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THE VILSMEIER-HAACK REACTION WITH 3,4-DISUBSTITUTED ISOXAZOLIN-5-ONES. A NEW SYNTHESIS OF 1,3-OXAZIN-6-ONES AND 1,3-OXAZINE-2,6-DIONES.

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Summary: A novel synthesis of 2-dimethylamino-3,4-disubstituted-6H-1,3-oxazin-6-ones by a Vilsmeier-Haack type reaction on isoxazolin-5-ones is presented.

Recently described is the preparation of a number of 2-amino-[1] and 2-phenyl-6H-1,3-oxazin-6-ones.[2] The synthetic potential of such a class of compounds is well documented.[3]

We report here on the syntheses by a Vilsmeier-Haack type reaction of 2-dimethylamino--3,4-disubstituted-6H-1,3-oxazin-6-ones 2, obtained in a single step from the readily available 3,4-disubstituted isoxazolin-5-ones 1.[4] This new class of heterocycle 2 is obtained in a pure state and in very good yields (68-85%).

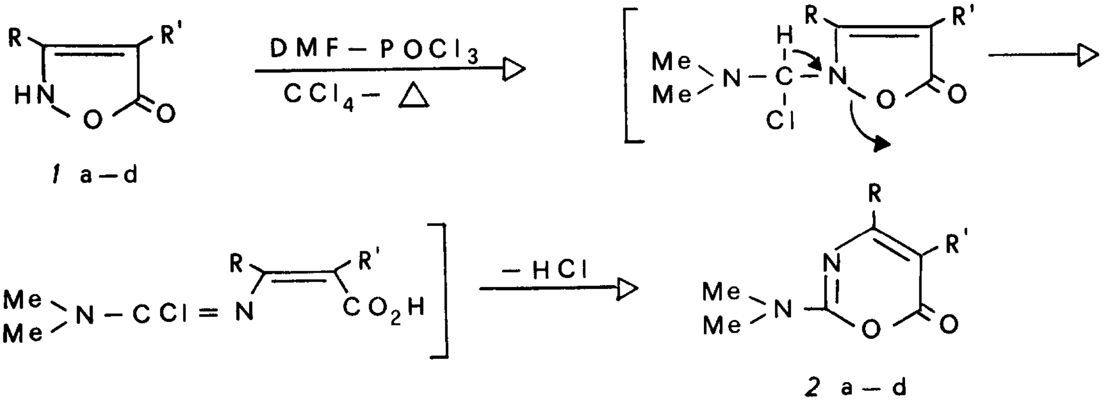
To the best of our knowledge only two reports concerning the syntheses of 1,3-oxazin-6-ones from isoxazolin-5-ones have been described in the literature,[5] while 2H-1,3-oxazines are known to be formed from isoxazolium salts.[6]

We suggest that the reaction proceeds by attack of the Vilsmeier reagent at position 2 of the isoxazolin-5-one, followed by ring-opening and cyclisation with hydrogen chloride elimination, as shown in Scheme 1.

The structures of the new compounds follow from analytical and spectroscopic data as well as from chemical behaviour.

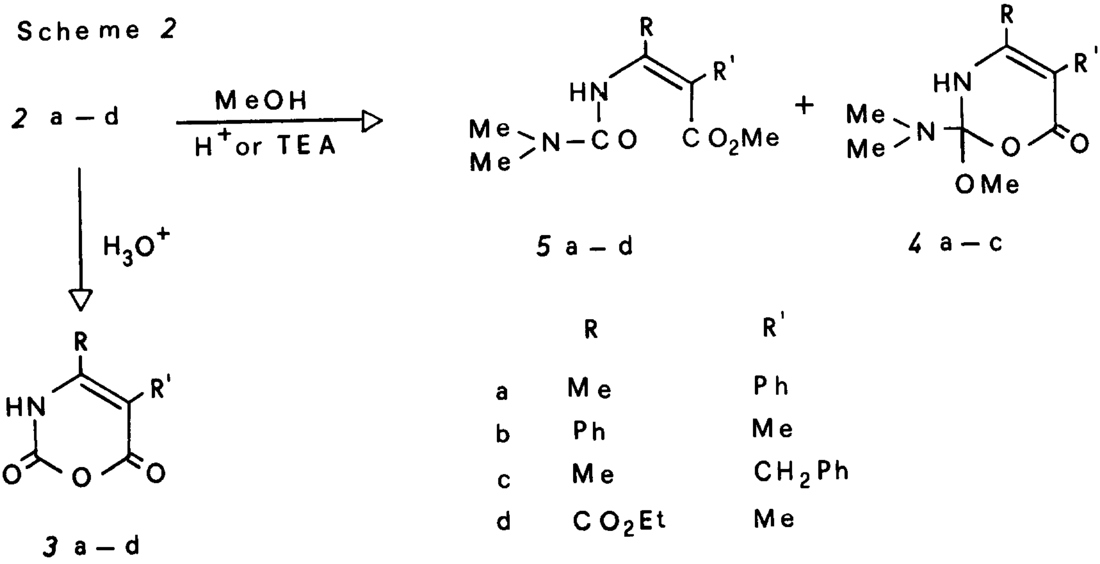
The 2-dimethylaminooxazinones 2 are stable compounds and do not react with alcohols or water. By refluxing in methanol and in the presence of p-toluenesulfonic acid or triethylamine, 2a,c slowly gave a mixture of two derivatives 5a-c and 4a-c (5/4 ratio 2:1). Only 5d was obtained from 2d.

Scheme 1



Derivatives 5, like 2-(acylamino)crotonic esters,[3] by refluxing in diphenyl ether gave the starting oxazinones 2 (40-45 % yields). The isomers 5 and 4 are stable in the reaction conditions. Furthermore the irradiation (high-pressure Hg-lamp, pyrex, acetone) of 5b gave the corresponding double bond isomer which differs from 4b, thus excluding the E-Z relationship between the series 5 and 4. In the case of products 4, in which is present a quaternary carbon atom (C_2) rather rare in the chemical literature,[7] the analysis of the fine structure for C_2 resulting from $^{13}C\{^1H\}$ selective decoupling experiments on OMe and NMe_2 groups strongly supports the structural assignments; on the other hand no fine structure was shown by C_6. By acidic treatment, the oxazinones 2a-d gave the corresponding 1,3-oxazine-2,6-diones 3a-d in 60-85% yields (Scheme 2).

Scheme 2



	R	R'
a	Me	Ph
b	Ph	Me
c	Me	CH_2Ph
d	CO_2Et	Me

This reaction greatly extends the range of substitution patterns obtainable for these biologically interesting heterocycles.[8] Compound 3d proved to be identical with an authentic sample synthesized by a literature method.[8] A partial list of characterization data is summarized in the Table.

Table. Characterisation of new compounds.[9]

Compd.	m.p. °C or b.p. °C (mm)	IR[10] (cm^{-1})	^{1}H-NMR[11] (δ ppm, $CDCl_3$)
2a[12]	55-56°	1725, 1610	7.33(m.5),3.2(s.6),2.1(s,3)
2b	110-111°	1728, 1603	7.5(m.5),3.2(s.6),2.08(s.3)
2c	96-97°	1725, 1605	7.25(m.5),3.8(s.2),3.18(s.6),2.19(s.3)
2d	53-54°	1740, 1720, 1600	44(q.2.7),3.2(s.6),2.08(s.3),1.42(t.3.7)
3a[13]	226°	3210, 1790, 1695	11.5(bs.1),7.35(m.5),2.1(s.3)
3b	192-193°	3250, 1780, 1712	11.5(bs.1),7.55(m.5),1.8(s.3)
3c	138-139°	3200, 1760, 1730	9.8(bs.1),7.22(m.5),3.73(s.2),2.2(s.3)
3d[8]	94-95°	3230, 1790, 1720	9.15(bs.1),4.53(q.2.7),2.37),(s.3),1.5(t.3.7)
4a	111-112°	3210, 1727, 1610	8.32(bs.1),7.3(m.5),3.75(s.3),2.76(bs.6), 2.28(s.3)
4b	134-135°	3200, 1718, 1655	7.35(m.6),3.58(s.3),3.12(s.6),1.88(s.3)
4c	122-123°	3150, 1718, 1652	7.23(m.5),7(bs.1),3.7(s.3),3.62(s.2),2.82(s.6), 2.23(s.3)
5a	142-143°	3150, 1685, 1660	11.7(bs.1),7.25(m.5),3.66(s.3),3.12(s.6), 2.22(s.3)
5b	107-108°	3160, 1690, 1660	11.2(bs.1),7.35(m.5),3.86(s.3),3.06(s.6),1.7(s.3)
5c	150-155° (0.1)	3160, 1690, 1675	11.8(bs.1),7.2(m.5),3.8(s.2),3.72(s.3), 3.12(s.6),2.5(s.3)
5d	98-99°	3200, 1730, 1690	11.2(bs.1),4.4(q.2.7),3.8(s.3),3.05(s.6), 1.85(s.3),1.34(t.3.7)

The Vilsmeier-Haack reaction on isoxazolin-5-ones appears to be quite general and the reactivity of oxazinones 2 is currently being investigated as well as the scope of the reaction on 3- and 4-substituted isoxazolin-5-ones.

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9) Satisfactory elemental analyses were obtained for all new compounds.

10) Perkin Elmer 377 Instrument, nujol mull for solid and liquid film for oils.

11) Varian EM 390 spectrometer; multiplicity, signal intensity (H) and coupling constant (hertz) indicated by values in parentheses.

12) Reaction conditions: CCl_4 (80 ml), DMF (15 mmol), $POCl_3$ (13 mmol), isoxazolin-5-one 1 (10 mmol). Reflux for 3h.

13) Reaction conditions: Dioxane (30 ml), H_2SO_4 4.5% (10 ml), 1,3-oxazin-6-one 2 (2 mmol). Reflux 1h.

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