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Three Distinct Reactions of 3,4-Dihydroisoquinolines with Azlactones: Novel Synthesis of Imidazoloisoquinolin-3-ones, Benzo[*a*]quinolizin-4-ones, and Benzo[*d*]azocin-4-ones

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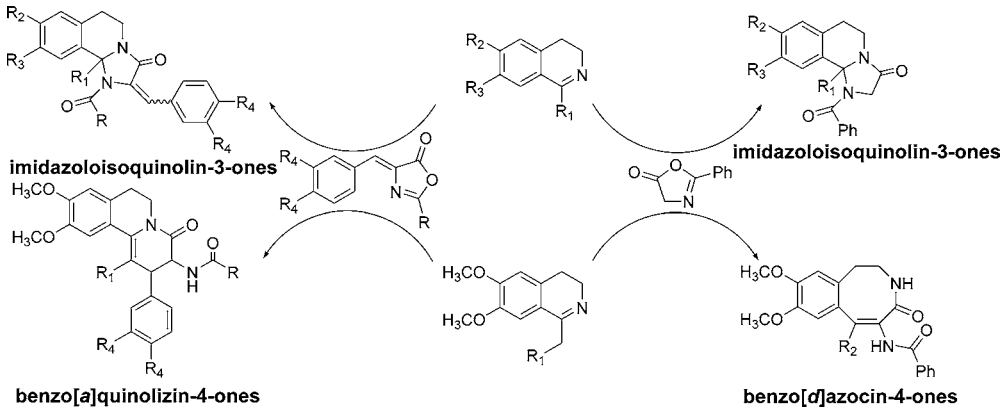
ABSTRACT



A facile and direct synthetic entry to tricyclic imidazoloisoquinolin-3-ones and benzo[*a*]quinolizin-4-ones is reported based on the ring annulation of 1-unsubstituted and 1-substituted dihydroisoquinolines with azlactones under neutral conditions in a one-step procedure. Bicyclic 2,3-dihydrobenzo[*d*]azocin-4-ones were also prepared using simple azlactone and 1-substituted dihydroisoquinolines in a one-pot reaction.

Azlactones[1] are versatile precursors for the asymmetric syntheses of α-amino acid derivatives, lactam, and arylpyruvic acid units which have been used for the synthesis of tetrahydro-*β*-carbolines[2] and lamellarin alkaloids.[3] Schulzeines A−C, new α-glucosidase inhibitors, isolated from the marine sponge *Penares schulzei*, were the first three benzo[*a*]-quinolizin-4-ones containing an amide moiety at the C-3 position.[4]

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Within the class of ring-fused isoquinolines, there have been no reports on the synthesis and biological activity of imidazoloisoquinolines. However, the related triazoloisoquinolines were reported to have some interesting pharmaceutical and agricultural properties.[5] The berberine,[6] emetine, and related ipecac alkaloids,[7] all containing benzo[*a*]quinolizine moieties,[8] are reported to possess interesting biological activities. Several methods for the preparation of the benzo[*a*]quinolizine ring system have been reported in the literature.[9] Benzazocine was found as a structural component of pentacyclic alkaloids which exhibited highly potent cytotoxicity.[10] It was also synthesized for biological study as an eight-membered B-ring of colchicine analogues.[11]

Various 1-substituted dihydroisoquinolines have been used for the synthesis of benzazocine,[12] benzo[*a*]quinolizines,[13] and thiazolo[2,3-*a*]isoquinolin-3-ones[14] related to imidazoloisoquinolin-3-ones.

Our group has been interested in the synthesis of some pyrroloisoquinoline alkaloid derivatives.[15] We now report a convenient synthesis of tricyclic imidazoloisoquinolin-3-ones **1**, benzo[*a*]quinolizin-4-ones **2**, and benzo[*d*]azocin-4-ones **3** (Figure 1). To generate heterocyclic structures relevant to the alkaloid targets, we have investigated the cyclocondensation of azlactones with various dihydroisoquinolines, both unsubstituted and 1-substituted.

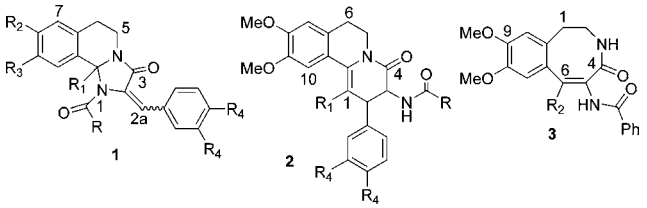

Figure 1. Structures of imidazoloisoquinolin-3-ones **1**, benzo[*a*]-quinolizin-4-ones **2**, and benzo[*d*]azocin-4-ones **3**.

Azlactones **4** were prepared directly from the reaction of benzaldehydes and *N*-acetylglycine or hippuric acid in the presence of sodium acetate and acetic anhydride.[1a] They were obtained in moderate yields after recrystallization from ethanol. The required 3,4-dihydroisoquinolines **5** and **6** were synthesized by the well-established Bischler−Napieralski reaction starting from the arylethylamine derivatives which were converted to the corresponding amide derivatives and then cyclized to imines **5** and **6** using $POCl_3$.[16]

With both key starting materials in hand, the reaction of the simple dihydroisoquinolines with azlactones in acetonitrile was investigated. When 3,4-dihydroisoquinoline **5a** was treated with azlactone **4a** (entry 1, Table 1) in acetonitrile under reflux for 12 h, a single product was obtained in good yield (88%). The product was characterized as imidazoloisoquinolin-3-one **1a** on the basis of spectroscopic and analytical data with a singlet at δ 6.56 (C-10b) in the ^{1}H NMR spectrum and the amide groups at 1713 and 1668 cm^{-1} in the IR spectrum. To further demonstrate the scope of this cyclocondensation reaction, the reaction of various azlactones **4a**−**d** and dihydroisoquinolines **5a**−**c** was investigated and the corresponding imidazoloisoquinolin-3-ones **1b**−**h** were obtained in yields ranging from 4 to 94% as shown in Table 1.

The mechanism for the formation of **1** is proposed to involve the acyl iminium salt **7** formed by the reaction of the imine group of the dihydroisoquinoline with the carbonyl group of azlactone followed by subsequent C−N bond formation to provide the imidazoloisoquinolin-3-ones **1** (Scheme 1).

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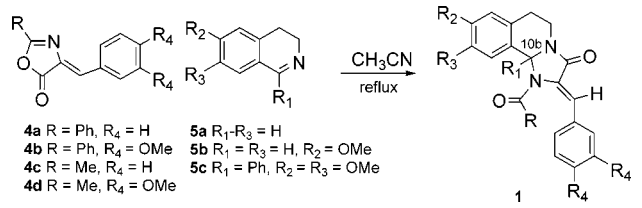
Table 1. Preparation of Imidazoloisoquinolin-3-ones **1**



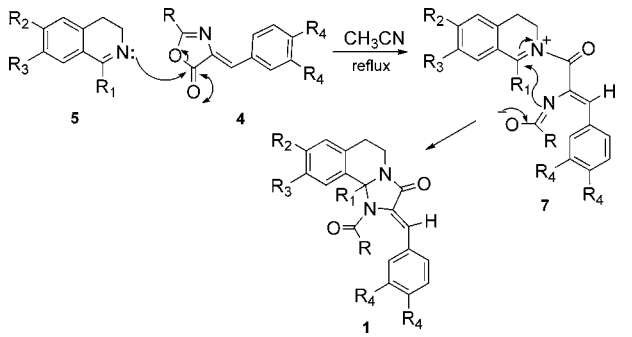
entry	azlactones	isoquinolines	time (h)	yield of **1** (%)
1	**4a**	**5a**	12	**1a** (88)
2	**4a**	**5b**	3	**1b** (94)
3	**4b**	**5a**	24	**1c** (78)
4	**4a**	**5c**	48	**1d** (17)[a]
5	**4c**	**5a**	24	**1e** (44)
6	**4c**	**5b**	3	**1f** (64)
7	**4d**	**5a**	24	**1g** (47)
8	**4c**	**5c**	48	**1h** (4)[b]

[a] 78% recovery of imine **5c** and 77% recovery of azlactone **4a**. [b] 80% recovery of imine **5c** and 50% recovery of azlactone **4c**.

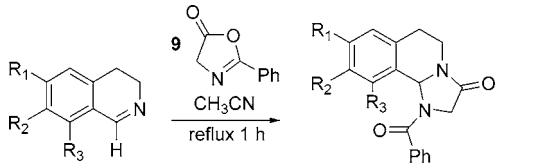
The following observations were made from the above reaction. The presence of an electron-donating group at position 6 of the dihydroisoquinoline **5** (R_2) increased the rate of the reaction presumably by increasing the nucleophilicity of the imine group, as shown in entries 2 and 6 where the reaction went to completion within 3 h. However, the presence of an electron-donating group on the aromatic ring of the azlactone deactivated the carbonyl reactivity resulting in a much slower rate of reaction as shown in entries 3 and 7 where a longer reaction time (24 h) was required. As expected, when the 1-position of the dihydroisoquinoline **5** is substituted with a phenyl group, only a low yield of the product was obtained as in entries 4 and 8. In general, azlactones **4** with a methyl side chain (R = Me) instead of a phenyl group gave lower yields of the product.

We next turned our attention toward the synthesis of other imidazoloisoquinolin-3-ones **8a**−**c** by treatment of 3,4-dihydroisoquinolines **5d**−**f** with a simple azlactone **9** in refluxing acetonitrile for 1 h. As indicated in Scheme 2, the low yield of products **8a**−**c** was observed. This could be due to the formation of other byproducts and decomposition of the simple azlactone **9**.

Scheme 1. Proposed Mechanism for the Formation of **1**

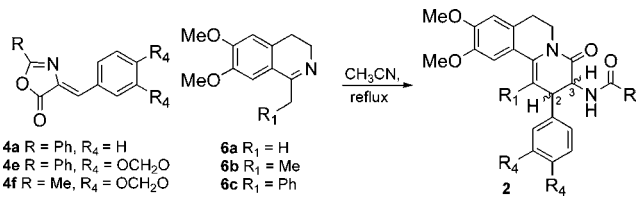


Scheme 2. Preparation of Imidazoloisoquinolin-3-ones **8**



Furthermore, a completely different pathway was observed when azlactones **4** were treated with various 1-alkyl-substituted 3,4-dihydroisoquinolines **6a**−**c** where an imine−enamine equilibrium is possible. For example, when 1-methyl dihydroisoquinoline **6a** (R_1 = H) was treated with azlactone **4a** in acetonitrile under reflux for 2 h, the benzo[*a*]-quinolizine-4-one **2a** was obtained in 89% yield as shown in entry 1, Table 2. The structure of the product was fully

Table 2. Preparation of Benzo[*a*]quinolizin-4-ones **2**



entry	azlactones	isoquinolines	yield of **2** (%, cis/trans)[a]
1	**4a**	**6a**	**2a** (89, 74:26)
2	**4a**	**6b**	**2b** (67, 39:61)
3	**4a**	**6c**	**2c** (83, 24:76)
4	**4e**	**6a**	**2d** (91, 78:22)
5	**4e**	**6b**	**2e** (77, 48:52)
6	**4e**	**6c**	**2f** (88, 44:56)
7	**4f**	**6a**	**2g** (74, 51:49)
8	**4f**	**6b**	**2h** (80, 36:64)

[a] All reaction times are 2 h.

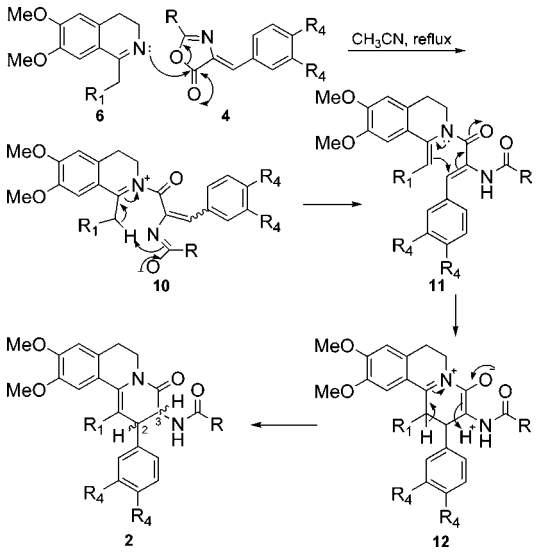
supported by spectroscopic data with absorption in the IR spectrum at 1683 and 1654 cm^{-1} for the two amide groups. The ratio of the cis/trans isomers was found to be 74:26 as judged by ^1H NMR (J = 7.6 Hz for the cis isomer and 14.3 Hz for the trans isomer).

The reaction was found to proceed well with other 1-ethyl and 1-benzyl dihydroisoquinoline derivatives (**6b**,**c**) and differently substituted azlactones **4** giving yields varying from 67 to 91% as shown in Table 2 entries 2−8. It was found that in the case where R_1 = H in **6a** the cis product predominated. When the steric bulk of the substituents increased (R_1 = Me, Ph), the trans isomer became the major product.

The formation of **2** is proposed to involve the acyliminium salt **10**, analogous to compound **7**, formed by the ring-

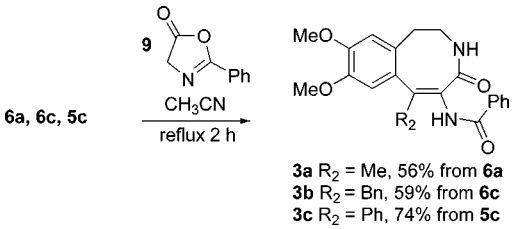
opening reaction at the carbonyl of azlactone **4** with C−N bond formation. With the alkyl substitution at the C-1 position, the acyliminium salt **10** will be readily converted to the corresponding enamide intermediate **11** which undergoes C−C bond formation to give the product **2** via the intermediate **12** as shown in Scheme 3.

Scheme 3. Proposed Mechanism for the Formation of **2**



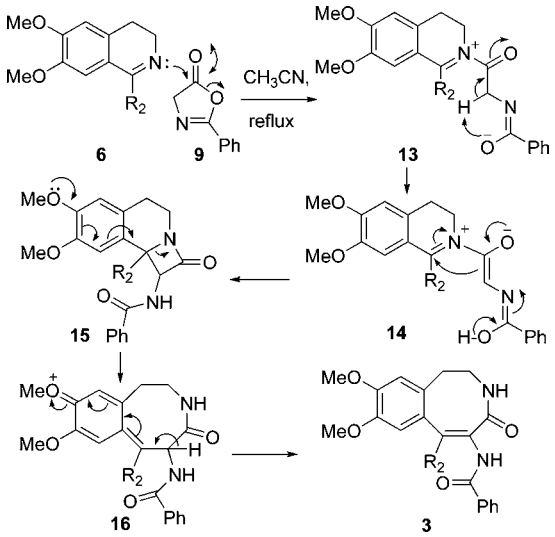
A completely different pathway was observed when various 1-substituted 3,4-dihydroisoquinolines **5c**, **6a**, and **6c** were treated with the azlactone **9** in acetonitrile at reflux for 2 h, and benzo[*d*]azocin-4-one derivatives **3** were instead obtained in moderate yield as shown in Scheme 4. The

Scheme 4. Preparation of Benzo[*d*]azocin-4-ones **3**



mechanism of the reaction was proposed to involve acyl iminium salt **13** which could lead to imidazoloisoquinolin-3-ones **8**, similar to the conversion of intermediate **7** to imidazoloisoquinolin-3-ones **1**, when 3,4-dihydroisoquinolines are unsubstituted. However, in the 1-substituted 3,4-dihydroisoquinolines, the formation of imidazoloisoquinolin-3-one was not favorable, and the iminium salt **13** could undergo proton transfer to generate enolate **14** followed by the β lactam ring formation to form lactam **15**. Alternatively, the lactam could be envisaged to form by the addition of the amido ketene, derived from the azlactones **9**, to imine. Cleavage of the C−N bond in the strained lactam assisted by the lone pair of an electron on oxygen could lead to intermediate **16** which could aromatize to give the benzo[*d*]azocin-4-one derivatives **3** (Scheme 5). All compounds

Scheme 5. Proposed Mechanism for the Formation of **3**



were fully characterized, and for compound **3a**, the amide absorptions were observed at 1666 and 1631 cm^{-1}. Dihydroisoquinolines with a phenyl substituent at C-1 (**5C**) seem to work slightly better than the C-1 alkyl-substituted dihydroisoquinolines (**6a** and **6c**).

In summary, we have devised a direct, highly efficient route with very simple reaction conditions to imidazoloisoquinolin-3-ones **1**, benzo[*a*]quinolizine-4-ones **2**, and benzo[*d*]azocin-4-ones **3**. The imidazoloisoquinolin-3-ones **1** could be readily obtained by the cyclocondensation reaction of azlactones **4** with C-1 unsubstituted 3,4-dihydroisoquinolines **5**. However, under similar conditions, the C-1 substituted 3,4-dihydroisoquinolines **6** led directly to benzo[*a*]quinolizine-4-ones **2** and benzo[*d*]azocin-4-ones **3** depending on the nature of C-1 substituents and azlactone substrates. Compounds **2** lend themselves to conversion to various products, and we are applying this methodology to the synthesis of related alkaloids and other biologically important benzo[*a*]-quinolizin-4-one derivatives.

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Supporting Information Available: Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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