Generation of 6-(Trifluoromethyl)-4,5-dihydro-2(3*H*)-pyridone and the Application to Synthesis of Some Fused Nitrogen Heterocycles Carrying a Trifluoromethyl Group on the Bridgehead Position via Radical Cyclization of Dihydropyridones

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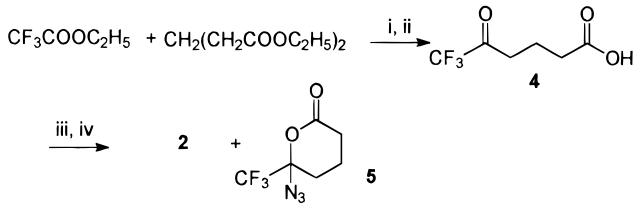
Staudinger/aza-Wittig reaction of 6,6,6-trifluoro-5-oxohexanoyl azide with PPh_3 or PBu_3 was examined. A reactive intermediate acyl imine **1** was trapped by methanol. Without nucleophile, isomerized enamide form **3** was obtained. *N*-Iodobenzoylation and *N*-haloalkylation of **3** and following radical cyclization via the 5-*exo* or 6-*exo* mode gave benzoindolizidinone, indolizidinone, and quinolizidinone derivatives **10**−**14**, which have a trifluoromethyl group at the bridgehead position adjacent to nitrogen. Although $LiAlH_4$ reduction of **10** and **11** gave a mixture of saturated benzoindolizidine **15** and amino alcohol **16**, reduction with BH_3/THF selectively gave the desired **15** and indolizidine **17** from **13**.

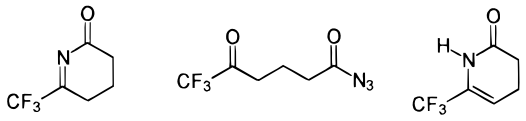
Trifluoromethylated nitrogen heterocycles are an attractive class of compounds because of their potential biological activities,[1] and many 5-membered and 6-membered aromatic nitrogen heterocycles have been prepared.[2−4] However, saturated compounds such as quinolizidines, indolizidines,[5] or pyrrolizidines[6] have been ignored by organofluorine chemists in spite of their wide range of biological activities observed among the naturally occurring alkaloids. Although these fused heterocycles are strong bases due to their rigid tertiary amine structures, introduction of a trifluoromethyl group near the nitrogen atom will reduce the basicity and may modify the biological activity. Since introduction of a trifluoromethyl group[7] into saturated heterocycles is considerably different from that into aromatic ones, we intended to develop a new general route to indolizidines and quinolizidines carrying a trifluoromethyl group on the bridgehead carbon of those skeletons, and 6-(trifluoromethyl)-4,5-dihydro-2(3*H*)-pyridone (**1**) was conceived as a reactive precursor to such fused heterocycles. In the last decade, we have been investigating the application of the Staudinger/aza-Wittig reaction of keto azides to cyclic imines,[8] and acyl imine should arise from the reaction of trifluoroketoacyl azide **2** with trialkylphosphines.[9]

Scheme 1[a]



[a] Key: (i) $NaOC_2H_5/C_2H_5OH$ reflux; (ii) 30% H_2SO_4/reflux; (iii) $SOCl_2$; (iv) $TMSN_3$.

We report here the formation of acyl imine **1** via Staudinger/aza-Wittig reaction and the further application of the obtained tautomerized product **3** to the synthesis of indolizidine and quinolizidine derivatives via radical cyclization.



Results and Discussion

(1) Staudinger/Aza-Wittig Reaction of 6,6,6-Trifluoro-5-oxohexanoyl Azide. As illustrated in Scheme 1, the starting keto acid, 6,6,6-trifluoro-5-oxohexanoic

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(2) 5-Membered-ring-nitrogen heterocycles: (a) Abdul-Ghani, M. M.; Tipping, A. E. *J. Fluorine Chem*. **1995**, *73*, 189. (b) Umada, A.; Okano, T.; Eguchi, S. *Synthesis* **1994**, 1457. (c) Meazza, G.; Zanardi, G. *J. Fluorine Chem*. **1994**, *67*, 183. (d) Barnes, K. D.; Hu, Y.; Hunt, D. A. *Synth. Commun*. **1994**, *24*, 1749. (e) Iwata, S.; Ishiguro, Y.; Utsugi, M.; Mitsuhashi, K.; Tanaka, K. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 2432. (f) Bouillon, J. P.; Ates, C.; Janousek, Z.; Viehe, H. G. *Tetrahedron Lett*. **1993**, *34*, 5075. (g) Takahashi, M.; Kotashima, H.; Saitoh, T. *Heterocycles* **1993**, *35*, 909. (h) Meazza, G.; Zanardi, G.; Piccardi, P. *J. Heterocycl. Chem*. **1993**, *30*, 365. (i) Okano, T.; Uekawa, T.; Morishima, N.; Eguchi, S. *J. Org. Chem*. **1991**, *56*, 5259.

(3) 6-Membered-ring-nitrogen heterocycles: (a) Eguchi, S.; Umada, A.; Okano, T. *Heterocycles* **1996**, *40*, 333. (b) Atkinson, R. S.; Coogan, P. M.; Cornell, C. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 157. (c) Bouillon, J. P.; Janousek, Z.; Viehe, H. G.; Tinant, B.; Declercq, J.-P. *Ibid*. **1995**, 2907. (d) Yamamoto, M.; Burton, D. J.; Swenson, D. C. *J. Fluorine Chem*. **1995**, *72*, 49. (e) Baumann, L.; Folkerts, A.; Imming, P.; Klindert, T.; Massa, W.; Steitz, G.; Wocadlo, S. *Liebigs Ann*. **1995**, 661. (f) Kobayashi, M.; Uneyama, K.; Hamada, N.; Kashino, S. *Tetrahedron Lett*. **1994**, *35*, 5235. (g) Bouillon, J. P.; Wynants, C.; Janousek, Z.; Viehe, H. G. *Heterocycles* **1994**, *37*, 915.

(4) A few examples of synthesis of CF_3-containing saturated nitrogen heterocycles have been also reported: Begue, J. P.; Bonnet-Delpon, D.; Lequeux, T. *Tetrahedron Lett*. **1993**, *34*, 3279.

(5) Michael, J. P. *Nat. Prod. Rep*. **1995**, *12*, 535.

(6) Robins, D. J. *Nat. Prod. Rep*. **1995**, *12*, 413.

(7) For a review on the synthesis of trifluoromethyl compounds, see: McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.

(8) (a) Okawa, T.; Eguchi, S. *Tetrahedron Lett*. **1996**, *37*, 81. (b) Okawa, T.; Eguchi, S.; Kakehi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 247. (c) Eguchi, S.; Yamashita, K.; Matsushita, Y.; Kakehi, A. *J. Org. Chem*. **1995**, *60*, 4006.

(9) Sasaki, T.; Eguchi, S.; Okano, T. *J. Am. Chem. Soc*. **1983**, *105*, 5912.

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acid (**4**), was prepared by Claisen condensation of ethyl trifluoroacetate and diethyl glutarate with sodium ethoxide followed by decarboxylative hydrolysis with 30% sulfuric acid as in Tatrow's preparation method for 5,5,5-trifluoro-4-oxopentanoic acid.[10] The total yield of the acid **4** from trifluoroacetate was 42% and somewhat lower than that of the latter acid. Although the succinate for the latter acid leads to a stable sodium enolate of the addition product that is difficult to deprotonate to a highly unstable conjugated dianion, the condensation product, diethyl 2-trifluoroacetylglutarate, still has a reactive site, which can be deprotonated to a nonconjugated dianion, and the further reaction with trifluoroacetate made the reaction more complicated and lowered the yield of the condensation product even if the equimolar amount of base was used. Conversion of acid **4** into acyl chloride with thionyl chloride followed by azidation with trimethylsilyl azide in THF gave a 1:1 mixture of desired acyl azide **2** and azido lactone **5** in 98% yield in total.[11] Contamination of **5** to **2** and the ratio were confirmed by the IR spectrum (1767 and 1717 cm^{-1} for **2** and 1782 cm^{-1} for **5**) and the ^1H NMR spectrum, in which the complicated absorptions of **5** were shown in addition to the simpler spectrum of **2**. Since acyl azide **2** was thermally unstable due to spontaneous Curtius reaction, the following reaction with trialkylphosphines was conducted without separation of **5** (Scheme 1).

At first, reaction of acyl azide **2** (1:1 mixture with lactone **5**) with triphenylphosphine was carried out in CH_3OH solution at room temperature. Accompanied by evolution of nitrogen indicating the formation of acyl iminophosphorane **6**, methoxy lactam **7** was isolated in 9% yield as a thermally unstable compound along with a nearly quantitative amount of triphenylphosphine oxide from the complex reaction mixture. As described in our earlier work,[9] cyclic acyl imine is a reactive intermediate, and the product seems to be isolated only as an adduct of an appropriate nucleophile such as methanol.

This was supported by the fact that cyclic enamide **3**, enamine−imine tautomer of cyclic imine **1**, was isolated in 49% yield with triphenylphosphine and in 34% yield with tributylphosphine, respectively, on the basis of the starting acid **4**, when this reaction was conducted in benzene without any nucleophile. Several attempts to obtain [4 + 2] adducts with some dienes including cyclopentadiene or Danishefsky diene were unsuccessful, and **3** was again isolated from the reaction mixture.

An alternative route employing the reaction of the 6,6,6-trifluoro-5-oxohexanoyl chloride and (trimethylsilylimine)triphenylphosphorane to avoid undesired formation of **5** gave a comparative yields of **3** (55% from PPh_3 and 38% from PBu_3) (Scheme 2).

(2) Radical Cyclization of Unsaturated Alkyl and Acyl Derivatives of Enamide 3. Although the acyl imine intermediate **1** was not isolated because of the spontaneous tautomerization, the enamide **3** can be still regarded as a precursor for the fused nitrogen heterocycles. Thus, **3** was derivatized with *o*-iodobenzoyl chloride and various haloalkylation reagents with a terminally halogenated side chain as summarized in Table 1. For activation of enamide nitrogen, sodium hydride was used. Nucleophilicity of amide nitrogen of **3** is somewhat declined by the trifluoromethyl group and the acylation, and alkylation reactions took long time to complete (several days for alkylation at room temperature). For the iodobenzylation of **3** with 2-iodobenzyl bromide, NaI was added for activation of benzyl bromide.[12]

Scheme 2

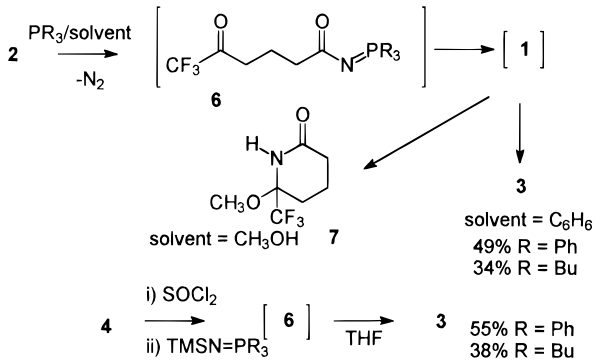
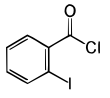
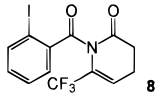
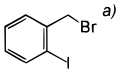
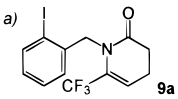
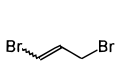
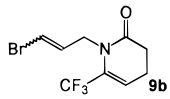
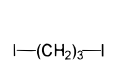
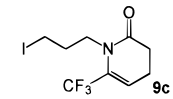
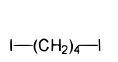
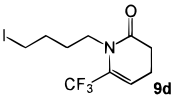


Table 1. Derivatization of Enamide 3

Halides	Products	Reaction temp.	Reaction time	Yields (%)
	 **8**	0 °C to r.t.	3 h	71
 *a)*	 **9a**	45 °C	2.5 d	60
	 **9b**	r.t.	3 d	77
	 **9c**	45 °C	3 d	60
	 **9d**	70 °C	2 d	76

a NaI was added for activation of benzyl bromide.

Radical cyclization of the *o*-iodobenzoyl derivative **8** and haloalkyl products **9a**−**d** with tributyltin hydride ($SnBu_3H$) and a catalytic amount of azobisisobutyronitrile (AIBN) gave the desired polycyclic products **10**−**14**, which were the normal 5-*exo* and 6-*exo* cyclization mode products, in good yields (Table 2).[13] To avoid simple reduction of halides, a benzene solution of $SnBu_3H$ and AIBN was slowly added into the reaction mixture and the reactions were completed in 8−10 h at 80 °C. Benzoindolizidindione **10** and benzoindolizidinone **11** were obtained from *o*-iodobenzoyl and *o*-iodobenzyl derivatives **8** and **9a**, respectively, in good yields. (*E*)- and (*Z*)-3-bromoallyl

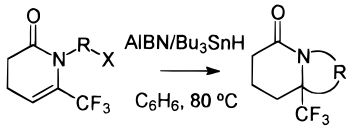
(10) Brown, P.; Burdon, J.; Tatrow, J. C. *Tetrahedron* **1960**, *10*, 164.

(11) The formation of azido lactone **5** was a result of the ring−chain tautomerism. Such an undesired formation of azido lactone was also observed in the preparation of *o*-acylbenzoyl azide: Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2149. For ring−chain tautomerism, see: Valters, R. E.; Flitsch, W. In *Ring−Chain Tautomerism*; Katritzky, A. R., Ed.; Plenum Press: New York, 1985.

(12) Rorig, K.; Johnston, J. D.; Hamilton, R. W.; Telinski, T. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 576.

(13) For reviews on free radicals in organic synthesis: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Jasperse, C. P.; Curran, D. P. *Chem. Rev.* **1991**, *91*, 1237. (c) Curran, D. P. *Synlett* **1991**, 63; (d) *Synthesis* **1988**, 417 and 489. (e) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

Table 2. Radical Cyclization of 8 and 9a−d with AIBN and Bu_3SnH



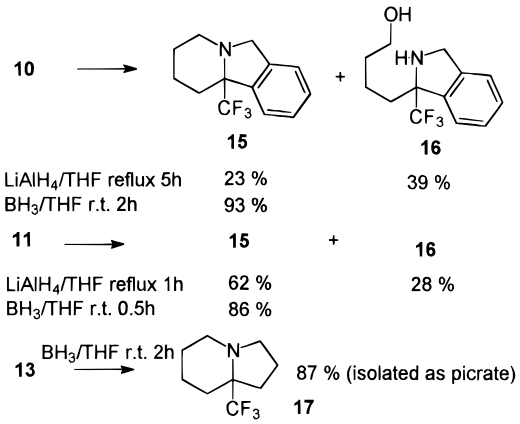
entry	Substrates	Products	Yield (%)
1	**8**	**10**	97
2	**9a**	**11**	92
3	**9b**$_{E,Z}$	**12**	64 from *E* 65 from *Z*
4	**9c**	**13**	84
5	**9d**	**14**	50

derivatives **9b**$_{E,Z}$ were separated by SiO_2 chromatography, and radical cyclization was conducted as the pure isomer forms. However, both *E*- and *Z*-isomers gave the same cyclization product **12** in almost the same yield (64 and 65%), indicating the fast inversion of vinyl radical or structural change from sp^2 radical to p radical (sp carbon). This cyclization of a vinyl radical intermediate may be important for synthesis of 1-/2-substituted indolizidine analogs. Both 3-iodopropyl and 4-iodobutyl derivatives afforded the saturated indolizidinone **13** and quinolizidinone **14**, respectively. However, the yield of quinolizidinone **14** is relatively lower (50%) than those of other cyclized products **10**−**13**, and a trace amount of the open-chain simple reduction product was also found in the reaction mixture. This is consistent with the previously reported less favored nature of the 6-*exo* radical cyclization.[14]

Reduction of the cyclized products to the alkaloid-related saturated compounds were firstly attempted with $LiAlH_4$. However, as the example of the reduction of **10**, a substantial amount of open-chain hydroxybutyl derivative **16** (39%) was isolated along with the desired tricyclic **15** (23%). The reduced basicity of the nitrogen caused by the adjacent CF_3 group makes the intermediate aminal (the first step in the reduction) unreactive for imine formation (the second intermediate to **15**), and it breaks down to the corresponding aldehyde, which is immediately reduced to **16**. Finally, more selective reduction of these cyclic amides and imides were achieved by BH_3/THF complex at room temperature. In this method, indolizidine **17** was also obtained in good yield (Scheme 3).

It is interesting that this cyclization strategy of haloalkyl dihydropyridone to indolizidine derivatives was also introduced by Shibasaki and co-workers recently.[15] Even without the trifluoromethyl group, cyclic acyl imine (dihydropyridone) is unstable and tautomerizes to the enamide form. Although the acyl imine intermediate cannot be used as a synthetic intermediate directly, the aza-Wittig route to dihydropyridone is still useful to prepare indolizidine and quinolizidine compounds with a trifluoromethyl group. Physical and biological properties of the trifluoromethylated cyclic amines are under investigation.

Scheme 3



Experimental Section

^1H and ^{13}C-NMR spectra of $CDCl_3$ or DMSO-d_6 solutions were recorded at 200 and 40 MHz with TMS as an internal standard. ^{19}F NMR spectra of $CDCl_3$ or DMSO-d_6 were recorded at 87.67 MHz. Chemical shifts of the ^{19}F NMR spectra were reported in ppm (δ) relative to internal $CFCl_3$.

6,6,6-Trifluoro-5-oxohexanoic Acid (4). Sodium (12.6 g, 663 mmol) was dissolved in anhydrous ethanol (140 mL). At 0 °C, ethyl trifluoroacetate (77.6 g, 546 mmol) was added in one portion to the above ethanol solution. Diethyl glutarate (25.0 g, 133 mmol) was added to the resulting solution, and the mixture was heated at 70 °C for 3 h. Then, diethyl glutarate (25.0 g, 133 mmol) was added to the mixture again, and the mixture was heated overnight at 70 °C. After cooling, 20% H_2SO_4 (300 mL) was added to the mixture, and then the mixture was extracted with Et_2O (150 mL × 4). Removal of the solvent under reduced pressure gave a crude product. Without purification, to the obtained ester was added 30% H_2SO_4 (300 mL), and the mixture was heated at reflux for 7 h. After cooling, the mixture was poured onto ice−water and extracted with Et_2O (100 mL × 4). The combined extracts were successively washed with saturated aqueous NaCl and water. The Et_2O solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Distillation gave pure carboxylic acid **4** as a colorless solid (20.5 g, 42%): bp 62−5 °C (4 Torr); mp 34−7 °C; ^1H NMR ($CDCl_3$) 2.02 (quint, J = 7.1 Hz, 2H), 2.47 (t, J = 7.1 Hz, 2H), 2.85 (t, J = 7.1 Hz, 2H), 10.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 17.28, 32.38, 35.27, 115.80 (q, J = 291 Hz), 179.60, 191.41 (q, J = 35 Hz); ^{19}F NMR ($CDCl_3$) −79.9 (s); IR (neat film) 1765, 1713 cm^{-1}; CI-MS *m/z* 185 ($M + H^+$, 100), 167 (13). Anal. Calcd for $C_6H_7F_3O_3$: C, 39.14; H, 3.83. Found: C, 39.02; H, 3.92.

6,6,6-Trifluoro-5-oxohexanoyl Azide (2). Carboxylic acid **4** (3.70 g, 20.0 mmol) was dissolved in oxalyl chloride (8 mL), and the solution was stirred for 2.5 h at room temperature. The excess of oxalyl chloride was removed under reduced pressure (IR (neat film) 1796, 1767 cm^{-1}). The residue was dissolved in anhydrous THF (10 mL), and trimethylsilyl azide (5 mL) was added dropwise at 0 °C to the solution. The mixture was stirred for 2 h at room temperature, and the

(14) 6-*exo*-Cyclization of 6-heptenyl radical is 100 times as slow as 5-*exo* cyclization of 5-hexenyl radical: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons: Chichester, 1995; p 152.

(15) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965.

solvent was removed under reduced pressure to give a 1:1 mixture of acyl azide **2** and cyclic azide **5**: ^{1}H NMR ($CDCl_3$) 1.88−2.15 (m, 4 H × 1/2), 2.02 (quint, J = 7.0 Hz, 2 H × 1/2), 2.40−2.66 (m, 1 H × 1/2), 2.45 (t, J = 7.0 Hz, 2 H × 1/2), 2.72−2.90 (m, 1 H × 1/2), 2.84 (t, J = 7.0 Hz, 2 H × 1/2); IR (neat film) 2135, 1782, 1767, 1717 cm^{-1}. This mixture was used for further reaction without purification.

6-Methoxy-6-(trifluoromethyl)-2-piperidinone (7). The mixture of **2** and **5** prepared from acid **4** (184 mg, 1.00 mmol) as above was dissolved in anhydrous methanol (6 mL). To the solution was added PPh_3 (300 mg, 1.14 mmol), and the resulting mixture was stirred at room temperature for 2 h. Removal of the solvent under reduced pressure and chromatography on a SiO_2 column (2:1 hexane−EtOAc) gave PPh_3O (274 mg, 98%) and **7** as a thermally unstable solid (17 mg, 9%): ^{1}H NMR ($CDCl_3$) 2.02 (m, 4H), 2.44 (m, 2 H), 3.39 (q, J = 0.8 Hz, 3 H), 6.70 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 16.70, 26.28, 31.19, 50.93, 85.68 (q, J = 31 Hz), 123.85 (q, J = 287 Hz), 173.56; IR (KBr) 1688 cm^{-1}; CI-MS m/z 198 (M + H$^+$; 100), 184 (33).

6-(Trifluoromethyl)-4,5-dihydro-2(1*H*)-pyridone (3). Method A. Acyl azide **2** prepared from keto acid **4** (3.7 g, 20 mmol) as above was dissolved in benzene (200 mL), and then triphenylphosphine (6.3 g, 24 mmol) was added in one portion. After the solution was stirred for 5 h at room temperature, the solvent was removed under reduced pressure to give a mixture. The residue was sublimed at 80−100 °C (0.2 Torr), and collected solid was recrystallized from Et_2O to give pure **3**: 1.52 g (49%); ^{1}H NMR ($CDCl_3$) 2.41−2.60 (m, 4 H), 5.71−5.79 (m, 1 H), 8.52 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 19.59, 29.39, 107.77 (q, J = 5 Hz), 120.32 (q, J = 271 Hz), 128.63 (q, J = 35 Hz), 171.56; ^{19}F NMR ($CDCl_3$) −71.0 (s); IR (KBr) 1709, 1688 cm^{-1}; EI-MS m/z 165 (M$^+$, 100), 137 (42). Anal. Calcd for $C_6H_6F_3NO$: C, 43.65; H, 3.66; N 8.48. Found: C, 43.76; H, 3.49; N, 8.43.

Method B. Acyl chloride prepared from acid **4** (184 mg, 1 mmol) was dissolved to anhydrous THF (2 mL), and then (trimethylsilyl)iminophosphorane (3.54 g, 2.34 mmol) was added in one portion. The resulting mixture was stirred for 1 h at room temperature and then diluted with water (10 mL). The mixture was extracted with Et_2O, and the combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was separated on a preparative SiO_2 TLC plate (hexane−EtOAc 1:1) to give pure **3** (90 mg, 55%).

1-(2′-Iodobenzoyl)-6-(trifluoromethyl)-3,4-dihydro-2(1*H*)-pyridone (8). To a solution of **3** (248 mg, 1.50 mmol) in THF (5 mL) was added NaH (66 mg, 1.65 mmol; 60% oil dispersion) in one portion at 0 °C. The resulting suspension was stirred for 1 h at room temperature. To the suspension was added *o*-iodobenzoyl chloride (600 mg, 2.25 mmol) and then the mixture was stirred for 3 h at room temperature. The mixture was poured into water and was extracted with CH_2Cl_2 after neutralization of the solution with hydrochloric acid. The combined extracts were dried over $MgSO_4$. The solvents were removed under reduced pressure, and the residue was chromatographed on a silica gel preparative TLC plate to give pure **8** as a colorless solid: 420 mg (71%); mp 114−5 °C; ^{1}H NMR ($CDCl_3$) 7.95 (ddd, J = 7.9, 1.0, 0.5 Hz, 1H), 7.43−7.48 (m, 2H), 7.40 (ddd, J = 7.9, 6.6, 1.0 Hz, 1H), 7.16 (ddd, J = 7.9, 6.6.1.5 Hz, 1H), 6.49−6.58 (m, 1H), 2.50−2.70 (m, 4H); ^{13}C NMR ($CDCl_3$) 19.61, 32.78, 120.73 (q, J = 273 Hz), 122.64 (q, J = 3.9 Hz), 128.36, 129.45, 132.49, 141.01, 140.83, 132.81, 132.81 (q, J = 36 Hz), 170.92, 170.98; IR (KBr) 1709 cm^{-1}; ^{19}F NMR ($CDCl_3$) −61.1 (s); CI-MS m/z 396 (M + H$^+$, 25), 231 (100). Anal. Calcd for $C_{13}H_9F_3INO_2$: C, 39.52; H, 2.30; N, 3.54. Found: C, 39.51; H, 2.24; N, 3.35.

1-(2′-Iodobenzyl)-6-(trifluoromethyl)-3,4-dihydro-2(1*H*)-pyridone (9a). A mixture of **3** (198 mg, 1.20 mmol), 2-iodobenzyl bromide (891 mg), NaH (60% oil dispersion: 58 mg, 1.44 mmol), and NaI (450 mg, 3.00 mmol) in THF (5 mL) was stirred at 45 °C for 60 h. The mixture was worked up as in the above case to obtain **9a** as a colorless solid: 274 mg (60%); mp 82−83 °C; ^{1}H NMR ($CDCl_3$) 7.84 (dd, J = 7.2, 1.2 Hz, 1H), 7.83 (td, J = 7.6, 1.3 Hz, 1H), 6.95 (t-like m, 1 H), 6.85 (d-like m, 1H), 6.16 (tq, J = 4.8, 0.7 Hz, 1H), 4.88 (s, 2H), 2.65−2.73 (m, 2H), 2.46−2.61 (m, 2H); ^{13}C NMR ($CDCl_3$) 19.19, 30.75, 51.32 (q, J = 2.6 Hz), 97.12, 114.33 (q, J = 5.7 Hz), 120.47 (q, J = 272 Hz), 125.46, 128.65, 128.99, 131.88 (q, J = 33 Hz), 138.79, 139.90, 170.46, 170.46; ^{19}F NMR ($CDCl_3$) −65.2 (s); 1688 cm^{-1}; CI-MS m/z 383 (M + 1 + H$^+$, 14), 382 (M + H$^+$, 100). Anal. Calcd for $C_{13}H_{11}F_3INO$: C, 40.97; H, 2.91; N, 3.68. Found: C, 40.88; H, 2.77; N, 3.76.

(*E*)- and (*Z*)-1-(3-Bromoprop-2-enyl)-6-(trifluoromethyl)-3,4-dihydro-2(1*H*)-pyridone (9b$_E$ and 9b$_Z$). As similar as above, a mixture of **3** (132 mg, 0.8 mmol), 1,3-dibromopropene (7:3 *E*,*Z*-mixture: 0.2 mL, *ca*. 2 mmol), and NaH (60% oil dispersion: 39 mg, 0.96 mmol) in THF (3 mL) was treated to give a mixture of **9b$_E$** and **9b$_Z$**, which were separated by SiO_2 preparative TLC (CH_2Cl_2).

9b$_E$: 123 mg (54%); colorless oil; ^{1}H NMR ($CDCl_3$) 6.34 (d, J = 6.0 Hz, 1H), 6.19 (dt, J = 13.8, 6.0 Hz, 1H), 6.09 (tq, J = 4.8, 0.8 Hz, 1H), 4.25 (d, J = 6.0 Hz, 2H), 2.60−2.52 (m, 2H), 2.33−2.48 (m, 2H); ^{13}C NMR ($CDCl_3$) 19.05, 30.70, 44.01 (q, J = 2.7 Hz), 110.14, 114.55 (q, J = 5.8 Hz), 120.66 (q, J = 272 Hz), 131.15 (q, J = 33 Hz), 132.12, 170.19; ^{19}F NMR ($CDCl_3$) −64.7 (s); IR (neat film) 1694 cm^{-1}; MS m/z 285 (M$^+$ + 2, 4), 283 (M$^+$, 4), 205 (18), 204 (100). Anal. Calcd for $C_9H_9BrF_3NO$: C, 38.05; H, 3.19; N, 4.93. Found: C, 38.09; H, 3.49; N, 4.60.

9b$_Z$: 52 mg (23%); colorless oil; ^{1}H NMR ($CDCl_3$) 6.28 (dt, J = 7.2, 1.9 Hz, 1H), 6.01−6.12 (m, 2H), 4.45 (dd, J = 5.2, 1.9 Hz, 2H), 2.54−2.62 (m, 2H), 2.33−2.48 (m, 2H); IR (neat film) 1694 cm^{-1}.

***N*-(3-Iodopropyl)-6-(trifluoromethyl)-3,4-dihydro-2(1*H*)-pyridone (9c).** Following the procedure described above, **9c** was obtained from a mixture of **3** (248 mg, 1.50 mmol), 1,3-diiodopropane (0.86 mL, *ca*. 7.5 mmol), and NaH (60% oil dispersion: 66 mg, 1.65 mmol) in THF (3 mL) as a thermally unstable colorless oil that turned brown on standing: 300 mg (60%); ^{1}H NMR ($CDCl_3$), 6.093 (tq, J = 4.8, 1.0 Hz, 1H), 3.73 (t, J = 7.2 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H), 2.56−2.50 (m, 2H), 2.46−2.28 (m, 2H), 2.11 (quint, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) 1.06, 19.07, 30.83, 32.42, 44.03 (q, J = 2.4 Hz), 114.56 (q, J = 5.9 Hz), 120.71 (q, J = 272 Hz), 131.52 (q, J = 32 Hz), 170.62; IR (neat film) 1696 cm^{-1}.

***N*-(4-Iodobutyl)-6-(trifluoromethyl)-3,4-dihydropyridin-2-one (9d).** Following the procedure described abve, **9d** was obtained from a mixture of **3** (165 mg, 1.00 mmol), 1,4-diiodobutane (0.66 mL, *ca*. 5.5 mmol), and NaH (60% oil dispersion: 44 mg, 1.1 mmol) in THF (3 mL) as a colorless oil: 264 mg (76%); ^{1}H NMR ($CDCl_3$), 6.10 (td, J = 4.9, 1.0 Hz, 1 H), 3.69 (t, J = 7.2 Hz, 2H), 3.19 (t, J = 7.0 Hz, 2H), 2.57−2.49 (m, 2H), 2.45−2.30 (m, 2H), 1.91−1.76 (m, 2H), 1.73−1.58 (m, 2H); ^{13}C NMR ($CDCl_3$) 5.67, 19.06, 29.68, 30.86, 30.91, 41.79 (q, J = 2.6 Hz), 114.70 (q, J = 5.9 Hz), 120.76 (q, J = 272 Hz), 131.62 (q, J = 32 Hz), 170.52; ^{19}F NMR ($CDCl_3$) −64.9 (s), IR (neat film) 1694 cm^{-1}; MS m/z 347 (M$^+$, 32), 220 (100). Anal. Calcd for $C_{10}H_{13}F_3INO$: C, 34.60; H, 3.78; N, 4.04. Found: C, 34.98; H, 3.82; N, 4.01.

10b-(Trifluoromethyl)-1,2-dihydro[2,1-*a*]isoindole-4,6-(3*H*,10b*H*)-dione (10). To a refluxing solution of **8** (316 mg, 0.80 mmol) in benzene (11 mL) was added a solution of AIBN (12 mg, 80 μmol) and Bu_3SnH (0.44 mL, *ca*. 1.6 mmol) in benzene (11 mL) dropwise over 5 h, and the resulting solution was further refluxed for 5 h. The solvent was removed under reduced pressure, and the residue was dissolved to Et_2O (20 mL) and 50% aqueous KF solution (5 mL). The mixture was stirred for 1 h at room temperature. Then the mixture was separated, and the aqueous layer was washed with Et_2O several times. The Et_2O extracts were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on a preparative SiO_2 TLC (1:1 hexane−EtOAc) to give pure **10** as a colorless solid: 207 mg (97%); mp 150−151 °C; ^{1}H NMR ($CDCl_3$) 8.00 (ddd, J = 7.4, 1.3, 0.8 Hz, 1H), 7.71 (td, J = 7.4, 1.3 Hz, 1H), 7.69−7.57 (m, 2H), 2.91−2.67 (m, 3H), 2.42−2.17 (m, 1H), 2.13−1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) 17.59 (q, J = 1.9 Hz), 27.47, 32.49, 67.00 (q, J = 29 Hz), 125.11 (q, J = 285 Hz), 122.93, 126.14, 130.05, 131.15, 135.07, 142.15, 165.74, 169.36; ^{19}F NMR ($CDCl_3$) −74.3 (s); IR (KBr) 1773, 1692 cm^{-1}; MS m/z

269 (M^+, 96), 201 (47), 200 (100). Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 57.87; H, 3.79; N, 5.18.

10b-(Trifluoromethyl)-1,2,6,10b-tetrahydropyrido[2,1-*a*]isoindol-4(3*H*)-one (11). Following the procedure described for the synthesis of **10**, **11** was obtained from a solution of **9a** (229 mg, 0.60 mmol) in benzene (9 mL) and a solution of AIBN (8 mg, 50 μmol) and Bu_3SnH (0.33 mL, *ca*. 1.2 mmol) in benzene (9 mL): 140 mg (92%); colorless solid; mp 100−101 °C; ^{1}H NMR ($CDCl_3$) 7.47−7.31 (m, 4H), 5.18 (d, J = 15.4 Hz, 1H), 4.62 (d, J = 15.4 Hz, 1H), 2.80−2.40 (m, 3H), 2.36−2.12 (m, 1H), 2.04−1.80 (m, 2H); ^{13}C NMR ($CDCl_3$) 17.14 (q, J = 1.8 Hz), 27.80, 29.78, 51.95, 69.91 (q, J = 28 Hz), 126.43 (q, J = 287 Hz), 123.15 (2C), 128.26, 130.05, 138.10, 138.44, 170.90; ^{19}F NMR ($CDCl_3$) −76.0 (s); IR (KBr) 1655 cm^{-1}; MS *m*/*z* 256 (M^+ + 1, 15), 255 (M^+, 92), 186 (100). Anal. Calcd for $C_{13}H_{12}F_3NO$: C, 61.18; H, 4.74; N, 5.49. Found: C, 61.20; H, 4.64; N, 5.75.

8a-(Trifluoromethyl)-3,7,8,8a-tetrahydro-5(6*H*)-indolizinone (12). Following the procedure described for the synthesis of **10**, **12** was obtained from a solution of **9b*E*** (142 mg, 0.50 mmol) in benzene (8 mL) and a solution of AIBN (8 mg, 50 μmol) and Bu_3SnH (0.27 mL, *ca*. 1.0 mmol) in benzene (8 mL): 66 mg (64%); colorless oil; ^{1}H NMR ($CDCl_3$) 6.22 (dt, J = 6.3, 1.9 Hz, 1H), 5.77 (dt, J = 6.3, 2.2 Hz, 1H), 4.67 (ddd, J = 16.4, 2.2, 1.9 Hz, 1H), 4.13 (ddd, J = 16.4, 2.2, 1.9 Hz, 1H), 2.66−2.36 (m, 3 H), 2.24−1.99 (m, 1H), 1.92−1.63 (m, 2H); ^{13}C NMR ($CDCl_3$) 16.50, 26.71, 29.36, 54.22, 71.34 (q, J = 29 Hz), 126.36 (q, J = 286 Hz), 127.94, 131.63, 171.14; ^{19}F NMR ($CDCl_3$) −76.7 (s); IR (neat film) 1669 cm^{-1}; MS *m*/*z* 205 (M^+, 1), 136 (100). Anal. Calcd for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.68; H, 5.16; N, 6.58.

As similar as above, **12** was also obtained from **9b*Z*** (23 mg, 82 μmol), Bu_3SnH (45 μL, *ca*. 0.17 mmol), and AIBN (1.5 mg, 9 μmol): 11 mg (65%).

8a-(Trifluoromethyl)-1,2,3,7,8,8a-hexahydro-5(6*H*)-indolizinone (13). Following the procedure described for the synthesis of **10**, **13** was obtained from a solution of **9c** (100 mg, 0.30 mmol) in benzene (5 mL) and a solution of AIBN (5 mg, 30 μmol) and Bu_3SnH (0.16 mL, *ca*. 0.6 mmol) in benzene (5 mL): 52 mg (84%); colorless oil; ^{1}H NMR ($CDCl_3$) 4.08−3.94 (m, 1H), 3.47 (ddd, J = 12.1, 9.6, 4.5 Hz, 1H), 2.59−2.29 (m, 4H), 2.16−1.41 (m, 6H); ^{13}C NMR ($CDCl_3$) 17.43, 20.25 (q, J = 1.7 Hz), 29.55, 29.72, 35.95, 46.20, 65.85 (q, J = 27 Hz), 127.32 (q, J = 287 Hz), 171.04; ^{19}F NMR ($CDCl_3$) −75.7 (s); IR (neat film) 1659 cm^{-1}; MS *m*/*z* 207 (M^+, 15), 138 (100). Anal. Calcd for $C_9H_{12}F_3NO$: C, 52.17; H, 5.84; N, 6.76. Found: C, 52.13; H, 6.00; N, 6.64.

9a-(Trifluoromethyl)-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizin-4-one (14). Following the procedure described for the synthesis of **10**, **14** was obtained from a solution of **9d** (104 mg, 0.30 mmol) in benzene (5 mL) and a solution of AIBN (5 mg, 30 μmol) and Bu_3SnH (0.16 mL, *ca*. 0.6 mmol) in benzene (5 mL): 33 mg (50%); colorless oil; ^{1}H NMR ($CDCl_3$) 4.72 (dqt, J = 13.0, 2.3, 1.3 Hz, 1H), 2.75 (br t, J = 13.0 Hz, 1H), 2.48 (t, J = 6.6 Hz, 2H), 2.25−2.05 (m, 2H), 1.96−1.34 (m, 8H); ^{13}C NMR ($CDCl_3$) 16.85 (q, J = 1.9 Hz), 20.25, 24.20, 32.22, 33.16, 38.53, 60.42 (q, J = 25 Hz), 127.72 (q, J = 290 Hz), 171.76; ^{19}F NMR ($CDCl_3$) −70.5; IR (neat film) 1653 cm^{-1}; MS *m*/*z* 222 (M^+ + 1, 12), 221 (M^+, 89), 152 (100). Anal. Calcd for $C_{10}H_{14}F_3NO$: C, 54.29; H, 6.38; N, 6.33. Found: C, 54.33; H, 6.63; N, 6.04.

10b-(Trifluoromethyl)-1,2,3,4,6,10b-hexahydropyrido-[2,1-*a*]isoindole (15). To a stirred solution of **10** (54 mg, 0.20 mmol) in THF (1 mL) was added BH_3/THF solution (1.0 M; 2 mL, 2.0 mmol) dropwise at −20 °C in 5 min, and then the solution was stirred at room temperature for 2 h. To the solution was added MeOH (2 mL), and the solvents were removed under reduced pressure. The pure amine **15** was obtained by preparative TLC (SiO_2, 1:1 hexane−EtOAc) as a colorless oil: 33 mg (50%); ^{1}H NMR ($CDCl_3$) 7.37−7.21 (m, 4H), 4.40 (d, J = 13.4 Hz, 1H), 4.20 (d, J = 13.4 Hz, 1H), 3.26 (br t, J = 14.8 Hz, 1H), 2.97 (br d, J = 14.8 Hz, 1H), 2.30−2.20 (m, 1H), 1.78−1.40 (m, 5H); ^{13}C NMR ($CDCl_3$) 18.74, 19.19, 27.95, 45.75, 57.34, 69.39 (q, J = 27 Hz), 122.84 (q, J = 7.2 Hz), 122.92, 127.65, 128.60, 139.95, 127.75 (q, J = 285 Hz), 141.58; MS *m*/*z* 241 (M^+, 7), 172 (100). Anal. Calcd for $C_{13}H_{14}F_3N$: C, 64.72; H, 5.85; N, 5.81. Found: C, 64.98; H, 5.74; N, 5.66.

$LiAlH_4$ Reduction of 10. To a stirred suspension of $LiAlH_4$ (35 mg, 0.9 mmol) in THF (2 mL) was added a solution of **10** (34 mg, 0.12 mmol) in THF (1 mL) at room temperature. The resulting mixture was refluxed for 4 h and then diluted with H_2O (25 mL). After addition of 20% aqueous NaOH (25 μL) and stirring for 30 min at room temperature, Et_2O (4 mL) and $MgSO_4$ were added into the mixture. Filtration and removal of the solvents followed by chromatography on a SiO_2 TLC plate (1:1 hexane−EtOAc) gave **15** (7 mg, 23%) and **16** (10 mg, 39%): colorless oil; ^{1}H NMR ($CDCl_3$) 7.39−7.23 (m, 4H), 4.45 (d, J = 13.8 Hz, 1H), 4.32 (d, J = 13.8 Hz, 1H), 3.62 (dt, J = 10.6, 6.4 Hz, 1H), 3.56 (dt, J = 10.6, 6.2 Hz, 1H), 2.10 (ddd, J = 14.0, 11.5, 5.5 Hz, 1H), 1.94 (ddd, J = 14.0, 11.7, 5.5 Hz, 1H), 1.761 (s, 2H), 1.54 (m, 2H), 1.41−1.24 (m, 1H), 1.16−0.93 (m, 1H); ^{13}C NMR ($CDCl_3$) 19.28, 32.68, 33.19, 52.16, 62.48, 72.75 (q, J = 27 Hz), 123.04, 123.83, 127.63, 127.65 (q, J = 285 Hz), 129.16, 137.71, 142.87; MS *m*/*z* 259 (M^+, 5), 186 (100). Anal. Calcd for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.22; N, 5.40. Found: C, 60.43; H, 6.09; N, 5.33.

8a-(Trifluoromethyl)indolizidine (17). To a stirred solution of **13** (39 mg, 0.2 mmol) in THF (1 mL) was added BH_3/THF solution (1.0 M; 2 mL, 2.0 mmol) dropwise. After the solution was stirred for 2 h at room temperature, workup as above gave crude **17** as a colorless oil. Picric acid EtOH solution (*ca*. 5%, 1 mL) was added to the crude **17**, and the resulting precipitates were collected. Recrystallization from MeOH gave **17**·picrate as yellow solid: 70 mg (87%); mp 176−180 °C dec; ^{1}H NMR ($CDCl_3$) 8.92 (s, 2H), 4.04 (ddd, J = 11.8, 8.8, 5.2 Hz), 3.78−3.37 (m, 3H), 2.71−2.49 (m, 2H), 2.31−1.76 (m, 8H); ^{13}C NMR ($CDCl_3$) 17.64, 17.81, 19.47, 25.43, 32.08, 48.43, 53.03, 68.98 (q, J = 28 Hz), 125.19 (q, J = 284 Hz), 129.21, 127.03, 141.89, 162.19; IR (KBr) 1634, 1562, 1366, 1273, 1175, 710 cm^{-1}; CI-MS *m*/*z* 194 (M + H$^+$, 100). Anal. Calcd for $C_{15}H_{17}F_3N_4O_7$: C, 42.66; H, 4.06; N, 13.27. Found: C, 42.44; H, 3.98; N, 13.57.

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