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A MILD BISCHLER–NAPIERALSKI-TYPE CYCLIZATION OF TRICHLOROMETHYL CARBAMATES FOR THE SYNTHESIS OF β-CARBOLINONES

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Abstract – A straightforward synthesis of β-carbolinones by the Bischler–Napieralski-type cyclization of the corresponding trichloromethyl carbamates, which does not require acids, bases, oxidants, or transition-metals to promote the cyclization, has been achieved.

INTRODUCTION

β-Carbolinone alkaloids are a diverse group of biologically active indole alkaloids, e.g., rhetsinine,[1] strychnocarpine,[2] bauerine C,[3] secofascaplysin A,[4] trigonostemonines A, B,[5] and milnamide C, F[6] (Figure 1). For example, strychnocarpine, a simple tetrahydro-β-carbolinone alkaloid isolated from *Strychnos elaeocarpa* in 1980,[2a] exhibits a high affinity for the peripheral type of benzodiazepine binding sites in rat brains.[2b] These β-carbolinones have been the target of syntheses because of their intriguing structural features and interesting biological activities.

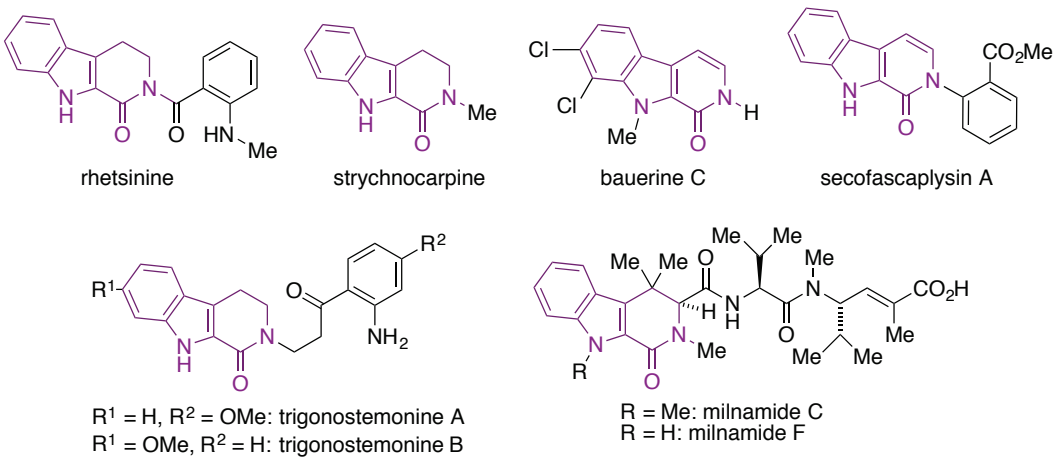
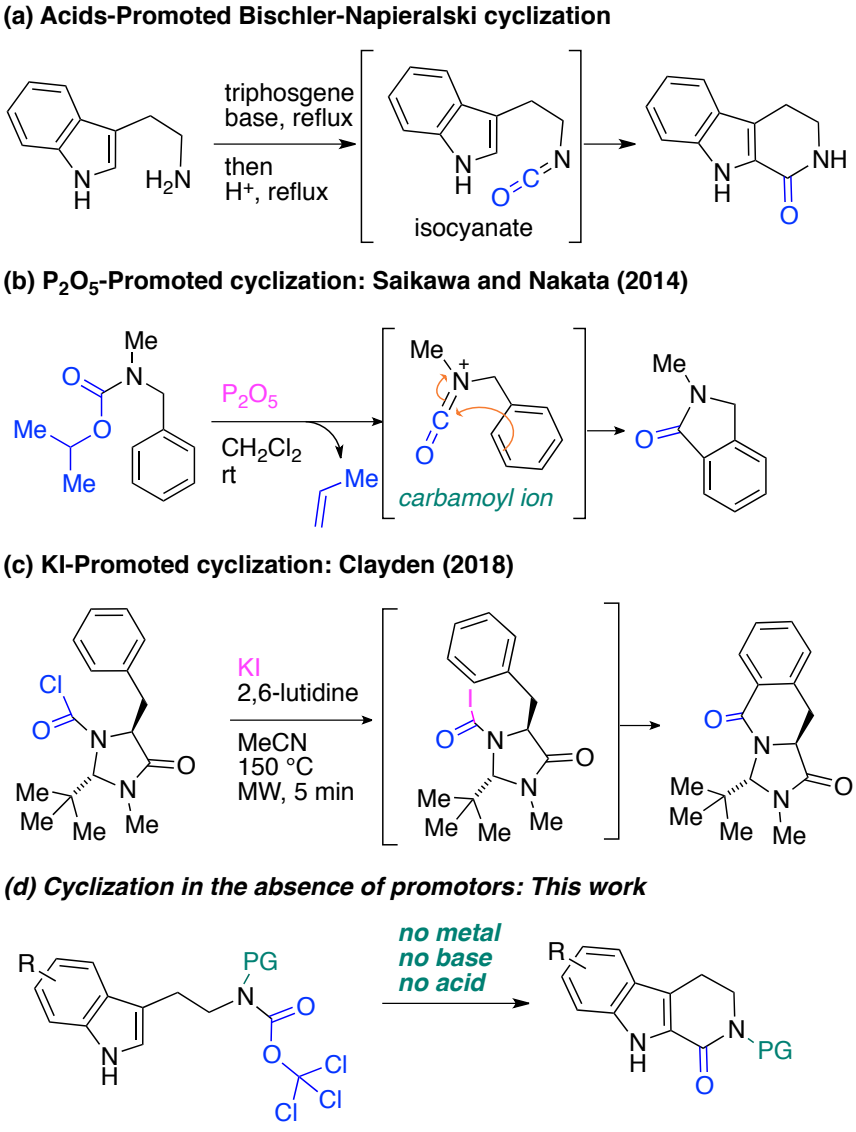


Figure 1. β-Carbolinone alkaloids

While most syntheses rely on acid-promoted Fischer indolization[7] or transition-metal-mediated approaches,[8] the most straightforward approach utilizes an isocyanate intermediate in a Bischler–Napieralski cyclization.[9] However, the difficult formation of the isocyanate intermediate in strong acidic conditions needs robust substrates, which are limited to primary amines (Scheme 1a).[10] Considering these cumbersome and multistep approaches, a more straightforward approach in the synthesis of β-carbolinones is highly desired.



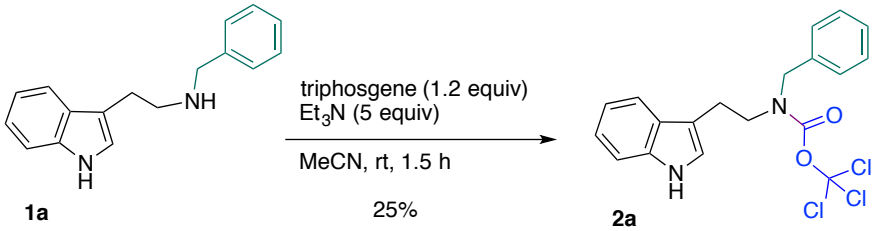
Scheme 1. Previously reported methods for Bischler–Napieralski cyclization

Recently, to circumvent these limitations, two pioneering reports on the mild Bischler–Napieralski-type cyclizations have been reported, including the P_2O_5-promoted generation of a carbamoyl ion at room temperature from isopropyl benzylcarbamates developed by Saikawa, Nakata, and co-workers (Scheme 1b),[11] and the KI-promoted generation of a carbamoyl ion from N-chloroformylimidazolidinones through halogen exchange reported by Clayden and co-workers (Scheme 1c).[12] These reactions are notable

because (i) they allow the generation of intermediates under mild reaction conditions and (ii) the precursors are stable and easily accessible from simple starting materials. However, conversion of the precursors to lactams requires additives and can limit the use of sensitive functional groups in the substrates. These constraints restrict the utility of the mild Bischler–Napieralski cyclizations, particularly for indole alkaloid synthesis. As part of our current interest in the synthesis of indole alkaloids,[13] we have recently determined an alternative protocol for the mild Bischler–Napieralski cyclization, which can be applicable to indole substrates. A cyclization of N-protected pyrano[3,2-*e*]tryptamines using triphosgene could afford β-carbolines through carbamoyl ions, leading to the total synthesis of fontanesine B for the first time.[14] In addition, we encountered a serendipitous isolation of the trichloromethyl carbamate derived from *N*-PMB pyrano[3,2-*e*]tryptamine. Hence, we proposed that trichloromethyl carbamates could be used as the substrate for the synthesis of a variety of lactams (Scheme 1d). To the best of our knowledge, there is no example of the cyclization of trichloromethyl carbamates to afford diverse lactams.[15,16] In this paper, we report that trichloromethyl carbamates are sufficiently reactive for C–C bond formation to occur efficiently in the absence of acids, bases, oxidants, and transition-metals.

RESULTS AND DISCUSSION

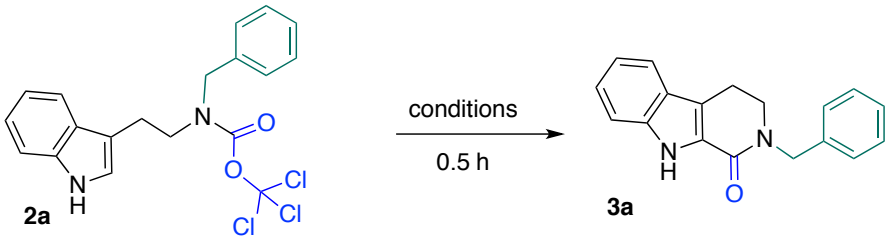
Initially, our investigations focused on confirming the accessibility and bench-stability of the trichloromethyl carbamates.[17] Stirring the amine **1a** with triphosgene (1.2 equiv) at room temperature in the presence of Et_3N as an acid scavenger afforded the trichloromethyl carbamate **2a** in 25% yield after aqueous work-up and silica gel column chromatography (Scheme 2). The trichloromethyl carbamate **2a** was stable when stored in a refrigerator as a solid for at least 6 months. With **2a** in hand, we subsequently examined the cyclization of the trichloromethyl carbamate **2a** to form the β-carbolinone **3a**.



Scheme 2. Synthesis of trichloromethyl carbamate **2a**

An evaluation of the promotors revealed that an additive was not necessary for the cyclization of **2a** (entries 1-10, Table 1). For example, heating in MeCN, without an additive, was effective in promoting cyclization, affording **3a** in 55% yield (entry 10, Table 1). Additionally, solvent effects were dramatically pronounced (entries 11–21) with DMSO being most effective in promoting the cyclization of **2a** (74% yield, entry 16).

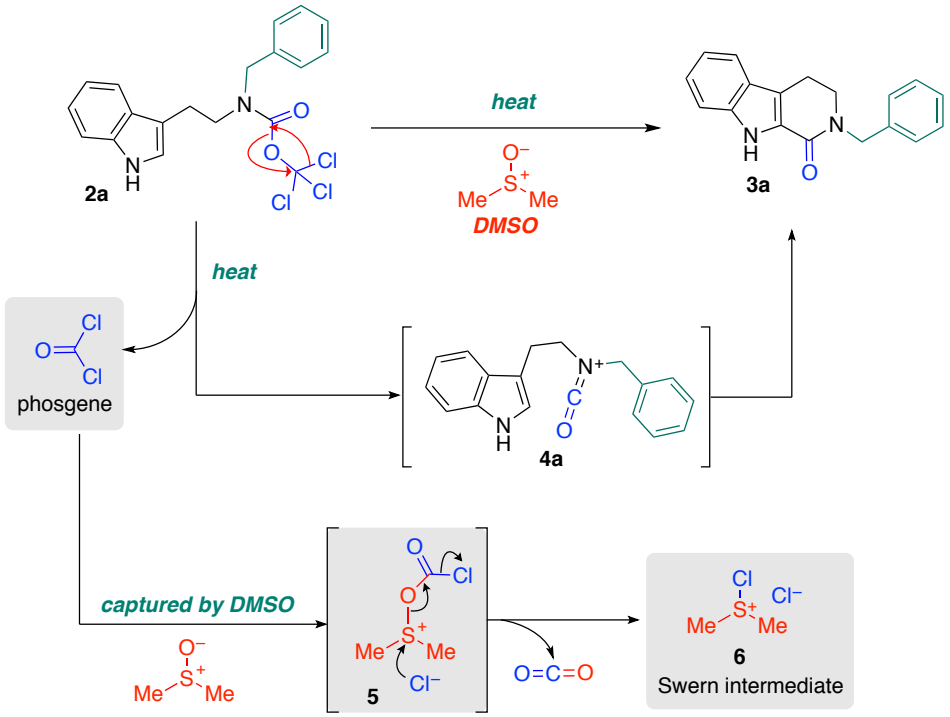
Table 1. Solvent and additive effects on the Bischler–Napieralski-type cyclization of trichloromethyl carbamate



entry	temp. (°C)	solvent	additive (equiv)	yield (%)[a]
1	80	MeCN	$POCl_3$ (2)	44
2	80	MeCN	AcOH (2)	64
3	80	MeCN	30% HBr in AcOH (2)	70
4	80	MeCN	$Cu(OTf)_2$ (2)	decomp.
5	rt	MeCN	P_2O_5 (2)	0
6	80	MeCN	P_2O_5 (2)	51
7	rt	MeCN	KI (1)	22
8	80	MeCN	KI (1)	49
9	80	MeCN	Et_3N (2)	34
10	80	MeCN	–	55
11	100	1,4-dioxane	–	trace
12	80	AcOEt	–	trace
13	80	benzene	–	31
14	100	toluene	–	39
15	100	DMF	–	66
16	***100***	***DMSO***	***–***	***74***
17	100	*tert*-BuOH	–	71
18	80	EtOH	–	0
19	60	MeOH	–	0
20	60	TFE	–	trace
21	80	$CHCl_3$	–	trace

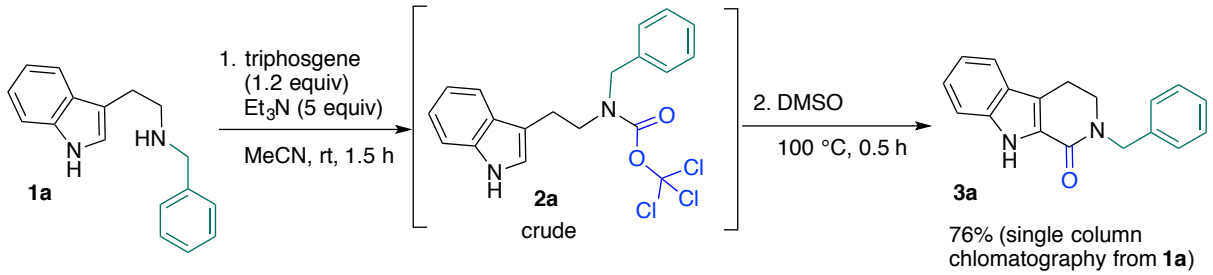
[a] Isolated yield.

From the results in Table 1, we suggested that DMSO would act as a phosgene scavenger.[18] The suggested mechanism for the Bischler–Napieralski-type cyclization in DMSO is shown in Scheme 3. Release of phosgene from **2a** generated the carbamoyl ion **4**, which underwent cyclization to give **3a**. DMSO reacted with phosgene to produce the intermediate **5**, which was attacked by chloride to give the Swern intermediate **6**,[19] enabling the occurrence of additive-free Bischler–Napieralski-type cyclization.



Scheme 3. Suggested mechanism for the Bischler–Napieralski-type cyclization in DMSO

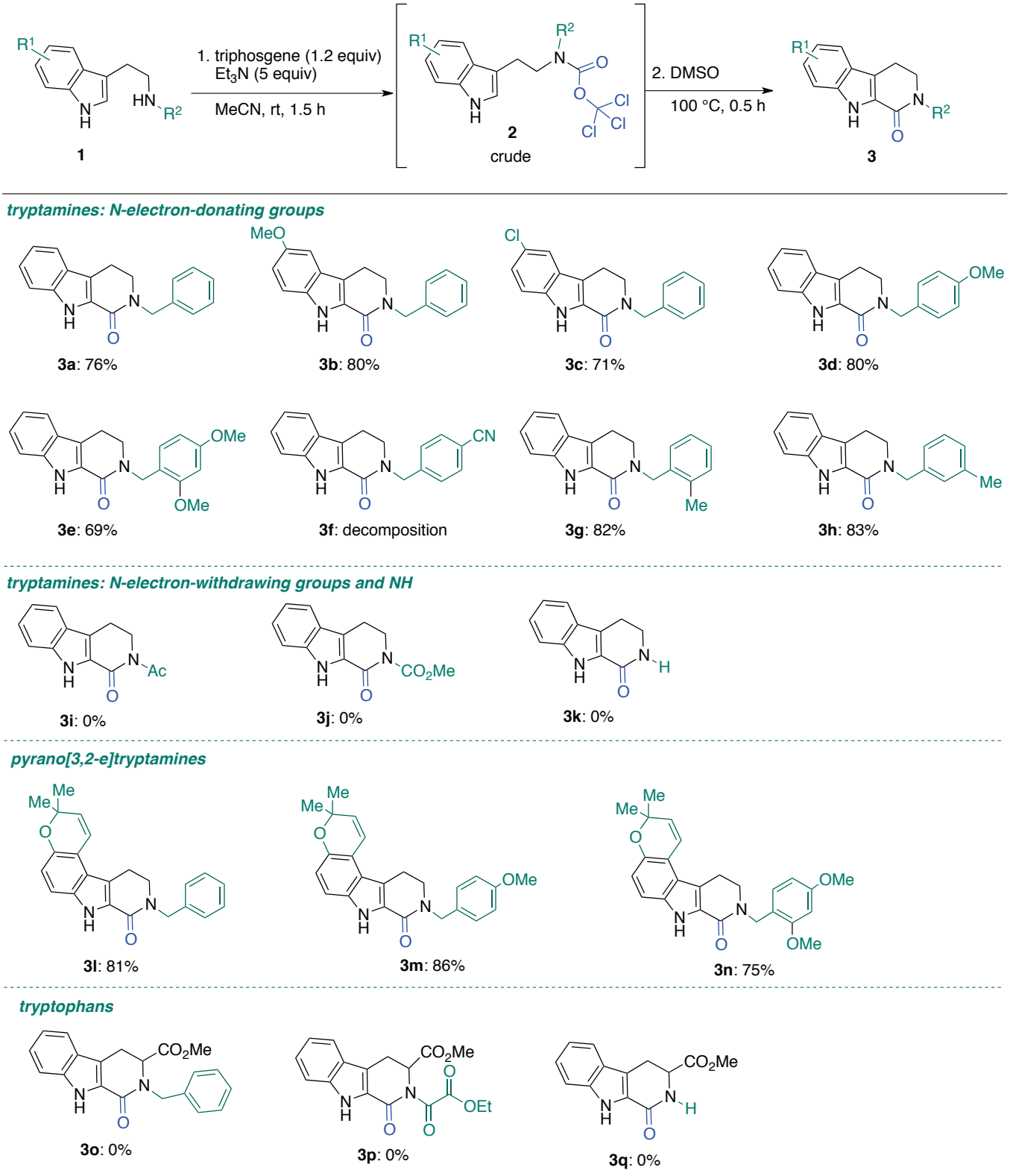
To investigate the scope of this reaction, we next attempted to prepare a wide range of trichloromethyl carbamates from their corresponding secondary amines. Although several trichloromethyl carbamates were successfully synthesized, intensive purification led to low yields (18–49%) as some of the carbamates were unstable. However, we found that the present cyclization could be applied to crude **2a** obtained from a simple aqueous work-up, affording **3a** in 76% yield (Scheme 4). Crude **2a** is sufficiently pure for use in the synthesis of **3a** without the need for intensive purification step, leading to higher yield.



Scheme 4. Alternative protocol for the Bischler–Napieralski-type cyclization via trichloromethyl carbamate

The scope of the cyclization is shown in Scheme 5. The cyclization was insensitive to substitution on the indole ring at the C5 position (**3a-c**). Various β-carbolinones with alkyl-substituted amines, such as benzyl (**3a-c**), 4-methoxybenzyl (**3d**), 2,4-dimethoxybenzyl (**3e**), and methyl-substituted benzyl (**3g** and **3h**) tryptamines, were obtained in good yield. However, decomposition of 4-cyanobenzyl tryptamine (**3f**)

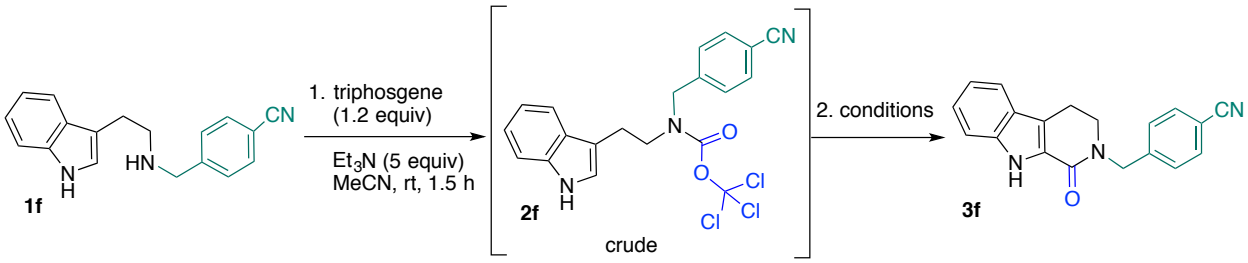
was observed. While no tryptamines with electron-withdrawing groups or unprotected tryptamine (**3i-k**) were obtained, a good yield was observed when pyranoindoles were used as a substrate (**3l-3n**). Additionally, when we employed tryptophans instead of tryptamines, no product was obtained (**3o-3q**).



Scheme 5. Scope and limitation of the Bischler–Napieralski-type cyclization

Unsuccessful reactions (**3i-k**, **3f**, and **3o-q**, Scheme 5) led us to rationalize that a more mild and efficient cyclization would require the identification of a suitable protecting group. We reasoned that the cyanobenzyl group might serve as a suitable protecting and activating group to enable a mild protocol for the Bischler–Napieralski-type cyclization *via* a cationic intermediate. Liu reported the effects of 2-cyanobenzyl ether for a stereospecific glycosylation reaction.[20] The 2-cyanobenzyl group participated in the stabilization of the oxocarbenium ion by coordinating with the cyano moiety in an intramolecular fashion. Thus, the cyclization of the 4-cyanobenzyl compound **2f** was expected to be more favorable by intermolecular coordination of the nitrile with the carbamoyl ion, which would reduce decomposition side reactions of the carbamoyl ion.

Table 2. Optimization of reaction conditions using **2f** as a substrate



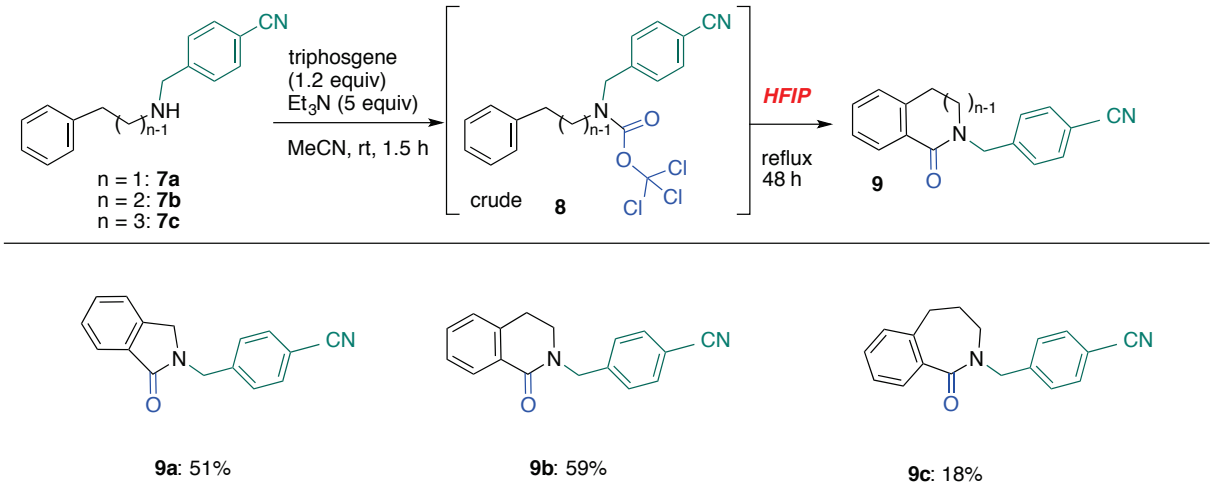
entry	temp. (°C)	solvent	time (h)	yield (%)[a]
1	rt	neat	168	93
2	rt	MeCN	3	0
3	rt	1,4-dioxane	3	0
4	rt	AcOEt	3.	0
5	rt	benzene	3	0
6	rt	toluene	3	0
7	rt	$CHCl_3$	3	0
8	rt	DMF	3	0
9	rt	DMSO	3	0
10	rt	H_2O	3	0
11	rt	concd. HCl	3	trace
12	rt	MeOH	3	0
13	rt	EtOH	3	0
14	rt	*i*-PrOH	3	0
15	rt	*n*-BuOH	3	0
16	rt	*tert*-BuOH	3	0
17	rt	TFE	3	82
18	60	TFE	0.1	78
19	***rt***	***HFIP***	***0.5***	***90***
20	60	HFIP	0.1	86

[a] Isolated yield.

To test this hypothesis, we prepared crude **2f** on a gram scale. Surprisingly, after 1 week at room temperature and open to air, the crude **2f** in a flask was spontaneously converted into **3f** in 93% yield (entry 1, Table 2), which supported our hypothesis and data in Scheme 5 (**3f**; decomposition).

An evaluation of solvents revealed 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was the most effective solvent among other solvents (entries 2-20), while the reaction in MeCN (entry 2, Table 2) resulted in no cyclization (entry 2). Therefore, the details of the nitrile effects are not clear and under investigation. In contrast to the optimized reaction conditions for **2a** reported in Table 1, 2,2,2-trifluoroethanol (TFE) and HFIP exhibited better performance than DMSO in the reaction of **2f**,[21] which indicated that this difference might be due to the performance of the stabilizer interacting with cationic intermediate in the cyclization.[22]

After establishing the mild Bischler–Napieralski cyclization using 4-cyanobenzyl (4-CNBn) tryptamine in HFIP, reactions of 4-CNBn-substituted amines **7a-c** were performed (Scheme 6). Pleasingly, under reflux conditions, 4-CNBn-substituted amines with different alkyl chains were compatible and gave the corresponding lactams **9a**, **9b**, and **9c** in 51%, 59%, and 18% yields, respectively. To the best of our knowledge, this is the first time that the formation of a benzazepinone has been realized by a Bischler–Napieralski cyclization.[23]



Scheme 6. Bischler–Napieralski-type cyclization of amines **7a-c**

In conclusion, we developed the Bischler–Napieralski-type cyclization of trichloromethyl carbamates in the absence of additives, giving β-carbolinones. Notably, our protocol enabled use of versatile trichloromethyl carbamates as a cyclization precursor. Furthermore, the cyclization also proceeded in HFIP at room temperature by the use of the 4-cyanobenzyl group as both protecting and activating groups. Further applications along these lines and the development of other activating groups are underway in our group.

EXPERIMETAL

Melting points were recorded with a Yamato MP21 and are uncorrected. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer and absorbance bands are reported in wavenumbers (cm^{-1}). The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer. Chemical shifts in ^{1}H-and ^{13}C-NMR are expressed in ppm (δ). All ^{13}C NMR spectra were determined with complete proton decoupling. Column chromatography and Flash column chromatography were performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.). High-resolution MS spectra were recorded with Micromass AutoSpec 3100 and JEOL JMS-T100LP mass spectrometers. All tryptamines were synthesized according to the literature.[13h] All reagents were obtained from commercial suppliers and used without further purification.

Trichloromethyl (2-(1*H*-indol-3-yl)ethyl)(benzyl)carbamate (2a).

Triphosgene (712 mg, 2.4 mmol, 1.2 equiv) was added to a mixture of **1a** (500 mg, 2 mmol) and Et_3N (1.4 mL, 10 mmol) in MeCN (20 mL) at room temperature and the mixture was stirring for 1.5 h. After addition of H_2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/6) to give **2a** (208 mg, 25%) as a yellow solid.

208 mg (0.51 mmol), 25%: Yellow solid: mp 200—202 °C; IR ($CHCl_3$): 3479, 1724, 1640 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.08 (br s, 1H), 7.53–7.57 (m, 1H), 7.33–7.38 (m, 4H), 7.21–7.23 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.99, 6.98 (two s, 1H), 4.57, 4.49 (two s, 2H), 3.01–3.07 (m, 2H), 3.01–3.07 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 150.3, 149.6, 136.4, 135.9, 135.7, 128.9, 128.3, 128.2, 128.1, 127.4, 127.3, 127.1, 122.4, 122.3, 119.7, 119.6, 118.7, 118.6, 112.2, 112.0, 111.5, 111.4, 55.2, 53.1, 51.0, 50.3, 24.5, 23.2 (There are amide rotamers); HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_2NaO_2$ $[M+H]^+$ 433.0253, 435.0224, found 433.0252, 435.0221.

2-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3a).

A solution of compound **2a** (824 mg, 2 mmol) in DMSO (15 mL) was heated at 100 °C for 0.5 h. After addition of H_2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/4) to give **3a** (409 mg, 74%) as a colorless powder.

409 mg (1.48 mmol), 74%: Colorless powder: mp 225—226 °C; IR ($CHCl_3$): 3229, 1711, 1640 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.32–7.38 (m, 4H), 7.26–7.30 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 4.81 (s, 2H), 3.65 (t, *J* = 6.9 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.5, 137.7, 137.5, 128.8, 128.1, 127.6, 127.0, 125.4, 125.0, 120.3, 120.2, 118.3, 112.5, 49.6, 47.5, 20.8 (two carbons are overlapped); HRMS (ESI): calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1341, found 277.1340.

General Procedure for the Synthesis of Carbolinones 3 (for 3a, 3b, 3c, 3d, 3e, 3g, and 3h).

Triphosgene (712 mg, 2.4 mmol) was added to a mixture of **1** (2 mmol) and Et_3N (1.4 mL, 10 mmol) in MeCN (20 mL) was added at room temperature and the mixture was stirring for 1.5 h. After addition of H_2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was used without further purification. A solution of crude **2** in DMSO (15 mL) was heated at 100 °C for 0.5 h. After addition of H_2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant mixture was purified by silica gel column chromatography (AcOEt/hexane = 1/4—1/6) to give **3**.

2-Benzyl-6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3b).

490 mg (1.6 mmol), 80%: Colorless powder: mp 200—201 °C; IR ($CHCl_3$): 3227, 1640 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.69 (br s, 1H), 7.28–7.38 (m, 6H), 6.93–6.95 (m, 2H), 4.82 (s, 2H), 3.84 (s, 3H), 3.64 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 6.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.7, 154.5, 137.7, 132.9, 128.8, 128.0, 127.6, 125.5, 117.8, 116.1, 113.5, 100.7, 55.9, 49.7, 47.6, 20.8 (three carbons are overlapped); HRMS (ESI): calcd for $C_{19}H_{19}N_2O_2$ $[M+H]^+$ 307.1447, found 307.1447.

2-Benzyl-6-chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3c).

442 mg (1.42 mmol), 71%: Colorless powder: mp 215—217 °C; IR ($CHCl_3$): 3460, 1641 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.90 (br s, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.29–7.37 (m, 6H), 7.20 (dd, *J* = 2.3, 8.6 Hz, 1H), 4.82 (s, 2H), 3.65 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 7.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.5, 137.4, 136.1, 128.9, 128.2, 128.0, 127.7, 126.2, 125.9, 125.3, 119.5, 117.6, 113.9, 49.8, 47.5, 20.6 (two carbons are overlapped); HRMS (ESI): calcd for $C_{18}H_{16}ClN_2O$ $[M+H]^+$ 311.0951, 313.0922, found 311.0951, 313.0923.

2-(4-Methoxybenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3d).

490 mg (1.6 mmol), 80%: Colorless powder: mp 240—241 °C; IR ($CHCl_3$): 3219, 1640 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.88 (br s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.25–7.28 (m, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.76 (s, 2H), 3.80 (s, 3H), 3.63 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.5, 159.2, 137.6, 129.8, 129.4, 127.2, 125.4, 124.9, 120.2, 120.1, 118.2, 114.2, 112.5, 55.4, 49.0, 47.3, 20.8 (two carbons are overlapped); HRMS (ESI): calcd for $C_{19}H_{18}N_2NaO_2$ $[M+Na]^+$ 329.1266, found 329.1267.

2-(2,4-Dimethoxybenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3e).

463 mg (1.37 mmol), 69%: Colorless powder: mp 209—211 °C; IR ($CHCl_3$): 3462, 1641 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.86 (br s, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.6 Hz, 2H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 1.7 Hz, 1H), 6.45 (dd, *J* = 2.3, 8.6 Hz, 1H), 4.78 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.69 (t, *J* = 6.9 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H);

^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.7, 160.4, 158.8, 137.6, 130.5, 127.4, 125.4, 124.7, 120.1, 118.2, 118.1, 112.7, 104.3, 98.6, 55.5, 55.4, 47.7, 44.0, 20.9 (one carbon is overlapped); HRMS (ESI): calcd for $C_{20}H_{20}N_2NaO$ $[M+Na]^+$ 359.1372, found 359.1371.

2-(2-Methylbenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3g).

478 mg (1.64 mmol), 82%: Colorless powder: mp 218—219 °C; IR ($CHCl_3$): 3462, 1641 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.27–7.30 (m, 2H), 7.18–7.22 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 4.81 (s, 2H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.36 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.4, 137.5, 136.9, 135.2, 130.7, 128.4, 127.6, 127.0, 126.2, 125.4, 125.0, 120.3, 120.2, 118.3, 112.5, 47.4, 47.0, 20.8, 19.3; HRMS (ESI): calcd for $C_{19}H_{18}N_2NaO$ $[M+Na]^+$ 313.1317, found 313.1321.

2-(3-Methylbenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3h).

482 mg (1.66 mmol), 83%: Colorless powder: mp 219—220 °C; IR ($CHCl_3$): 3446, 1640 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.77 (br s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 6.9 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.09–7.18 (m, 4H), 4.79 (s, 2H), 3.65 (t, *J* = 6.9 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.6, 138.5, 137.6, 128.7, 128.6, 128.3, 127.1, 125.4, 125.1, 124.9, 120.3, 120.1, 118.2, 112.6, 49.6, 47.5, 21.5, 20.8 (one carbon is overlapped); HRMS (ESI): calcd for $C_{19}H_{18}N_2NaO$ $[M+Na]^+$ 313.1317, found 313.1314.

General Procedure for the Synthesis of Carbolinones (3l-n).

Triphosgene (356 mg, 1.2 mmol) was added to a mixture of **1** (1 mmol) and Et_3N (0.7 mL, 5 mmol) in MeCN (15 mL) was added at room temperature and the mixture was stirring for 1.5 h. After addition of H_2O (15 mL), the whole was extracted with AcOEt (3 x 30 mL), washed with brine (2 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was used without further purification. A solution of crude **2** in DMSO (10 mL) was heated at 100 °C for 0.5 h. After addition of H_2O (10 mL), the whole was extracted with AcOEt (3 x 30 mL), washed with brine (2 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant mixture was purified by silica gel column chromatography (AcOEt/hexane = 1/4—1/6) to give **3**.

9-Benzyl-3,3-dimethyl-7,9,10,11-tetrahydropyrano[3,2-*e*]pyrido[3,4-*b*]indol-8(3*H*)-one (3l).

291 mg (0.81 mmol), 81%: Colorless powder: mp 254—257 °C; IR ($CHCl_3$): 3460, 1641 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.50 (br s, 1H), 7.29-7.34 (m, 4H), 7.24 (t, *J* = 6.9 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.75 (d, *J* = 9.8 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 1H), 5.67 (d, *J* = 9.8 Hz, 1H), 4.66 (s, 2H), 3.54 (t, *J* = 6.9 Hz, 2H), 3.08 (t, *J* = 6.9 Hz, 2H), 1.33 (s, 6H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 161.0, 146.6, 138.5, 133.7, 130.4, 129.1, 128.4, 128.1, 127.7, 121.4, 119.8, 116.7, 115.5, 113.3, 113.2, 75.5, 49.1, 47.6, 27.5, 22.5 (three carbons are overlapped); HRMS (ESI): calcd for $C_{23}H_{23}N_2O_2$ $[M+H]^+$ 359.1760, found 359.1760.

9-(4-Methoxybenzyl)-3,3-dimethyl-7,9,10,11-tetrahydropyrano[3,2-*e*]pyrido[3,4-*b*]indol-8(3*H*)-one (3m).

335 mg (0.86 mmol), 86%: Colorless powder: mp 186—187 °C; IR ($CHCl_3$): 3462, 1638 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.42 (br s, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 9.2 Hz, 1H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 1H), 6.73 (d, *J* = 9.7 Hz, 1H), 5.60 (d, *J* = 9.7 Hz, 1H), 4.72 (s, 2H), 3.80 (s, 3H), 3.60 (t, *J* = 7.2 Hz, 2H), 3.14 (t, *J* = 7.5 Hz, 2H), 1.43 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.3, 159.1, 147.1, 133.2, 130.1, 129.6, 129.4, 128.0, 121.6, 119.6, 116.9, 116.1, 114.1, 113.6, 112.5, 75.5, 55.4, 48.9, 47.1, 27.3, 22.8 (three carbons are overlapped); HRMS (ESI): calcd for $C_{24}H_{25}N_2O_3$ $[M+H]^+$ 389.1865, found 389.1868.

9-(2,4-Dimethoxybenzyl)-3,3-dimethyl-7,9,10,11-tetrahydropyrano[3,2-*e*]pyrido[3,4-*b*]indol-8(3*H*)-one (3n).

315 mg (0.75 mmol), 75%: Colorless powder: mp 209—211 °C; IR ($CHCl_3$): 3460, 1719, 1687, 1638, 1614 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.86 (br s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 9.2 Hz, 1H), 6.76 (t, *J* = 9.5 Hz, 2H), 6.47 (d, *J* = 2.3 Hz, 1H), 6.44 (dd, *J* = 2.3, 8.6 Hz, 1H), 5.60 (d, *J* = 9.7 Hz, 1H), 4.75 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.67 (t, *J* = 7.5 Hz, 2H), 3.14 (t, *J* = 6.9 Hz, 2H), 1.43 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.6, 160.4, 158.7, 147.0, 133.4, 130.4, 129.9, 128.3, 121.6, 119.7, 118.1, 116.8, 115.8, 113.4, 112.7, 104.3, 98.6, 75.2, 55.5, 47.5, 44.0, 27.4, 22.9 (two carbons are overlapped); HRMS (ESI): calcd for $C_{25}H_{27}N_2O_4$ $[M+H]^+$ 419.1971, found 419.1973.

2-(4-Cyanobenzyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (3f) (Table 2).

Triphosgene (712 mg, 2.4 mmol) was added to a mixture of **1f** (551 mg, 2 mmol) and Et_3N (1.4 mL, 10 mmol) in MeCN (20 mL) was added at room temperature and the mixture was stirring for 1.5 h. After addition of H_2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was used without further purification. A solution of the crude **2f** in HFIP (5 mL) was stirred at room temperature for 0.5 h. The resultant mixture was purified by silica gel column chromatography (AcOEt/hexane = 3/1—5/1) to give **3f** (541 mg, 90%) as colorless powder.

541 mg (1.79 mmol), 90%: Colorless powder: mp 273—274 °C; IR ($CHCl_3$): 3199, 1647 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 11.65 (br s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.02 (t, *J* = 6.9 Hz, 1H), 4.76 (s, 2H), 3.61 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.3, 144.6, 138.0, 133.0, 128.9, 127.2, 125.3, 124.8, 120.7, 120.1, 119.4, 118.4, 113.1, 110.4, 49.3, 48.3, 20.7 (two carbons are overlapped); HRMS (ESI): calcd for $C_{19}H_{16}N_3O$ $[M+H]^+$ 302.1293, found 302.1297.

General Procedure for the Synthesis of Carbolinones 9 (Scheme 6).

Triphosgene (712 mg, 2.4 mmol) was added to a mixture of **7** (2 mmol) and Et_3N (1.4 mL, 10 mmol) in

MeCN (20 mL) was added at room temperature and the mixture was stirring for 1.5 h. After addition of H_2O (20 mL), the whole was extracted with AcOEt (3 x 50 mL), washed with brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was used without further purification. A solution of the crude **8** in HFIP (5 mL) was stirred under reflux. The resultant mixture was purified by silica gel column chromatography (AcOEt/hexane = 1/4) to give **9**.

2-(4-Methylbenzyl)isoindolin-1-one (9a).

254 mg (1.02 mmol), 51%: Colorless powder: mp 136—138 °C; IR ($CHCl_3$): 2231, 1686 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.50 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.40-7.42 (m, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.86 (s, 2H), 4.30 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.8, 142.6, 141.1, 132.8, 132.2, 131.9, 128.7, 128.4, 124.2, 123.0, 118.6, 111.8, 49.7, 46.2 (two carbons are overlapped); HRMS (ESI): calcd for $C_{16}H_{12}N_2NaO$ $[M+Na]^+$ 271.0847, found 271.0848.

2-(4-Methylbenzyl)-3,4-dihydroisoquinolin-1(2*H*)-one (9b).

310 mg (1.18 mmol), 59%: Colorless powder: mp 79—82 °C; IR ($CHCl_3$): 2232, 1708, 1647, 1609 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.42-7.44 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 4.82 (s, 2H), 3.50 (t, *J* = 6.9 Hz, 2H), 2.97 (t, *J* = 6.9 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.9, 143.2, 138.1, 132.6, 132.2, 129.0, 128.6, 128.5, 127.3, 127.2, 118.8, 111.5, 50.6, 46.1, 28.2 (two carbons are overlapped); HRMS (ESI): calcd for $C_{17}H_{14}N_2NaO$ $[M+Na]^+$ 285.1004, found 285.1000.

2-(4-Methylbenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (9c).

100 mg (0.36 mmol), 18%: Colorless powder: mp 109—111 °C; IR ($CHCl_3$): 2232, 1632 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 1.7, 7.5 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.38 (td, *J* = 1.7, 7.5 Hz, 1H), 7.33 (dt, *J* = 1.2, 7.4 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 1H), 4.82 (s, 2H), 3.19 (t, *J* = 6.3 Hz, 2H), 2.75 (t, *J* = 6.9 Hz, 2H), 1.87 (q, *J* = 6.9 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.7, 143.8, 137.3, 135.5, 132.6, 131.3, 128.9, 128.8, 128.5, 127.2, 118.8, 111.6, 50.4, 46.3, 30.3, 29.3 (two carbons are overlapped); HRMS (ESI): calcd for $C_{18}H_{16}N_2NaO$ $[M+Na]^+$ 299.1160, found 299.1158.

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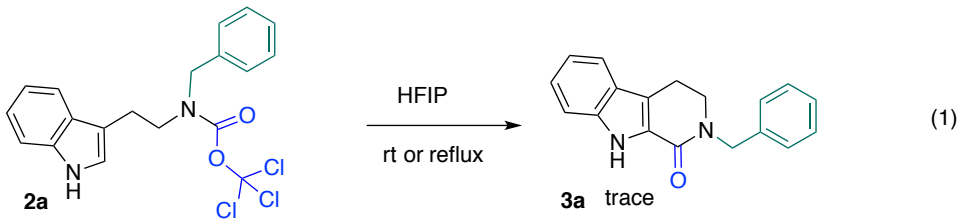

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