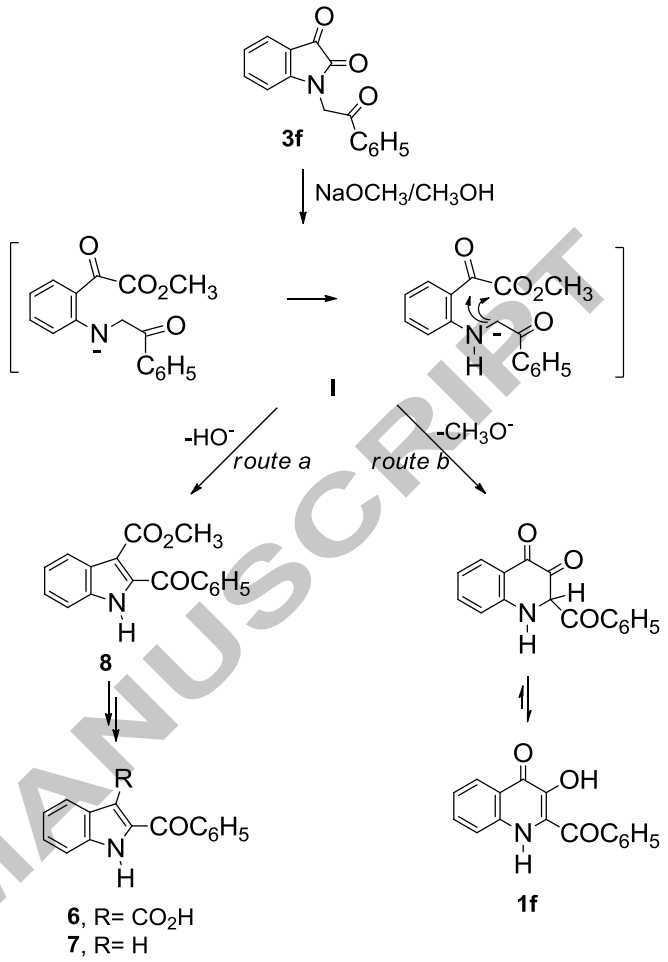

**Scheme 3.** Proposed mechanism for the alkoxide promoted rearrangement of alkyl isatinacetates **3b-e**

To determine the behavior of *N*-substituted isatins with other electron-withdrawing substituents, we explored the performance of *N*-phenacylisatin **3f** (**3**, X= $C_6H_5$). This reaction was studied by Rekhter in 1993.[17] Employing 3 equivalents of sodium methoxide at room temperature and further acidification the author obtained 2-benzoylindole-3-carboxylic acid **6**.

Bearing this in mind, we decided to study this reaction in different conditions. Under mild conditions 2-benzoylindole-3-carboxylic acid (**6**) was obtained as main product together with 2-benzoylindole (**7**) and methyl 2-benzoylindole-3-carboxylate (**8**). Under more drastic conditions indoles **6** and **7** were the sole products isolated (Scheme 4, *route a*). 2-Benzoyl-3-hydroxy-4-oxo-1,4-dihydroquinoline (**1f**) could only be obtained with poor yields (25%) by treatment of **3f** with sodium methoxide (ratio 1:1) at 90 °C, 1-2 min (Scheme 4, *route b*), together with acid **6** as main product (66%).

For the transformation **3f** → **6-8**, we propose a reaction mechanism in which the indole nucleus would be generated through an addition-elimination reaction by nucleophilic attack of the intermediate carbanion **I** on the keto carbonyl. The ester **8** formed, would be transformed into acid **6** (probably by alkoxide promoted *O*-alkylester cleavage).[18] Finally, decarboxylation of **6** would result in compound **7** (Scheme 4, *route a*).

When comparing the behavior of alkyl isatinacetates **3b-e** (see above), and isatinacetamides (**3**, X= $NR^1R^2$)[7b] with the behavior of the *N*-phenacyl derivative **3f,** the observed differences could be justified taking into account the intermediate carbanion **I** stabilization. The phenacyl group, a strong electron acceptor, causes a strongly stabilized carbanion **I**, that preferentially attacks the more electrophilic carbonyl mainly leading to compounds with indole nucleus (**6-8**) (Scheme 4, *route a*). However, esters and amides of isatinacetic acid (**3**, X= OR, $NR^1R^2$) have the alkoxycarbonyl or carboxamido group, with less electron acceptor effect, thus originating less stable intermediate carbanions, that preferentially attack the ester carbonyl leading to 3-hydroxy-4-oxo-1,4-dihydroquinolines **1** as main products (Scheme 3).



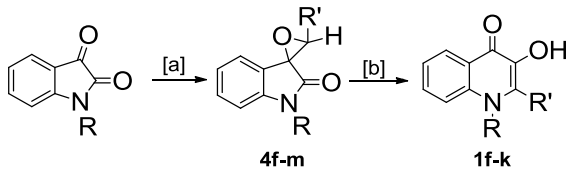

**Scheme 4.** Proposed mechanism for the alkoxide promoted rearrangements of N-phenacylisatin (3f)

We also studied the reaction of *N*-4-nitrobenzylisatin **3g** (**3**, COX= 4-$NO_2C_6H_4$) with alkoxides under different conditions. In all cases isatin was obtained as a major product. The *N*-dealkylation would be the result of nucleophilic attack of alkoxide on the benzylic methylene. In no case compounds with indole structure or 4-quinolinone **1g** could be isolated. This indicates that the presence of a carbonyl to stabilize the intermediate carbanion **I** is required in such alkoxide promoted rearrangements.

Finally, we decided to use a new approach using spiroepoxyoxindoles **4** as intermediaries. Recently we reported a study of reactions of alkylation of isatin[19] where we observed that reaction path depends on the nature of the alkylating agent and the reaction conditions. Employing NaOEt/EtOH at low temperatures (0-5 °C), alkylating agents having acidic methylenes (such as nitrobenzyl bromide or phenacyl bromide) lead to spiroepoxyoxindoles **4f,g** *via* Darzens' condensation[12] (Scheme 5, Table 2). At room temperature (20-25 °C) compounds **4** were transformed into the corresponding 3-hydroxy-4-oxo-1,4-dihydroquinolines **1f** and **1g** with good to excellent yields (92% and 73% respectively). The proposed mechanism involves as fundamental step a 1,2 nucleophilic migration of the carbon attached to the electron-withdrawing group (R') (Scheme 6).

The same behavior was observed employing isatin and 4-chlorophenacyl bromide as starting products. According to the reaction conditions the corresponding epoxide **4h** and the 4-

quinolinone **1h** were obtained with good yields (93% and 81% respectively).



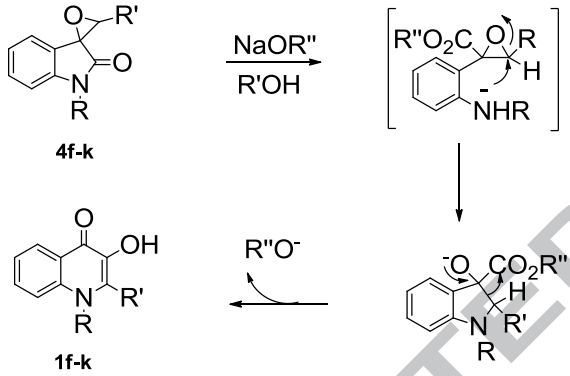

**Scheme 5.** Synthetic route to hydroxyquinolinones **1f-k** *via* spiroepoxyoxindoles **4**

[a] $XCH_2R'/NaOC_2H_5$, 0-5 °C. [b] $NaOC_2H_5$, 25 °C

**Table 2.**

Spiroepoxyoxindoles **4f-m** synthesized

| Compound 4 | R | R' |
|---|---|---|
| **f** [Ref. 19] | H | $C_6H_5CO$ |
| **g** [Ref. 19] | H | 4-$NO_2C_6H_4$ |
| **h** | H | 4-$ClC_6H_4CO$ |
| **i** | $CH_3$ | $C_6H_5CO$ |
| **j** | $CH_3$ | 4-$ClC_6H_4CO$ |
| **k** | $CH_3$ | 4-$CH_3C_6H_4CO$ |
| **l** | $CH_3$ | $CO_2CH_3$ |
| **m** | $CH_3$ | 4-$NO_2C_6H_4$ |




**Scheme 6.** Mechanism for rearrangement of **4**→**1**

To extend the scope of the reaction above to the synthesis of *N*-substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines we studied the reaction of *N*-methylisatin with various alkylating agents. Reactions using methyl chloroacetate or 4-nitrobenzyl bromide in the presence of sodium ethoxide at room temperature led to the corresponding epoxides **4l** (77%) and **4m** (66%) as final products. However, when using phenacyl halides under similar conditions the initially formed spiroepoxyoxindoles **4i-k** were slowly consumed by transforming into the corresponding 2-aroyl-3-hydroxy-1-methyl-4-oxo-1,4-dihydroquinolines **1i-k** (Scheme 5). Considering the proposed mechanism, the **4** → **1** rearrangement (Scheme 6) would be favored by the carbanionic character acquired by the migratory carbon due to the stability conferred by the strong electron acceptor group (ArCO).

It was interesting to analyze the stereochemical results of the epoxidation reaction. Epoxides **4i-l** were obtained in the form of *E* diastereomer. On the other hand, in the case of epoxide **4m**, both stereoisomers were isolated by chromatographic methods with similar yields (Figure 3; *Z*, 30% and *E*, 36%). Confirmation of the structures was performed by 2D spectroscopy (HSQC, HMBC and NOESY, see Supplementary material).

Regarding epoxides, it is accepted that *E* isomers are generally the most stable,[20] because the interactions between the R' group and the isatin carbonyl are minimal. In particular, this is important in the case of compounds **4** when R'= COAr, $CO_2CH_3$, in which carbonyl groups interactions would destabilize the *Z* diastereomers. This interaction could be reduced in the 4-nitrophenyl derivative **4m** as a result of a suitable orientation of the aryl group by rotation of the Ar-C bond thus explaining why both diastereomers are obtained.

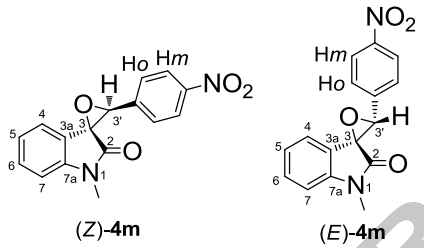
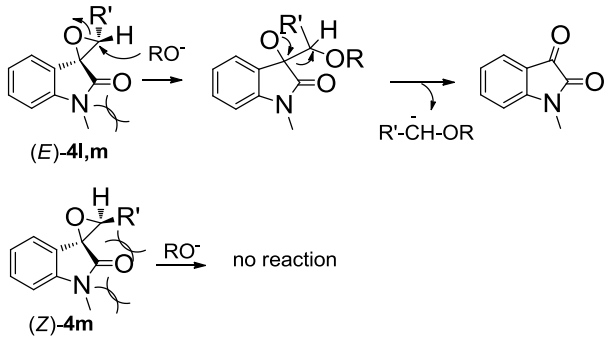



**Figure 3.** (*Z, E*)-**4m** diastereomers

Finally, in order to force the rearrangement of **4** to **1**, the previously isolated *E,Z*-**4m** and *E*-**4l** epoxides, were subjected to the reaction with alkoxides under more drastic conditions. We were not able to achieve the rearrangement, demonstrating the importance of a strong electron withdrawing benzoyl group for the rearrangement to occur. However, the stereochemistry of the epoxide was crucial to its behavior under the reaction conditions. When *E*-**4l,m** isomers were treated at different temperatures (40-70 °C) a mixture of compounds was obtained, being *N*-methylisatin the main product. In contrast, under similar conditions, the diastereomer *Z*-**4m** remained unchanged. The different behavior of spiroepoxyoxindoles with nucleophiles has been reported.[20b] In this case, it could be explained considering that for *E* diastereomers, the oxirane ring carbon (C-3') would be the sterically favored site for nucleophilic attack by the alkoxide, regenerating *N*-methylisatin (in a "retro-epoxidation" type reaction). In the *Z* isomer, that attack would be prevented by the steric hindrance caused by R' (Scheme 7).




**Scheme 7.** Behavior of spiroepoxyoxindoles (*Z*)-**4m** and (*E*)-**4l,m** towards alkoxides

## 3. Conclusion

In summary, we have presented here the synthesis of a series of 2-substituted 3-hydroxy-4-oxo-1,4-dihydroquinolines (**1**), an important class of heterocyclic compounds for their potential applications. We have used three different synthetic approaches and have determined their scope and limitations. The use of a compound with the preformed 4-quinolinone nucleus (kynurenic acid) as a precursor gave poor results. However, two methods based on rearrangement reactions allowed us to obtain properly substituted 4-quinolinones **1**. The alkoxide promoted rearrangement of alkyl isatinacetates led to 2-alkoxycarbonyl derivatives **1b-e** as the main products. 2-Benzoyl derivatives **1f,h-k** were obtained with good to excellent yields by the alkoxide promoted reaction of isatin (or *N*-methylisatin) with

phenacyl halides at room temperature. This reaction led initially to the benzoyl substituted spiroepoxyoxindoles **4** (*via* Darzens' condensation) which were smoothly transformed into the corresponding 2-benzoylquinolinones **1**. The determination of the configuration of the spiroepoxioxindoles **4** by spectroscopic methods allowed us to correlate their chemical behavior to their stereochemical features.

## Acknowledgments

This work was financially supported by the Universidad de Buenos Aires.

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## Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.