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On the structure of compounds obtained from the reaction of amines with 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione

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Abstract—Recent literature data on the reaction of aromatic amines with 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione need to be corrected.

1. Introduction

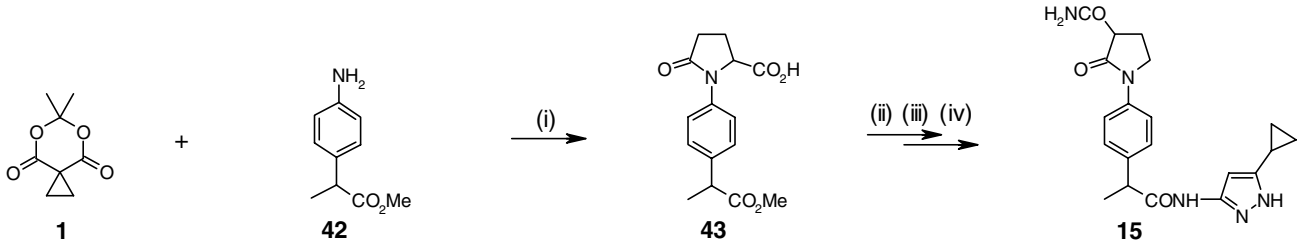
In a recent article on new inhibitors of CDK2/cyclin kinase, Pevarello et al. described the synthesis of acid **43**, named and drawn as a pyroglutamic acid. This product, in further reactions, yielded a compound named and drawn as the pyrrolidone-3-carboxamide **15** (Scheme 1).[1] In another paper on VCAM/VLA-4 antagonists, Tilley et al. reported the synthesis of pyroglutamic acid **11** whose thermal decarboxylation in DMSO gave pyrrolidinone **12** (Scheme 2).[2]

We have been paying attention to these results because of our interest in pyrrolidinone chemistry.[3] These reactions were unusual in the field of the general reactivity of Meldrum's acid derivative **1**, and the easy decarboxylation of **11** to **12** was not common in the pyroglutamic acid chemistry.[3] Thus, we wished to verify the structure of pyrrolidinones **11** and **43**.

2. Discussion

Meldrum's derivative **1** is a member of a series of cyclopropane compounds substituted on the same carbon by two electron-withdrawing groups. Ring opening addition reaction between various nucleophiles and these reagents has been known for a long time (Scheme 3).[4] In the case of spiro diester **1**, this addition has already been realized with pyrroles,[5] guanines,[6] Meldrum's acid[7] or acetamidomalonic esters[8] as nucleophile.

These reactions were extended by Danishefsky and coworkers[9] who described that the initial homoconjugate



Scheme 1. Reagents and conditions:[1] (i) toluene, 60 °C, 12 h; (ii) HOBT ammonium salt, EDCI, THF/DMF; (iii) MeOH/H_2O, Na_2CO_3; (iv) $HetNH_2$, EDCI, CH_2Cl_2, 20 °C.

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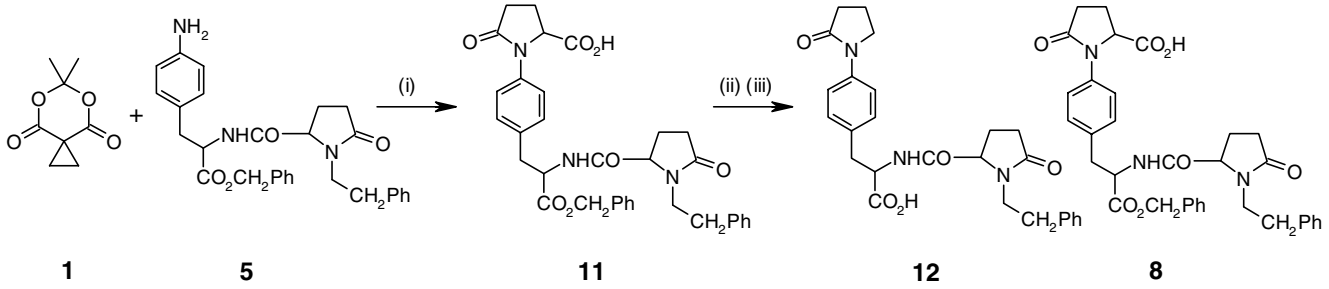
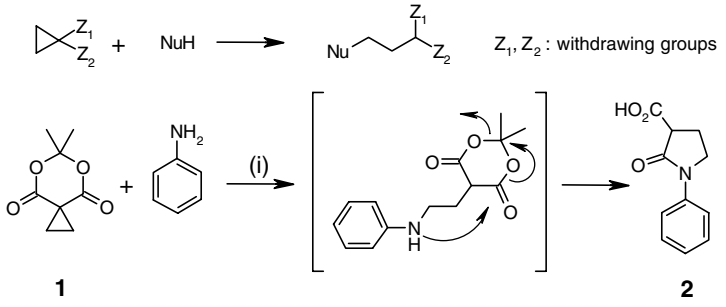


Scheme 2. Reagents and conditions:[2] (i) CH_2Cl_2, reflux, 4 h; (ii) H_2, Pd(C); (iii) DMSO, 100 °C, 12 h.



Scheme 3. Reaction conditions:[9] (i) neat, 20 °C, 12 h.

addition of aniline to the electrophilic cyclopropane ring of **1** was followed by attack of the substituted aniline on the Meldrum's ring. Compound **2** was thus obtained in 80% yield (Scheme 3).

Pevarello et al.[1] and Tilley et al.[2] also reacted the Meldrum's acid derivative **1** with aniline derivatives. However, they described that pyroglutamic acids **43** and **11**, respectively, would be obtained from anilines **42** and **5**, instead of 2-pyrrolidone-3-carboxylic acids **7** and **8**, which should have been obtained (Scheme 2, Fig. 1) in accordance with the literature. Because Tilley did not report physical data, we focussed on the NMR data described by Pevarello et al.[1]

We have compared in Table 1, the pyrrolidinone part of the ^{1}H NMR spectrum described for compound **43**[1] (**43**-*described*) with the spectrum of authentic pyroglutamic acid **3**[11,12] obtained by malonic synthesis[13] (Scheme 4).

Two multiplet signals centered at 2.30 and 2.65 ppm were assigned to the four protons Ha and Hb of pyroglutamic acid **3**. For lactam **43**-*described*, these protons appeared at 2.25 and 3.78 ppm, respectively. This fairly large difference was emphasized for the Hc protons which were observed at 3.46 ppm for **43**, contrasting to 4.78 ppm for **3**.

The structures **3** and **43**-*described* are both *N*-phenyl pyroglutamic acids. The difference of substituents of the phenyl group was not sufficient to explain the difference of chemical shifts for the protons Ha, Hb and especially Hc of these two acids. Moreover the computated chemical shifts[16] for the five protons of a pyroglutamic structure **43** (**43**-*calculated*) are very close to the values of the authentic pyroglutamic acid **3**, but very different from the values for **43**-*described*.[1] Thus, we conclude that the product **43** is not a *N*-phenyl pyroglutamic acid.

Because of the literature reports suggesting that the spiro diester **1** could react with anilines to give 2-pyrrolidinone-3-carboxylic acid **2**, we looked if the structure of compound obtained by Pevarello was **7**, belonged

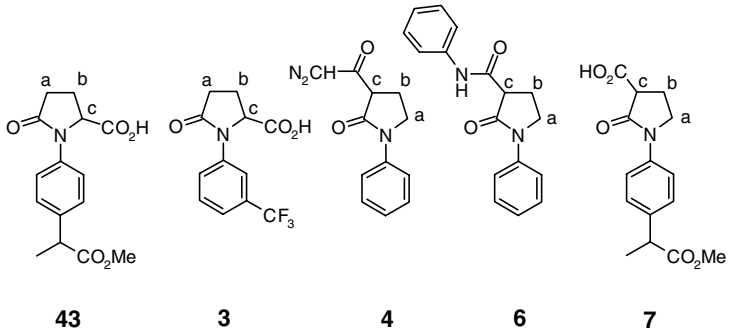
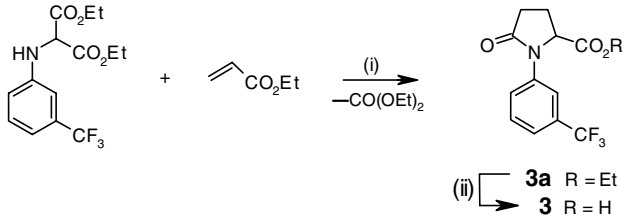


Figure 1. Numbering used in NMR descriptions of Table 1.

Table 1. ^{1}H NMR spectra of selected compounds

No	ppm				
43 (*described*)[1]	2.25 (m, 2Hb)		3.46 (dd, $J = 9.1$, 7.9 Hz, Hc)	3.78 (m, 2Ha)	
3[11,12]	2.20–2.40 (m, Hb_1)	2.45–2.90 (m, 2Ha, Hb_2)			4.78 (dd, $J = 9.0$, 3.1 Hz, Hc)
43 (*calculated*)[16]	2.23–2.42 (m, Hb_1)	2.54–2.81 (m, 2Ha, Hb_2)			4.78 (dd, $J = 8.1$, 3.5 Hz, Hc)
4[10]	2.20–2.31 (m, Hb_1)	2.68–2.80 (m, Hb_2)	3.53 (q, $J = 3$ Hz, Hc)	3.78–3.98 (m, 2Ha)	
6[12,14]	2.45–2.63 (m, Hb_1)	2.63–2.83 (m, Hb_2)	3.67 (t, $J = 9.4$ Hz, Hc)	3.91 (dd, $J = 8.3$, 5.8 Hz, 2Ha)	
7 (*calculated*)[16]	2.10–2.28 (m, Hb_1)	2.28–2.48 (m, Hb_2)	3.43 (dd, $J = 8.1$, 6.8 Hz, Hc)	4.09 (dd, $J = 7.4$, 6.9 Hz, 2Ha)	



Scheme 4. Reagents and conditions: (i) EtONa, EtOH, reflux, 12 h; (ii) NaOH, H_2O, reflux, 5 h.

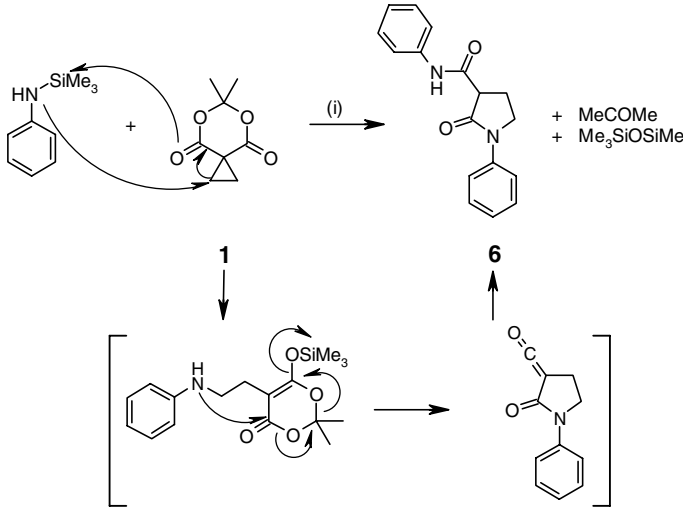
to this chemical family (Fig. 1). We have compared in Table 1 the pyrrolidinone part of the ^{1}H NMR spectrum for **43**-*described* with the spectra of lactam **4**[10] and of pure 2-pyrrolidinone-3-carboxylic amide **6**[12,14] synthesized in one-step from the reaction of *N*-trimethylsilylaniline with **1** (a possible mechanism[15] for this reaction is given in Scheme 5).

In the ^{1}H NMR spectra of **4** and **6**, two multiplet signals in the range 2.20–2.83 ppm were assigned to the two protons Hb; the proton Hc was observed in the range 3.53–3.67 ppm and the signal in the range 3.78–3.91 ppm was attributed to the two protons Ha. Peaks with identical chemical shifts and integrated intensities were also observed for **43**-*described*. Besides, computed spectrum[16] of the structure **7** gave very similar results for the five protons of the pyrrolidinone ring.

We have first shown that compound **43** is not a pyroglutamic acid derivative. We propose that the pyrrolidinone-3-carboxylic acid **7** was produced from the reaction between the Meldrum's acid derivative **1** and the aniline **42**. This formula is in accordance with the general results of Danishefsky and co-workers,[9] and experimental ^{1}H NMR spectrum is compatible with a pyrrolidinone structure.

3. Conclusion

We have shown that the assigned formula for compound **43**[1] needed to be corrected to structure **7**. In the same way, it was obvious that formula **11**[2] needs to be corrected by a pyrrolidinone-3-carboxylic acid (that will also justify the easy decarboxylation of **11** to **12** which was not common in the pyroglutamic acid chemistry).[3]



Scheme 5. Reaction conditions: (i) neat, 80 °C, 24 h.

These modifications in the structure of **43** and **11** do not influence the formulas of **12** and **15**.

4. Experimental

Melting points were determined using an electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were recorded on a Perkin–Elmer 700 spectrometer. Microanalyses were performed by the 'Service Central de Microanalyses' of CNRS in Vernaison, France.

4.1. Ethyl *N*-(3-trifluoromethylphenyl)pyroglutamate (3a)

Ethyl acrylate (26 g, 0.26 mol) was added to a stirred solution of diethyl {[3-(trifluoromethyl)phenyl]amino} malonate (80 g, 0.25 mol) and sodium ethoxide (0.26 mol) in ethanol (100 mL). The solution was refluxed for 12 h. After cooling at 0 °C, the mixture was acidified, and then concentrated. The solid was discarded, solvents were evaporated and the product was distilled to give 51 g (68%) of a slightly yellow oil, bp (0.1 mmHg): 127–128 °C; IR (neat): ν (cm^{-1}) 1740, 1705, 1610, 1590, 1495, 1455; ^{1}H NMR ($CDCl_3$): δ (ppm) 1.19 (t, $J = 7.0$ Hz, 3H), 2.20–2.40 (m, 1H), 2.48–2.95 (m, 3H), 4.22 (q, $J = 7.0$ Hz, 2H), 4.5–4.9 (m, 1H), 7.2–7.9 (m, 4H).

Anal. Calcd for $C_{14}H_{14}NO_3F_3$: C, 55.82; H, 4.68; N, 4.65; F, 18.92. Found: C, 55.86; H, 4.89; N, 4.76; F, 18.90.

4.2. *N*-(3-Trifluoromethylphenyl)pyroglutamic acid (3)

A stirred mixture of ester **3a** (9 g, 0.030 mol) and sodium hydroxide (1.2 g, 0.030 mol) in water (30 mL) was refluxed for 5 h. After cooling at room temperature, the solution was washed with diethyl ether. The aqueous phase was strongly stirred by using a large magnetic bar, and then acidified by adding slowly 2 M HCl. The solid obtained was recrystallized (acticarbon) from ethanol/water (1/1) to give acid **3**, 5.2 g (63%), mp (ethanol/water): 125–126 °C; IR (Nujol): ν (cm^{-1}) 1725, 1640, 1610, 1590, 1495; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.20–2.40 (m, 1H), 2.45–2.90 (m, 3H), 4.78 (dd, $J = 9.0$, 3.1 Hz, 1H), 5.62 (s, 1H, deuterium oxide exchangeable), 7.10–7.80 (m, 4H).

Anal. Calcd for $C_{12}H_{10}NO_3F_3$: C, 52.75; H, 3.69; N, 5.13; F, 20.86. Found: C, 52.46; H, 3.66; N, 5.47; F, 20.42.

4.3. 2-Oxo-*N*,1-diphenyl-3-pyrrolidinecarboxamide (6)

A stirred mixture of **1** (10 g, 0.059 mol) and *N*-trimethylsilylaniline (19 g, 0.115 mol) was heated at 80 °C for 24 h (N_2) to give a stick paste and an oil containing acetone and hexamethyldisiloxane. Methanol (50 mL) was added and the mixture was stirred at room temperature for 2 h. The precipitate was filtered, and then washed with ether to give 4.6 g of **6** as a white solid (29%), mp (methanol): 204–206 °C; IR (Nujol): ν (cm^{-1}) 1685, 1660, 1645, 1595, 1550, 1490; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.45–2.63 (m, 1H), 2.63–2.83 (m, 1H), 3.67 (t, $J = 9.4$ Hz, 1H), 3.91 (dd, $J = 8.3$, 5.8 Hz, 2H), 7.11 (tt, $J = 7.3$, 1.6 Hz, 1H), 7.23 (tt, $J = 7.3$, 1.9 Hz, 1H), 7.34 (tt, $J = 8.1$, 1.9 Hz, 2H), 7.42 (tt, $J = 7.4$, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ (ppm) 20.3 (CH_2), 46.9 (CH_2), 48.7 (CH), 120.0 (CH), 120.8 (CH), 124.4 (CH), 125.9 (CH), 129.2 (CH), 129.3 (CH), 137.9 (C), 138.7 (C), 165.5 (C), 171.8 (C).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.49; H, 5.69; N, 10.21.

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