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Enhancement of the carbamate activation rate enabled syntheses of tetracyclic benzolactams: 8-oxoberbines and their 5- and 7-membered C-ring homologues†

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A route to the direct amidation of aromatic-ring-tethered *N*-carbamoyl tetrahydroisoquinoline substrates was developed. This route enabled general access to 8-oxoberberines and their 5- and 7- membered C-ring homologues. It overcomes the undesired tandem side-reactions that result in the destruction of the isoquinoline backbone, which inevitably occurred under our previously reported superacidic carbamate activation method.

Introduction

The design of a synthetic strategy directed toward natural products does not always include its extension into the syntheses of their derivatives.

The protoberberine alkaloids, which constitute an important family of benzylisoquinoline alkaloids, display various biological and medicinal properties.[1] The nor- and homoforms of protoberberines also exhibit potent antimalarial and anti-inflammatory activities.[2] The total synthesis of naturally occurring protoberberines and their derivatives has therefore been a topic of great interest to synthetic organic chemists.[3] In some synthetic strategies,[4] 8-oxoberbines are used as intermediates, which can be converted into their reduced berbine counterparts *via* redox reactions (Fig. 1).[4]

The Pictet–Spengler-type intramolecular cyclization reaction[3b,c,5] is one of the key methods available for the construction of tetracyclic structures of the protoberberines (Fig. 1(a)), although other synthetic approaches have been reported,[3–5] including S_N2-type cyclization reactions (Fig. 1(b)),[3d] the Friedel–Crafts type reaction (Fig. 1(c)),[4a] and the transition-metal-catalyzed carbonylation reaction (Fig. 1(d)).[4b–d] Indeed, this biomimetic approach[6] has been successful in the preparation of natural products and their analogues bearing electron-rich aromatic rings. However, as in the case of general electrophilic aromatic substitution reactions, the intramolecular cyclization reaction is limited by the ring size and the reactivities of the aromatic rings. The D-ring is essentially activated by electron-donating groups such as the methoxy groups when the iminium ion is used as an electrophile. Similarly, synthetic routes to the 5-membered C-ring homologues (*i.e.*, the isoindoloisoquinolines) and the 7-membered C-ring homologues (*i.e.*, the homoprotoberberines) have also been developed.[7] Although these approaches are effective for electron-rich substrates, similar issues were encountered for the reactions of electron-deficient rings when electrophilic aromatic substitution approaches were employed for the construction of a C-ring.[7a] Therefore, the development of a general approach to protoberberine and its homologues of different ring sizes is challenging.

As a direct amidation method for aromatic rings, the activation of urea or carbamate in the presence of trifluoromethanesulfonic acid (TfOH) has been developed (Scheme 1(a)).[8] The obtained reactive intermediate, a carba-

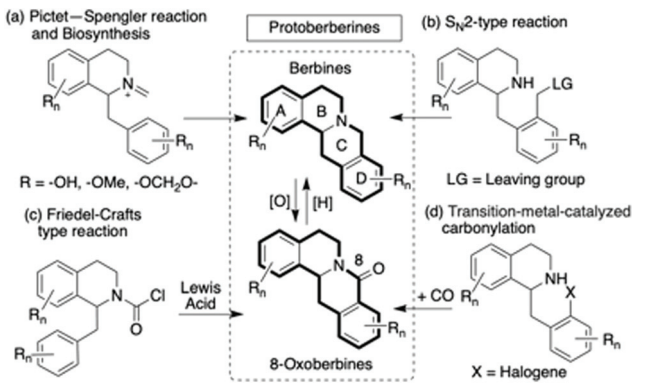

Fig. 1 Structures of protoberberine alkaloids and their traditional synthetic strategies.

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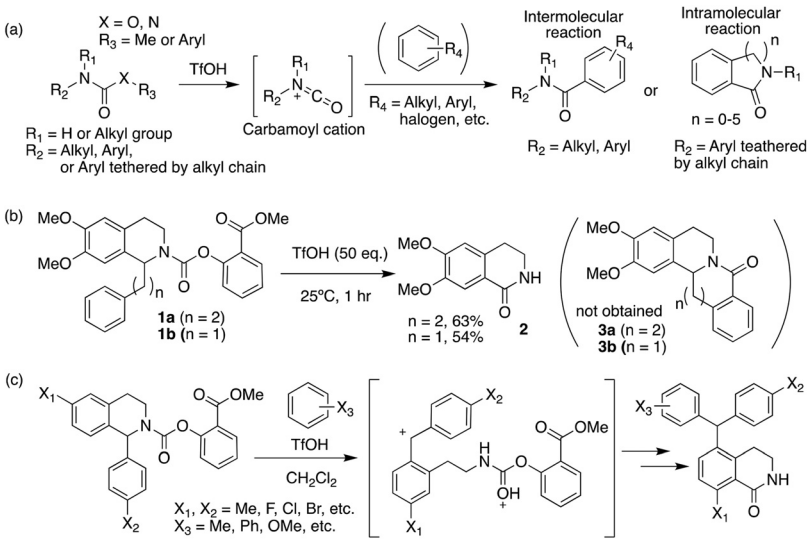


Scheme 1 (a) Previously developed direct amidation method *via* carbamoyl cations. (b) Our previous approach to form unexpected product **2**. (c) Benzylic C–N bond scission of tetrahydroisoquinolines in the presence of TfOH.

moyl cation, has been shown to exhibit sufficient electrophilicity to react with deactivated aromatic compounds,[8c] and to form energetically demanding medium-sized cyclic compounds.[8f] In a series of synthetic studies into the construction of benzolactams, we attempted to apply these reaction conditions to the construction of protoberberines and their homologues using **1a** and **1b** as substrates (Scheme 1(a)). However, the desired transformation did not take place, and instead, 3,4-dihydroisoquinolone (**2**) was obtained instead of **3** (Scheme 1(b)). The formation of this undesired product is similar to our previously reported reaction of benzylic C–N bond cleavage-initiated tandem triarylmethane formation (Scheme 1(c)).[9] In this reaction, the benzylic C–N bond is cleaved in the presence of a superacid, and the resulting carbocations act as strong electrophiles. However, to achieve the synthesis of the homoprotoberberine backbone, such benzylic C–N bond cleavage must be avoided. Thus, we herein report on a general synthetic route to 8-oxoberbines and their homologues, avoiding this undesired reaction.

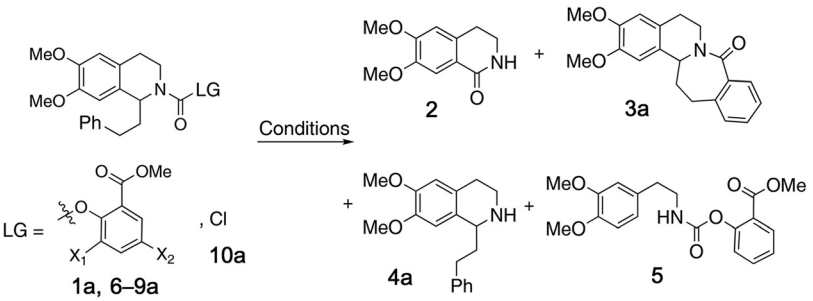
Results and discussion

Initially, we examined the reaction conditions to determine the mechanism leading to the formation of **2** (Table 1, entries 1–5). The reaction did not proceed in the presence of trifluoroacetic acid (TFA) even when it was used as the reaction solvent (entry 1), thereby indicating that a stronger acid is required for the conversion to be successful. Using 1.4 eq. of TfOH (entry 2), the desired conversion did not occur, but partial decomposition of the carbamate moiety took place to afford **4a** (entry 2).[10] In contrast, a large excess of TfOH (10 eq.) caused the conversion of **1a** into **2** and the formation of a trace amount of **3a** (entry 3). Harsher conditions (*i.e.*, 50 eq. TfOH) decreased the yields of both products **2** and **3a** (entry 4). In addition, a shorter reaction time at a lower temperature (entry 5) afforded product **5**, which indicated that detachment of the phenethyl group proceeds prior to cyclization, as shown in Fig. 2.[11]

Based on the above results, a mechanism leading to the formation of **2** can be proposed, as shown in Fig. 2, pathway (a). More specifically, the reaction is initiated by protonation of the carbamate nitrogen atom, and subsequent benzylic C–N bond cleavage affords a carbocation, which is trapped by the tethered aromatic ring. Based on the results of our previous study,[9] further protonation of the carbamate moiety would be expected. Following the cyclization of the tethered aromatic ring, an indanyl cation is released *via* a retro-Friedel–Crafts alkylation, and the resulting intermediate **5-H**$^+$ is then activated by the acid to afford cyclized product **2** in the rate-determining step.[8c] To suppress the formation of product **2**, the activation of the carbamate group (step B in Fig. 2, pathway (b)) should be faster than the Friedel–Crafts reaction (step A), which is caused by the C–N bond scission reaction.

The leaving group was then optimized to enhance the activation rate of the carbamate group (Table 1, entries 6–11). Although the conventional method required a temperature of 25 °C (entry 3), leaving groups bearing an electron-withdrawing group successfully activated the carbamate residue at 0 °C. The amount of acid and the position of the nitro group were important to control the activation rate and the yield of **3a**. More specifically, substrate **6a** afforded the desired product **3a** in a 77% yield (entry 8). The optimal amount of acid equally depends on the formation of **2** and **4a** (entries 6–9). Based on entries 6 and 7, it can be considered that more than seven equivalents of acid are required to suppress the triflate anion attack on the reactive cationic intermediate, which leads to the decomposition of the carbamate moiety. This result is sugges-

Table 1 Screening of the reaction conditions and leaving groups



	Substrate			Condition				Yield[b] (%)				
Entry[a]		X_1	X_2	Acid (eq.)	Solvent	Temp. (°C)	Time	**2**	**3a**	**4a**	**5**	Recovery
1	**1a**	H	H	TFA (50)	None	25	24 h	0	0	0	0	96
2	**1a**	H	H	TfOH (1.4)	CH_2Cl_2	25	18 h	0	0	48[c]	0	25[c]
3	**1a**	H	H	TfOH (10)	CH_2Cl_2	25	1 h	78	2	0	0	0
4	**1a**	H	H	TfOH (50)	None	25	1 h	63	0	0	0	0
5	**1a**	H	H	TfOH (50)	None	0	5 m	Trace	0	0	64	0
6	**6a**	NO_2	H	TfOH (5)	CH_2Cl_2	0	2 h	3[c]	66[c]	28[c]	0	0
7	**6a**	NO_2	H	TfOH (7)	CH_2Cl_2	0	30 m	4[c]	71[c]	17[c]	0	0
8[d]	**6a**	NO_2	H	TfOH (10)	CH_2Cl_2	0	5 m	19	77	0	0	0
9	**6a**	NO_2	H	TfOH (50)	None	0	5 m	59	8	0	0	0
10	**7a**	H	NO_2	TfOH (10)	CH_2Cl_2	0	40 m	53	24	0	0	0
11	**8a**	H	CO_2Me	TfOH (10)	CH_2Cl_2	0	10 m	44	48	0	0	0
12	**9a**	CO_2Me	H	TfOH (10)	CH_2Cl_2	0	5 m	24	58	0	0	0
13[e,f]	**10a**	—		$AlCl_3$ (1.1)	Benzene	80	20 h	0	25	0	0	0

[a] 0.3 mmol scale reaction. [b] Isolated yield, unless otherwise noted. [c] The yields were determined by ^{1}H-NMR spectroscopy without isolation. [d] The reaction was also conducted on the 1.3 mmol scale. The products **2** and **3a** were obtained in 16 and 76% yield respectively. [e] The reaction condition previously shown in ref. 4*a*. [f] Demethylated products were obtained in total 19% yield.

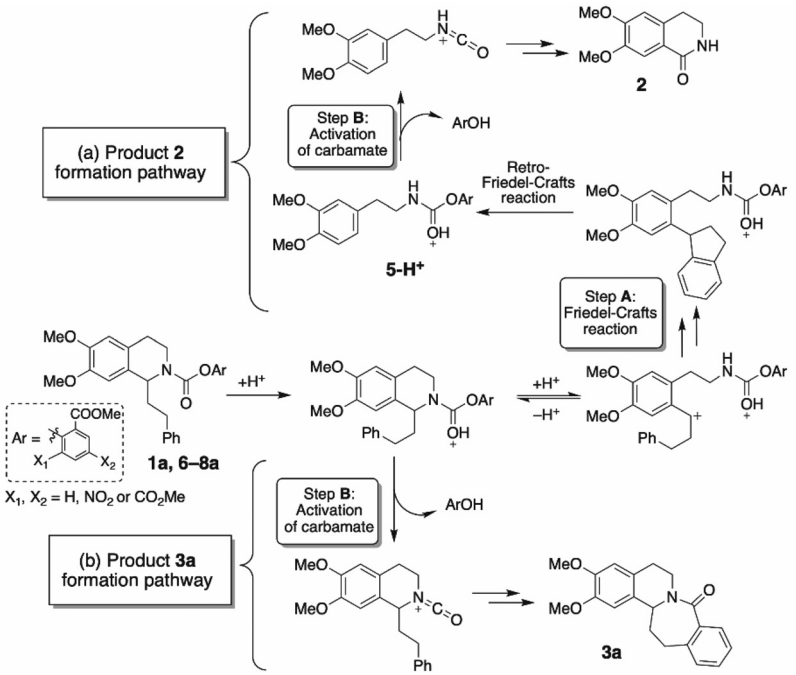


Fig. 2 Branching of the reaction pathway to form undesired product **2** and desired product **3a**.

tive of the fact that several equivalents of acids are used for not only the protonation of substrates and the cleaved leaving group (3-nitro salicylic acid methyl ester) but also for the solvation of triflates to reduce the activity of the free anion. In the case of the other leaving group, substrate **7a** afforded **3a** in 24% yield together with **2** (53% yield) (entry 10). In addition, substrate **8a**, bearing a leaving group as previously reported by Sumita and Ohwada *et al.*,[12] afforded **3a** in a moderate yield (48%, entry 11). The positional change of the ester group improved the yield of **3a** by only 10% (entry 12). These results point to the salicylate leaving group bearing a nitro group at the C3 position with 10 equivalents of acid being optimal, such that it was therefore employed for the substrate scope investigation. In addition, a previously reported method, namely the Lewis-acid-promoted reaction of carbamoyl chloride **10a**, was examined (entry 13), which afforded **3a** in a low yield (25%) together with the formation of demethylated products (total 19% yield) and a complex mixture of polymerized side-products. The limitation of the method is also discussed in the ESI.†

To elucidate the effect of the nitro group position, an energy diagram was constructed for the C–O bond dissociation reaction using a model system of **1′**, **6′**, and **7′** at the PCM(CH_2Cl_2)-M06-2X/6-311+G**//PCM(CH_2Cl_2)-M06-2X/6-31G* level of theory[13,14] using the Gaussian16 program (Fig. 3(a)).[15] The proposed activation mechanism is based on the discussion described in ref. 7*c*. Thus, the installation of the nitro group at the C3-position of methyl salicylate decreased the activation free energy by 4.5 kcal mol^{-1}, while substitution at the C5-position resulted in a 1.7 kcal mol^{-1} decrease. This difference between the C3- and C5-nitro leaving groups was attributed to the charge separation of the transition state (Fig. 3(b)).[16] Since the nitro group withdraws the electron of the leaving group to become negatively charged, the charge is highly separated at the transition state of the C5-nitro substrate, and the dipole moment of the structure changes from 13.0 D (**INT-7′**) to 18.2 D (**TS-7′**) during activation. Conversely, the negative charge of the nitro group and the positive charge of the carbamoyl cation are related in the transition state of the C3-nitro substrate. In this case, the dipole moment of the structure changes from 12.9 D (**INT-6′**) to 6.6 D (**TS-6′**), indicating that the instability of the system derived from the charge separation of **INT-6′** is reduced in transition state **TS-6′**.

Next, the substrate scope was investigated for 5-, 6-, 7-, and 8-membered ring formation (Table 2). Samples of substrate **6**

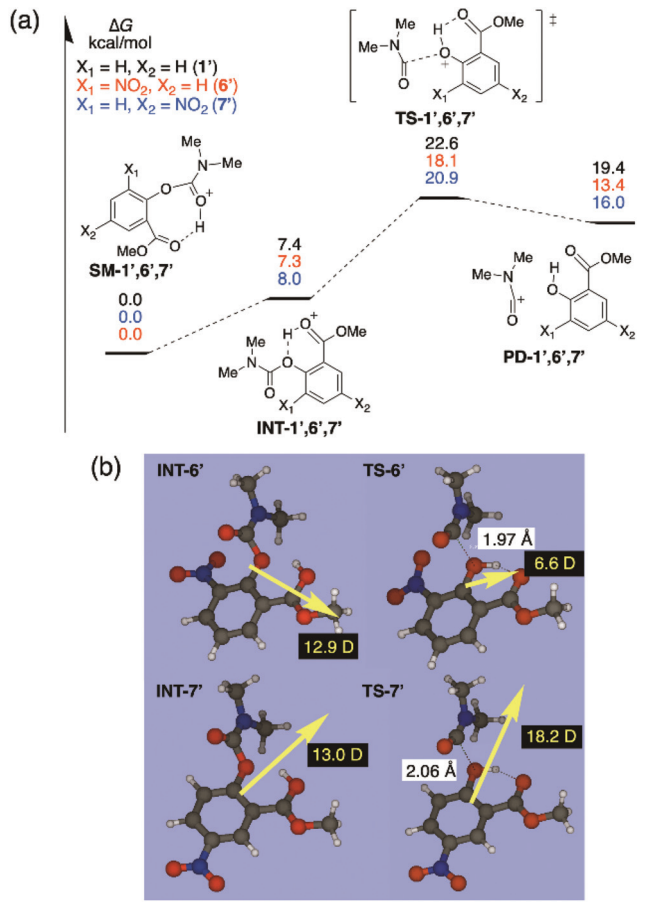
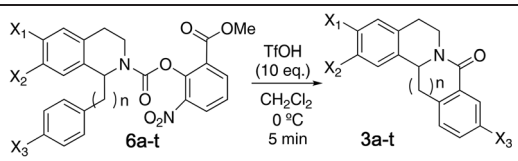


Fig. 3 (a) Energy diagram of the C–O bond scission reaction of the model system. (b) Structures of the intermediates and transition states. The dipole moments (PCM(CH_2Cl_2)-M06-2X/6-311+G**) and C–O bond lengths are also displayed.

Table 2 Substrate scope for syntheses of protoberberine backbone and its homologues



Entry[a]	Substrate	*n*	X_1	X_2	X_3	Product	Yield[b] (%)
1	**6c**	0	H	H	H	**3c**	78
2	**6d**	0	H	H	Me	**3d**	96
3	**6e**	0	H	H	Cl	**3e**	74
4	**6f**	0	OMe	OMe	H	**3f**	74
5	**6g**	0	H	Me	H	**3g**	97
6	**6h**	0	H	Cl	H	**3h**	88
7	**6i**	1	H	H	H	**3i**	91
8	**6j**	1	H	H	Me	**3j**	93
9	**6k**	1	H	H	Cl	**3k**	92
10	**6b**	1	OMe	OMe	H	**3b**	89
11	**6l**	1	H	Me	H	**3l**	98
12	**6m**	1	H	Cl	H	**3m**	96
13	**6n**	2	H	H	H	**3n**	92
14	**6o**	2	H	H	Me	**3o**	87
15	**6p**	2	H	H	Cl	**3p**	57
16	**6a**	2	OMe	OMe	H	**3a**	77
17	**6q**	2	H	Me	H	**3q**	82
18	**6r**	2	H	Cl	H	**3r**	92
19	**6s**	3	H	H	H	**3s**	8
20	Substrate **6t**					Product **3t**	76

[a] Approx. 0.3 mmol scale reaction. [b] Isolated yield.

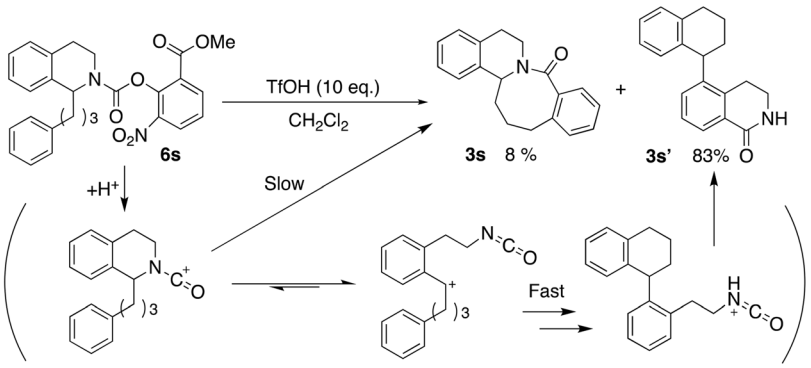


Fig. 4 Competition between 8-membered ring formation and rearrangement followed by C–O bond scission of the carbamate moiety.

were synthesized using known methods from phenethylamine derivatives (for details, see the ESI†). In particular, for 5-, 6-, and 7-membered ring synthesis, the cyclized products were obtained at good to high yields (entries 1–18). Interestingly, even aromatic rings deactivated by a chloro group were suitable for the electrophilic aromatic substitution reaction (entries 3, 9, and 15). However, our attempt at 8-membered ring synthesis was less efficient than the corresponding reactions for the preparation of the smaller rings (entry 19).

In the case of **6s**, benzylic C–N bond cleavage afforded rearranged product **3s′** in an 83% yield (Fig. 4). Considering that 7-membered ring formation did not result in this undesired reaction caused by C–N bond scission (entry 13), it appears that the activation reaction of the carbamate group is faster than the C–N bond scission of the carbamate substrate, and hence there should be another pathway to C–N bond scission promoted by the carbamoyl cation intermediate. Since formation of the 8-membered ring is approximately 50 times slower than 7-membered ring formation,[8f] the undesired reaction proceeds readily.

Comparison of the 6- and 7-membered ring formation reaction rates were then examined intramolecularly (Table 2, entry 20), where it was found that 6-membered ring formation dominated to afford product **3t**. This is in good agreement with the previously reported relative cyclization rate, which indicated that the 6-membered ring formation reaction is approximately 10^4 times faster than 7-membered ring formation.[8f] We also note that isomerization of the benzyl proton was not observed, indicating that 6-membered ring formation is significantly faster than C–N bond cleavage.

Conclusion

In summary, we investigated the transformation of 1,2,3,4-tetrahydroisoquinoline derivatives into 8-oxoberbines and their homologues in the presence of TfOH. Due to the fact that previous synthetic methods caused an unexpected reaction to produce dihydroisoquinolones *via* a tandem reaction involving benzylic C–N bond cleavage, Friedel–Crafts alkylation, retro-Friedel–Crafts alkylation, activation of the carbamate, and Friedel–Crafts type amidation, the reaction was modified based on analysis of the reaction mechanism. It was found that modification of the leaving group enhanced the activation rate of the carbamate group, enabling us to synthesize 8-oxoberberines and their 5–7 membered C-homologues substituted by electron-donating groups and a chloro group. Our route therefore represents a synthetic strategy directed toward a natural product that also can also be extended to the syntheses of its derivatives. Synthesis of further complex structures employing this method is ongoing.

Conflicts of interest

The author declare no competing financial interest.

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