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A new synthesis of functionalized imidazol-2-ones

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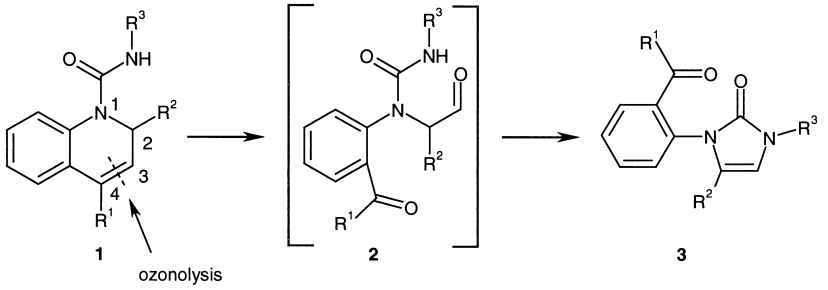
Abstract

The novel preparation of imidazol-2-ones in four steps from quinolines via an oxidative ring rearrangement is reported.

The imidazol-2-one ring is a frequently occurring motive in many interesting, biologically active, natural and non-natural molecules.[1–5] In general, the starting point for the construction of the imidazol-2-one skeleton is a coupling between an appropriately functionalized α-amino carbonyl compound and isocyanate; the resulting intermediate is then cyclized to the corresponding imidazol-2-one, preferentially employing acid catalysis.[1,3,6] Alternatively, α-substituted carbonyl derivatives with a leaving group may be reacted with substituted urea derivatives.[5]

Recently, we reported a convenient solid phase synthesis of substituted 2,3-dihydro-quinoline-4-ones, which required the preparation of intermediates **1** bound to polystyrene (R^1 = O-linker-polystyrene).[7] In this paper, we report the synthesis of C(4) substituted derivatives of **1** in solution and their conversion to substituted imidazol-2-ones by an elegant oxidative ring rearrangement (Scheme 1).



Scheme 1.

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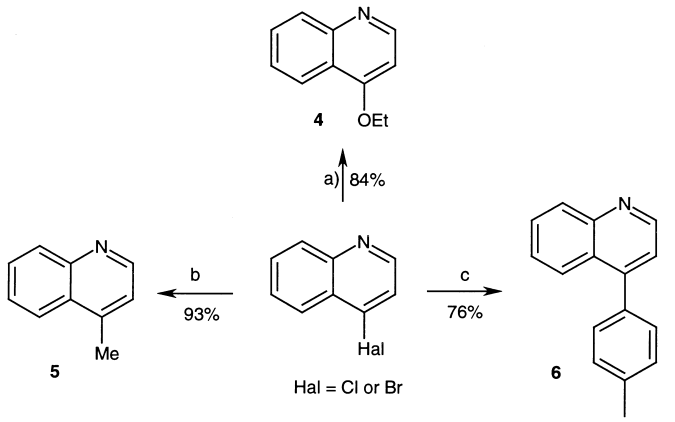
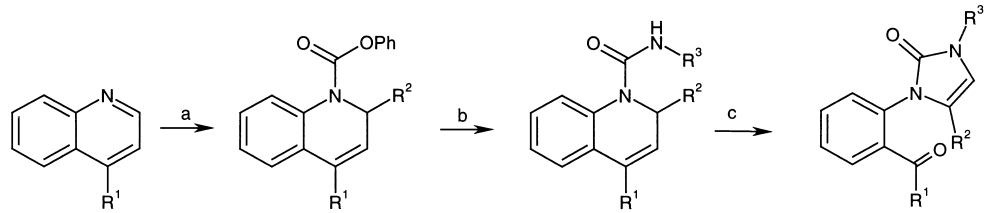
We envisioned that oxidative cleavage of the C(3)–C(4) double bond of **1** would result in an intermediate aldehyde **2**, which would readily cyclize to form a substituted imidazol-2-one **3**. Herein, we demonstrate the generality of this transformation, which allows the convenient synthesis of highly functionalized imidazol-2-ones. A number of representative quinolines **4–6** were readily prepared as shown in Scheme 2. The 4-ethoxyquinoline **4** was prepared via reaction of 4-chloroquinoline with sodium ethoxide, while substituted quinolines **5** and **6** were easily prepared through cuprate addition to 4-chloro-quinoline[8] and a Suzuki coupling reaction of 4-bromo-quinoline, respectively.[9,10]



Scheme 2. (a) Hal = Cl: 4 equiv. NaOEt, EtOH, dioxane, 80°C, 24 h. (b) Hal = Cl: 4 equiv. CuBr, 8 equiv. MeMgCl, THF, –78°C, 3 h then rt overnight. (c) Hal = Br: 3.4 equiv. K_2CO_3, 1.5 equiv. 4-methylbenzeneboronic acid, $Pd(OAc)_2$ catalyst, dioxane/H_2O (6:1), 100°C, 2 h

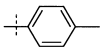
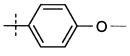
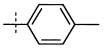
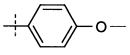
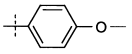
Nucleophilic addition of a number of different Grignard reagents to the C=N double bond of quinolines **4–6** in the presence of phenyl chloroformate provided functionalized dihydro quinolines **7–11** (Scheme 3).[7,11] Treatment of **7–11** with aliphatic or aromatic magnesium amides (generated in situ by reacting the amine with 1 equiv. of ethylmagnesium bromide in THF at room temperature) resulted in the clean exchange of the phenolate and formation of ureas **1**.[7] With compounds **1** in hand we were able to attempt their envisioned conversion to **3**. Indeed,



Scheme 3. (a) 1.1 equiv. R^2MgBr, 1.1 equiv. ClC(O)OPh, THF, –78°C, 0°C, rt. (b) 3 equiv. R^3NH_2, 3 equiv. EtMgBr, dioxane, 100°C, 2 h. (c) O_3, CH_2Cl_2, –78°C, then dimethyl sulfide, then 5% CF_3COOH in CH_2Cl_2, 0.25 h

when compounds **1a–m** (see Table 1) were treated carefully with ozone at –78°C for 1–2 min, followed by addition of excess dimethyl sulfide, concentration, and subsequent treatment with CF_3COOH (5% in CH_2Cl_2) cyclization ensued, and compounds **3a–m** were obtained in moderate to good yields (Table 1). For the success of this reaction it was crucial to avoid any excess of ozone since it led to diminished yields of **3**, presumably through overoxidation.[12]

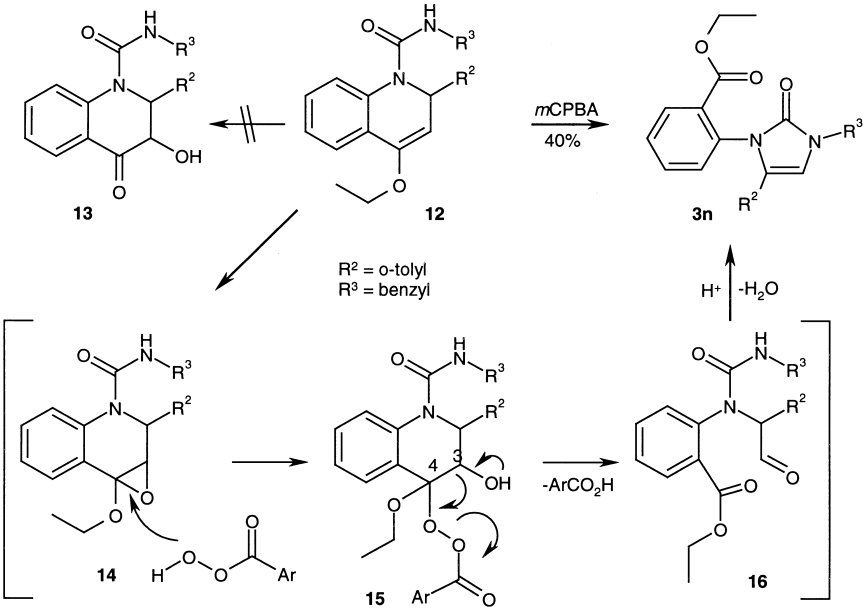
Table 1
Yields of products **1a–m** and **3a–m** (Scheme 3). [a]Yields refer to isolated compounds with satisfactory ^{1}H NMR and MS. [b]Yields refer to transformation of **1→3**

entry	R1	R2	R3	Yield[a)] **1**	Yield[a,b)] **3**
a	OEt	Me		75%	47%
b				80%	34%
c				68%	51%
d				98%	50%
e				80%	55%
f				92%	50%
g				97%	41%
h				98%	20%
i				95%	59%
j				98%	53%
k				74%	39%
l	Me			89%	44%
m		Me		93%	31%

As can be seen in Scheme 3 and Table 1, the corresponding intermediates **7–11** and **1a–m** were obtained in good yields. In an attempt to improve the moderate yields of the oxidative ring rearrangement (**1→3**), we also oxidized **1m** via bishydroxylation with OsO_4/NMO, followed by treatment of the diol with $NaIO_4$. However, **3m** was obtained in comparable yield to the ozonolysis protocol.

Interestingly, oxidation of enol ether **12** with 2 equiv. of *m*CPBA also resulted in formation of imidazolone **3n**, rather than the expected hydroxy ketone **13**, a transformation that can be

rationalized by the mechanism outlined in Scheme 4. Thus, ring opening of intermediate epoxide **14** with *m*CPBA, followed by oxidative fragmentation of the C(3)–C(4) bond of **15** could lead to the formation of aldehyde **16**, which could cyclize under the acidic conditions of the reaction to produce **3n**. The use of 1 equiv. of *m*CPBA gave similar results, but in addition to **3n**, unreacted **12** was recovered due to incomplete reaction.



Scheme 4.

In summary, we have found a new and elegant synthesis for substituted imidazol-2-ones. Starting from quinolines, substituted 1,2-dihydro-quinolines were synthesized in three steps. These intermediates are then converted to imidazol-2-ones by the key transformation, an oxidative ring rearrangement.[13]

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12. (a) The use of several ozone indicators[12b] did not allow us to stop the ozonolysis prior to overoxidation taking place. The intermediate ozonide appears to be very prone to overoxidation. In practice, the ozonolysis was stopped every 10 s, and a small sample was treated with dimethyl sulfide and analyzed by TLC. Upon clean conversion of all starting material, normally after 1–2 min, the reaction was worked up. (b) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
13. Typical procedure: Compound **1a** (322 mg, 1 mmol) was dissolved in CH_2Cl_2 (30 ml) and cooled to –78°C. Ozone was bubbled through the reaction mixture until all starting material was consumed, normally after 1–2 min.[12] Dimethyl sulfide (0.1 ml) was added and the reaction mixture was stirred for 0.2 h at 25°C. Trifluoroacetic acid (1.5 ml) was added and the reaction mixture was stirred for 0.25 h at 25°C, diluted with benzene, concentrated and purified by chromatography (SiO_2, EtOAc:hexane (3:7)) to give compound **3a** (158 mg).