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Synthesis of spiro[pyrrolidine or piperidine-3,9′-xanthenes] by anionic cycloacylation of carbamates

Domingo Quintás, Alberto García and Domingo Domínguez*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Facultad de Química, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

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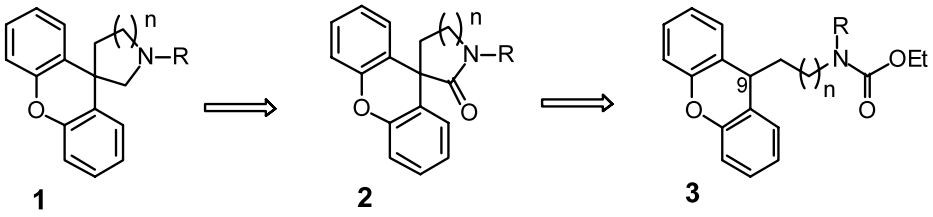
Abstract—Xanthene spiropyrrolidines and spiropiperidines were synthesized by a process in which the key step was intramolecular trapping of a xanthen-9-yl anion by a carbamate side-chain situated at the same position.

The title compounds (**1**, $n=1$, 2) have been reported to have antibacterial and antifungal activities and to affect the central nervous system.[1] Spiropyrrolidinones have also been reported to have sedative, analeptic and hypotensive activities.[2] All previously reported synthesis of these spiro systems have been based on the intermolecular reaction of xanthen-9-yl anions with aminoalkylating agents such as *N*-ethoxycarbonylaziridine,[3] 1-ethyl-3-chloropyrrolidine,[2] 3-dimethylaminoethyl chloride[1] or, for piperidine derivatives, 3-dimethylaminopropyl chloride.[1] Of these syntheses, the most direct one is the approach of Stamm et al.,[3] but it affords only spiropyrrolidinones in moderate yields.

In this paper we report an alternative approach to these pharmacologically interesting compounds in which the five or six-membered aza-ring is assembled by a versatile anionic cycloacylation process[4] consisting of intramolecular trapping of the xanthen-9-yl anion by a carbamate side-chain situated at the same position (Scheme 1). The required carbamate-bearing intermediates **3** are easily prepared from readily available aldehydes (**5** or **8**), and the xanthenospirolactams **2** obtained in the key step are easily reduced to the desired products **1**.

Aldehyde **5** has previously been prepared from 9-hydroxyxanthene by a multistep procedure.[5] In this work we introduced the acetaldehyde unit by means of a direct nucleophilic substitution reaction. It is well known that the hydroxy group at the doubly benzylic position of xanthene can be easily replaced by nucleophiles such as alcohols, amines, amides and active methylene compounds;[6] we found that secondary and tertiary enamides can be introduced in the same way. In the case of tertiary enamides, the acyl immonium intermediate can either be trapped in situ by a second nucleophile (e.g. ethanol) or hydrolyzed to an aldehyde group. By means of the latter option, a 95% yield of aldehyde **5** was obtained by reaction of 9-hydroxyxanthene **4** with *N*-methyl-*N*-vinyl acetamide in glacial acetic acid at rt for 12 h (Scheme 2).



Scheme 1.

Keywords: spiroxanthenes; pyrrolidines; piperidines; anionic cyclization; cycloacylation.
* Corresponding author. Fax: +34-981-595012; e-mail: qomingos@usc.es

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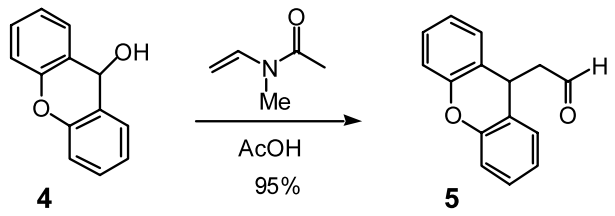
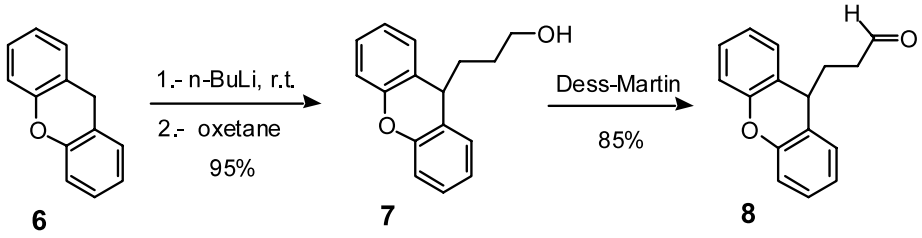


Scheme 2.

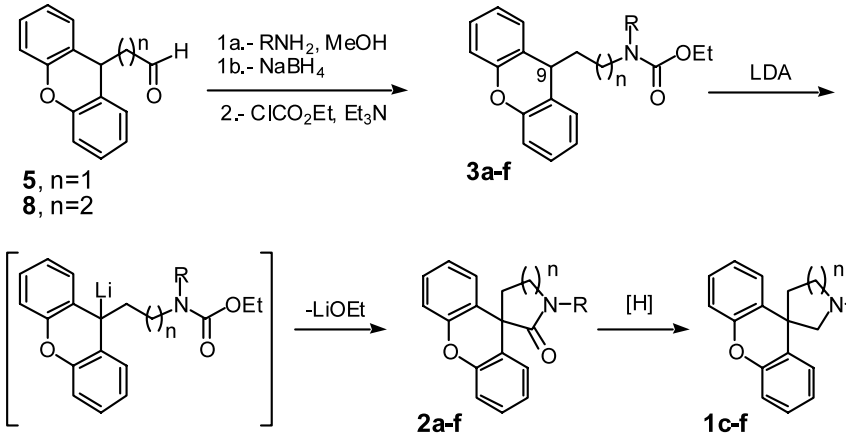
Aldehyde **8** was also prepared by a procedure that is much more efficient than the previously reported five-step synthesis from 9-hydroxyxanthene.[5] Envisaging that the corresponding alcohol might be obtained as the result of nucleophilic opening of the oxetane ring by xanthen-9-yl lithium, we reacted commercially available xanthene **6** with *n*-BuLi for 1 h at rt and treated the resulting solution with oxetane. This gave a 95% yield of alcohol **7**,[5] which upon oxidation with Dess–Martin periodinane afforded aldehyde **8** in 85% yield (Scheme 3).

Transformation of the aldehydes **5** and **8** into the required carbamates was performed by conventional chemistry (Scheme 4): condensation with the appropriate primary amine in methanol, followed by reduction with $NaBH_4$, gave the secondary amines, which were treated with ethyl chloroformate to obtain carbamates **3a–c** (from propionaldehyde **8**) and **3d–f** (from acetaldehyde **5**) in the overall yields listed in Table 1.[7]

We now approached the key step of the planned synthesis: conversion of position 9 of compounds **3** into an anion susceptible to intramolecular attack by the electrophilic carbonyl group, resulting in the formation of xanthenospirolactams **2** and concomitant loss of ethoxide (Scheme 4). When 1 equivalent of LDA was added at −78°C to carbamate **3a**, an intensely red solution



Scheme 3.

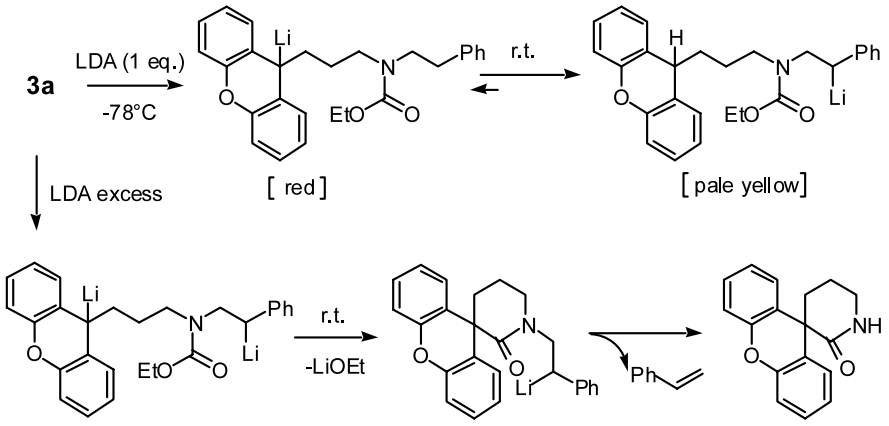


Scheme 4.

Table 1. Preparation of carbamates **3**, their cyclization to xanthenospirolactams **2**, and reduction to **1**

Compound **3**	R	% Yield[a] of **3**	Equiv. of LDA	% Yield[a] of **2**[8]	% Yield[a] of **1**[9]
a ($n=2$)	CH_2CH_2Ph	60	1	S.M.	
a ($n=2$)	CH_2CH_2Ph		2.5	60 (R = H)	
b ($n=2$)	Bn	70	2.5	55 (R = H)	
c ($n=2$)	Bu	76	2.5	85	60
d ($n=1$)	CH_2CH_2Ph	96	1.2	42	50
d ($n=1$)	CH_2CH_2Ph		2.5	52 (R = H)	47 (R = H)
e ($n=1$)	Bn	93	1.2	75	98
f ($n=1$)	Bu	90	2.5	85	80

[a] Yields refer to pure isolated products.



Scheme 5.

formed but only starting material was recovered after 6 h of stirring at low temperature, and the same result was obtained when 1 equiv. of $BF_3{\cdot}OEt_2$ was added to activate the carbonyl. When the reaction was allowed to warm to rt after LDA addition, the solution turned from red to pale yellow, but again only starting material was recovered. Only when LDA was added in excess (2.5 equiv.) and the temperature was raised to rt and stirred for 6 h did cyclization take place, and subsequent β-elimination afforded the secondary lactam **2** ($n=2$, R = H).

We interpret the above results as follows. The red solution obtained at low temperature indicates formation of an anion by deprotonation of position 9, but no reaction occurs (Scheme 5). When the temperature is raised, equilibrium between the xanthen-9-yl anion and the benzylic anion of the nitrogen substituent is shifted very much to the latter, giving the pale yellow solution, and since cyclization is now effectively precluded and β-elimination is slow for the acyclic carbamate, only starting material is recovered after quenching. However, when a second equivalent of LDA is added, both benzylic positions are deprotonated and cyclization occurs, followed by the easier β-elimination from the cyclic lactam (better leaving-group ability than the carbamate in the open derivative).

Similar behavior was observed with carbamate **3b**: stirring with 2.5 equivalent of LDA for 12 h at rt achieved cyclization but an unexpected *N*-debenzylation occurred since the major product isolated was the unsubstituted lactam **2** ($n=2$, R = H). No *N*-dealkylation process was observed with carbamate **3c**; in this case, treatment with 2.5 equiv. of LDA[10] at −78°C, followed by stirring at rt for 3 h, afforded the expected spiropiperidone **2c** in an excellent 85% yield (Table 1).

Cyclization to five-membered rings proved to be faster, and occurred even at −78°C. When carbamate **3d** was treated with 1.2 equiv. of LDA at −78°C for 3 h, a 42% yield of spiropyrrolidinone **2d** was obtained along with starting material (50%) and traces of the secondary spiropyrrolidinone **2** ($n=1$, R = H).[11] Stirring **3d** at rt for 6 h following addition of 2.5 equiv. of LDA at −78°C afforded a 52% yield of *N*-dealkylated spiropyrrolidinone **2** ($n=1$, R = H). Cyclization of the *N*-benzyl carbamate **3e** was achieved in 75% yield by treatment with 1.2 equiv. of LDA at −78°C for 2.5 h;[7,8] in this case cyclization took place at low temperature and **2e** suffered no *N*-debenzylation, unlike the homologous carbamate **3b**. Similar treatment of carbamate **3f**, but using a greater excess of LDA (2.5 equiv.), afforded an 85% yield of the cyclized pyrrolidinone **2f**.[7,10]

Finally, reduction of the carbonyl group of lactams **2** with $BH_3{\cdot}SMe_2$ or LAH in refluxing THF[9] afforded the corresponding spiropiperidine **1c** and spiropyrrolidines **1d–f** (Table 1).

Summing up, we have developed an efficient new synthetic route from xanthene or xanthone to two pharmacologically interesting families, xanthene spiropyrrolidines and xanthene spiropiperidines.

Acknowledgements

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7. All new compounds were fully characterized spectroscopically and had satisfactory elemental analyses or HRMS data.
8. **The following cycloacylation procedure was typical**. To a solution of carbamate **3e** (1.02 g, 2.63 mmol) in 30 mL of dry THF at −78°C was added 3.16 mmol LDA (1.2 equiv.). The red solution so obtained was kept at that temperature for 2.5 h and then quenched with aq. NH_4Cl. The solvents were evaporated and the residue was dissolved in EtOAc and washed with water. Chromatography of this crude on a SiO_2 column using a 4:1 mixture of hexane and ethyl acetate as eluent afforded 0.67 g of **2e** (75% yield) as a white solid. Mp 165–166°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43–7.36 (m, 5H), 7.28–7.21 (m, 2H), 7.11 (d, $J=8.6$, 2H), 7.12–7.01 (m, 4H), 4.72 (s, 2H), 3.43 (t, $J=7.0$, 2H), 2.38 (t, $J=7.0$, 2H). ^{13}C-DEPT NMR (250 MHz, $CDCl_3$) δ 174.8 (C), 150.9 (2×C), 136.2 (C), 128.9 (2×C), 128.6 (2×CH), 128.4 (2×CH), 127.9 (CH), 126.5 (2×CH), 124.4 (2×C), 123.6 (2×CH), 116.7 (2×CH), 48.9 (C), 47.6 (CH_2), 43.6 (CH_2), 40.1 (CH_2). IR ν_{max} 3060–2860, 1684, 1480. EI-MS m/z (%) 341 (17), 250 (94), 208 (53), 207 (53), 194 (100). HRMS for $C_{23}H_{19}NO_2$ calcd 341.1415, found 341.1419.
9. (a) **The following procedure was typical for reduction of lactams with $BH_3{\cdot}SMe_2$**: To a solution of the spiropyrrolidinone **2e** (250 mg, 0.73 mmol) in 20 mL of dry THF was added $BH_3{\cdot}SMe_2$ complex (0.44 mL, 4.4 mmol). The reaction mixture was refluxed under argon for 6 h and then cooled to 0°C, 10 mL of aqueous KOH were added and the resulting mixture was refluxed for 10 min and cooled. The solvents were removed under vacuum, the residue was taken up in ethyl acetate, and the organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated to dryness. Chromatography of this residue on a SiO_2 column using an 85:15 mixture of hexane and ethyl acetate afforded the spiropyrrolidine **1e** (235 mg, 98%) as a white solid. Mp 239–241°C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74 (dd, $J=7.8$ and 1.4, 2H), 7.41 (d, $J=7.0$, 2H), 7.33 (t, $J=7.0$, 2H), 7.25 (t, $J=7.1$, 1H), 7.21 (td, $J=7.8$ and 1.5, 2H), 7.11 (td, $J=7.5$ and 1.4, 2H), 7.01 (dd, $J=8.0$ and 1.4, 2H), 3.75 (s, 2H), 3.04 (s, 2H), 3.02 (t, $J=7.1$, 2H), 2.51 (t, $J=7.1$, 2H). ^{13}C-DEPT NMR (250 MHz, $CDCl_3$) δ 150.0 (2×C), 139.6 (C), 130.0 (2×C), 128.9 (2×CH), 128.7 (2×CH), 128.5 (2×CH), 127.8 (2×CH), 127.3 (CH), 123.5 (2×CH), 116.2 (2×CH), 74.9 (CH_2), 60.2 (CH_2), 55.9 (CH_2), 48.7 (CH_2), 43.6 (C). IR ν_{max} 3100–2940, 1572, 1484. EI-MS m/z (%) 327 (100), 236 (13), 208 (49), 207 (58), 133 (88). HRMS for $C_{23}H_{21}NO$ calcd 327.1623, found 327.1638. (b) Lactams **2** ($n=1$, R = H) and **2c** were reduced by treatment with LAH for 24 h in refluxing THF, which gave **1** ($n=1$, R = H)[1] and **1c** in moderate yields (Table 1).
10. We choose to use an excess of LDA since it is not deleterious and gives higher yields.
11. Compound **2** ($n=1$, R = H) was previously prepared by reaction of the xanthen-9-yl anion with *N*-ethoxycarbonylaziridine, which involves a cyclization of intermediate isocyanates that is related to the processes described in the present paper; see Ref. 3a.