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Synthesis of benzoindoloquinolizines via a Cu(I)-mediated C–N bond formation

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ABSTRACT

An effective synthesis of the multi ring-fused benzoindoloquinolizines has been accomplished by Cu(I)-mediated and MW-assisted C–N_{amide} bond formation of benzo[*a*]quinolizin-4-ones. The deamination of tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolines was also studied and was found to give benzoquinolizines. The benzo[*a*]quinolizin-4-ones were prepared based on the annulations of C-1 substituted 3,4-dihydroisoquinolines and azlactones.

1. Introduction

The benzo[*a*]quinolizine ring system **1** is an important heterocyclic framework that can be found in numerous biologically active compounds[1] including alangiumkaloid A **2**, an oxoprotoberberine alkaloid, and isoalangioside **3**, isolated from a Thai folk medicinal plant, *Alangium salviifolium*.[2,3] Schulzeine A **4** and its analogues Schulzeines B–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] The synthetic benzo[*a*]chinolizinone (Ro 41-3696) **5** was reported as an effective non-sedative hypnotic for the induction and maintenance of sleep.[5] 2-Amidobenzo[*a*]quinolizine **6** was synthesized as a novel dipeptidyl peptidase IV (DPP-IV) inhibitors (Fig. 1).[6]

The classical approaches for the synthesis of the benzo[*a*]quinolizine ring system involved the Dieckmann condensation of 1,2-dialkylesters of dihydroisoquinolines, the Bischler–Napieralski cyclization of arylethylpyridinones, and the reaction of 3,4-dihydroisoquinolines with α,β-unsaturated ketones.[7] Other new methods have been reported in the literature.[8] We have also reported a facile and direct synthetic entry to tricyclic imidazoloisoquinolinones and benzo[*a*]quinolizin-4-ones based on the annulations of 1-unsubstituted and 1-substituted dihydroisoquinolines **7** with azlactones **8** under neutral conditions.[9]

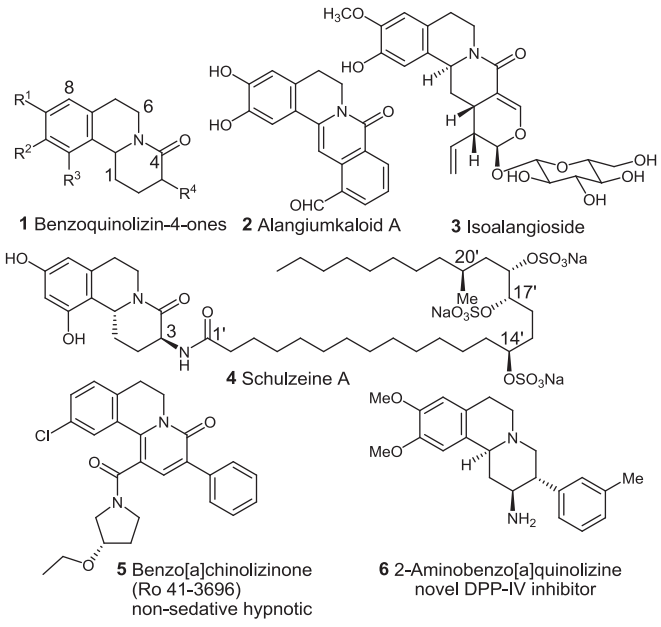

Fig. 1. Example of natural product alkaloids and biologically synthetic compounds containing benzoquinolizine system.

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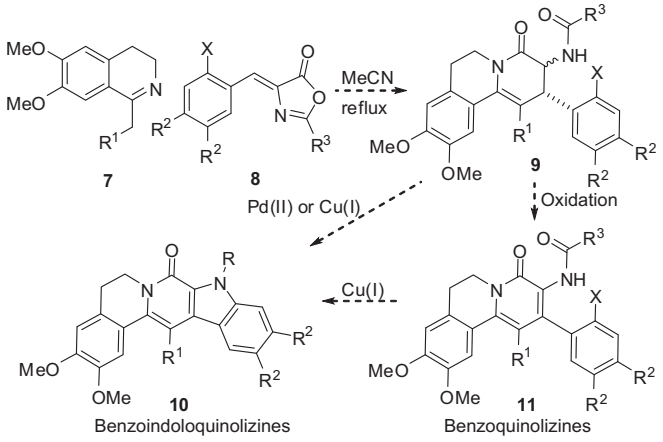
In continuation of our interests in the palladium- and copper-mediated formation of *O*- and *N*-aryl bonds[10,11] in general and particularly the C–N bond formation of indole alkaloids,[12] we have studied, in this work, the Pd(II)-catalyzed and Cu(I)-mediated $C-N_{amide}$ bond formations of tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolines **9** and benzo[*a*]quinolizin-4-ones **11** in order to obtain the multi ring-fused benzoindoloquinolizines **10** as shown in Scheme 1.



Scheme 1. Synthesis of multi ring-fused benzoindoloquinolizinone.

2. Results and discussion

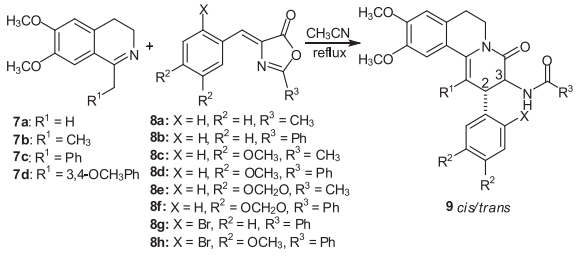
2.1. Synthesis of tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolines 9

The reaction of azlactones **8** with various 1-substituted 3,4-dihydroisoquinolines **7** in refluxing acetonitrile gave the corresponding 3,4-dihydropyridin-2(1*H*)-ones as a mixture of *cis*/*trans* tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolines **9** in moderate to good yields as shown in Table 1. It was found that when the substituent R^3 on the azlactones **8** was a phenyl group, the corresponding products **9** were obtained in higher yields than in the cases where R^3 was a methyl group. In the cases where the substituent R^1 on the 3,4-dihydroisoquinolines **7** was a proton (R^1=H) the *cis*-products predominated, however, increasing the steric bulk of the substituents where R^1=CH_3 and Ph derivatives, the trans isomers became the major products. The cyclocondensation of azlactones **8** (R^3=CH_3) with hindered 1-benzyl-3,4-dihydroisoquinolines **7** (R^1=Ph, 3,4-$(OCH_3)_2C_6H_3$) gave cyclocondensation products **9** in poor yield (entries 5–7 and 9–11). However, the yields could be improved with longer reaction times.

The structure of *cis*-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolines **9a** was assigned by interpretation of spectral data. The IR spectrum exhibited absorptions at 1683 and 1654 cm^{-1} indicating the presence of two amide carbonyl groups, which corresponded to two peaks of carbonyl groups in the ^{13}C NMR spectrum at δ 165.3 and 170.0. In addition, the IR spectrum exhibited a secondary amide absorption at 3396 cm^{-1}. The ^1H NMR showed a coupling constant of 7.6 Hz for *H*-2 and *H*-3 inferring the cis-relationship. ^1H NMR of the *trans*-**9a** exhibited trans-relationship of *H*-2 and *H*-3 with larger coupling constant of 13.4 Hz.

The ^1H NMR chemical shift assignment for *cis*-**9a** was confirmed by a detailed observation of NOE effects (Fig. 2). In particular, irradiation at the frequency of the signal at δ 5.06 (*H*-3) enhanced the signal at δ 4.40 (*H*-2, 9%) and δ 6.84 (N*H*, 3%). In addition, irradiation at the frequency of the signal at δ 4.40 (*H*-2) enhanced the signal at δ 6.02 (*H*-1, 4%), thus confirming the chemical shifts and the stereochemical assignment between *H*-3 and *H*-2 as having a cis-relationship. Similarly, the ^1H NMR chemical shift assignment for

Table 1
Synthesis of tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolines **9**[a]



7a: R^1 = H
7b: R^1 = CH_3
7c: R^1 = Ph
7d: R^1 = 3,4-OCH_3Ph

8a: X = H, R^2 = H, R^3 = CH_3
8b: X = H, R^2 = H, R^3 = Ph
8c: X = H, R^2 = OCH_3, R^3 = CH_3
8d: X = H, R^2 = OCH_3, R^3 = Ph
8e: X = H, R^2 = OCH_2O, R^3 = CH_3
8f: X = H, R^2 = OCH_2O, R^3 = Ph
8g: X = Br, R^2 = H, R^3 = Ph
8h: X = Br, R^2 = OCH_3, R^3 = Ph

Entry	X	R^1	R^2	R^3	Yield % **9**[b] (*cis*/*trans*)
1	H	H	H	Ph	**a** 89 (74:26)
2	H	H	OCH_3	Ph	**b** 79 (84:16)
3	H	CH_3	OCH_3	CH_3	**c** 65 (40:60)
4	H	CH_3	OCH_3	Ph	**d** 86 (40:60)
5	H	Ph	H	CH_3	**e** 42 (17:83)
6	H	Ph	OCH_3	CH_3	**f** 35[c] (0:100)
7	H	Ph	OCH_2O	CH_3	**g** 45[d] (20:80)
8	H	Ph	OCH_3	Ph	**h** 80 (36:64)
9	H	3,4-$(OMe)_2$Ph	H	CH_3	**i** 34 (27:73)
10	H	3,4-$(OMe)_2$Ph	OCH_3	CH_3	**j** 45[e] (16:84)
11	H	3,4-$(OMe)_2$Ph	OCH_2O	CH_3	**k** 39[f] (15:85)
12	H	3,4-$(OMe)_2$Ph	H	Ph	**l** 86 (35:65)
13	H	3,4-$(OMe)_2$Ph	OCH_3	Ph	**m** 85 (32:68)
14	H	3,4-$(OMe)_2$Ph	OCH_2O	Ph	**n** 84 (38:62)
15	Br	H	H	Ph	**o** 98 (78:22)
16	Br	H	OCH_3	Ph	**p** 80 (76:24)
17	Br	CH_3	H	Ph	**q** 70 (71:29)
18	Br	CH_3	OCH_3	Ph	**r** 77 (56:44)

[a] All reaction times were 2 h.
[b] Isolated yields of pure product after PTLC on silica.
[c] Reaction time was 7 h, **9f**, 41% (17:83).
[d] Reaction time was 7 h, **9g**, 68% (18:82).
[e] Reaction time was 12 h, **9j**, 62% (21:79).
[f] Reaction time was 12 h, **9k**, 80% (19:81).

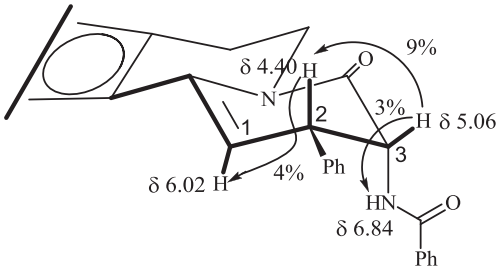


Fig. 2. NOEs effects observed for *cis*-**9a** ($CDCl_3$, 400 MHz).

trans-**9a** was confirmed by a detailed observation of NOE effects. It was found that irradiation of the signal at δ 5.16 (*H*-3) did not enhance the signal at δ 4.04 (*H*-2), thus confirming the stereochemical assignment between *H*-2 and *H*-3 as having a trans-relationship.

2.2. Survey of C–N bond formation of tetrahydro-2*H*-pyrido [2,1-*a*]isoquinolines 9

Various approaches for the synthesis of indole ring systems have been reported in the literature.[12a,13] We sought to develop the synthesis of benzoindoloquinolizines **10** via the C–N bond formation of the corresponding tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolines **9**. Initially, our approach to synthesize the indole ring was inspired by the recent findings of palladium-catalyzed C–H activation/C–N bond formation.[13,14] First, we examined the possibility of C–H activation of tetrahydro-2*H*-pyrido[2,1-*a*]isoquinoline **9a** using $Pd(OCOCF_3)_2$ as the catalyst in the presence of $Cu(OAc)_2$ and $AgOCOCF_3$ as reoxidant at 80–85 °C under an argon atmosphere in