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A SIMPLE SYNTHESIS OF Δ^2-OXAZOLINES, Δ^2-OXAZINES, Δ^2-THIAZOLINES AND Δ^2-IMIDAZOLINES

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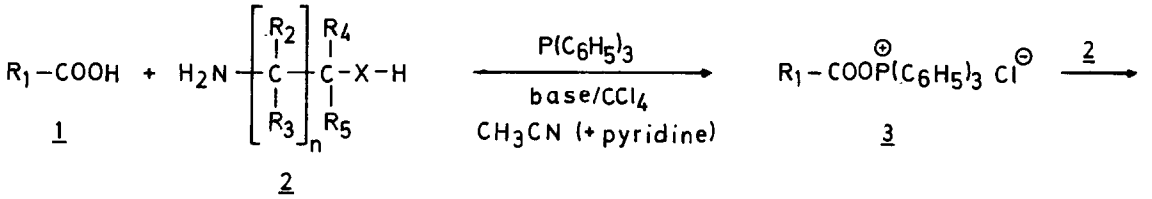
Summary - Carboxylic acids react with amino alcohols, amino mercaptans or diamines in the presence of triphenylphosphine, CCl_4 and tert. bases to afford in 50-75% yield the corresponding Δ^2-oxazolines, Δ^2-oxazines, Δ^2-thiazolines and Δ^2-imidazolines.

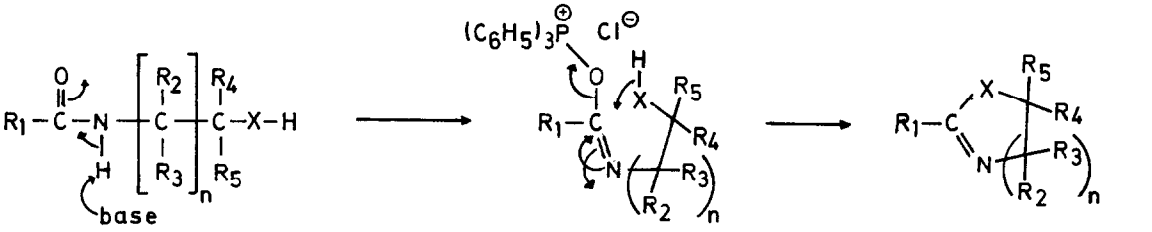
A recent publication[1], which came only now to our notice, prompts us to publish part of our own investigations on the synthesis of Δ^2-oxazolines[2], Δ^2-oxazines[3], Δ^2-thiazolines[4] and Δ^2-imidazolines[5].

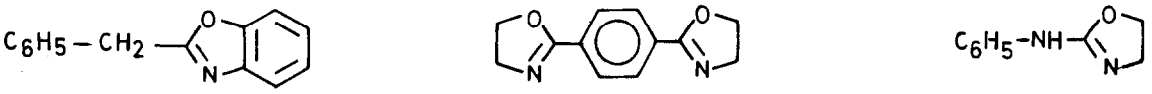
Although these derivatives of carboxylic acids have very interesting biological and chemical properties, e.g. as starting materials for the corresponding aromatic heterocycles[6] or in the case of Δ^2-oxazolines as protecting groups for the carboxylic acid moiety[2], the hitherto known methods[2-5] for their preparation require either vigorous conditions or aggressive reagents like $SOCl_2$. These methods are therefore not suitable for the conversion of rather labile carboxylic acids like prostaglandins into the aforementioned cyclic derivatives

We have found that aliphatic and aromatic carboxylic acids 1 can be readily converted in one reaction step in ca. 50-75% yield into their corresponding Δ^2-oxazolines, Δ^2-oxazines, Δ^2-thiazolines and Δ^2-imidazolines by reaction with amino alcohols, amino mercaptans and diamines 2 in the presence of ca. 3 equivalents each of triphenylphosphine, triethylamine, diisopropylethylamine or DBU and excess CCl_4 in acetonitrile[7] or better in acetonitrile-pyridine (1:1) at room temperature. In this process, the starting carboxylic acids 1 and the

amine moieties 2 are first converted via the activated triphenyl-phosphonium esters 3 into the intermediate amides 4[8] which are subsequently cyclized in situ to the desired derivatives 6.







Since apparently the carboxylate anions as well as the amides 4 are preferentially activated by the triphenylphosphine-CCl_4 reaction cascade[7] in the presence of tert. bases, it is not necessary to protect aliphatic or aromatic hydroxyl, amino or sulfonamide groups present in the carboxyl 1 - or amine 2 - moiety. Thus benzoic acid 1a (compare Table 1) and trisamine 2d furnished the corresponding Δ^2-oxazoline 6d in 73% yield. Employing carboxylic acids containing hydroxy (or amino) groups as in m-hydroxy benzoic acid 1e or prostaglandin $PGF_{2\alpha}$[9], 3 equivalents of triphenylphosphine in acetonitrile-pyridine (1:1) are added within 3-4 hours to 1, ethanolamine 2a and 3 equivalents of triethylamine, DBN or DBU and CCl_4 in acetonitrile-pyridine. Using smaller amounts of strong tertiary bases effects S_N2-displacement of aliphatic hydroxyl groups in 1 or 2 by chlorine[7]. Phenylacetic acid 1j and 3-amino-1-propanol 2j were readily converted into the 1,3- Δ^2-oxazine 6j in 51% yield. An aromatic 1,2-hydroxy-

amine like o-aminophenol and phenylacetic acid condensed to 2-benzylbenzoxazol 7, mp. 32°C[10], in 56%, terephthalic acid to the bis-Δ^2-oxazoline 8, mp. 235°C[11] in 50% yield. Starting with the amide 4 (R_1 = C_6H_5NH; R_2-R_5 = H; n = 1; X = O), the Δ^2-oxazoline 9, mp. 122°C[12], was obtained in 75% yield.

Reaction of benzoic acid with D(-)2-amino-2-phenylethanol 2b furnished the Δ^2-oxazoline 6b as well as traces of the isomer 6c. Hydrolysis of 6b with aqueous hydrochloric acid afforded pure D(-) 2b, mp. 75-77°C, thus proving the preferential activation of the amide carbonyl group in 4b (X = O, n = 1) to 5. The isomeric compound 6c is probably formed by transformation of the amino alcohol 2b to the corresponding ethyleneimine[7], formation of the N-benzoyl-ethyleneimine and rearrangement to 6b and 6c. The reaction of benzoic acid with 2-mercaptoethylamine 2k (X = S, n = 1) furnished the Δ^2-thiazoline 6k in 45% yield. If the S-triphenyl-phosphonium amide salt had been formed as intermediate instead of 5 (X = S), the corresponding Δ^2-oxazoline 6a would have been obtained instead of 6k.

Employing triphenylphosphine-azoester[13], $[(C_6H_5)_3\overset{\oplus}{P}\text{-}O\text{-}\overset{\oplus}{P}(C_6H_5)_3]\ 2CF_3SO_3^{\ominus}$/ triethylamine[14] or triphenylphosphine-2,2'-dipyridyldisulfide[15] as reagents gave the derivatives 6 in about the same yields as with triphenylphosphine/ CCl_4, $CBrCl_3$, CBr_4 or C_2Cl_6. However, as yet no conversion of 1 or 4 to 6 could be effected using a commercial sample of polymeric triarylphosphine instead of triphenylphosphine.

For purification, the sensitive end products 6 were hitherto mostly distilled. They can, however, be readily chromatographed with only minute hydrolysis to the corresponding amides 4 if deactivated alumina (A IV - V) or E. Merck silicagel containing 40% H_2O are employed.

Using these methods, drugs containing carboxyl groups like the aforementioned prostaglandins, diuretics and antiinflammatory agents, e.g. indomethacin, can be easily converted into their corresponding derivatives 6, some of which possess very interesting intrinsic biological activities[9].

Table 1

	1	2						6[a]	
	R_1	R_2	R_3	R_4	R_5	n	X	yield (%)	mp. (bp.)
a	C_6H_5	H	H	H	H	1	O	71.7	(110°C/0.5 mbar)
b	C_6H_5	C_6H_5	H	H	H	1	O	64	
c	C_6H_5	H	H	C_6H_5	H	1	O		
d	C_6H_5	CH_2OH	CH_2OH	H	H	1	O	73	140°C
e	3-hydroxy phenyl	CH_3	CH_3	H	H	1	O	67.5	159-161°C
f	3-amino phenyl	H	H	H	H	1	O	63	125-127°C
g	3-pyridyl	CH_3	CH_3	H	H	1	O	73.8	(120°C/0.5 mbar)
h	benzyl	H	H	H	H	1	O	51.7	(95°C/0.3 mm)
i	benzyl	CH_3	CH_3	H	H	1	O	68.7	(155-160°C/15 mm)
j	benzyl	H	H	H	H	2	O	51.4	(125°C/0.2 mm)
k	C_6H_5	H	H	H	H	1	S	45	(150°C/1.5 mbar)
l	C_6H_5	H	H	H	H	1	NH	46.1	97-99°C (185°C/1 mbar)

[a] all compounds showed the expected analytical and spectral data

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