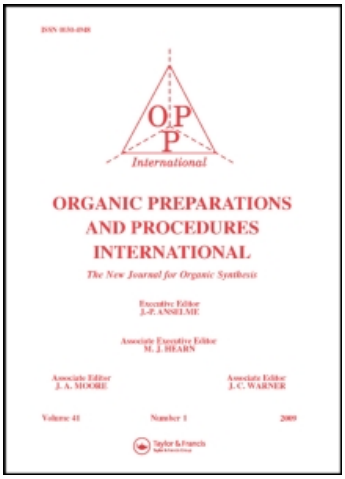

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 2-DIMETHYLAMINO-5-(α-CHLOROALKENYL)-13-OXAZIN-6-ONES

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To cite this Article Beccalli, Egle M. and Marchesini, Alessandro(1993) 'SYNTHESIS OF 2-DIMETHYLAMINO-5-(α-CHLOROALKENYL)-13-OXAZIN-6-ONES', Organic Preparations and Procedures International, 25: 2, 234 — 237
To link to this Article: DOI: 10.1080/00304949309457953
URL: http://dx.doi.org/10.1080/00304949309457953

SYNTHESIS OF 2-DIMETHYLAMINO-5-(α-CHLOROALKENYL)-1,3-OXAZIN-6-ONES

Submitted by (05/11/92)

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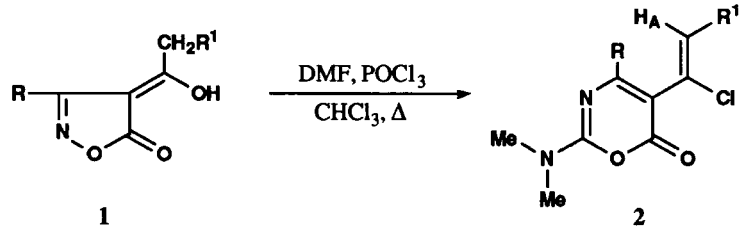
We previously described the synthesis of 2-dialkylamino-1,3-oxazin-6-ones[1] and 2-dimethylamino-5-alkenyl-1,3-oxazin-6-ones[2] from isoxazolin-5-ones and 4-alkylideneisoxazolin-5-ones respectively, by a Vilsmeier-Haack type reaction. We now report the results obtained when the Vilsmeier-Haack reaction is carried out on 4-(α-hydroxyalkylidene)isoxazolin-5-ones (**1**). The starting isoxazolones **1b** and **1d** are known compounds and compounds **1a** and **1c** were prepared according to reported methods.[3,4]

When the reaction was carried out with 2.5 equiv. of the Vilsmeier reagent, the sole products were the 2-dimethylamino-5(α-chloroalkenyl)-1,3-oxazin-6-ones (**2a-d**, Table 1). While only one stereoisomer of **2b** is isolated, a 2:1 mixture (approx. ^{1}H NMR) of two isomers of **2a** was obtained;



1 2

a) R = *n*-Pr, R^1 = Me b) R = Ph, R^1 = Me c) R = *n*-Pr, R^1 = H d) R = Ph, R^1 = H

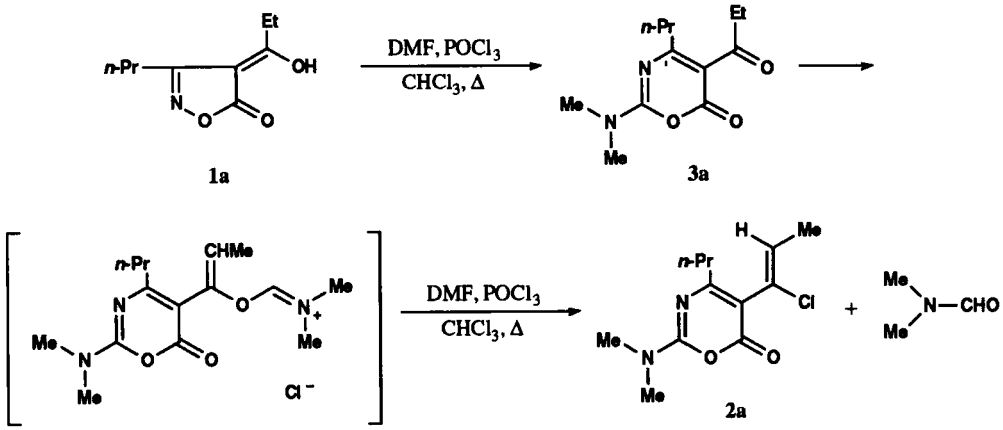
the major isomer was easily isolated in the pure state by crystallization. The chemical shift of the olefinic proton for the major isomer of **2a** is at δ 5.73 and at δ 6.05 for the minor one. In agreement with the known deshielding effect of the chlorine atom,[5] we suggest the Z stereochemistry for the major isomer of **2a**. The same stereochemistry was proposed for **2b**. If the reaction of **1a** is carried out with one equivalent of the Vilsmeier reagent, the reaction mixture contained not only oxazinones **2a** and unreacted isoxazolones **1a**, but also a new compound, isolated in low yield (see Experimental Section) and shown to be the 2-dimethylamino-5-propionyl-1,3-oxazin-6-ones (**3a**). This compound arises from initial attack of the Vilsmeier reagent on position 2 of the isoxazolone ring.[1,2]

Compound **3a** reacts with the Vilsmeier reagent to give oxazinone **2a**, which supports 5-ketooxazinones **3** as intermediates in the formation of the 5-chloroalkenyloxazinones **2** from isoxazolones **1**. The formation of derivatives **2** from compounds **3** may be rationalized, as in the formation of α-chlorostyrene from acetophenone,[6] by electrophilic attack of the Vilsmeier reagent on the carbonyl oxygen followed by a nucleophilic displacement of dimethylformamide by chloride ion from the intermediate. Furthermore, compounds **2** like α-chlorostyrene,[6] do not react further with the Vilsmeier reagent.

TABLE 1. Mps, Yields, Elemental Analyses and Spectral Data.

Cmpd.	Yield (%)	mp (°C) bp (torr)	Elemental Analysis Calcd. (Found) C	H	N	IR (cm^{-1})	^1H NMR (δ)
1a	86	99-100[a]	59.00 (59.11)	7.15 (7.19)	7.65 (7.71)	1708, 1670	1.02 (3H, t, J = 7, $-CH_3$); 1.29 (3H, t, J = 8,$-CH_3$); 1.73 (2H, m,$-CH_2$); 2.73 (4H, m, 2-CH_2); 8.86 (1 H, s,-OH)[b]
1c	62	80-81[c]	56.79 (56.87)	6.55 (6.61)	8.28 (8.33)	1758, 1680	1.12 (3H, t, J = 7.5, $-CH_3$); 1.79 (2H, m, $-CH_2$); 2.51 (3H, s, CH_3-C=); 2.74 (2H, t, J = 8, $-CH_2$);11.45 (1 H, s,-OH)[b]
2a[d]	80	69-70[e]	56.14 (56.30)	6.67 (6.71)	10.91 (10.85)	1750 sh, 1726	0.93 (3H, t, J = 7.4, $-CH_3$); 1.64 (2H, m, $-CH_2$);1.88 (3H, d, J = 6.6, CH_3-CH=); 2.41 (2H, t, J = 7.4, $-CH_2$); 3.12 (3H, s, N-CH_3); 3.14 (3H, s, N-CH_3); 5.73 (1H, q, J = 6.6, -CH=)
2b	88	136-137[a]	61.97 (62.01)	5.20 (5.22)	9.63 (9.71)	1734	1.75 (3H, d, J = 6.6, CH_3-CH=); 3.19 (3H, s, N-CH_3); 3.22 (3H, s, N-CH_3); 5.60 (1 H, q, J = 6.6, H_A); 7.40 (3H, m, Ar); 7.75 (2H, m, Ar)
2c	39	44-45[f]	54.44 (54.49)	6.23 (6.27)	11.54 (11.63)	1748	0.95 (3H, t, J = 7.5, $-CH_3$); 1.66 (2H, m, $-CH_2$); 2.47 (2H, m, $-CH_2$); 3.12 (3H, s, N-CH_3); 3.16 (3H, s, N-CH_3); 5.35 (1H, d, J = 1.1, H_A); 5.69 (1H,d, J = 1.1, H_B)
2d	41	120-121[a]	60.77 (60.83)	4.73 (4.77)	10.12 (10.22)	1745, 1619	3.19 (3H, s, N-CH_3);3.23 (3H, s, N-CH_3); 5.25 (1H, d, J = 1.4, H_A); 5.52 (1H, d, J = 1.4, H_B);7.43 (3H, m, Ar); 7.76 (2H, m, Ar)
3a	30	140-145/0.5	60.48 (60.52)	7.61 (7.55)	11.76 (11.83)	1745	0.96 (3H, t, J = 7.4, $-CH_3$); 1.09(3H, t, J = 7.5,$-CH_3$); 1.61 (2H, m, $-CH_2$); 2.78 (4H, m, 2-CH_2); 3.19 (3H, s, N-CH_3);3.27 (3H, s, N-CH_3)

a) From CH_2Cl_2-Et_2O. b) Exchanges with D_2O. c) From Et_2O. d) 2:1 mixture of isomers. e) Pure major isomer isolated by crystallization from hexane. The olefinic proton of the minor isomer gives a quartet (J = 6 Hz) centered at δ 6.05. f) From hexane.



EXPERIMENTAL SECTION

Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 298 instrument, in Nujol mull for solids and liquid film for oils. 1H NMR spectra were recorded on a Bruker WP80SY spectrometer with TMS as an internal standard in $CDCl_3$ or on a Bruker AC 300. Column chromatography was performed on Merck Kieselgel 60, 0.063-0.2 mm. The drying agent was Na_2SO_4. Evaporation was carried out under vacuum in a rotary evaporator. Compounds **1b** and **1d** were prepared according to literature procedures.[3,7]

Synthesis of Isoxazolin-5-ones 1a,c (Table 1) were prepared by the previously reported method[3,4] from the corresponding 3-substituted isoxazolin-5-ones (20 mmol) and the appropriate orthoester (40 mmol). **1a** from 3-propylisoxazolin-5-one and triethyl orthopropionate and **1c** from 3-propylisoxazolin-5-one and triethyl orthoacetate.

Vilsmeier-Haack Reaction of 4-(α-Hydroxyalkylidene)isoxazolin-5-ones 1a-d.- Chloroform (80 mL, EtOH free) was cooled in an ice bath and DMF (1.85 g, 25 mmol) and phosphorus oxychloride (3.83 g, 25 mmol) were added. The isoxazolin-5-one (1) (10 mmol) was then added and, after warming at room temperature, the reaction mixture was stirred under reflux for 3 hrs. The reaction mixture was evaporated, water (70 mL) was added, the mixture neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was dried, filtered and evaporated. Column chromatography of the residue (eluent 30:1 CH_2Cl_2-Et_2O gave pure **2** (Table 1).

Vilsmeier-Haack Reaction of 1a with One Equivalent of Vilsmeier Reagent.- The reaction was carried out as described above on 10 mmol of **1a**, but 0.74 g (10 mmol) of DMF and 1.53 g (10 mmol) of $POCl_3$ were used. After heating under reflux for 3 hrs, the usual work-up followed by column chromatography (eluent CH_2Cl_2) gave **2a**, 0.39 g (15 %) and **3a** oil, 0.72 g (30%).

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THE SYNTHESIS OF TWO BICYCLO[4.3.0]NONANE DERIVATIVES

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(08/05/92)

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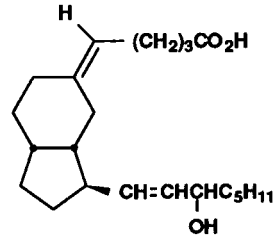
The synthesis of homocarbaprostacyclins such as **1**[1] necessitated access to appropriate bicyclo[4.3.0]nonane derivatives. An earlier successful application[1] of oxidative ring contraction to the generation of analogous bicyclo[3.3.0]octane derivatives led us to adopt a similar approach to the present case.



1

Following a literature procedure,[3] 2,7-dihydroxynaphthalene was catalytically hydrogenated to the bicyclo[4.4.0]decane-3,9-diol (**2**). The stereochemistry of this compound has not been assigned though the derived diketone **5** has been shown[4] to undergo reactions dependent upon the indicated *cis*-ring junction. Analogy with the stereochemical course of reduction of 2-naphthol[5] predicts the hydroxyl orientation depicted for **2**. In our hands diol **2** was best converted to dione **5** by oxidation with pyridinium dichromate in dimethylformamide. Oxidative ring contraction of decalindione **5** with thallic nitrate in acetic acid gave a 27% yield of keto-acid **6**. The course of such ring contractions is determined by the preferred direction of enolisation of the carbonyl group. In the present case, the *cis*-ring junction directs thallation to C-2 and hence the preferential