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A Practical Synthesis of the Chronic Renal Disease Agent, 4,5-Dihydro-3*H*-1,4,8b-triazaacenaphthylen-3-one Derivatives, Using Regioselective Chlorination of Ethyl 5-methylimidazo[1,2-*a*]pyridine-3-carboxylate with *N*-Chlorosuccinimide

Tomomi Ikemoto,[a,*] Tetsuji Kawamoto,[b] Kiminori Tomimatsu,[b] Muneo Takatani[b] and Mitsuhiro Wakimasu[b]

[a]*Chemical Development Research Division, Takeda Chemical Industries Ltd, 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan*
[b]*Pharmaceutical Research Division, Takeda Chemical Industries Ltd, 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan*

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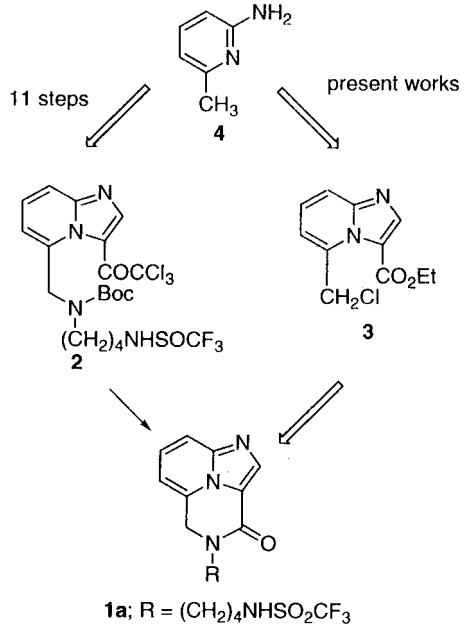
Abstract—A convenient synthesis of the chronic renal disease agent, trifluoro-*N*-[4-(3-oxo-3,5-dihydro-4*H*-1,4,8b-triazaacenaphthylen-4-yl)butyl]methanesulfonamide (**1a**), for large scale has been developed via ethyl 5-(chloromethyl)imidazo[1,2-*a*]pyridine-3-carboxylate (**3**), which was given by the regioselective chlorination of ethyl 5-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**6**) with *N*-chlorosuccinimide (NCS) using AcOEt as a solvent in 83% yield. The condensation of **3** and primary amines gave 4,5-dihydro-3*H*-1,4,8b-triazaacenaphthylen-3-one derivatives (**1**) in good yields. The present synthesis of **1a** was accomplished in five steps from 2-amino-6-methylpyridine (**4**) without requiring a chromatographic method.

Introduction

Trifluoro-*N*-[4-(3-oxo-3,5-dihydro-4*H*-1,4,8b-triazaacenaphthylen-4-yl)butyl]methanesulfonamide (**1a**) is an agent for chronic renal disease.[1a] It was shown to have potent platelet derived growth factor (PDGF) inhibitory activity and to inhibit the reduction in GFR in 5/6 nephrectomized rats and spontaneously hypercholesterolemic (SHC) rats. In the first synthesis of **1a**, the deprotection of the Boc group of 5-(*N*-Boc-aminomethyl)imidazo[1,2-*a*]pyridines (**2**) trichloroacetylated at the 3-position with hydrogenchloride successively effected the intramolecular coupling to produce the desired **1a**. One problem during the development of **1a** in clinical evaluations was the availability of large amounts of the raw drug substance, because the reported synthesis[1] required 12 steps to give **1a** in 6% overall yield via **2**. In particular, this method required repeated chromatographic purifications. Hence, an efficient synthesis of **1a** for large scale without chromatography was required. Our retrosynthetic analysis of **1a** is depicted in Scheme 1. Kurata et al. have reported[2] that the treatment of ethyl



Scheme 1.

Keywords: 4,5-dihydro-3*H*-1,4,8b-triazaacenaphthylen-3-one derivative; regioselective chlorination; ethyl 5-methylimidazo[1,2-*a*]pyridine-3-carboxylate; *N*-chlorosuccinimide.

* Corresponding author. Tel.: +6-6300-6840; fax: +6-6300-6251; e-mail: lkemoto_tomomi@takeda.co.jp

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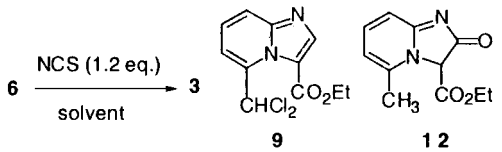
Table 1. Chlorination of **6** with NCS in various solvents



9 **12**

Entry	Solvent	Conditions	Product yields (%)[a]			
			6	**3**	**9**	**12**
1	CCl_4[b]	Reflux,7 h	26	55	4	ND[c]
2	AcOEt	rt,24 h	ND	83	1	2
3	THF	rt,4 h	3	76	4	6
4	DMF	rt,4 h	ND	1	18	ND
5	MeCN	rt,4 h	ND	5	5	7
6	AcOH	rt,4 h	ND	1	ND	83

[a] Determined by HPLC.
[b] Addition of AIBN.
[c] ND=Not detected.

5-bromomethyl-2-(methylthio)imidazo[1,2-*a*]pyridine-3-carboxylate with primary amines gave 4,5-dihydro-2-methylthio-4-substituted-3*H*-1,4,8b-triazaacenaphthylen-3-one derivatives. Namely, ethyl 5-(halomethyl)imidazo[1,2-*a*]pyridine-3-carboxylate was regarded as a synthetic intermediate of **1a**. In a previous report,[3] 5-(chloromethyl)imidazo[1,2-*a*]pyridine-3-carboxylate (**3**) was prepared from 2-amino-6-methylpyridine (**4**), that is, bromination of 2-methyl-6-pivaloylaminopyridine with *N*-bromosuccinimide (NBS) in the presence of 2,2′-azobis-isobutyronitrile (AIBN), followed by treatment with acid, reaction with ethyl 2-chloro-3-oxopropanoate (**5**), and chlorination using thionyl chloride. However, the reported preparation suffered from poor availability of **1a** and the use of expensive reagents. Hence, we planned the regioselective chlorination of ethyl 5-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**6**). Although many imidazo[1,2-*a*]pyridines[4] having useful biological activities and as a biochemical fluorescent marker were derived from the substituents at the 3-position, there were few reports[5] regarding electrophilic reactions of imidazo[1,2-*a*]pyridine blocked at the 3-position. Halogenation was only reported by Hand and Paudler[5] that treatments of 3-methylimidazo[1,2-*a*]pyridine (**7**) or 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**8**) with NBS in chloroform gave the apparent nucleophilic and the succinimide substituents at the 2-position, respectively. However, we thought that the desired reaction should occur because the methyl group of **6** was activated by the ester group at the 5-position. In this paper, we describe the regioselective chlorination of **6** with *N*-chlorosuccinimide (NCS) to **3**, and the convenient synthesis of **1a** using **3**.

Results and Discussion

Regioselective chlorination of 6 to 3

The yields of **5** were generally lower,[6] but the potassium salt of **5** (**5·K**) could be synthesized in 88% yield by an improved method whereby a mixture of ethyl chloroacetate and ethyl formate reacted with potassium *t*-butoxide in diisopropyl ether (IPE). Subsequently, the neutralization of **5·K** with H_2SO_4 in ethanol, followed by the addition of **4**, yielded **6** in 60% yield. We examined the reactions of **6** with NCS in a variety of solvents, as shown in Table 1. At first, the reaction of **6** with NCS (1.2 equiv.) and a catalyzed AIBN in refluxing carbon tetrachloride could give a mixture of chloromethyl derivatives, such as **3** and ethyl 5-(dichloromethyl)imidazo[1,2-*a*]pyridine-3-carboxylate (**9**), but could not give the usual apparent nucleophilic substituents at the 2-position (**10** and **11**), as shown in Fig. 1. Moreover, the reactions of **6** with NCS in ethyl acetate or tetrahydrofuran gave **3** regioselectively in 83 and 76% yield, respectively, together with **9** and ethyl 5-methyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridine-3-carboxylate (**12**) as minor products. On the other hand, the chlorination of **6** with NCS in acetic acid as a solvent afforded different regioselectivity to give **12** in 83% yield (Scheme 2).

The thermostability of **3** was examined for large-scale operation. The residue of **3** was 58% when **3** as an oil was kept for one week at 25°C, while the sulfuric acid salt (**3·H_2SO_4**) of **3** as a crystalline powder entirely remained. The structure of product (**13**) isolated by HPLC (column; SEP-PAK; Waters, mobile phase; acetonitrile–water) was determined by LC-MS, ^{1}H NMR analysis, and elemental analysis. Therefore, shorter reaction time was required to avoid the production of **13** for practical preparation. We examined the influence of various acids on the reaction of **6** and NCS in THF, as shown in Table 2, because it has been reported[7] that NCS would give the protonated species in the presence of a stronger acid, that is, the elimination ability of a protonated succinimide group was higher than that of a succinimide group. As a result, the rates of the reactions to chloromethyl derivatives were higher by the addition of a catalystic amount (0.2 equiv.) of a stronger acid, such as methanesulfonic acid, hydrogenchloride, and trifluoroacetic acid (entry 3, 4, 5). The addition of equimolecular methanesulfonic acid or hydrogenchloride accelerated the reaction rates; however, refluxing condition was required because the powder salts of **6** were precipitated. From these results, it was considered that the addition of 0.2 equiv. trifluoroacetic acid was the optimized condition. Although the reaction of **6** with NCS in AcOEt at room

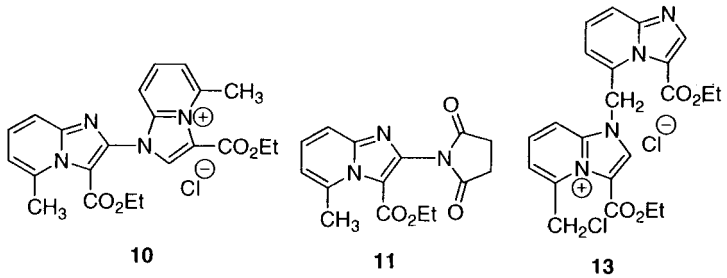
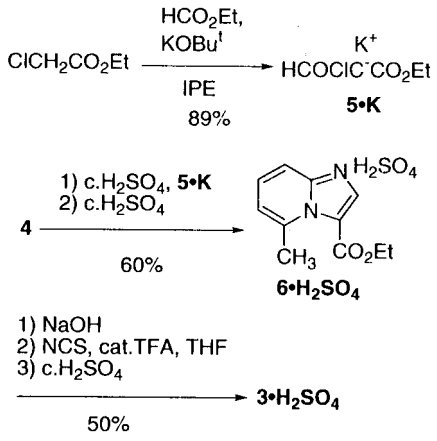


Figure 1.

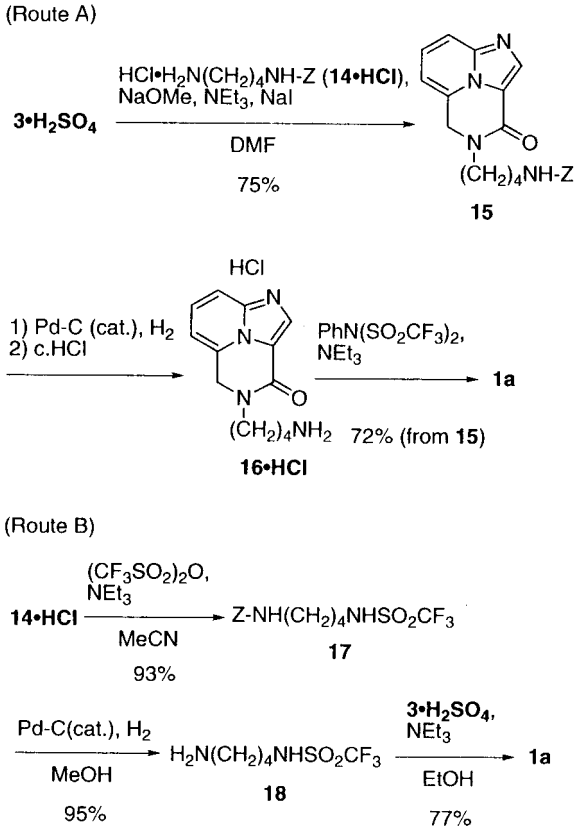


Scheme 2.

Table 2. The reaction of **6** with NCS (1.2 equiv.) in THF

Entry	Additive (eq)	Conditions	Yields (%)[a]			
			6	**3**	**9**	**12**
1	–	rt, 4 h	3	76	4	6
2	–	Reflux, 1 h	ND[b]	66	15	2
3	$MeSO_3H$ (0.2)	rt, 2 h	ND	56	20	11
4	HCl–IPE (0.2)	rt, 2 h	2	56	23	5
5	TFA (0.2)	rt, 2 h	1	67	4	12
6	AcOH (0.2)	rt, 4 h	4	74	3	3
7	$MeSO_3H$ (1.0)	Reflux, 1 h	2	52	18	8
8	HCl–IPE (1.0)	Reflux, 1 h	1	22	ND	17
9	TFA (1.0)	rt, 3 h	ND	22	49	15
10	AcOH (1.0)	rt, 4 h	14	59	3	5

[a] Yields were determined by HPLC.
[b] ND=Not detected.



Scheme 3.

temperature required longer time (24 h) in the absence of acid, the addition of 0.2 equiv. trifluoroacetic acid shortened the reaction time (2 h) to give **3·H_2SO_4** in 50% isolated yield. On the other hand, the addition of acetic acid (0.2 and 1.0 equiv.) did not affect the regioselectvity of **6** to give the chloromethyl derivatives (entry 6, 10) (Scheme 3).

Synthesis of 1

The coupling of **3·H_2SO_4** and the primary amine **14·HCl**[8] (1 equiv.) using triethylamine (4 equiv.) as a base in DMF for 3 h at 70°C under nitrogen atmosphere gave **15** in 24% yield accompanied with a by-product. This by-product was thought to be the oxidation product (**19**) of **15**, because imide **20·HCl** was recovered from the mother solution in the next step, as shown in Fig. 2. Optimization of the coupling reaction was examined as shown in Table 3. As a result, the neutralization of **3·H_2SO_4** and **14·HCl** (1 equiv.) with 28% NaOMe in MeOH (2 equiv.) in DMF, followed by the addition of sodium iodide (1 equiv.) and triethylamine (1 equiv.) at 40°C was carried out under nitrogen atmosphere to give the desired **15** in 80% yield (75% isolated yield). Moreover, alkylamines or benzylamines also afforded the desired **1** in good yields when the coupling reactions of **3** and various amines were examined, as shown in Table 4. Aniline did not effect the intramolecular

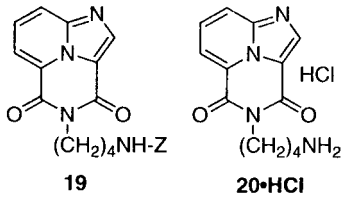


Figure 2.

Table 3. The condensation of **3** and **14·HCl**

Entry	Additives	Solvent	Conditions	Yields (%)[a]	
				15	**3**
1	NEt_3	DMF	70°C, 3 h	24	5
2	NaI, NEt_3	DMF	70°C, 1 h	34	ND[b]
3	NaI, NEt_3	EtOH	75°C, 3 h	52	ND
4	DBU, NaI, NEt_3	DMF	40°C, 5 h	60	2
5	NaOMe, NaI, NEt_3	DMF	40°C, 1.5 h	80	1
6	NaOMe, NaI, K_2CO_3	DMF	40°C, 1.5 h	70	1

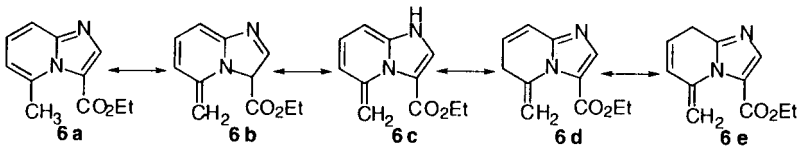
[a] Yields were determined by HPLC.
[b] ND=Not detected.

Table 4. Reactions of **3** with amines (RNH_2)

Entry	R	Conditions	Isolated yield (%)
1[a]	$TfNH(CH_2)_4$	Reflux, 4 h	**1a**, 77
2	Me	40°C, 3 h	**1b**, 70
3	*n*-Bu	40°C, 2 h	**1c**, 88
4	$PhCH_2$	40°C, 3 h	**1d**, 83
5	4-$ClC_6H_4CH_2$	40°C, 3 h	**1e**, 81
6	4-$MeOC_6H_4CH_2$	40°C, 3 h	**1f**, 78
7[b]	Ph	90°C, 3 h	**1g**, 70

[a] EtOH was used as a solvent.
[b] K_2CO_3 (2 equiv.) was used as a base.

Table 5. Calculations of HOMO for **6**

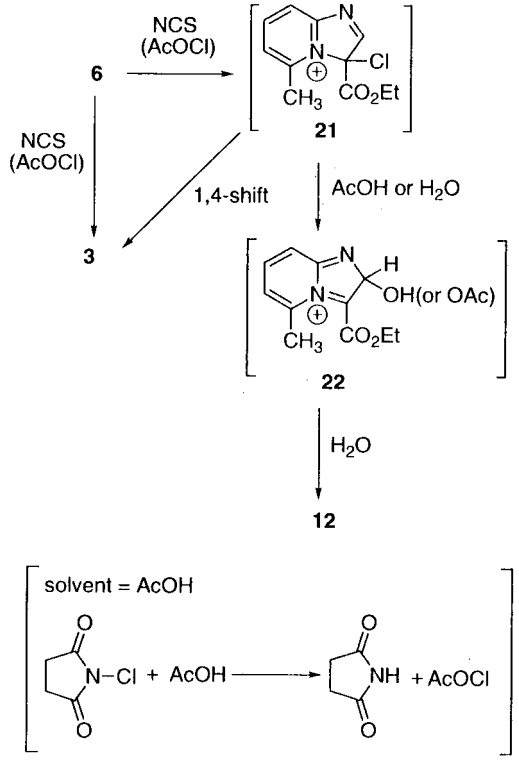


	N(1)	C(2)	C(3)	N(4)	C(5)	C(6)	C(7)	C(8)	C(9)	Me
6a	0.153	0.007	0.292	0.001	0.151	0.053	0.100	0.138	0.034	0.006
6b	0.002	0.022	0.001	0.184	0.045	0.120	0.052	0.152	0.074	0.319
6c	0.065	0.054	0.032	0.142	0.024	0.142	0.028	0.218	0.032	0.253
6d	0.022	0.151	0.194	0.078	0.026	0.011	0.134	0.066	0.087	0.087
6e	0.001	0.164	0.114	0.104	0.075	0.046	0.063	0.021	0.147	0.204

amidation to get ethyl 5-(phenylaminomethyl)imidazo[1,2-*a*]pyridine-3-carboxylate. Aniline derivative (**1g**) was obtained by the reaction using potassium carbonate (2 equiv.) instead of triethylamine at 90°C. The reaction of **3** and *N*-(4-aminobutyl)(trifluoro)methanesulfonamine (**18**, 1 equiv.) preparated from **14·HCl** gave **1a** in 77% yield (route B). The hydrogenation of **15** in MeOH at 50°C for 2 h gave **16·HCl**. Compound **1a** was given by the treatment of **16·HCl** with triethylamine and *N*-phenyltrifluoromethanesulfonimide in 72% yield (from **15**, route A).

Reaction mechanism of 6 to 3 or 12

Different results attained by the treatment of **6** with NCS were of interest in connection with the reaction mechanism. The different regioselectivity of 8-hydroxyimidazo[1,2-*a*]pyridine was interpreted by various MO calculations[9] using the MNDO method. In order to interpret the regioselective chlorination of **6** with NCS due to solvents, we calculated the frontier π-electron densitiy of five tautomers of **6** using the AM1 method developed by Dewar.[10] These calculations showed that the highest-occupied molecular orbital (HOMO) of **6** was at the 3-position (**6a** and **6d**) and the carbon of the methyl group (**6b**, **6c** and **6e**), as shown in Table 5. These data suggest, therefore, that electrophilic attack would occur at these positions (the 3-position or methyl group or both). The mechanism of formation of **3** and **12** from **6** was thought to be, as shown in Scheme 4. Namely, the carbon at the 3-position attacked NCS (or AcOCl)[11] to give the cationic intermediate **21** and the successive 1,4-chlorine shift produced the chloromethyl derivatives, while Hand and Paudler[5] have deduced that the bromonations of **7** or **8** with NBS passed through the 1-bromoimidazo[1,2-*a*]pyridium by the calculation. Another possible explanation might be that the carbon of the methyl group at the 5-position directly attacked NCS to give the chloromethyl derivatives. In the case of acetic acid as a solvent, acetic acid (quenching water) nucleophilically substituted the intermediate **21** at the 2-position to form the cation **22** leading to **12**. These mechanisms are worthy of further study.



Scheme 4.

Conclusion

A practical preparation of an agent for chronic renal disease, **1a** has been developed on large scale. The reaction of **6** with NCS afforded the unusual results to give regioselectively **3**. The coupling of **3** and the primary amines successively produced the 4,5-dihydro-4-substituted-3*H*-1,4,8b-triazaacenaphthylen-3-one derivatives. Our synthesis of **1a** was accomplished in five steps from 2-amino-6-methylpyridine (**4**) without requiring chromatographic purification.

Experimental

Melting points were recorded on a Yanagimoto micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. Column chromatography was performed with a Wakogel C-200 (75–150 μm). HPLC was performed on a YMC-Pack ODS-A302 column (6i.d.×150 mm) with 0.05 M KH_2PO_4 aqueous solution–MeCN (55:45) at 25°C. Detection was effected with a Shimadzu SPD-10A

spectrophotometric detector at 254 nm. Elemental analyses and mass spectra were analyzed by Takeda Analytical Research Laboratories Ltd.

Ethyl 5-methylimidazo[1,2-*a*]pyridine-3-carboxylate sulfuric acid salt (6·H_2SO_4). A mixture of ethyl formate (334 g, 4.5 mol) and ethyl chloroacetate (552 g, 4.5 mol) was added to a suspension of potassium *t*-butoxide (505 g, 4.5 mol) and IPE (5 L) at 0°C, and the whole was stirred for 24 h at room temperature. The resulting precipitates were collected by filtration to give ethyl 2-chloro-3-oxopropanoate potassium salt (**5·K**, 761 g, 88%) as an orange solid.

To a solution of concentrated H_2SO_4 (80 mL, 1.6 mol) and EtOH (1.5 L) at 0°C were added **5·K** (596 g, 3.1 mol) and 2-amino-6-methylpyridine (**4**, 108 g, 1.0 mol), and the whole was refluxed for 5 h. After cooling and concentration, AcOEt (1 L) was poured into the residue and extracted with water. The aqueous layer was neutralized with 2N-NaOH solution and extracted with AcOEt (1 L). The AcOEt extract was washed with water and concentrated in vacuo. EtOH was poured into the residue, and concentrated H_2SO_4 (51 mL) was added at 0°C. The resulting precipitates were collected by filtration, washed with IPE, and dried at room temperature to give **6·H_2SO_4** (194 g, 60% from **4**) as a white solid; mp 125–126°C. Anal. Calcd for $C_{11}H_{14}N_2O_6S$: C, 43.70; H, 4.67; N, 9.27; S, 10.61. Found: C, 43.47; H, 4.75; N, 9.16; S, 10.89. ^{1}H NMR (D_2O): δ 1.23 (t, *J*=7.1, 3H), 2.62 (s, 3H), 4.28 (d, *J*=7.1, 2H), 7.16 (d, *J*=7.3, 1H), 7.68 (d, *J*=8.9, 1H), 7.80 (dd, *J*=7.3, 8.9, 1H), 8.40 (s, 1H). IR (Nujol, cm^{-1}): 1732, 1655, 1552, 1531.

Ethyl 5-(chloromethyl)imidazo[1,2-*a*]pyridine-3-carboxylate sulfuric acid salt (3·H_2SO_4). After a suspension of **6·H_2SO_4** (2.50 kg, 8.3 mol) and AcOEt (25 L) was neutralized with 8N-NaOH, the AcOEt extract was concentrated. AcOEt (25 L) was poured into the residue, successively NCS (1.33 kg, 10.0 mol) and TFA (64.4 mL, 0.8 mol) were added. After the reaction mixture was stirred at 30°C for 2 h, 1N-HCl solution (10 L) was poured into the reaction mixture. The aqueous layer was neutralized with 30% NaOH solution (4.5 L) and extracted with IPE (50 L). The IPE extract was washed with water and concentrated in vacuo. MeCN (14 L) was poured into the residue, and concentrated H_2SO_4 (394 mL, 6.0 mol) was added at 0°C. The resulting precipitates were collected by filtration, washed with IPE, and dried at room temperature to give **3·H_2SO_4** (1.40 kg, 50%) as a white solid; mp 155–157°C. Anal. Calcd for $C_{11}H_{13}N_2O_6SCl$: C, 39.33; H, 3.89; N, 8.32; S, 9.52; Cl, 10.53. Found: C, 38.97; H, 3.92; N, 8.16; S, 9.59; Cl, 10.60. ^{1}H NMR (D_2O): δ 1.41 (t, *J*=7.2, 3H), 4.49 (d, *J*=7.1, 2H), 5.41 (s, 2H), 7.70 (d, *J*=5.4, 1H), 8.04–8.08 (m, 2H), 8.66 (s, 1H). IR (Nujol, cm^{-1}): 1731, 1651, 1550, 1529.

Oil **3** was held for one week at room temperature. The residue was separated by HPLC (column; SEP-PAK; Waters; mobile phase; acetonitrile–water (15:85); detective; 254 nm) to give **13** as a white solid. LC-MS (EI); 441 (M^+), 139 (M^+). Anal. Calcd for $C_{22}H_{22}N_4O_4Cl_2\cdot1.5H_2O$: C, 52.33; H, 5.00; N, 11.10; Cl, 14.04. Found: C, 52.39; H, 4.96; N, 11.10; Cl, 13.80. ^{1}H NMR ($CDCl_3$): δ 26 (t, *J*=7.1, 3H), 1.39 (t, *J*=7.1, 3H), 4.17 (q, *J*=7.1, 2H), 4.43 (q, *J*=7.1, 2H), 5.51 (s, 2H), 7.05 (s, 2H), 7.60 (dd, *J*=7.1, 8.8, 1H), 7.84 (d, *J*=8.8, 1H), 7.86 (d, *J*=7.1, 1H), 7.97 (d, *J*=6.6, 1H), 8.12 (s, 1H), 8.24 (dd, *J*=6.6, 6.9, 1H), 8.34 (s, 1H), 8.86 (d, *J*=9.1, 1H).

Benzyl 4-(3-oxo-3,5-dihydro-4*H*-1,4,8b-triazaacenaphthylen-4-yl)butylcarbamate (15). After 28% NaOMe in MeOH (2.32 L, 12.0 mol) was added to a suspension of **3·H_2SO_4** (1.35 kg, 4.0 mol), benzyl 4-aminobutylcarbamate hydrogenchloride (**14·HCl**, 1.04 kg, 4.0 mol) and DMF (6 L), triethylamine (560 mL) and NaI (600 g) was added. The reaction mixture was stirred at 40°C for 1 h. After cooling, water was poured into the reaction mixture, and extracted with AcOEt (14 L). The AcOEt extract was washed with water and concentrated in vacuo. The residue was triturated with AcOEt (2.4 L), collected by filtration, washed with IPE, and dried at room temperature to give **15** (1.13 kg, 75%) as a white solid; mp 108–110°C. Anal. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.81. Found: C, 66.61; H, 6.02; N, 14.78. ^{1}H NMR ($CDCl_3$): δ 1.59–1.73 (m, 4H), 3.26 (m, 2H), 3.57 (m, 2H), 4.96 (s, 2H), 5.09 (s, 2H), 6.70 (d, *J*=6.9, 1H), 7.24–7.34 (m, 7H), 7.49 (d, *J*=9.1, 1H), 8.15 (s, 1H). IR (Nujol, cm^{-1}):1709, 1660, 1537.

The following compounds were prepared in a manner similar to that for **15**:

4-Methyl-3,5-dihydro-4H-1,4,8b-triazaacenaphthylen-3-one (**1b**): A white solid, mp 171–172°C. Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.18; H, 4.54; N, 22.49. ^{1}H NMR ($CDCl_3$): δ 3.13 (s, 3H), 5.00 (s, 2H), 6.72 (d, *J*=7.0, 1H), 7.31 (dd, *J*=7.0, 9.1, 1H), 7.52 (d, *J*=9.1, 1H), 8.17 (s, 1H). IR (KBr, cm^{-1}):1631, 1556, 1538, 1313, 1151.

4-Butyl-3,5-dihydro-4H-1,4,8b-triazaacenaphthylen-3-one (**1c**): A light brown oil. EI-MS: 229 (M^+). ^{1}H NMR ($CDCl_3$): δ 0.98 (t, *J*=7.3, 3H), 1.42 (m, 2H), 1.65 (m, 2H), 3.58 (t, *J*=7.4, 2H), 5.00 (s, 2H), 6.73 (d, *J*=7.0, 1H), 7.31 (dd, *J*=7.0, 9.0, 1H), 7.52 (d, *J*=9.0, 1H), 8.17 (s, 1H). IR (neat, cm^{-1}):1637, 1536, 1465, 1336, 1301, 1213, 1153.

4-Benzyl-3,5-dihydro-4H-1,4,8b-triazaacenaphthylen-3-one (**1d**): A white solid, mp 141–142°C. Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.85; H, 4.84; N, 15.98. ^{1}H NMR ($CDCl_3$): δ 4.79 (s, 2H), 4.86 (s, 2H), 6.65 (d, *J*=7.0, 1H), 7.24–7.38 (m, 6H), 7.51 (d, *J*=9.1, 1H), 8.24 (s, 1H). IR (KBr, cm^{-1}):1650, 1535, 707.

4-(4-Chlorobenzyl)-3,5-dihydro-4H-1,4,8b-triazaacenaphthylen-3-one (**1e**): A white solid, mp 161–163°C. Anal. Calcd for $C_{16}H_{12}N_3OCl$: C, 64.54; H, 4.06; N, 14.11; Cl, 11.91. Found: C, 64.42; H, 4.05; N, 14.10; Cl, 11.80. ^{1}H NMR ($CDCl_3$): δ 4.76 (s, 2H), 4.86 (s, 2H), 6.67 (d, *J*=7.0, 1H), 7.24–7.35 (m, 5H), 7.53 (d, *J*=9.1, 1H), 8.24 (s, 1H). IR (KBr, cm^{-1}):1643, 1525, 1305, 1199, 781.

4-(4-Methoxybenzyl)-3,5-dihydro-4H-1,4,8b-triazaacenaphthylen-3-one (**1f**): A white solid, mp 138–139°C. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.57; H, 5.34; N, 14.26. ^{1}H NMR ($CDCl_3$): δ 3.80 (s,

3H), 4.73 (s, 2H), 4.84 (s, 2H), 6.65 (d, *J*=6.9, 1H), 6.89 (dd, *J*=6.6, 1.9, 1H), 7.24–7.33 (m, 4H), 7.51 (d, *J*=9.1, 1H), 8.23 (s, 1H). IR (KBr, cm^{-1}):1641, 1540, 1508, 1249, 742.

4-Phenyl-3,5-dihydro-4H-1,4,8b-triazaacenaphthylen-3-one (**1g**): A white solid, mp 219–220°C. Anal. Calcd for $C_{15}H_{11}N_3O{\cdot}0.1H_2O$: C, 71.75; H, 4.50; N, 16.73. Found: C, 71.86; H, 4.50; N, 16.73. ^1H NMR ($CDCl_3$): δ 5.36 (s, 2H), 6.79 (d, *J*=7.0, 1H), 7.30–7.50 (m, 6H), 7.61 (d, *J*=9.1, 1H), 8.30 (s, 1H). IR (KBr, cm^{-1}): 1643, 1527, 1502, 1303, 721.

Trifluoro-*N*-[4-(3-oxo-3,5-dihydro-4*H*-1,4,8b-triazaacenaphthylen-4-yl)butyl]methanesulfonamide (1a). To a solution of **15** (960 g, 2.5 mol) and MeOH (10 L) was added 5% Pd–C (100 g), and the suspension was stirred at 50°C for 6 h under hydrogen atmosphere. After cooling and Pd–C was removed by filtration, concentrated HCl (258 mL, 2.5 mol) was added and concentrated. MeOH (10 L) and THF (10 L) were added to the residue at 0–5°C and stirred for 4 h at the same temperature. The resulting precipitates were collected by filtration, washed with IPE, and dried at room temperature to give **16·HCl** (710 g, 97%) as a white solid. Concentration of the mother solution, successively recrystallization from EtOH yielded **20·HCl** as a white solid. **20·HCl** (18.7 g, 2%); mp. decomposition (223°C). Anal. Calcd for $C_{13}H_{15}N_4O_2Cl{\cdot}0.1H_2O$: C, 52.65; H, 5.17; N, 18.90; Cl, 11.97. Found: C, 52.45; H, 5.19; N, 18.66; Cl, 11.73. ^1H NMR (D_2O): δ 1.72–1.84 (m, 4H), 3.10–3.15 (m, 2H), 4.13–4.17 (m, 2H), 7.96 (dd, *J*=7.3, 9.1, 1H), 8.16–8.22 (m, 2H), 8.56 (s, 1H). IR (Nujol, cm^{-1}): 1656, 1627, 1545.

N-Phenyltrifluoromethanesulfonimide (1.24 kg, 3.5 mol) was added to a mixture of **16·HCl** (604 g, 2.2 mol), triethylamine (783 mL, 5.7 mol) and DMF (6.1 L). After the reaction mixture was stirred at room temperature for 1 h, AcOEt (5 L) was poured into the reaction mixture and extracted with 1N HCl (6 L×2). The aqueous layer was neutralized with 6N NaOH solution and extracted with 2-butanone–AcOEt (1: 1, 12 L×3). The organic extract was washed with water and concentrated in vacuo. The residue was triturated with AcOEt (3 L), collected by filtration, washed with IPE, and dried in vacuo at 40°C to give **1a** (505 g, 61%) as a white solid. Compound **1a** (90 g, 11%) was recovered from the mother solution; mp 176–178°C. Anal. Calcd for $C_{14}H_{15}N_4O_3SF_3$: C, 44.68; H, 4.02; N, 14.89. Found: C, 44.40; H, 3.97; N, 14.74. ^1H NMR ($CDCl_3$): δ 1.63–1.98 (m, 4H), 3.41 (m 2H), 3.63 (m, 2H), 5.02 (s, 2H), 6.74 (d, *J*=7.3, 1H), 7.33 (dd, *J*=7.3, 8.8, 1H), 7.54 (d, *J*=8.8, 1H), 8.18 (s, 1H). IR (Nujol, cm^{-1}): 1641, 1541, 1508.

Benzyl 4-{[(trifluoromethyl)sulfonyl]amino}butylcarbamate (17). To a mixture of **14** (3.50 g, 15.7 mmol), Et_3N (2.63 mL, 18.9 mmol), and MeCN (35 mL) was dropped Tf_2O (2.65 mL, 15.7 mmol) under 0°C, and the whole was stirred for 2 h at 0°C. After concentrated, AcOEt (40 mL) was poured into the residue and washed with water, 0.5N HCl solution, sat. $NaHCO_3$ solution, and brine. After concentration, the residue was triturated with petroleum ether, collected by filtration, washed with petroleum ether, and dried in vacuo at room temperature to give **17** (5.20 g, 93%) as a white solid; mp 45–46°C. Anal. Calcd for $C_{13}H_{17}N_2O_4SF_3$: C, 44.06; H, 4.80; N, 7.90. Found: C, 43.97; H, 4.94; N, 7.78. ^1H NMR ($CDCl_3$): δ 1.59 (m, 4H), 3.19–3.23 (m, 2H), 3.28 (m, 2H), 5.09 (s, 2H), 6.24 (brs, 1H), 7.35–7.39 (m, 5H). IR (Nujol, cm^{-1}): 3419, 1695, 1545.

***N*-(4-Aminobutyl)(trifluoro)methanesulfonamine (18).** To a solution of **17** (2.00 g, 5.5 mmol) and MeOH (20 mL) was added 10% Pd–C (0.20 g), and the suspension was stirred at room temperature for 2 h under hydrogen atmosphere. After Pd–C was removed by filtration, the mother solution was concentrated. The residue was triturated with IPE, collected by filtration, washed with IPE, and dried in vacuo at room temperature to give **18** (1.18 g, 95%) as a white solid; mp 110–114°C. Anal. Calcd for $C_5H_{11}N_2O_2SF_3$: C, 27.27; H, 5.03; N, 12.72. Found: C, 27.46; H, 5.14; N, 12.74. ^1H NMR ($CDCl_3$): δ 1.59–1.67 (m, 4H), 1.74–1.82 (m, 2H), 2.80–2.86 (m, 2H), 3.19–3.25 (m, 2H). IR (Nujol, cm^{-1}): 1628, 1543.

Ethyl 5-methyl-2-oxo-2,3-dihydroimidazo[1,2-a]pyridine-3-carboxylate (12). To a suspension of **6** (2.00 g, 9.8 mmol) and AcOH (20 mL) was added NCS (1.57 g, 11.8 mmol), and the whole was stirred for 4 h at room temperature. Water was poured into the reaction mixture and extracted with 2-butanol. After the 2-butanol extract was concentrated in vacuo to give a solid (0.81 g). The residue (300 mg) was purified by silica gel column chromatography (CH_2Cl_2–MeOH=4:1) to give **12** (280 mg, 35%) as a white solid; mp 126–128°C. Anal. Calcd for $C_{11}H_{12}N_2O_3{\cdot}0.1H_2O$: C, 59.50; H, 5.63; N, 12.62. Found: C, 59.47; H, 5.50; N, 12.75. ^1H NMR (DMSO-d_6): δ; keto:enol=1:1.16; keto form; 1.23 (t, *J*=7.3, 3H), 2.34 (s, 3H), 4.27 (q, *J*=7.3, 2H), 5.77 (s, 1H), 6.82 (d, *J*=7.3, 1H), 7.01 (d, *J*=7.3, 1H), 7.84 (dd, *J*=8.3, 7.3, 1H), enol form; 1.26 (t, *J*=7.3, 3H), 2.55 (s, 3H), 4.20 (q, *J*=7.3, 2H), 7.08 (d, *J*=7.3, 1H), 7.24 (d, *J*=7.3, 1H), 7.60 (dd, *J*=8.3, 7.3, 1H), 12.17 (bs, 1H). IR (Nujol, cm^{-1}): 1687, 1653, 1554, 1532.

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