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Synthesis of 3-aryl-3-hydroxypyrrolidin-2-ones and 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-pyrrolo-[3,4-*c*]quinoline-1,4-dione derivatives from the Baylis–Hillman adducts of isatins

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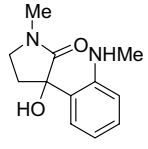
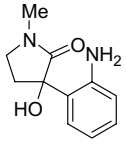
Abstract—We prepared some 3-aryl-3-hydroxypyrrolidin-2-ones and tricyclic 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-pyrrolo[3,4-*c*]quinoline-1,4-diones starting from the Baylis–Hillman adducts of isatin derivatives.

Recently, synthesis of 3,4-disubstituted pyrrolidin-2-one derivatives has been investigated extensively[1,2] in connection with the design of conformationally restricted analogs of bioactive amino acids[2] and with the usefulness as intermediates in the synthesis of bioactive non-proteinogenic amino acids.[2f] Especially, the synthesis of 3-hydroxypyrrolidin-2-one derivatives received much attention,[1h,i,3,4a–c] which involved the trials of oxidation of chiral pyrrolidin-2-one[3] or synthesis from the Baylis–Hillman adduct of α-keto esters.[4a–c] A new tryptamine-related alkaloid, chimonamidine (**1**, Fig. 1), was isolated from the seeds of *Chimonanthus praecox Link* and the structure including absolute configuration was elucidated by spectroscopic analysis and biomimetic total synthesis from tryptamine.[3] Recently, the structure of donaxaridine (**2**), an alkaloid isolated from *Arundo donax*, has been elucidated as having the same backbone with that of chimonamidine,[5a] which was assigned before as the wrong structure (shown in parentheses).[5b–d]



Chimonamidine (**1**)



Donaxaridine (**2**)

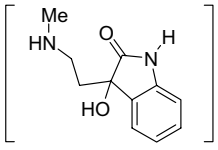


Figure 1.

During the investigations on the chemical transformations of the Baylis–Hillman adducts,[6,7] we envisioned that we could prepare the interesting 3-aryl-3-hydroxypyrrolidin-2-one derivatives. Thus, we thought an efficient synthetic route for the preparation of *ortho*-aminoaryl-substituted pyrrolidinone derivatives, which have similar backbone with those of the natural products, chimonamidine and donaxaridine (Scheme 1). If we used the Baylis–Hillman adducts of isatin,[7] we could synthesize our desired compound easily via the Michael addition, condensation, and the following ring-opening sequences.

The synthesis of the Baylis–Hillman adducts of isatin **3** has been already published by us and other groups independently (Scheme 2).[7] With the Baylis–Hillman adduct **3a** in our hand, we examined the reaction of **3a** and benzylamine.[2,8] As expected, the reaction of benzylamine and **3a** in MeOH at room temperature gave a diastereomeric mixture of **4a**-*syn* and **4a**-*anti* in 57% and 31% yield, respectively (Scheme 2 and entry 1 in Table 1).[9] Similarly, we could obtain **4b** and **4c** and the results are summarized in Table 1. In all cases, the *syn* isomers were obtained as the major products. The stereochemistry of **4b**-*syn* was confirmed by NOE experiments as shown in Figure 2.

Keywords: 3-Aryl-3-hydroxypyrrolidin-2-ones; Pyrrolo[3,4-*c*]quinolinones; Baylis–Hillman adducts; Isatins.
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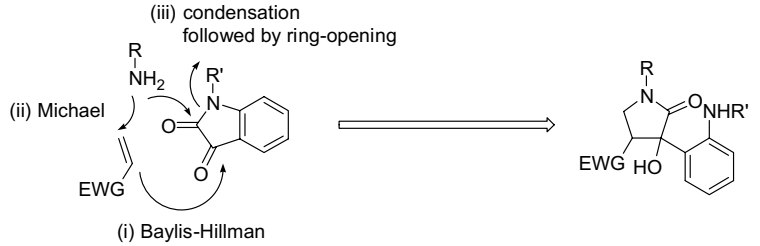
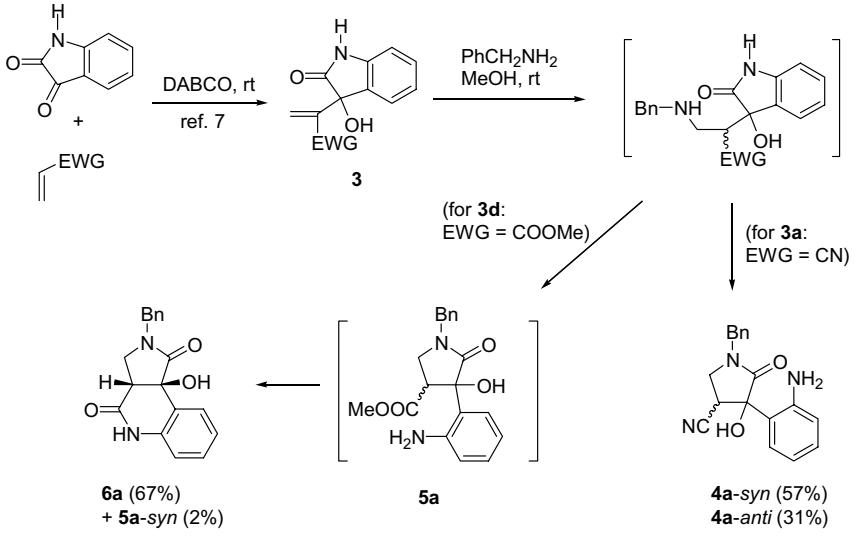
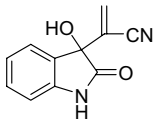
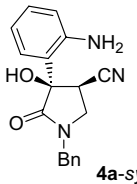
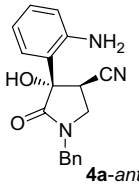
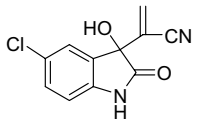
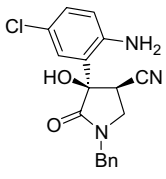
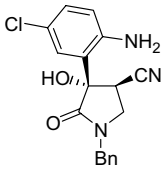
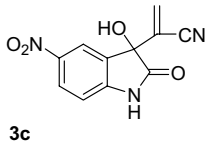
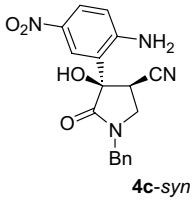
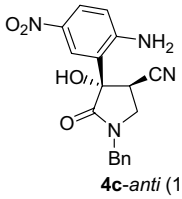


Scheme 1. Synthetic approaches for chimonamidine analogs.



Scheme 2.

Table 1. The reaction of Baylis–Hillman adducts of acrylonitrile and benzylamine[a]

Entry	Substrate	Time (h)	Product (%)	
1	 **3a**	20	 **4a**-*syn* (57)	 **4a**-*anti* (31)
2	 **3b**	10	 **4b**-*syn* (49)	 **4b**-*anti* (18)
3	 **3c**	2	 **4c**-*syn* (57)	 **4c**-*anti* (19)

[a] Conditions: $BnNH_2$ (1.2 equiv), MeOH, rt.

However, the situation was different for the Baylis–Hillman adducts derived from methyl acrylate (Scheme 2 and Table 2). Indeed, when the Baylis–Hillman adduct **3d** was used as the starting material, low yield (2%) of

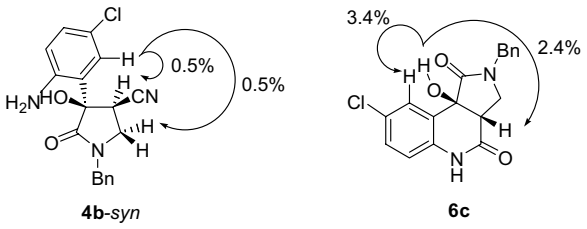


Figure 2. NOE results of **4b**-*syn* and **6c**.

expected 3-hydroxypyrrolidin-2-one derivative **5a**-*syn* was obtained together with tricyclic 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-pyrrolo[3,4-*c*]quinolone-1,4-dione **6a** (67%) as the major product (entry 1 in Table 2).[10,11] Compound **6a** was formed in a one-pot reaction via the sequential Michael addition of benzylamine to the Baylis–Hillman adduct **3d**, intramolecular cyclization and concomitant ring opening of lactam of isatin moiety,[5b–d] and eventual formation of new lactam ring (Scheme 2). Similarly, we obtained **6b** from the reaction of **3d** and *p*-methoxybenzylamine and **6c** from **3e** and benzylamine. The stereochemistry of compounds **6** was confirmed by NOE experiments having **6c** as an example (Fig. 2). But the situation was different for **3f**, which afforded a diastereomeric mixture of **5d**. However, the relative geometry is inverted with respect to **3a**–**c**, the *anti*-product being the major component of the reaction mixture. In this case, we could not find the formation of the corresponding tricyclic compound **6d**. The whole results are summarized in Table 2.

In summary, we disclosed the synthesis of 3-aryl-3-hydroxypyrrolidin-2-ones and tricyclic 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-pyrrolo[3,4-*c*]quinoline-1,4-diones starting from the Baylis–Hillman adducts of isatin derivatives. The evaluation of biological activities and further chemical transformations of the synthesized compounds are currently underway.

Acknowledgments

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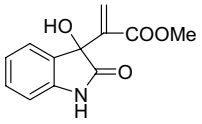
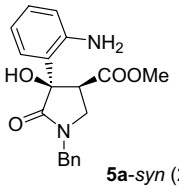
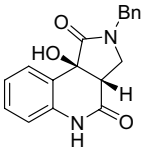
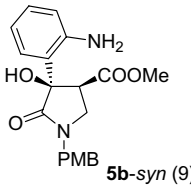
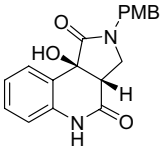
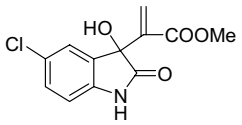
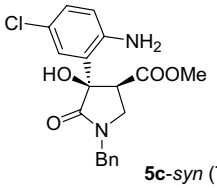
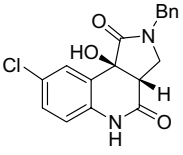
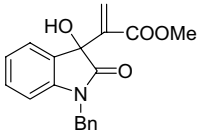
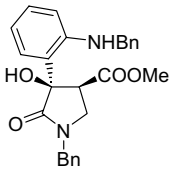
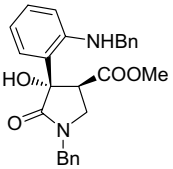
References and notes

1. For the synthesis and biological activities of pyrrolidinone derivatives, see: (a) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M.

Table 2. The reaction of Baylis–Hillman adducts of methyl acrylate and benzylamines[a]

Entry	Substrate	Time (h)	Product (%)	
1	 **3d**	4	 **5a**-*syn* (2)	 **6a** (67)
2[b]	**3d**	2	 **5b**-*syn* (9)	 **6b** (69)
3	 **3e**	2	 **5c**-*syn* (7)	 **6c** (68)
4	 **3f**	20	 **5d**-*syn* (8)	 **5d**-*anti* (76)

[a] Conditions: $BnNH_2$ (1.2 equiv), MeOH, rt.
[b] 4-Methoxybenzylamine was used instead of benzylamine (PMB is 4-methoxybenzyl).

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9. Compound **4a**-*syn*: 57%; white solid, mp 225–226 °C (dec.); IR (KBr) 3433, 2249, 1697, 1620 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ 3.25 (dd, $J = 10.5$ and 6.3 Hz, 1H), 3.45 (dd, $J = 10.5$ and 2.4 Hz, 1H), 3.88 (dd, $J = 6.3$ and 2.4 Hz, 1H), 4.53 (d, $J = 14.7$ Hz, 1H), 4.72 (d, $J = 14.7$ Hz, 1H), 4.76 (br s, 2H), 6.59 (t, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 7.8$ Hz, 1H), 6.85 (d, $J = 7.8$ Hz, 1H), 7.08 (s, 1H), 7.09 (t, $J = 7.8$ Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ 34.58, 44.81, 45.74, 78.13, 116.19, 116.63, 117.01, 121.09, 125.48, 126.90, 127.05, 127.78, 128.63, 134.06, 145.27, 170.99; ESIMS *m*/*z* 308 (M^++H). Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.27; H, 5.62; N, 13.55.
Compound **4a**-*anti*: 31%; white solid, mp 161–163 °C; IR (KBr) 3498, 3386, 3259, 2249, 1689, 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.33 (dd, $J = 9.6$ and 7.8 Hz, 1H), 3.56 (dd, $J = 9.6$ and 8.1 Hz, 1H), 3.66 (dd, $J = 8.1$ and 7.8 Hz, 1H), 4.55 (s, 2H), 4.65 (br s, 2H), 5.38 (br s, 1H), 6.63–6.72 (m, 2H), 6.81 (d, $J = 7.8$ Hz, 1H), 7.13 (t, $J = 7.8$ Hz, 1H), 7.24–7.27 (m, 2H), 7.33–7.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.92, 45.65, 47.31, 81.51, 116.72, 118.34, 118.90, 120.21, 126.40, 128.35, 128.41, 129.11, 130.23, 134.36, 146.37, 172.38; ESIMS *m*/*z* 308 (M^++H). Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.31; H, 5.69; N, 13.46.
10. For the synthesis and biological activity of pyrrolo[3,4-*c*]quinolone derivatives, see: (a) Kravchenko, D. V.; Kuzovkova, Y. A.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Balakin, K. V.; Ivachtchenko, A. V. *J. Med. Chem.* **2005**, *48*, 3680; (b) Cappelli, A.; Anzini, M.; Vomero, S.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Menziani, M. C.; De Benedetti, P. G.; Giorgi, G.; Ghelardini, C.; Collina, S. *Bioorg. Med. Chem.* **2002**, *10*, 779.
11. Compound **5a**-*syn*: 2%; IR (film) 3367, 1732, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.18 (dd, $J = 10.5$ and 6.6 Hz, 1H), 3.43–3.47 (m, 1H), 3.71 (s, 3H), 3.73–3.75 (m, 1H), 4.66 (s, 2H), 6.63 (t, $J = 7.5$ Hz, 1H), 6.71 (d, $J = 7.8$ Hz, 1H), 6.84 (d, $J = 7.5$ Hz, 1H), 7.11 (t, $J = 7.5$ Hz, 1H), 7.21–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 45.52, 47.44, 47.48, 52.18, 80.42, 117.72, 117.81, 123.46, 125.96, 127.97, 128.56, 128.74, 129.69, 135.04, 145.80, 171.00, 172.80; ESIMS *m*/*z* 341 (M^++H).
Compound **6a**: 67%; white solid, mp 199–201 °C; IR (KBr) 3309, 3236, 3147, 1677 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ 3.17 (dd, $J = 9.3$ and 8.1 Hz, 1H), 3.28 (t, $J = 8.1$ Hz, 1H), 3.58 (dd, $J = 9.3$ and 8.1 Hz, 1H), 4.38 (d, $J = 14.7$ Hz, 1H), 4.53 (d, $J = 14.7$ Hz, 1H), 6.13 (s, 1H), 6.94 (dd, $J = 8.1$ and 1.2 Hz, 1H), 7.07–7.14 (m, 3H), 7.22–7.28 (m, 4H), 7.86 (dd, $J = 7.8$ and 1.5 Hz, 1H), 10.19 (br s, 1H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ 44.54, 46.03, 46.81, 74.01, 115.06, 119.55, 122.46, 126.88, 126.97, 127.52, 127.92, 129.10, 134.77, 135.77, 167.41, 172.08; ESIMS *m*/*z* 309 (M^++H). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.21; H, 5.32; N, 9.01.