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Spiroannelation Reactions of 3-Trifluoroacetyl- and other 3-Acyl-1-methyl-lactams

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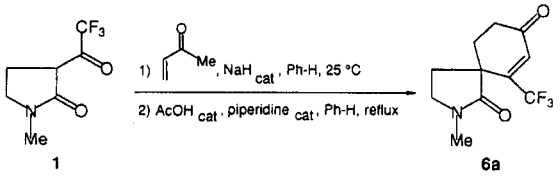
Dedicated to Prof. K. Kieslich on the occasion of his 65th birthday.

Abstract. 3-Trifluoroacetyl- and other 3-acyl-1-methyl-lactams (**1–5**) undergo the Robinson annelation with α,β-unsaturated ketones to produce spirocyclic cyclohexenones (**6**), their precursors hydroxycyclohexanones (**7**) or 3-acyl-3-oxobutyl-lactams (**8**) depending on the substitution.

Because of their unique biological properties, trifluoromethylated compounds are targets of continuing interest [1]. The Robinson annelation [2, 3] has great synthetic potential in constructing complex polycyclic and particularly spirocyclic frameworks but only few examples of Robinson annelation are reported for trifluoroacetylated derivatives [4, 5]. We have already applied it to the readily available 1-methyl-3-trifluoroacetyl-2-pyrrolidinone **1** [6] and obtained the spirocyclohexenone **6a** (Scheme 1). This compound was subsequently trifluoroacetylated in *alpha* position to the enone carbonyl giving the corresponding 1,3-diketone which was heterocyclized with bis-nucleophiles [7, 8].

Now we have obtained spiroannelations using α,β-unsaturated ketones and 3-trifluoroacetyl or other 3-acyl-1-methyl-lactams. Since the annelation combines two steps – a Michael addition followed by cyclocondensation – two procedures were tried, namely a one pot reaction (Method 1) or a two-step process with isolation of the Michael adduct.



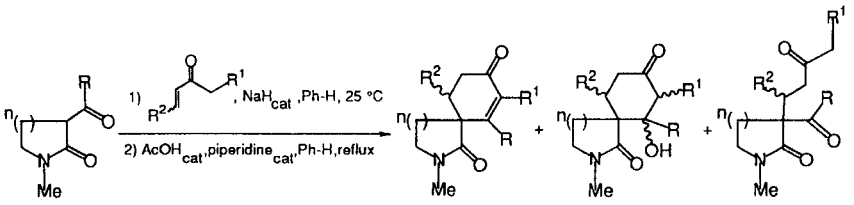
1 6a

Scheme 1

Thus, 3-acyl-lactams **1–5** were treated with the α,β-unsaturated ketone in the presence of a catalytic amount of sodium hydride (except entry **a** [c]) of Table 1) then, after addition of catalytic amounts of acetic acid and piperidine, the mixture was refluxed in benzene during several hours (Method 1: Scheme 2, Table 1).

The spirocyclic cyclohexenones **6a,c–e,g,h** were obtained in modest to good yield using methyl vinylketone except for entries **e** and **f** where intermediates **7f** and **8e,f** could be detected or isolated (Table 1).

Following the two step procedure (Method 2) 3-acyl-lactams **1–3,5** were treated first with α,β-unsaturated ketone and sodium hydride (catalytic amount) to produce, after chromatography on silica gel or distillation under reduced pressure, the Michael adduct **8a,e,f,h** or in one case the spirocyclic hydroxycyclohexanone **7a**. The intermediates **7a**, **8a,b,e,f,h** underwent cyclization and dehydration upon refluxing in benzene in the presence of catalytic amounts of acetic acid and piperidine



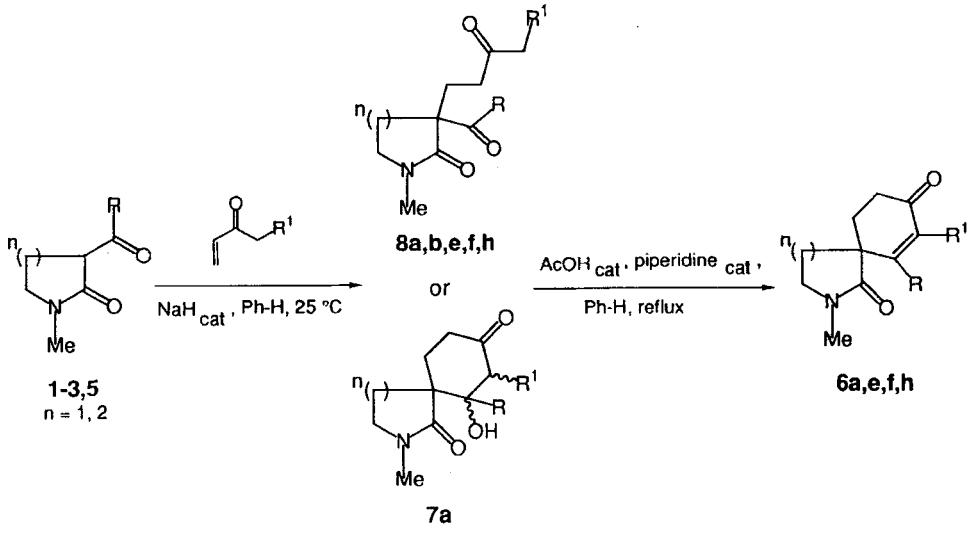
1-5 n = 1,2 **6a,c-e,g,h** **7b,f** **8b,e,f**

Scheme 2

Table 1 Data of spirocyclic cyclohexenones (**6**) hydroxycyclohexanones (**7**) and 3-acyl-3-oxobutyl-lactams (**8**)

Lactam	n	R	R^1	R^2	Entry	Conv. (%)	Yield **6** (%) [a]	Yield **7** (%) [a]	Yield **8** (%)
1	1	CF_3	H	H	**a**	100 [b]	65	–	–
						80 [c]	32	–	–
			Me	H	**b**	100 [b]	–	59 (57/43)	23 [d]
			H	Ph	**c**	95 [b]	52 (58/42)	–	–
			H	Me	**d**	80 [b]	49 (85/15)	–	–
2	2		H	H	**e**	~ 90 [b]	~ 15 [e]	–	~ 10 [e]
3	1	C_6H_5	H	H	**f**	100 [b]	–	45 (53/47)	34
4		p-$CF_3C_6H_4$	H	H	**g**	100 [b]	67	–	–
5		CO_2Et	H	H	**h**	~ 40 [b]	~ 20 [e]	–	–

[a] Diastereoselectivity: (major/minor); [b] catalytic amount of NaH; [c] 1 eq. of NaH;
[d] hydrate of trifluoroacetylated lactam; [e] detected by ^{1}H-NMR.



Scheme 3

to give spirocyclic cyclohexenones **6a,e,f,h** (Method 2: Scheme 2, Table 2).

The substitution pattern of the α,β-unsaturated ketone has influence on the outcome of the reaction. When the substituent R^1 is a methyl group, heterocycle **6b** was not obtained using Method 1 (Table 1). On the other hand, the nature of the substituent R^2 has no significant influence on the reaction. When R^2 is a phenyl or methyl group, azaspiro[4,5]dec-6-enes **6c** and **6d** were isolated as a diastereoisomeric mixture. The selectivity can be modified by varying the steric hindrance of R^2 (Table 1, entries **c** and **d**). The amount of the base was also important. As we found, it is advantageous to use only a catalytic amount of sodium hydride. >Indeed, when

Table 2 Spirocyclic cyclohexanones **6a,e,f,h**

Lactam	n	R	R^1	Entry	Conv. (%)	Yield **8** (%)	Yield **7** (%) [a]	Cpd	Conv. (%)	Yield **6** (%)
1	1	CF_3	H	**a**	100	58 [b,e]	–	**8a** [e]	100	87
					100	–	63 [c] (95/5)	**7a**	100	95
			Me	**b**	–	–	–	**8b** [e]	90	[d]
2	2		H	**e**	70	42	–	**8e**	100	43
3	1	C_6H_5	H	**f**	100	48	–	**8f**	100	83
5		CO_2Et	H	**h**	100	51	–	**8h**	100	75

[a] Diastereoselectivity: (major/minor); [b] the crude was chromatographed on silica gel; [c] the crude was first distilled under reduced pressure then recrystallized; [d] cyclization into **7b** (86 %, (~ 55/45)[a]) but no dehydration into **6b**; [e] hydrate of trifluoroacetylated lactam

using one equivalent of NaH, it was not only necessary to work at 0 °C but the conversion was incomplete and the yield low (Table 1, entry **a** [b,c]).

Generally, 3-acyl-lactams **3–5** could be employed to prepare new cyclohexenones **6f,g,h** depending on the substituent R and the conditions (Methods 1 and 2). It is worth noting the influence of a phenyl group substituted in *para* position by a trifluoromethyl group. In this case, under the same conditions, the cyclohexenone **6g** was the only reaction product, while the annelation with 3-benzoyl-NMP **3** gave a mixture of cyclohexanone **7f** and of the Michael adduct **8f** (Table 1).

These examples illustrate that the Robinson annelation can be applied to 3-trifluoroacetyl and 3-benzoyl-lactams which constitutes a useful procedure for the preparation of heterospirocyclic compounds **6**.

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Experimental

Melting points were taken using a Dr. Tottoli apparatus and are uncorrected. IR and mass spectra were measured on a Perkin-Elmer 1710 and A Finnigan Mat TSQ 70 apparatus, respectively. The ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were run on a Bruker AM 500 spectrometer at 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) or with Varian VXR-200 and Gemini-200 spectrometers at 200 MHz (^{1}H), 188.2 MHz (^{19}F) and 50.3 MHz (^{13}C), in $CDCl_3$ solution, using 5 mm probes. The TMS signal was taken as an internal reference for the ^{1}H and ^{13}C spectra, while $CFCl_3$ was used as an internal reference for the ^{19}F spectra. Most of the ^{13}C-NMR spectra were obtained from proton coupled or proton noise decoupled spectra. For molecules **6c**, **6e**, **7a**, **6f** and **7f**, unambigous assignments were obtained by use of the two-dimensional ^{1}H–^{13}C heteronuclear chemical shift correlation spectroscopy [9, 10]. For the ^{1}J connectivities, we have assumed an average one bond carbon-proton coupling constant of about 135 Hz (fixed delays durations: $\Delta_1 = 1/2\ (^1J_{CH}) = 3.6$ msec; $\Delta_2 = 1/4\ (^1J_{CH}) = 1.8$ m sec). For the long-range ^{1}H–^{13}C connectivities, we have chosen averaged ^{13}C–^{1}H coupling constant of about 12.5 Hz (fixed delays: $\Delta_1 = 1/2\ (^nJ_{CH}) = 40$ msec; $\Delta_2 = 1/4\ (^nJ_{CH}) = 20$ msec. The two-dimensional data matrix were submitted to a Lorentz–Gauss transformation [9, 10] in the t_1 dimension and to a sinusoïdal multiplication [9, 10] in the t_2 dimension prior to Fourier transformation („power" spectrum calculation in all cases). We have also used the double-quantum filtered correlation spectroscopy (DQF-COSY) [9–12] to verify or to assign some of the ^{1}H resonances. The DQF-COSY experiments have been acquired using the TPPI (Time-Proportional Phase Incrementation) [9, 10, 12] and transformed in the phase-sensitive mode [9, 10, 12]. Chemical shifts are in ppm on the δ scale, and coupling constants J are given in Hz. The following abbreviations are used S, s singlet, D, d doublet, T, t triplet, Q, q quartet, q_t quintet, s_x sextet, s_p septuplet and m multiplet; capitalized characters indicating one bond couplings.

The commercial α,β-unsaturated ketones and 3-acyl-lactams (except compounds **4** and **5**) were distilled before use. Benzene was dried over sodium using benzophenone as indicator.

General procedures for Robinson spiroannelation reactions

Method 1

3-Acyl-lactam **1-5** (1 eq.) and α,β-unsaturated ketone (1.1 eq.) were added simultaneously to a suspension of NaH (0.025 eq.) in dry benzene (1 ml/1 mmol) at 20 °C. After 3 hours, acetic acid (0.04 eq.) and piperidine (0.04 eq.) were added, and the mixture was refluxed for several hours (5–20 hrs). The volatiles were then removed and the residue was chromatographed on silica gel (mixture of ether/petroleum ether or methanol/ether) to give cyclohexenone **6a,c–e,g,h**, cyclohexanone **7b,f**, or lactam **8b,e,f**.

Method 2

3-Acyl-lactam **1–3** or **5** (1 eq.) and α,β-unsaturated ketone (1.1 eq.) were added simultaneously to a suspension of NaH (0.025 eq.) in dry benzene (1 ml/1 mmol) at 20 °C. The mixture was stirred for several hours (5–12 hrs) then filtered on silica gel. After evaporation of volatiles, the crude material was chromatographed on silica gel (ether or mixture of methanol/ether) or distilled under reduced pressure to give cyclohexanone **7a** or lactam **8a,b,e,f,h**.
These intermediates (1 eq.) were then treated with acetic acid (0.04 eq.) and piperidine (0.04 eq.) in refluxing benzene (1 ml/1 mmol) during several hours (5–20 hrs). After evaporation, the residue was chromatographed on silica gel (mixture of methanol/ether) to give cyclohexenone **6a,e,f,h**.

Spiroannelations of 1-methyl-3-trifluoroacetyl-2-pyrrolidinone (1)

Reaction with methyl vinyl ketone (method 1 and 2)

The reactions of 1-methyl-3-trifluoroacetyl-2-pyrrolidinone **1** with methyl vinyl ketone were previously reported [7].

Reaction with ethyl vinyl ketone (method 1)

The reaction of 1-methyl-3-trifluoroacetyl-2-pyrrolidinone **1** (0.98 g, 5 mmol) with ethyl vinyl ketone (1.1 eq.) gave after chromatography (eluent: 85% ether/petroleum ether then 5% methanol/ether) the cyclohexanone **7b** as a mixture (57/43) of diastereoisomers (0.82 g, 59%) and the pyrrolidinone **8b** (0.32 g, 23%).

2,7-Dimethyl-1,8-dioxo-6-hydroxy-6-trifluoromethyl-2-aza-spiro[4,5]decane (**7b**)

Minor diastereoisomer: m.p. 75–77 °C. – IR (KBr): 3400–3100, 2955, 2893, 1729, 1670, 1507, 1456, 1407, 1257. – MS: 279 (M^+), 210, 196, 195, 153, 126, 112, 69. – ^{19}F-NMR: –69.0 (s). – ^{1}H-NMR: 1.19 (3H, dq, 6.7/^5J_F = 2.0), 1.7–1.8 (1H, m), 2.2–2.3 (2H, m), 2.4–2.6 (3H, m), 2.64 (1H, qm, 6.6), 2.90 (3H, s), 3.4–3.5 (2H, m), 6.54 (OH, d, 1.6). – ^{13}C-NMR: 7.2 (Qdq, 129.4/4.5/^4J_F = 2.3), 23.7 (Tm, 132.8/^4J_F = 2.3), 29.7 (Q, 138.9), 30.5 (Tm, 132.4), 36.2 (Tm, 132.9), 45.8 (Tm, 140.8), 46.7 (Sm), 47.0 (Dqd, 129.5/7.1/3.0), 82.2 (qm, ^2J_F = 26.1), 125.2 (Qd, ^1J_F = 287.5/1.7), 177.4 (Sm), 205.9 (Sm, ^4J_F = 1.2). – Anal. Calcd. for $C_{12}H_{16}F_3N_1O_3$ (279.26): C 51.61; H 5.77; N 5.02; Found: C 51.74; H 5.75; N 4.98.

Major diastereoisomer: m.p. 151–152 °C. – IR (KBr): 3500–3300, 1723, 1674. – ^{19}F-NMR: –72.1 (s). – ^{13}C-NMR: 7.7, 28.2, 30.0, 35.6, 37.5, 45.9, 46.0, 48.9, 81.0, 125.1, 173.3, 209.4.

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-1-methyl-3-oxobutyl-2-pyrrolidinone (**8b**)

M.p. 95–96 °C. – ^{19}F-NMR: –80.2 (s) and –85.1 (s). – ^{1}H-NMR: 1.04 (3H, t, 7.3), 1.8–2.0 (2H, m), 2.1–2.3 (1H, m), 2.42 (2H, q, 7.4), 2.5–2.6 (2H, m), 2.6–2.8 (1H, m), 2.89 (3H, s), 3.3–3.5 (2H, m), 3.66 (OH, brs), 7.70 (OH, brs). – ^{13}C-NMR: 7.3, 26.1, 26.7, 29.3, 35.4, 37.2, 47.0, 50.6, 96.1, 122.6, 175.8, 210.3.

Reaction with 4-phenyl-but-3-ene-2-one (*Method 1*)

The reaction of 1-methyl-3-trifluoroacetyl-2-pyrrolidinone **1** (0.98 g, 5 mmol) with 4-phenyl-but-3-ene-2-one (1.1 eq.) gave after chromatography (eluent: 45% ether/petroleum ether) the cyclohexenone **6c** as a mixture (58/42) of diastereoisomers (0.84 g, 52%).

1,8-Dioxo-2-methyl-10-phenyl-6-trifluoromethyl-2-azaspiro [4,5]dec-6-ene (**6c**)

Minor diastereoisomer: m.p. 111–113 °C. – IR (KBr): 3045, 2960, 2911, 2892, 1693, 1652, 1499, 1474, 1459, 1437, 1404, 1278. – MS: 323 (M^+), 303, 254, 246, 219, 191, 144, 91, 77. – ^{19}F-NMR: –61.6 (s). – ^{1}H-NMR (500 MHz): 1.86 (1H, ddd, 8.6/8.5/8.3), 2.1–2.2 (1H, m), 2.33 (1H, dd, 13.3/8.8), 2.58 (3H, s), 2.73 (1H, dd, 16.4/3.0), 2.95 (1H, dd, 15.9/15.2), 3.01 (1H, dd, 10.0/9.3), 3.90 (1H, dm, 13.9), 6.56 (1H, s), 7.23 (2H, m), 7.31 (3H, m). – ^{13}C-NMR (125.8 MHz): 23.5 (Tm, 134.8), 29.7 (Q, 138.6), 38.6 (Tdm, 131.9/12.0), 45.0 (Dm, 132.4), 46.0 (Tm, 144.1), 52.2 (Sm), 122.9 (Qd, $^{1}J_F$ = 277.3/6.8), 128.35 (Dm, 160.3), 128.41 (3C, Dm, 160.3), 131.7 (Dqd, 166.6/$^{3}J_F$ = 5.6/2.6), 136.8 (Sm), 149.1 (qdm, $^{2}J_F$ = 28.9/3.6), 172.1 (Sm), 196.7 (Std, 6.4/2.6). – Anal. Calcd for $C_{17}H_{16}F_3N_1O_2$ (323.31): C 63.15; H 4.98; N 4.33; Found: C 62.61; H 4.94; N 4.27.
Major diastereoisomer: m.p. 89–92 °C. – IR (KBr): 3032, 2955, 2926, 2889, 1691, 1635, 1497, 1474, 1457, 1405, 1277. – ^{19}F-NMR: –63.1 (s). – ^{1}H-NMR: 1.74, 2.10, 2.48, 2.64, 2.6–2.7, 2.95, 3.39, 3.67, 6.67, 7.2–7.4. – ^{13}C-NMR: 26.1, 29.8, 40.4, 45.6, 50.3, 51.1, 122.8, 128.33, 128.37, 128.39, 131.9, 137.4, 146.3, 170.2, 197.3.

Reaction with pent-3-ene-2-one (*Method 1*)

The reaction of 1-methyl-3-trifluoroacetyl-2-pyrrolidinone **1** (0.98 g, 5 mmol) with pent-3-ene-2-one (1.1 eq.) gave after chromatography (eluent: 80% ether/petroleum ether then 10 % methanol/ether) the cyclohexenone **6d** as a mixture (85/15) of diastereoisomers (0.64 g, 49%).

2,10-Dimethyl-1,8-dioxo-6-trifluoromethyl-2-azaspiro[4,5] dec-6-ene (**6d**)

Major diastereoisomer: m.p. 85–86 °C. – IR (KBr): 2971, 2910, 2895, 1681, 1635, 1507, 1488, 1463, 1402, 1264. – MS: 261 (M^+), 241, 219, 192, 172, 161, 134, 99, 69, 42. – ^{19}F-NMR: –63.4 (s). – ^{1}H-NMR (500 MHz): 1.08 (3H, d, 6.6), 2.06 (1H, ddd, 14.8/8.7/5.5), 2.25–2.40 (2H, m), 2.67 (1H, ddd, 14.6/9.5 / 6.1), 2.90 (3H, s), 3.09 (1H, ddq, 15.5/14.9/3.0), 3.40–3.50 (2H, m), 6.56 (1H, q, $^{4}J_F$ = 1.1); ^{13}C-NMR: 15.4 (Qm, 125.8), 26.0 (Tm, 134.1/$^{4}J_F$ = 2.1), 29.6 (Q, 138.5), 39.9 (Dm, 132.1), 41.4 (Tdm, 133.6/5.2), 46.4 (Ttq, 142.4/6.8/3.5), 49.3 (Sm), 122.7 (Qd, $^{1}J_F$ = 276.6/6.7), 131.4 (Dqd, 166.0/$^{3}J_F$ = 5.5/2.5), 146.5 (qm, $^{2}J_F$ = 28.1), 170.0 (Sm), 197.4 (Sm). – Anal. Calcd for $C_{12}H_{14}F_3N_1O_2$ (261.24): C 55.17; H 5.40; N 5.36; Found: C 54.80; H 5.21; N 5.24.
Minor diastereoisomer: ^{19}F-NMR: –66.4 (s).

Spiroannelation of 1-methyl-3-trifluoroacetyl-2-piperidinone (2)

Method 2

The reaction of 1-methyl-3-trifluoroacetyl-2-piperidinone **2** (1.05 g, 5 mmol) with methyl vinyl ketone (1.1 eq.) gave first the diketone **8e** (0.59 g, 42%) after chromatography (eluent: ether). This intermediate (0.41 g, 1.5 mmol) was then cyclized into cyclohexenone **6e** (0.17 g, 43%. – chromatography: eluent 5% methanol/ether) contamining by cyclohexanone **7e** as a mixture (68/32) of diastereoisomers (VPC: 5%).

1-Methyl-3-(3-oxobutyl)-3-trifluoroacetyl-2-piperidinone (**8e**)

B.p. 75–85 °C/0.01 mm Hg. – IR (film): 2951, 2883, 1755, 1716, 1639, 1503, 1405, 1359, 1212. – MS: 279 (M^+), 222, 210, 209, 189, 182, 140, 112, 69. – ^{19}F-NMR: –72.5 (s). – ^{1}H-NMR (500 MHz): 1.68–1.74 (1H, m), 1.90–1.96 (1H, m), 2.08–2.16 (2H, m), 2.12 (3H, s), 2.16–2.24 (1H, m), 2.35 (1H, m), 2.55 (1H, ddd, 18.5/7.6/5.7), 2.73 (1H, ddd, 18.4/7.5/7.3), 2.91 (3H, s), 3.36–3.42 (2H, m). – ^{13}C-NMR: 18.8 (Tm, 131.7), 27.3 (Ttm, 131.3/4.1), 28.6 (Tm, 127.4/$^{4}J_F$ = 1.2), 29.8 (Q, 127.3), 34.6 (Qt, 138.8/1.5), 38.6 (Tm, 124.7), 49.4 (Tm, 141.7), 55.7 (Sm), 115.4 (Qd, $^{1}J_F$ = 294.2/1.4), 166.8 (Sm), 190.3 (qm, $^{2}J_F$ = 29.4), 207.6 (Sm).

1,9-Dioxo-2-methyl-7-trifluoromethyl-2-azaspiro[5,5]undec-7-ene (6e)

IR (film): 2952, 2881, 1698, 1644, 1505, 1460, 1404, 1328, 1260. – MS: 261 (M^+), 241, 233, 205, 166, 148, 126, 79, 69. – ^{19}F-NMR: –62.2 (s). – ^{1}H-NMR (500 MHz): 1.90–1.97 (1H, m), 1.97–2.03 (1H, m), 2.03–2.11 (1H, m), 2.16 (1H, ddd, 13.8/8.5/4.9), 2.2–2.3 (1H, m), 2.46 (1H, ddd, 16.8/9.1/4.7), 2.62 (1H, ddd, 13.7/9.0/4.9), 2.70 (1H, ddd, 16.9/8.4/4.9), 2.98 (3H, s), 3.32 (1H, dddd, 12.2/5.5/2.0/2.0), 3.45 (1H, ddd, 12.1/12.0/4.6), 6.48 (1H, q, $^{4}J_F$ = 1.0). – ^{13}C-NMR (125.8 MHz): 18.8 (Tm, 130.8), 29.7 (Tm, 132.9), 32.3 (Tm, 130.7), 32.9 (Tddm, 132.4/6.8/3.5), 35.5 (Qd, 138.6/2.3), 44.2 (Sm), 49.6 (Tm, 139.3), 122.9 (Qd, $^{1}J_F$ = 277.0/6.7), 131.5 (Dqm, 165.0/$^{3}J_F$ = 2.9), 149.3 (qm, $^{2}J_F$ = 28.7), 169.1 (Sm), 197.2 (Sm).

1,9-Dioxo-7-hydroxy-2-methyl-7-trifluoromethyl-2-azaspiro [5,5]undecane (7e)

Major diastereoisomer: ^{19}F-NMR: –63.7 (d, 8.8). Minor diastereoisomer: ^{19}F-NMR: –66.8 (d, 9.1).

Spiroannelations of 3-benzoyl-1-methyl-2-pyrrolidinone (3)

Method 1

The reaction of 3-benzoyl-1-methyl-2-pyrrolidinone **3** (1.02 g, 5 mmol) with methyl vinyl ketone (1.1 eq.) gave after chromatography (eluent: 3 % methanol/ether) the cyclo-

hexanone **7f** as a mixture (53/47) of diastereoisomers (0.61 g, 45%) and the pyrrolidinone **8f** (0.46 g, 34%).

1,8-Dioxo-6-hydroxy-2-methyl-6-phenyl-2-azaspiro[4,5] decane (**7f**)

Minor diastereoisomer: m.p. 161–162 °C. – IR (KBr): 3500–3200, 2950, 2926, 2882, 1693, 1674, 1497, 1457,1445, 1415. – MS: 273 (M^+), 255, 203, 168, 153, 112, 105, 98, 77. – ^{1}H-NMR (500 MHz): 1.61 (1H, ddd, 13.2/9.2/8.4), 1.71 (1H, ddd, 13.1/8.9/8.2), 1.97 (1H, ddd, 13.4/7.3/1.6), 2.28 (1H, dddd, 14.4/5.4/2.1/1.7), 2.32–2.40 (3H, m), 2.57 (3H, s), 2.82 (1H, ddd, 9.5/9.4/2.5), 3.25 (OH, brs), 3.36–3.46 (1H, m), 4.13 (1H, d, 14.1), 7.26–7.34 (3H, m), 7.47 (2H, dd, 7.0/1.6). – ^{13}C-NMR (125.8 MHz): 27.1 (Ttm, 133.1/3.0), 29.6 (Q, 138.0), 33.3 (Tm, 132.3), 38.0 (Tm, 128.6), 46.1 (Tm, 139.4), 50.9 (Sm), 51.3 (Td, 131.6/2.8), 78.7 (Sm), 125.5 (Ddd, 160.9 /6.7/5.8), 127.7 (Dm, 160.0), 127.9 (Dd, 159.3/6.6), 143.0 (St, 6.8), 175.9 (Sm), 212.2 (Sm).– Anal. Calcd for $C_{16}H_{19}N_1O_3$ (373.33): C 70.31; H 7.01; N 5.12; Found: C 69.94; H 7.14; N 4.93.

Major diastereoisomer: IR (KBr): 3392, 3057, 2973, 2885, 1720, 1660, 1508, 1498, 1464, 1452, 1444, 1394. – ^{1}H-NMR (500 MHz): 1.78 (1H, ddd, 13.6/6.4/2.4), 2.06–2.18 (2H, m), 2.26–2.34 (1H, m), 2.44 (1H, ddd, 14.5/12.5/6.4), 2.55 (1H, dm, 14.8), 2.59 (3H, s), 2.65 (1H, dd, 14.3/2.1), 2.82 (1H, ddd, 13.7/13.7/5.0), 3.06 (1H, ddd, 8.9/8.8/3.7), 3.15 (1H, dd, 14.1/ 2.6), 5.69 (1H, d, 2.7), 7.26–7.36 (5H, m). – ^{13}C-NMR: 26.2, 29.1, 31.5, 36.6, 46.0, 48.1, 50.6, 79.6, 125.4, 127.4, 127.6, 142.1, 176.5, 207.6.

3-Benzoyl-1-methyl-3-(3-oxobutyl)-2-pyrrolidinone (**8f**)

M.p. 76–77 °C. – IR (KBr): 2990, 2962, 2936, 2882, 1719, 1691, 1673, 1595, 1577, 1506, 1460, 1305. – MS: 273 (M^+), 227, 203, 168, 105, 98, 77, 43. – ^{1}H-NMR (500 MHz): 1.95 (1H, ddd, 13.1/8.1/5.6), 2.08 (3H, s), 2.24–2.38 (2H, m), 2.50 (1H, ddd, 17.9/ 9.3/5.6), 2.60 (1H, ddd, 17.9/9.7/5.7), 2.70 (1H, ddd, 13.1/8.1/5.5), 2.92 (3H, s), 3.4–3.5 (2H, m), 7.41 (2H, dd, 8.1/7.4), 7.51 (1H, tt, 7.4/1.1), 7.96 (2H, dm, 8.2). – ^{13}C-NMR (125.8 MHz): 28.3 (Tm, 131.4), 29.5 (Q, 127.2), 29.7 (Ttt, 134.6/6.5/3.5), 29.8 (Q, 138.3), 38.5 (Tm, 125.9), 46.4 (Ttq, 143.1/6.7/3.0), 59.5 (Sm), 128.1 (Dd, 161.9/7.6), 128.5 (Ddd, 160.4/7.4/6.3), 132.2 (Dt, 161.8/7.7), 135.8 (St, 7.6), 172.8 (Sm), 198.5 (Sm), 207.4 (Sm).

Method 2

The reaction of 3-benzoyl-1-methyl-2-pyrrolidinone **3** (1.02 g, 5 mmol) with methyl vinyl ketone (1.1 eq.) gave first the diketone **8f** (0.66 g, 48%) after chromatography (eluent: 5% methanol/ether). This intermediate (0.55 g, 2 mmol) was then cyclized into cyclohexenone **6f** (0.42 g, 83%. - chromatography: eluent: 5% methanol/ether).

1,8-Dioxo-2-methyl-6-phenyl-2-azaspiro [4,5] dec-6-ene (**6f**)

M.p. 137–139 °C. – IR (KBr): 3045, 2982, 2952, 2900, 2864, 1683, 1669, 1622, 1596, 1571, 1504, 1477, 1448, 1403. – MS: 254 (M^+), 227, 200, 199, 178, 170, 141, 128, 115, 102, 77. – ^{1}H-NMR: 2.0-2.2 (2H, m), 2.2–2.4 (1H, m), 2.4–2.6 (2H, m), 2.8–3.0 (2H, m), 2.85 (3H, s), 3.2–3.4 (1H, m), 6.11 (1H, s), 7.22 (2H, dm, 6.0), 7.3–7.4 (3H, m). – ^{13}C-NMR (125.8 MHz): 30.0 (Q, 138.3), 30.4 (Tdd, 134.1/3.3/3.2), 33.1 (Ttt, 131.7/8.4/4.3), 33.6 (Ttd, 130.3/4.7/3.5), 46.1 (Ttq, 142.8/6.0/3.0), 49.3 (Sm), 126.9 (Ddd, 161.2/7.1/6.1), 128.3 (Ddm, 160.1/5.8), 128.7 (Dt, 161.3/7.7), 129.9 (D, 162.5), 138.3 (Sdtm, 6.9/5.9), 161.6 (Sm), 174.1 (Sm), 198.2 (Sm). – Anal. Calcd for $C_{16}H_{17}N_1O_2$ (255.32): C 75.27; H 6.71; N 5.49; Found: C 75.28; H 7.01; N 5.59.

Spiroannelation of 3-(p-trifluoromethylbenzoyl)-1-methyl-2-pyrrolidinone (4)

Method 1

The reaction of 3-(p-trifluoromethylbenzoyl)-1-methyl-2-pyrrolidinone **4** (0.41 g, 1.5 mmol) with methyl vinyl ketone (1.1 eq.) gave after chromatography (eluent: 5% methanol/ether) the cyclohexenone **6g** (0.32 g, 67%).

1,8-Dioxo-2-methyl-6-(p-trifluoromethyl-phenyl)-2-azaspiro [4,5] dec-6-ene (**6g**)

M.p. 150–152 °C.,– IR (KBr): 2930, 2882, 1681, 1671, 1609, 1570, 1501, 1471, 1451, 1432, 1325. – MS: 323 (M^+), 322, 295, 267, 238, 178, 141, 84, 57, 49. – ^{19}F-NMR: –63.3 (s). – ^{1}H-NMR: 2.0–2.3 (3H, m), 2.4–2.6 (2H, m), 2.87 (3H, s), 2.9–3.1 (2H, m), 3.3–3.4 (1H, m), 6.13 (1H, s), 7.36 (2H, d, 8.1), 7.63 (2H, dq, 8.2/^4J_F = 0.7). – ^{13}C-NMR: 29.80 (Tm, 134.2), 29.83 (Q, 138.4), 32.6 (Tm, 135.6), 33.3 (Tm, 127.2), 45.9 (Ttq, 142.3/5.6/2.9), 49.2 (Sm), 108.8 (Qt, ^1J_F = 356.0/ 4.1), 125.1 (Ddq, 170.6/6.0/^3J_F = 3.8), 127.4 (Dd, 163.8/6.4), 130.4 (qt, ^2J_F = 32.7/7.7), 130.6 (D, 164.5), 141.9 (Sqm, ^5J_F = 1.3), 159.8 (Sm), 173.6 (Sm), 197.6 (Sm).

Spiroannelation of ethyl 3-oxalyl-1-methyl-2-pyrrolidinone (5)

Method 2

The reaction of ethyl 3-oxalyl-1-methyl-2-pyrrolidinone **5** (1.00 g, 5 mmol) with methyl vinyl ketone (1.1 eq.) gave first the diketone **8h** (0.69 g, 51%) after chromatography (eluent 5% methanol/ether). This intermediate (0.40 g, 1.5 mmol) was then cyclized into cyclohexenone **6h** (0.28 g, 75%. – chromatography: eluent 10% methanol/ether) contamining by the pyrrolidinone **8h** (VPC: mixture 85/15).

Ethyl 3-oxalyl-1-methyl-3-(3-oxobutyl)-2-pyrrolidinone (**8h**)

IR (KBr): 2984, 2937, 2893, 1732, 1720, 1718, 1687, 1444, 1370, 1271. – MS: 269 (M^+), 239, 196, 168, 126, 86, 84, 73, 43. – ^{1}H-NMR (500 MHz): 1.36 (3H, t, 7.2), 1.91 (1H, ddd, 13.4/7.8/4.5), 2.13 (3H, s), 2.16–2.20 (2H, m), 2.48 (1H, ddd, 18.0/9.1/6.0), 2.59 (1H, ddd, 13.4/9.0/6.7), 2.68 (1H, ddd, 18.0/8.9/6.5), 2.88 (3H, s), 3.44–3.52 (2H, m), 4.31 (2H, q, 7.2). – ^{13}C-NMR: 13.5 (Qt, 127.4/2.6), 26.9 (Tdd, 131.8/5.7 /5.0), 27.2 (Tm, 135.9), 28.0 (Q, 132.7), 28.3 (Q, 133.1), 37.9 (Tm, 127.2), 46.4 (Ttq, 143.3/6.9/3.4), 57.9 (Sm), 62.1 (Tq, 149.1/4.5), 160.4 (St, 3.1), 171.5 (Sm), 192.4 (Sm), 207.0 (Sqt, 5.8/2.8).

6-Carboethoxy-1,8-dioxo-2-methyl-2-azaspiro[4,5]dec-6-ene (**6h**)

IR (film): 2982, 2937, 2907, 2877, 1721, 1687, 1679, 1505, 1475, 1449, 1406, 1303. – MS: 251 (M^+), 223, 196, 178, 166, 150, 121, 91, 45. – ^{1}H-NMR (500 MHz): 1.30 (3H, t, 7.1), 2.00 (1H, ddd, 13.5/4.7/4.5), 2.19 (1H, ddd, 12.9/8.3/3.3),

2.34–2.44 (2H, m), 2.48 (1H, ddd, 13.1/12.7/4.2), 2.70 (1H, ddd, 17.0/4.5/4.5), 2.92 (3H, s), 3.45–3.51 (1H, m), 3.53 (1H, ddd, 9.7/9.6/3.3), 4.25 (2H, q, 7.2), 6.81 (1H, s). – ^{13}C-NMR: 13.4 (Qt, 127.0/2.6), 27.7 (Tm, 134.5), 29.6 (Q, 138.0), 30.8 (Tm, 131.0), 33.3 (Tdd, 131.0/3.6/3.3), 46.1 (Ttq, 141.8/6.4 / 2.9), 46.5 (Sm), 61.2 (Tq, 148.4/4.4), 133.9 (Ddm, 162.3/1.7), 149.1 (Sm), 165.0 (Sm), 174.8 (Sm), 198.1 (Sm).

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