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Effect of Base and Acyl Chloride on Regioselectivity of Acylation of 8,8-Pentamethylene-2-methyl-7,9-dioxa-1-azaspiro[4.5]dec-1-ene 1-Oxide

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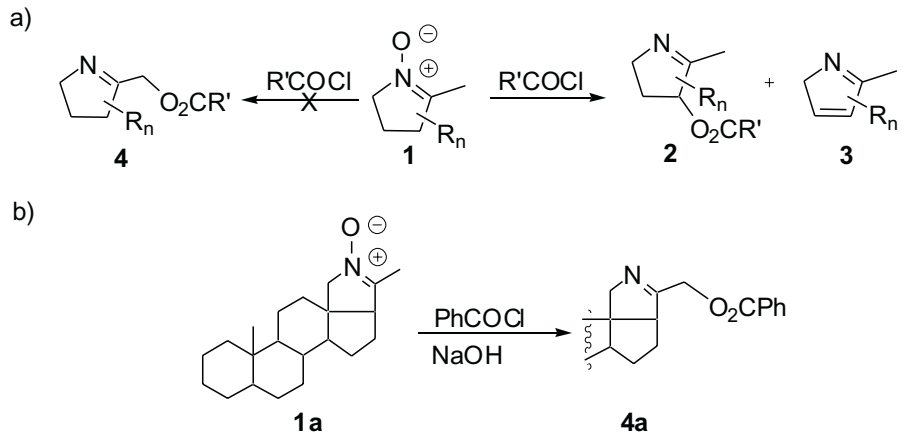
Acylation of 2-methyl-7,9-dioxa-1-azaspiro[4.5]dec-1-ene 1-oxide **(5)** in the presence of pyridine gives 3-acyloxy-2-methyl-1-pyrroline derivatives **6** independently of kind of acid chloride, while treatment of **5** with benzoyl or *p*-nitrobenzoyl chloride and triethylamine affords mainly 2-benzoyloxymethyl- **8a** and 2-*p*-nitrobenzoyloxymethyl-1-pyrroline **8b**, respectively. Acetylation of **5** was base-independent.

Key words: 2-methyl-1-pyrroline 1-oxide, acylation, regioselectivity

2-Methyl-1-pyrroline 1-oxide derivatives **1** react with acyl chlorides to give 3-acyloxy-1-pyrrolines **2** [1–5] and 2*H*-pyrroles **3** [3–5] in a ratio dependent on structure of **1** and reaction conditions. (The pyrrolines **2** react frequently with acylating agent used in excess to give *N*-acyl-3-acyloxy-2-methylenepyrrolidines [1–3]). This reaction might also furnish 2-acyloxymethyl-1-pyrroline **4**, but for unclear reasons its formation has not been observed (Scheme 1a). The only exception is benzoylation of steroidal derivative of 2-methyl-1-pyrroline 1-oxide, which affords exclusively **4a** (Scheme 1b) [6].

Scheme 1



4 **1** **2** **3**

1a **4a**

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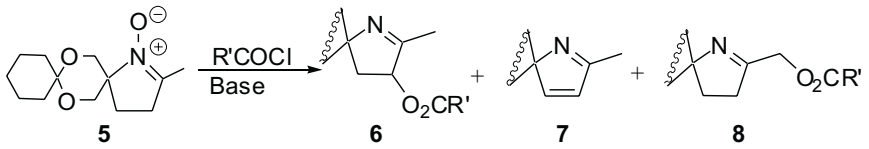
RESULTS AND DISCUSSION

We undertook studies on acylation of the title 2-methyl-1-pyrroline 1-oxide **5** [7] in hope to obtain acyloxy 1-pyrrolines, which would be used for preparation of polyhydroxylated pyrrolidines. Unexpectedly we realized that, in contrast to literature findings, it is possible to obtain selectively not only 3-acyloxy-1-pyrrolines **6** (a **2**-type product) but also 2-acyloxymethyl-1-pyrrolines **8** (a **4**-type product) by a proper choice of base and acylating reagent. Results of these studies are collected in Table 1.

Table 1. Acylation of 2-methyl-1-pyrroline 1-oxide **5**.



5 **6** **7** **8**

Entry	No of product, R'	Base	**6:7:8**[a] (summary yield)	Product[b], Yield
1	**a**, Ph	Pyr[c]	87:13:0 (54%)	**6a** (oil),[d] 40%; **7** (oil), 8%
2	**a**, Ph	TEA[e]	15:0:85 (68 – 80%)	**8a** (oil),[d] 60%
3	**a**, Ph	DBN[f]	60:20:20 (20%)	———
4	**b**, *p*-$C_6H_4NO_2$	Pyr[c]	80:20:0 (49%)	**6b** (oil),[d] 35%
5	**b**, *p*-$C_6H_4NO_2$	TEA[e]	15:0:85 (71 – 85%)	**8b** (M.p.103–107 ºC),[g] 65%
6	**c**, 3,4-$C_6H_3(OMe)_2$	Pyr	90:10:0 (51%)	**6c** (oil),[d] 31%
7	**c**, 3,4-$C_6H_3(OMe)_2$	TEA[e]	60:20:20 (48%)	———
8	**d**, Me	Pyr[c]	79:21:0 (57%)	**6d** (oil),[d] 41%
9	**d**, Me	TEA[e]	79:21:0 (54%)	———

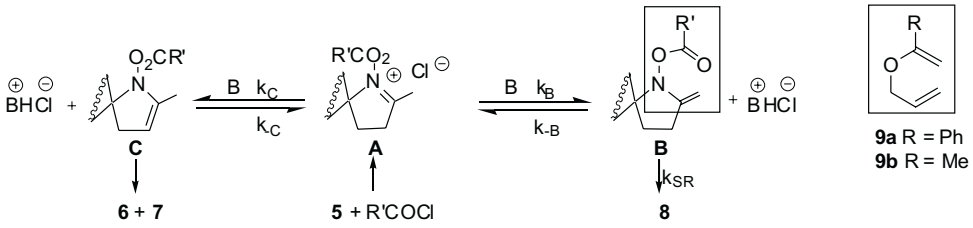
[a] Determined from ^{1}H NMR spectra. [b] Isolated product. [c] R'COCl/Pyr = 1:1. [d] Isolated by column chromatography. [e] R'COCl/TEA = 1:2. [f] PhCOCl/DBN = 1:1. [g] Isolated by crystallization from ethyl acetate – hexane mixture.

Benzoylation of **5** was examined in detail. In the presence of pyridine (Pyr) this reaction proceeded similarly to **1** to give 3-benzoyloxy-2-methyl-pyrroline **6a** contaminated with **7** (Table 1, entry 1) independently of amount of pyridine. However, the replacement of pyridine by triethylamine (TEA), a base stronger than pyridine, dramatically changed the reaction course to yield 2-benzoyloxymethyl-1-pyrroline **8a** as the major product (Table 1, entry 2). This reaction was somewhat capricious and use of 2 equiv. of TEA was required to obtain reproducible results. The employment of 1,8-diazabicyclo[4.3.0]non-5-ene (DBN), a base stronger than TEA, unexpectedly resulted in formation of **6a** as the major product together with **7** and **8a** in low summary yield (Table 1, entry 3). Probably in this case DBN acts rather as a nucleophile [8] than as a base and reacts with the chloride to furnish a derivative, which is weaker base than DBN itself. Next **5** was submitted to reaction with various acid chlorides in the presence of pyridine or TEA. The former acylation was acid chloride-independent to give 3-acyloxy-2-methyl-1-pyrrolines **6** contaminated with **7** (Table 1, entries 1, 4, 6 and 8). By contrast, acylation conducted in the presence of

TEA was acyl chloride-dependent. *p*-Nitrobenzoylation proceeded as the benzoylation to furnish **8b** as the major product (Table 1, entry 5). However, the reaction with 3,4-dimethoxybenzoyl chloride afforded **6c** as the major product; **7** and **8c** were by-products detected by ^{1}H NMR of the reaction mixture (Table 1, entry 7). Acetylation emerged to be base-independent to provide the same **6c**/**7** mixture in the presence of both TEA and pyridine (Table 1, entries 8 and 9).

Acylation of **5**, similarly to other nitrones [4,9], includes following steps (Scheme 2): *O*-acylation, deprotonation leading to enamine **B** and/or **C** and [3,3]-sigmatropic (hetero-Cope) rearrangement (SR) yielding **6** and/or **8**, respectively (in general case **2** and/or **4**). A way of formation of **3** has never been discussed.

Scheme 2



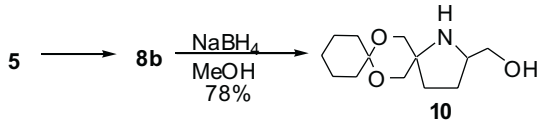
Based on this Forrester and co-workers have considered two possibilities of the exclusive formation of **2** from **1** [10]: (i) *endo*-enamine **C** is formed faster than *exo*-one **B** or (ii) **B** and **C** are in equilibrium, however, the latter rearranges into **2** faster than **B** into **3**. In the case of benzoylation of **1a** (Scheme 1b) generation of intermediate **C** from **1a** is strongly disfavored since this would contain highly strained system of two fused five-membered rings with bridgehead double bond at junction of two rings, so only *exo*-enamine **B** is formed and consequently **3a** [6,10].

In light of our results described herein Forrester's proposals seem to be invalid. In contrast to Forrester's suggestion (i), we assume by analogy to a deprotonation of methyl-alkyl ketones, that B arises faster than **C** ($k_B > k_C$), but under thermodynamic control more stable **C** is formed as the major intermediate. Indeed, a semiempirical PM3 [11] calculations reveal that **C** is lower in energy than **B** by *ca.* 3 kcal/mol independently of kind of R' and substituents at the 5 position. (The calculation was performed for simpler analogues of **B** and **C**, which would be formed during acetylation and benzoylation of 2-methyl-7,9-dioxa-1-azaspiro[4.5]dec-1-ene 1-oxide and 2,5,5-trimethyl-1-pyrroline 1-oxide.) Thus the product ratio (Table 1) depends mostly on values of k_{SR} and k_{-B}; **B** is converted into **8** when $k_{SR} > k_{-B}$ while $k_{SR} < k_{-B}$ gives rise to formation of **6** and **7** *via* more stable **C**. The outcomes of Table 1 indicate that following relations between k_{SR} and k_{-B} take place: (i) $k_{-B}^{Pyr} > k_{SR}^{Ar} > k_{-B}^{TEA}$ (Ar = Ph, *p*-$C_6H_4NO_2$), (ii) $k_{-B}^{Pyr} > k_{SR}^{Me} < k_{-B}^{TEA}$, (iii) $k_{-B}^{Pyr} > k_{-B}^{TEA}$ and (iv) $k_{SR}^{Ar} > k_{SR}^{Me}$. The inequity (iii) seems to be evident as it means that protonation of **B** by a stronger

acid ($pK_{a_{Pyr}}$ = 12.5 in MeCN [12]) is faster than its protonation by the weaker one ($pK_{a_{TEA}}$ = 18.5 in MeCN [13]). The relation (iv) is consistent with literature findings; (α-phenylvinyl)-allyl ether **9a**, isoelectronic with **Ba** undergoes [3,3]-sigmatropic rearrangement easier than (α-methylvinyl)-allyl ether **9b**, isoelectronic with **Bd** [14]. Additionally, our results showing that both **Ba** and **Bb** rearrange faster than **Bc** ($k_{SR}^{p-O_2NC_6H_4} \approx k_{SR}^{Ph} > k_{SR}^{3,4-(MeO)_2C_6H_3}$) are qualitatively compatible with results of kinetic studies on [3,2]-sigmatropic rearrangement of allyl-phenyl sulphoxides, which reveal that electron-donating substituents on phenyl ring decreases the rate of this reaction [15].

The formation of product **8** offers new synthetic utility of 2-methyl-1-pyrroline 1-oxides in pyrrolidine synthesis. Thus **8b** is smoothly reduced by sodium borohydride to yield 2-hydroxymethylpyrrolidine **10**, which could be difficult to obtain by other methods (Scheme 3).

Scheme 3



In summary, we have found out that 2-methyl-1-pyrroline 1-oxides **5** might be selectively converted into 3-acyloxy-2-methyl-1-pyrrolines **6** or 2-(aroyloxymethyl)-1-pyrrolines **8** by manipulation with the kind of base and acid chloride. The effect of these reagents on acylation of **5** is rationalized in terms of kinetic and thermodynamic control, respectively.

EXPERIMENTAL

General: ^1H and ^{13}C NMR spectra were measured with a Varian GEMINI 2000 spectrometer at 200 MHz and 50 MHz, respectively, as $CDCl_3$ solution. Coupling constants are in Hz and chemical shifts in ppm in respect to internal TMS or residual $CHCl_3$. In APT spectra resonances corresponding to CH_3 and CH are marked by (–). IR spectra were recorded with a Specord M80 (Carl-Zeiss Jena) spectrometer. Mass spectra (EI, Electron Impact; ESI, Electrospray Ionization) were obtained from an AMD 604 instrument. Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used for TLC. Column chromatography was performed on Marchery Nagel MN-Kieselgel 60 (200–300 mesh).

*General procedure for the reaction of **5** with acyl chlorides.* A solution of an acyl chloride (1.1 mmol) in dry dichloromethane (DCM, 3 mL) was added dropwise to an ice-cold solution of **5** (0.24 g, 1 mmol) and the corresponding amine (amounts are given in Table 1) in dry DCM (5 mL). This mixture was kept at 0ºC until **5** was no more detected by TLC, usually *ca.* 2 h. The reaction mixture was quenched by addition of saturated aqueous potassium bicarbonate (3 mL), an organic phase was separated and then washed with water and dried with $MgSO_4$. DCM was distilled off under reduced pressure and an residual amine was removed in *vacuum*. The residue was chromatographically separated from tars (silica gel, chloroform/acetone, 85/15, v/v) to give a **6**/**7**/**8** mixture. A product ratio was determined from ^1H NMR spectra (Table 1); the following proton signals were used for determination of quantity of components: **6** – δ 5.67–5.91 (3-H), **7** – δ 6.38 (3-H) and/or δ 7.82 (4-H), **8** – δ 4.95–5.07 (CH_2-OCOAr). The compounds

6a–**d**, **7, 8a** were isolated by column chromatography (silica gel, chloroform/acetone, 85/15, v/v) and **8b** was purified by crystallization from hexane-ethyl acetate mixture. Yields and properties of **6**, **7** and **8** are reported in Table 1.

3-Benzoyloxy-2-methyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]dec-1-ene (**6a**). ^{1}H NMR (δ): 1.19–1.65 (8H, m), 1.85–1.95 (2H, m), 2.02 (1H, dd, ^{3}J = 4.6, ^{2}J = 14.8), 2.07 (3H, s), 2.53 (1H, dd, ^{3}J = 8.2, ^{2}J = 14.8), 3.38 (1H, dd, ^{4}J = 1.6, ^{2}J = 11.3), 3.49 (1H, dd, ^{4}J = 1.6, ^{3}J = 11.3), 4.07 (2H, m), 5.87 (1H, dd, ^{3}J = 4.6, ^{3}J =8.2), 7.45 (3H, m), 7.97 (2H, m); ^{13}C NMR (δ, APT): 17.46(–), 22.35, 22.50, 25.50, 28.64, 35.98, 38.95, 66.84, 67.59, 71.72, 79.72(-), 97.97, 128.37(-), 129.24, 129.55(-), 133.29(-), 165.48, 173.74. IR/cm^{-1}: 2987, 2856, 1728, 1590, 1210, 1136, 1086. HRMS (EI, 70eV): 343.1783 calculated for $C_{20}H_{25}NO_4$, found 343.1800.

2-Methyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]dec-1,3-diene (**7**). ^{1}H NMR (δ): 1.24–2.10 (10H, m), 2.26 (3H, s), 3.34 (2H, d, ^{2}J = 12.0), 4.35 (2H, d, ^{2}J = 12.0), 6.38 (1H, d, ^{3}J = 5.0), 7.82 (1H, d, ^{3}J = 5.0). IR/cm^{-1}: 2940, 2864, 1644, 1448, 1384, 1368, 1284, 1106. HRMS (EI, 70eV): 221.1416 calculated for $C_{13}H_{19}NO_2$, found 221.1409.

2-Benzoyloxymethyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]dec-1-ene (**8a**). ^{1}H NMR (δ): 1.32–1.57 (8H, m), 1.95 (4H m), 2.63 (2H, m), 33.37 (2H, d, ^{2}J = 11.6 Hz), 3.97 (2H, d, ^{2}J = 11.6 Hz), 4.95 (2H, s), 7.38 (3H, m), 7.96 (2H, m). ^{13}C NMR (δ, APT): 22.21, 22.39, 25.37, 28.73, 30.10, 34.42, 35.67, 63.78, 66.30, 73.37, 97.80, 128.23(-), 129.08, 129.50(-), 133.12(-), 165.64, 175.28. IR (KBr)/cm^{-1}: 2940, 2864, 1730, 1642, 1528, 1156, 1102. HRMS (EI, 70eV): 343.1783 calculated for $C_{20}H_{25}NO_4$, found 343.1793.

3-*p*-Nitrobenzoyloxy-2-methyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]dec-1-ene (**6b**). ^{1}H NMR (δ): 1.42–1.66 (8H, m), 1.90 (2H, m), 2.04 (1H, dd, ^{3}J = 4.6, ^{2}J = 14.8), 2.12 (3H, s), 2.62 (1H, dd, ^{3}J = 8.4, ^{3}J = 14.8), 3.40 (1H, dd, ^{4}J = 2.0, ^{2}J = 11.4), 3.49 (1H, dd, ^{4}J = 2.0, ^{2}J = 11.4), 4.13 (2H, m), 5.91 (1H, dd, ^{3}J = 4.6, ^{2}J = 8.4), 8.15–8.31 (4H, m).^{13}C NMR (δ, APT): 17.55(-), 22.46, 22.61, 25.58, 28.52,36.32, 39.05, 66.88, 67.67, 72.04, 80.83(-), 98.20, 123.64(-), 130.80(-), 134.69, 150.78, 163.79, 173.17. IR/cm^{-1}: 3020, 2944, 1730, 1532, 1348, 1268, 1104. HRMS (EI, 70eV): 388.1634 calculated for $C_{20}H_{24}N_2O_6$, found 388. 1628.

2-*p*-Nitrobenzoyloxymethyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]dec-1-ene (8b). ^{1}H NMR (δ): 1.41–1.67 (8H, m), 1.88 (2H, m), 2.10 (2H, m), 2.71 (2H, m), 3.44 (2H, d, ^{2}J = 11.6), 4.06 (2H, d, ^{2}J = 11.6), 5.07 (2H,s), 8.25 (4H, m). ^{13}C NMR (δ, APT): 22.43, 22.61, 25.58, 29.03, 30.40, 34.64, 35.85, 66.52(2x), 73.78, 98.06, 123.57(-), 130.88(-), 134.76, 150.67, 164.06, 173.95. IR(KBr)/cm^{-1}: 3112, 2940, 1730, 1528, 1348, 1276, 1104. HRMS (EI, 70eV): 388.1634 calculated for $C_{20}H_{24}N_2O_6$, found 388.1615.

3-(3,4-Dimethoxybenzoyloxy)-2-methyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]dec-1-ene (6c). ^{1}H NMR (δ): 1.15–2.25 (10H, m), 2.09 (3H, s), 2.01 (1H, dd, ^{3}J = 4.7, ^{2}J = 14.7), 2.56 (1H, dd, ^{3}J = 8.3, ^{3}J = 14.7), 3.40 (1H, dd, ^{4}J = 2.0,^{2}J = 11.4), 3.52 (1H, dd, ^{4}J = 2.0, ^{2}J = 11.4), 3.89 (3H, s), 3.91 (3H, s), 4.05 (1H, d, ^{2}J = 11.4), 4.13 (1H, d, ^{2}J = 11.4), 5.86 (1H, dd, ^{3}J = 4.7, ^{3}J = 8.3), 7.24 (3H, m). ^{13}C NMR (δ, APT): 17.40(-), 22.29, 22.44, 25.43, 28.69, 35.78, 38.76, 55.86(-)(2x), 66.66, 67.52, 71.49, 79.43(-), 97.95, 110.06(-), 111.76(-), 123.60(-), 121.51, 148.52, 153.20, 165.19, 174.32. IR/cm^{-1}: 3035, 2935, 1726, 1530, 1344, 1259, 1200, 1104. HRMS (EI, 70eV): 403.1995 calculated for $C_{22}H_{29}NO_6$, found 403.2016.

3-Acetyloxy-2-methyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]dec-1-ene (6d). ^{1}H NMR (δ): 1.35–1.70 (8H, m), 1.88 (3H, m), 2.02 (3H, s), 2.07 (3H, s), 2.47 (1H, dd, ^{3}J = 8.5, ^{3}J = 14.6), 3.33 (1H, dd, ^{4}J = 2.1, ^{2}J = 11.3), 3.43 (1H, dd, ^{4}J = 2.1, ^{2}J = 11.3), 3.75 (2H, m), 5.63 (1H, dd, ^{3}J = 4.8, ^{3}J = 8.5). ^{13}C NMR (δ, APT): 17.28(-), 20.77(-), 22.39, 22.54, 25.52, 28.58, 36.09, 38.77, 66.07, 67.45, 71.47, 79.19(-), 98.08, 168.98, 174.57. IR/cm^{-1}: 2940, 1744, 1650, 1448, 1370, 1234, 1156, 1108. HRMS (EI, 70eV): 281.1627 calculated for $C_{15}H_{23}NO_4$, found 281.1606.

2-Hydroxymethyl-8,8-pentamethylene-7,9-dioxa-1-azaspiro[4.5]decane (10). Sodium borohydride (0.15 g, 4.0 mmol) was added to a solution of **8b** (0.34 g, 0.88 mmol) in MeOH (2 mL) and the mixture was stirred overnight at room temperature. MeOH was removed under reduced pressure and residue was treated with Et_2O (3×3 mL). Ethereal solutions were combined and dried over sodium sulphate. Et_2O was removed and a residue was purified by column chromatography (silica gel, $CHCl_3$:MeOH/9:1, v/v) to

afford **10** (0.17 g, 78%) as colourless oil. ^{1}H NMR (δ): 1.38–1.90 (14H, m), 3.13 (2H, brs), 3.32–3.45 (2H, m), 3.51–3.59 (3H, m), 3.68 (1H, d, ^{2}J = 11.4), 3.75 (1H, d, ^{2}J = 11.2). ^{13}C NMR(δ, APT): 22.33, 22.37, 25.43, 25.96, 29.85, 30.71, 34.51, 57.81(-), 58.38, 64.59, 66.84, 68.76, 97.86. IR/cm^{-1}: 3324, 3243, 2945,1644, 1245, 1115. HRMS (ESI): 242.1751 calculated for $C_{13}H_{24}NO_3$ ($M+H^+$), found 242.1751.

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