Heterocyclization of 5-Trifluoroacetyltricyclo[4.3.1.1^{3,8}]undecan-4-one to Some Trifluoromethylated 5-Membered Nitrogen Heterocycles[1]

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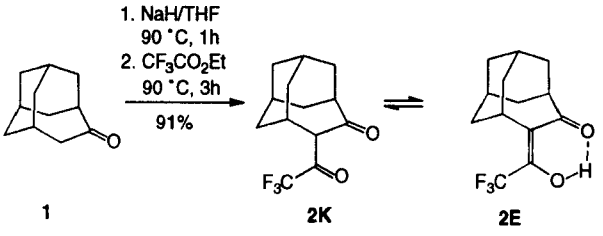
Heterocyclization of 5-trifluoroacetyltricyclo[4.3.1.1^{3,8}]undecan-4-one into isoxazole and pyrazole derivatives as a novel type of trifluoromethylated 5-membered nitrogen heterocycles is reported.

An increasing interest has been paid for several years to the chemistry of organic trifluoromethyl compounds due to their unique physical properties, specific chemical reactivity, and their remarkable potential biological activity.[2] The synthesis of trifluoromethyl heterocycles using a readily available building block with a trifluoromethyl group has often been found to be superior to either selective introduction of a trifluoromethyl group into heterocyclic compounds or conversion of a carboxy group into the trifluoromethyl group.[3] As an extension of our studies on the synthesis of heterocycles fused with polycyclic skeletons,[4] we report in this paper heterocyclization of the titled 1,3-diketones readily derived from 4-homoadamantanone, which provided a facile route to some trifluoromethylated derivatives of homoadamantano [4,5]fused 5-membered nitrogen heterocycles.

Trifluoroacetylation of 4-homoadamantanone (tricyclo[4.3.1.1^{3,8}]undecan-4-one) (**1**) with sodium hydride and ethyl trifluoroacetate in THF at 90°C for 3 h in a sealed tube afforded 5-trifluoroacetyl derivative **2** as colorless crystals in 91% yield after chromatography on silica gel. In $CDCl_3$, **2** revealed a very low field signal at $\delta = 16.3$ (s, 1H, OH) in the ^{1}H NMR spectrum, and characteristic signals at $\delta = 119.05$ (q, $^1J_{C,F} = 282$ Hz, CF_3), 169.73 (q, $^2J_{C,F} = 34$ Hz, =COH), and 208.71 (s, C=O) in the ^{13}C NMR spectrum,[5] indicating the shown enolic form **2E** (100%) as the major tautomeric form (Scheme 1).

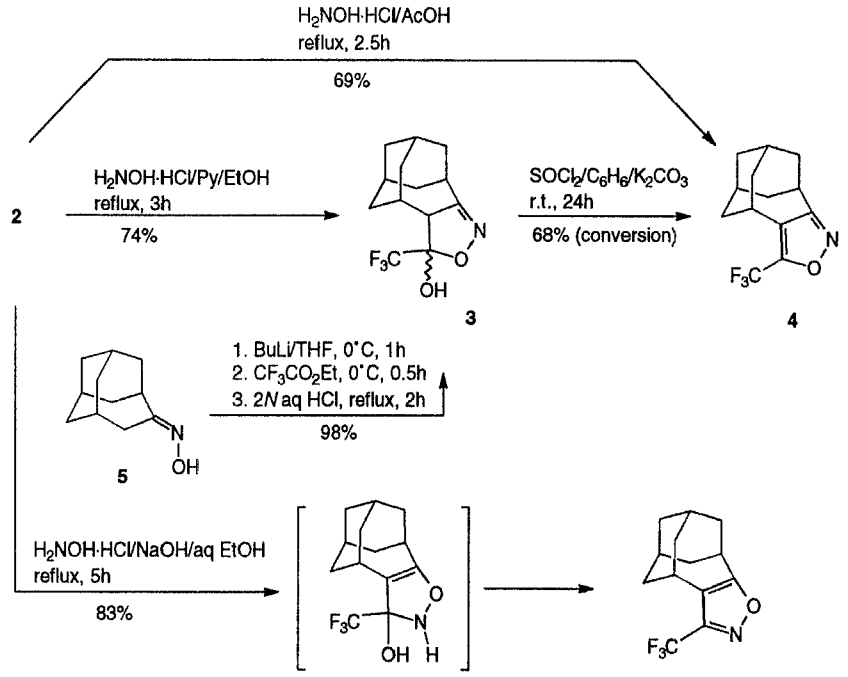


Scheme 1

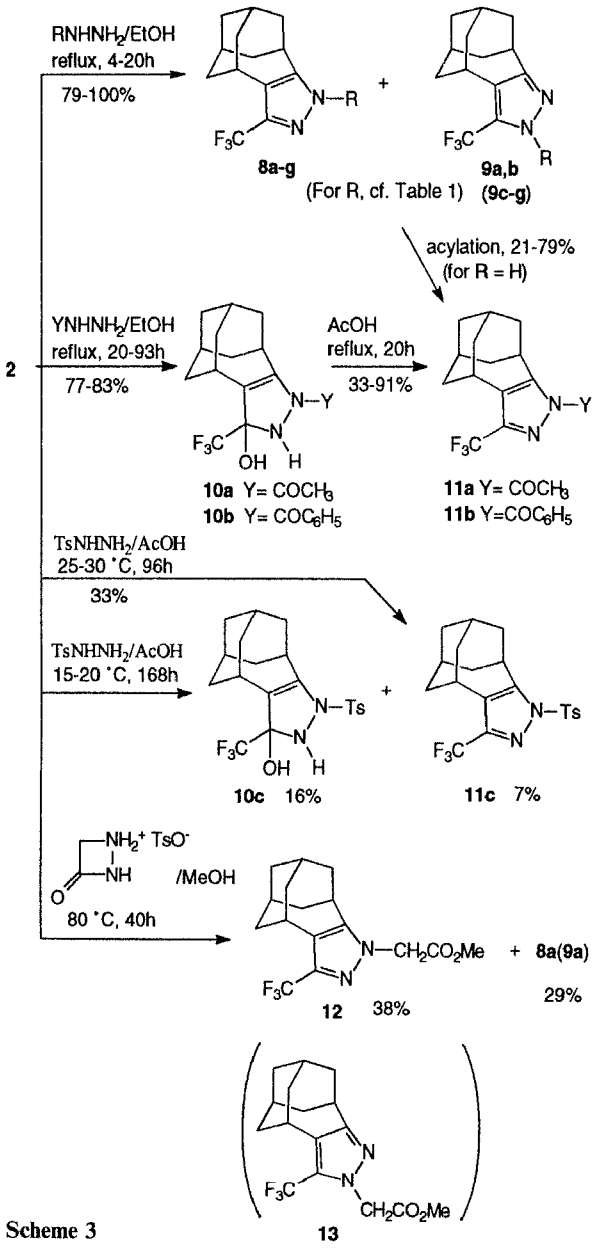
In order to prepare isoxazole derivatives, compound **2** was heated with $H_2NOH \cdot HCl$ in 1:1 pyridine/EtOH under reflux for 3 h. A crystalline product was obtained in 74% yield. This compound was characterized as a hydroxyisoxazoline derivative **3** based on the analysis and spectral data. This assignment was supported also by an alternative synthesis from the known oxime **5**[6] as depicted in Scheme 2. The reaction of **2** with $H_2NOH \cdot HCl$ in AcOH under reflux for 2.5 h afforded isoxazole **4** in 69% yield. The structure was supported by spectral data and an alternative synthesis of **4** from **3**. Thus, stirring of a mixture of **3**, K_2CO_3, and $SOCl_2$ in benzene at r.t. for 24 h afforded isoxazole **4** (68% based on ^{1}H NMR analysis). The dehydration of **3** did not occur by simple heating in benzene under reflux for 5 h, although clean dehydration of 5-perfluoroalkyl-5-hydroxyisoxazolines was reported under these conditions.[7,8] On the other hand, reaction of **2** with $H_2NOH \cdot HCl$ in aq NaOH–EtOH under reflux for 5 h afforded regioisomeric isoxazole **7** as a colorless oil in 83% yield. Thus, we could prepare both regioisomeric oxazoles **4** and **7** selectively using appropriate reaction conditions (Scheme 2).

Next we examined synthesis of pyrazole derivatives as summarized in Scheme 3.[9] The reaction of **2** with hydrazine dihydrochloride in refluxing EtOH gave pyrazole **8a** (or **9a**) as crystals quantitatively, but the same reaction with hydrazine sulfate in aq NaOH–EtOH[10] gave the same pyrazole in somewhat lower yield (54%). The ^{13}C NMR spectrum of this pyrazole in $CDCl_3$ revealed only one quartet signal assignable to CF_3 at $\delta = 122.50$ ($J_{C,F} = 269$ Hz) and the ^{1}H NMR spectrum had no diagnostic signals. Hence, this pyrazole seems to exist as one of the possible tautomeric forms **8a** and **9a** in $CDCl_3$ but further analysis was not possible at this stage.

The reaction of **2** with methylhydrazine afforded a 93:7 mixture of **8b** and **9b** in 95% yield. The ratio was determined by the characteristic ^{1}H NMR signals at $\delta = 3.79$ (d, long range $J_{H,H} = 0.6$ Hz, 2.8H) and 3.85 (q, long range $J_{H,F} = 1.2$ Hz, 0.2H) due to the NMe of **8b** and **9b**, respectively. The presence of long range coupling between the NMe and F groups,[11] as well as a lower chemical shift of the NMe group in **9b**, supported the assignment. But the separation of these regioisomers was not achieved by chromatography. The reactions of **2** with aryl hydrazines afforded regioselectively the corresponding pyrazole derivatives **8c–g** in good yields (Table 1). The structural assignments were based on the signals due to the pyrazole ring carbons at ca. $\delta = 137$, 126, and 151 which are very similar to those of **8b** in the ^{13}C NMR spectra. The selective formation of this regioisomer is in accord with the higher reactivity of the trifluoromethylated carbon with the more nucleophilic amino group.[12,13] The reactions of **2** with acylhydrazines in refluxing EtOH afforded intermediate products **10a,b** which can be dehydrated to the corresponding pyrazoles **11a,b** on heating in AcOH (Scheme 3 and Table 1).[14] Acylation of **8a (9a)** afforded also **11a,b**[15,16] selectively. The reaction of **2** with tosylhydrazine in AcOH at 25–30°C for 96 h gave pyrazole **11c** in 33% yield, but the same reaction in AcOH at 15–20°C for 168 h yielded pyrazoline **10c** and pyrazole **11c** in 16 and 7% yields, respectively (Scheme 3 and Table 1). The reaction of **2** with 3-oxo-1,2-diazetidinium tosylate (Taylor's reagent)[16] in MeOH at 80°C for 40 h in a sealed tube afforded a complex mixture, from which *N*-methoxycarb-



Scheme 2



Scheme 3

onylmethylpyrazole **12** was obtained in 38% yield, together with unsubstituted pyrazole **8a (9a)** (29%) after chromatography (Scheme 3). The regioisomer **13** was not obtained. The structure of **12** was supported by the spectral data. In particular, the shown regiochemistry was confirmed by the NOESY spectrum, i.e., an NOE was observed clearly between signals at $\delta = 2.76-2.87$ (m, 1H, C3-bridgehead H) and 4.88 (s, 2H, NCH_2COO).

It is well known that DMNP [3,5-dimethyl-1-(4-nitrophenyl)pyrazole] is a nonlinear optical material having a large SHG (second harmonic generation) value (16 times compared with urea). Hence, the SHG as well as THG (third harmonic generation) values of above pyrazole derivatives were measured by a powder method but none of them had larger values than those of urea.[17,18]

The work described herein demonstrates that trifluoroacetylhomoadamantanone **2** is a useful building block for synthesis of trifluoromethyl-substituted homoadamantano [4,5]fused 5-membered nitrogen heterocycles.

Microanalyses were performed with a Perkin-Elmer 2400S elemental analyzer. Compounds **2–4, 7, 8a–g, 10a–c, 11a–c** and **12** gave C,H,N analysis ±0.47%. Flash chromatography was performed with a silica gel column (Fuji-Davison BW-300). TLC was performed with Kieselgel 60 F_{254} (Merck, Art 5715). All reagents were of commercial quality.

5-Trifluoroacetyltricyclo[4.3.1.1^{3,8}]undecan-4-one (2):
A mixture of 4-homoadamantanone **(1)** (176 mg, 1.07 mmol) and NaH (60% in mineral oil, 185 mg, 4.62 mmol) in anhydr. THF (4 mL) was heated in a sealed tube at 90 °C for 1 h under N_2. To the cooled mixture was added CF_3CO_2Et (324 mg, 1.76 mmol) at r.t. and the mixture was again heated at 90 °C for 3 h in the sealed tube under N_2. The cooled mixture was diluted with EtOH (1 mL) to decompose the excess NaH, neutralized with 2N aq HCl, and extracted with Et_2O (15 mL × 4). The combined Et_2O extracts were washed with 5% aq $NaHCO_3$, water, sat. aq NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel; 20:1, he-

Table 1. Pyrazoles and Pyrazolines **8–12** Prepared

Entry	Educt	R (or Y) of Hydrazine	React. Time(h)[a]	Product	Yield (%)[b]
1	**2**	H	4	**8a (9a)**[c]	100
2	**2**	Me	20[d]	**8b + 9b**[e]	95
3	**2**	Ph	4	**8c**	96
4	**2**	4-MeC_6H_4	9	**8d**	99
5	**2**	4-ClC_6H_4	12	**8e**	88
6	**2**	4-$NO_2C_6H_4$	10	**8f**	84
7	**2**	3-$NO_2C_6H_4$	8	**8g**	79
8	**2**	MeCO	20	**10a**	77
9	**10a**		20[f]	**11a**	33
10	**2**	PhCO	93	**10b**	83
11	**10b**		20[f]	**11b**	93
12	**2**	*p*-Ts	168[g]	**10c + 11c**	16 + 7
13	**2**	*p*-Ts	96[h]	**11c**	33
14	**2**	T-reagent[i]	40[j]	**12 + 8a(9a)**	38 + 29

[a] Heated to reflux in EtOH.
[b] Isolated yields.
[c] As a tautomeric system.
[d] At r.t.
[e] A 93 : 7 ratio by ^1H NMR analysis.
[f] Heated to reflux in AcOH.
[g] At 15–20 °C in AcOH.
[h] At 25–30 °C in AcOH.
[i] 3-Oxo-1,2-diazetidinium tosylate.
[j] At 80 °C in MeOH.

xane/EtOAc) to afford the product **2** as colorless crystals (254 mg, 91 %); mp 58–60 °C.

IR (KBr): ν = 2920, 1620, 1447, 1306, 1186, 951 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.62–2.18 (m, 12 H), 2.72–2.82 (m, 1 H), 2.87–3.01 (m, 1 H), 16.3 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.29, 27.74, 31.86, 34.84, 35.77, 45.33, 116.65, 119.05 (q, J = 282 Hz), 169.73 (q, J = 34 Hz), 208.71.

MS (EI, 70 eV): m/z (%) = 261 (6.9), 260 (M^+, 31), 242 (9.7), 191 (100), 134 (23).

5-Hydroxy-5-trifluoromethyl-4-oxa-3-azatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2-ene (3):

Method A:

A mixture of **2** (130 mg, 0.50 mmol) and $H_2NOH \cdot HCl$ (43 mg, 0.60 mmol) in EtOH (3 mL) and pyridine (3 mL) was heated to reflux for 3 h. The cooled mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (5 mL × 4). The combined extracts were washed with water and dried (Na_2SO_4). Solvent removal under reduced pressure gave a solid residue which was recrystallized from hexane to afford **3** as colorless crystals (101 mg, 74%); mp 159–162 °C.

Method B:

To a stirred solution of the *anti*-oxime **5**[6] (90 mg, 0.50 mmol) in THF (4 mL) was added BuLi (0.62 mL of 1.6 M hexane solution, 1.0 mmol) at 0 °C under N_2. The stirring was continued for 1.5 h, and CF_3CO_2Et (92 mg, 0.50 mmol) was added to the mixture. After further stirring for 0.5 h, the mixture was diluted with 2 N aq HCl (3 mL, 6 mmol) and heated to reflux for 2 h. The cooled mixture was neutralized with sat. $NaHCO_3$ and extracted with Et_2O (10 mL × 4). The combined extracts were dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a residue which was purified by flash chromatography (silica gel; 10 : 1, hexane/EtOAc) to afford **3** as colorless crystals (135 mg, 98 %).

IR (KBr): ν = 3183, 1626, 1453, 1173, 1026, 1003, 953 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.45–2.20 (m, 12 H), 2.40 (t, J = 5.2 Hz, 1 H), 3.09 (s, 1 H), 3.19 (t, J = 5.6 Hz, 1 H), 3.57 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.93, 27.39, 27.58, 30.83, 31.76, 32.22, 35.85, 39.27, 40.91, 60.90, 103.30 (q, J = 32 Hz), 122.79 (q, J = 284 Hz), 169.61.

MS (EI, 70 eV): m/z (%) = 275 (M^+, 17), 274 (1.1), 258 (9.2), 257 (4.4), 256 (3.3), 206 (100).

5-Trifluoromethyl-4-oxa-3-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2,5-diene (4):

Method A:

A mixture of **2** (130 mg, 0.50 mmol) and $H_2NOH \cdot HCl$ (43 mg, 0.60 mmol) in AcOH (3 mL) was heated to reflux for 2.5 h. The cooled mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (5 mL × 4). The combined extracts were dried (Na_2SO_4). Removal of the solvent under reduced pressure gave **4** as an oil which, on storage in a refrigerator, solidified as faintly yellowish crystals (89 mg, 69 %); mp 44–46 °C.

Method B:

To a stirred mixture of **3** (68 mg, 0.25 mmol) and K_2CO_3 (5 mg, 36 mmol) in benzene (4 mL) was added $SOCl_2$ (320 mg, 2.69 mmol) at r.t. under N_2. The stirring was continued for 24 h, the mixture was diluted with water (10 mL) and extracted with hexane (10 mL × 3). The combined extracts were dried (Na_2SO_4). Solvent removal under reduced pressure gave a faintly yellowish solid of a 1 : 2 mixture of **3** and **4** (^1H NMR analysis) (66 mg, 68 % conversion of **3** to **4**).

IR (KBr): ν = 2924, 1651, 1310, 1145, 741 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.54–2.25 (m, 12 H), 3.20 (t, J = 5.6 Hz, 1 H), 3.31 (t, J = 5.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.03, 27.84, 30.31, 34.04, 35.20, 119.37 (q, J = 270 Hz), 127.15 (q, J = 40 Hz), 171.75.

MS (EI, 70 eV): m/z (%) = 257 (M^+, 16), 238 (12), 229 (1.4), 188 (8.2), 160 (100).

5-Trifluoromethyl-3-oxa-4-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene (7):

To a solution of $H_2NOH \cdot HCl$ (43 mg, 0.60 mmol) and **2** (130 mg, 0.50 mmol) in EtOH (4 mL) was added NaOH (28 mg, 0.70 mmol) in H_2O (0.5 mL), and the mixture was heated to reflux for 5 h. The cooled mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with sat. aq NaCl and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave an oily residue which was purified by flash chromatography (silica gel; 10 : 1, hexane/CH_2Cl_2) to afford **7** as a colorless oil (107 mg, 83 %).

IR (KBr): ν = 2292, 1636, 1468, 1179, 1142 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.62–2.35 (m, 12 H), 2.91 (t, J = 5.3 Hz, 1 H), 3.10–3.36 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.53, 29.19, 31.84, 32.84, 34.60, 36.50, 121.39 (q, J = 271 Hz), 121.41, 152.94 (q, J = 36 Hz), 182.39.

MS (EI, 70 eV): m/z (%) = 257 (M^+, 87), 238 (74), 229 (42), 188 (94), 160 (100).

5-Trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene (8a) or 5-Trifluoromethyl-3,4-diazatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2,5-diene (9a):

Method A:

A mixture of **2** (130 mg, 0.50 mmol) and $H_2NNH_2 \cdot 2HCl$ (63 mg, 0.60 mmol) in EtOH (2 mL) was heated to reflux for 4 h. The cooled mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (5 mL × 4). The combined extracts were dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid residue which was crystallized from CH_2Cl_2 to afford the pyrazole **8a (9a)** as colorless crystals (128 mg, 100 %); mp 194–197 °C.

Method B:

To a solution of **2** (130 mg, 0.50 mmol) and $H_2NNH_2 \cdot H_2SO_4$ (78 mg, 0.60 mmol) in EtOH (2.0 mL) was added 10 % aq NaOH (0.6 mL) and the mixture was stirred for 18 h at r.t. Workup as above gave **8a (9a)** (69 mg, 54 %).

IR (KBr): ν = 3157, 2916, 1446, 1176, 1122, 1011 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60–2.06 (m, 10 H), 2.18 (unsym s, 2 H), 3.06 (m, 2 H), 11.38 (brs, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.92, 28.71, 30.17, 33.84, 34.94, 36.28, 122.50 (q, J = 269 Hz), 125.19, 137.82 (q, J = 36 Hz), 152.79.

MS (EI, 70 eV): m/z (%) = 256 (M^+, 44), 255 (4.7), 241 (6.7), 237 (5.2), 187 (7.3), 83 (100).

Pyrazoles 8b–g; General Procedure:

A mixture of **2** (130 mg, 0.50 mmol) and the appropriate hydrazine (0.60 mmol) in EtOH (5 mL) was stirred under the conditions shown in Table 1. Removal of the solvent under reduced pressure gave crude pyrazoles which were purified by flash chromatography (silica gel; 1–20:1, hexane/AcOEt). The yields and reaction conditions are listed in Table 1.

3-Methyl-5-trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene **(8b)**:

Colorless crystals; mp 106–108 °C (hexane/EtOAc). Ca. 7% **9b** contamination based on ^{1}H NMR analysis.

IR (KBr): ν = 2926, 1157, 1107, 937, 739 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60–2.08 (m, 10 H), 2.19 (brs, 2 H), 2.97–3.10 (m, 2 H), 3.79 (d, J = 0.6 Hz, 2.8 H), 3.85 (q, J = 1.2 Hz, 0.2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.95, 28.72, 29.75, 33.67, 34.88, 36.20, 36.69, 122.57 (q, J = 268 Hz), 125.96, 136.45 (q, J = 35 Hz), 151.00.

MS (EI, 70 eV): m/z (%) = 270 (M^+, 100), 269 (7.8), 255 (12), 201 (16), 227 (17), 213 (54).

3-Phenyl-5-trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene **(8c)**:

Colorless crystals; mp 92–95 °C (hexane/EtOAc).

IR (KBr): ν = 2914, 1597, 1165, 1118, 706, 704 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.56 (s, 2 H), 1.73–2.10 (m, 8 H), 2.21 (brs, 2 H), 3.01–3.20 (m, 2 H), 7.32–7.54 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.03, 28.64, 29.70, 33.62, 34.70, 36.18, 123.40 (q, J = 269 Hz), 125.98, 126.69, 129.61, 138.39 (q, J = 36 Hz), 139.03, 151.61.

MS (EI, 70 eV): m/z (%) = 332 (M^+, 100), 331 (11), 313 (4.7), 275 (31), 263 (18).

3-p-Tolyl-5-trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene **(8d)**:

Colorless crystals; mp 119–121 °C (hexane/EtOAc).

IR (KBr): ν = 2919, 1516, 1387, 1231, 1159, 824 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72–2.13 (m, 10 H), 2.21 (brs, 2 H), 2.41 (s, 3 H), 2.98–3.17 (m, 2 H), 7.25 (s, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.12, 27.04, 28.67, 29.71, 33.66, 34.76, 36.24, 122.55 (q, J = 269 Hz), 125.77, 126.43, 130.10, 136.78, 138.22 (q, J = 36 Hz), 138.95, 151.40.

MS (EI, 70 eV): m/z (%) = 346 (M^+, 100), 345 (9.1), 331 (12), 327 (6.4), 277 (11).

3-p-Chlorophenyl-5-trifluoromethyl-3,4-diazatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene **(8e)**:

Mp 125–128 °C (hexane/EtOAc), colorless crystals.

IR (KBr): ν = 2917, 1501, 1464, 1130, 837 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.64–2.13 (m, 10 H), 2.22 (brs, 2 H), 2.95–3.18 (m, 2 H), 7.42–7.36 (m, 2 H), 7.41–7.50 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.00, 28.60, 29.76, 33.59, 34.63, 36.13, 123.36 (q, J = 269 Hz), 125.94, 127.12, 129.78, 134.80, 137.71, 138.85 (q, J = 36 Hz), 151.51.

MS (EI, 70 eV): m/z (%) = 368 (35), 366 (M^+, 100), 365 (7.3), 347 (3.3), 331 (2.9), 297 (7.0).

3-p-Nitrophenyl-5-trifluoromethyl-3,4-diazatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene **(8f)**:

Mp 223–225 °C (hexane/EtOAc), faintly yellowish crystals.

IR (KBr): ν = 2920, 1599, 1528, 1348, 1128, 858 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70–2.12 (m, 10 H), 2.26 (brs, 2 H), 3.14 (d, J = 3.2 Hz, 2 H), 7.57 (m, 2 H), 8.37 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.97, 28.51, 29.92, 33.47, 34.42, 35.99, 122.10 (q, J = 269 Hz), 125.18, 126.09, 128.09, 140.13 (q, J = 36 Hz), 144.13, 147.46, 151.80.

MS (EI, 70 eV): m/z (%) = 378 (100), 377 (M^+, 95), 376 (6.3), 358 (7.2), 347 (9.6), 331 (3.0), 308 (16).

3-m-Nitrophenyl-5-trifluoromethyl-3,4-diazatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene **(8g)**:

Mp 113–117 °C (hexane/EtOAc), faintly yellowish crystals.

IR (KBr): ν = 2922, 1535, 1350, 1130, 733, 685 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.73–2.14 (m, 10 H), 2.26 (brs, 2 H), 3.01–3.22 (m, 2 H), 7.64–7.79 (m, 2 H), 8.23–8.35 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.98, 28.54, 29.95, 33.50, 34.48, 36.03, 120.89, 122.14 (q, J = 269 Hz), 123.47, 127.67, 130.64, 131.51, 139.77 (q, J = 38 Hz), 148.97, 151.76.

MS (EI, 70 eV): m/z (%) = 377 (M^+, 100), 376 (5.6), 361 (2.8), 358 (9.1), 308 (7.1).

3-Acetyl-5-hydroxy-5-trifluoromethyl-3,4-diazatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6)-ene (10a):

A mixture of **2** (130 mg, 0.50 mmol) and acetic hydrazide (44 mg, 0.60 mmol) in EtOH was heated to reflux for 20 h. Removal of the solvent under reduced pressure gave a solid which was purified by flash chromatography (silica gel; 25:1, hexane/EtOAc) to afford **10a** as colorless crystals (121 mg, 77%); mp 117–119 °C (hexane/EtOAc).

IR (KBr): ν = 3314, 2915, 1678, 1449, 1170, 1007 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.53–2.14 (m, 12 H), 2.32 (s, 3 H), 2.36–2.52 (m, 1 H), 3.04 (t, J = 5.4 Hz, 1 H), 3.40 (s, 1 H), 5.76 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.20, 26.83, 27.05, 27.56, 31.42, 32.10, 33.32, 36.03, 40.16, 40.68, 61.29, 92.02 (q, J = 33 Hz), 123.90 (q, J = 286 Hz), 167.55, 174.37.

MS (EI, 70 eV): m/z (%) = 316 (M^+, 5.1), 273 (50), 256 (15), 247 (4.9), 204 (100).

3-Benzoyl-5-hydroxy-5-trifluoromethyl-3,4-diazatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6)-ene (10b):

A mixture of **2** (130 mg, 0.50 mmol) and benzoic hydrazide (82 mg, 0.60 mmol) in EtOH (5 mL) was heated at 80 °C for 93 h in a sealed tube. Removal of the solvent under reduced pressure gave a solid which was purified by flash chromatography (silica gel; 20:1, hexane/EtOAc) to afford **10b** as colorless crystals (150 mg, 83%); mp 139–141 °C (hexane/EtOAc).

IR (KBr): ν = 3337, 2907, 1657, 1422, 1350, 1161, 723, 708 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44–2.20 (m, 12 H), 2.42–2.54 (m, 1 H), 2.96–3.08 (m, 1 H), 3.47 (s, 1 H), 6.28 (s, 1 H), 7.34–7.57 (m, 3 H), 7.80–7.93 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.95, 27.60, 31.58, 32.20, 33.32, 35.99, 39.65, 40.76, 60.85, 77.47, 93.62 (q, J = 32 Hz), 124.17 (q, J = 286 Hz), 128.22, 130.75, 132.63, 133.75, 167.72.

MS (EI, 70 eV): m/z (%) = 378 (M^+, 90), 377 (2.0), 361 (6.5), 359 (4.1), 309 (100).

5-Hydroxy-3-*p*-toluenesulfonyl-5-trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6)-ene (10c) and 3-*p*-Toluenesulfonyl-5-trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene (11c):

A mixture of **2** (130 mg, 0.50 mmol) and *p*-toluenesulfonhydrazide (112 mg, 0.60 mmol) in AcOH (3 mL) was stirred at 15–20 °C for 168 h. The mixture was basified with 20% aq NaOH and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid which was purified by flash chromatography (silica gel; 10:1, hexane/EtOAc) to afford **10c** as colorless crystals (35 mg, 16%); mp 139–141 °C (hexane/EtOAc), and **11c** (15 mg, 7%) as colorless crystals; mp 110–113 °C (hexane/EtOAc). The same reaction at 25–30 °C for 96 h in another run and workup as above afforded only **11c** (68 mg, 33%).

Compound **10c**:

IR (KBr): ν = 3499, 2930, 1346, 1294, 1174, 1142, 1047, 667, 590 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.43–2.17 (m, 12H), 2.23 (t, J = 5.0 Hz, 1H), 2.43 (s, 3H), 3.00 (t, J = 5.4 Hz, 1H), 3.34 (s, 1H), 4.77 (s, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.71, 26.81, 27.06, 27.44, 31.34, 32.02, 33.15, 35.81, 39.55, 40.43, 61.87, 94.83 (q, J = 32 Hz), 123.36 (q, J = 284 Hz), 129.10, 129.68, 135.65, 144.98, 168.65.

MS (EI, 70 eV): m/z (%) = 428 (M^+, 71), 359 (100), 273 (10), 244 (7.3), 204 (22), 91 (47).

Compound **11c**:

IR (KBr): ν = 2916, 1595, 1392, 1196, 671 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.50–2.25 (m, 12H), 2.40–2.50 (m, 3H), 2.98 (brs, 1H), 3.90–4.05 (m, 1H), 7.35–7.42 (m, 2H), 7.82–7.93 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.84, 27.04, 28.38, 29.00, 32.90, 33.84, 35.79, 123.34 (q, J = 284 Hz), 128.34, 130.59, 134.96, 141.14 (q, J = 38 Hz), 146.55, 154.64, 168.67.

MS (EI, 70 eV): m/z (%) = 410 (M^+, 15), 391 (6.7), 346 (100), 254 (14), 199 (17).

3-Acetyl-5-trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene (11a):

Method A:

A mixture of **8a (9a)** (51 mg, 0.20 mmol) and $NaOAc \cdot 3H_2O$ (27 mg, 0.20 mmol) in AcOH (3 mL) was heated to reflux for 1 h. The cooled mixture was poured onto ice–water and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a solid residue which was purified by flash column chromatography (silica gel; 100:3, hexane/EtOAc) to give **11a** as colorless crystals (47 mg, 79%); mp 102–105°C (hexane).

Method B:

A solution of **10a** (34 mg, 0.11 mmol) in AcOH (1 mL) was heated to reflux for 20 h. The cooled mixture was diluted with water and extracted with hexane (5 mL × 4). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a residue which was purified by flash column chromatography (silica gel; 100:3, hexane/EtOAc) to give pure **11a** as colorless crystals (11 mg, 33%).

IR (KBr): ν = 2928, 1750, 1321, 1225, 1128, 963 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.70–2.04 (m, 10H), 2.20 (brs, 2H), 2.71 (s, 3H), 3.02 (t, J = 5.2 Hz, 1H), 4.33 (t, J = 5.6 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.88, 26.97, 28.62, 28.82, 33.03, 34.05, 36.08, 121.56 (q, J = 270 Hz), 130.02, 140.42 (q, J = 37 Hz), 155.31, 172.85.

MS (EI, 70 eV): m/z (%) = 298 (M^+, 9.9), 279 (2.1), 255 (100), 241 (11), 227 (2.9).

3-Benzoyl-5-trifluoromethyl-3,4-diazatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene (11b):

Method A:

To a stirred mixture of **8a (9a)** (51 mg, 0.20) and pyridine (24 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) was added PhCOCl (42 mg, 0.30 mmol) at r.t. and the mixture was heated to reflux for 0.5 h. The cooled mixture was diluted with water and extracted with CH_2Cl_2 (5 mL × 3). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid which was purified by flash column chromatography (silica gel; 40:1, hexane/EtOAc) to afford **11b** as colorless crystals (36 mg, 21%); mp 144–146°C (hexane).

Method B:

A solution of **10b** (54 mg, 0.14 mmol) in AcOH (2 mL) was heated to reflux for 20 h in a sealed tube. The cooled mixture was diluted with water and extracted with hexane (5 mL × 4). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave practically pure **11b** as a crystalline solid (46 mg, 91%) which was identical with the sample obtained by Method A.

IR (KBr): ν = 2903, 1327, 1185, 693 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.72–2.12 (m, 10H), 2.24 (brs, 2H), 3.09 (brs, 1H), 4.01 (t, J = 5.1 Hz, 1H), 7.40–7.55 (m, 2H), 7.58–7.69 (m, 1H), 7.93–8.05 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.01, 28.66, 29.26, 33.21, 34.14, 36.14, 121.65 (q, J = 270 Hz), 128.54, 129.56, 132.21, 132.35, 133.98, 141.37 (q, J = 36 Hz), 156.24, 168.66.

MS (EI, 70 eV): m/z (%) = 360 (M^+, 99), 359 (64), 341 (32), 330 (100), 291 (8.5), 255 (18).

3-Methoxycarbonylmethyl-5-trifluoromethyl-3,4-diazatetracyclo-[7.3.1.1^{7,11}.0^{2,6}]tetradeca-2(6),4-diene (12):

A stirred mixture of **2** (130 mg, 0.50 mmol) and 3-oxo-1,2-diazetidinium tosylate[16] (122 mg, 0.50 mmol) in MeOH (5 mL) was heated to 80°C for 40 h in a sealed tube. Removal of the solvent under reduced pressure gave a solid residue which was dissolved in MeOH/EtOAc (1:10, 22 mL). The solution was washed with 5% aq $NaHCO_3$, sat. aq NaCl, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid residue which was purified by flash column chromatography (silica gel; 10:1–1:5, hexane/CH_2Cl_2) to afford unreacted **2** (17 mg, 13% recovery), **12** as colorless crystals (54 mg, 33%, 38% based on consumed **2**); mp 122–125°C (CH_2Cl_2), and **8a (9a)** (32 mg, 25%, 29% based on consumed **2**), successively. Compound **8a (9a)** was identical with the sample prepared from **2** and $H_2NNH \cdot 2HCl$.

IR (KBr): ν = 2924, 1748, 1389, 1229, 1161, 1134, 1121, 1105, 1061 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.74–2.60 (m, 10H), 2.40–2.60 (m, 2H), 2.76–2.87 (m, 1H), 3.00–3.12 (m, 1H), 3.77 (s, 3H), 4.88 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.00, 28.73, 30.19, 33.37, 34.72, 36.19, 51.16, 52.89, 122.33 (q, J = 269 Hz), 126.34, 137.80 (q, J = 36 Hz), 151.89, 168.32.

MS (EI, 70 eV): m/z (%) = 329 (31), 328 (M^+, 100), 271 (19), 269 (42), 259 (13), 213 (16), 199 (14).

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