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Direct synthesis of 2-oxazolines from carboxylic acids using 2-chloro-4,6-dimethoxy-1,3,5-triazine under mild conditions

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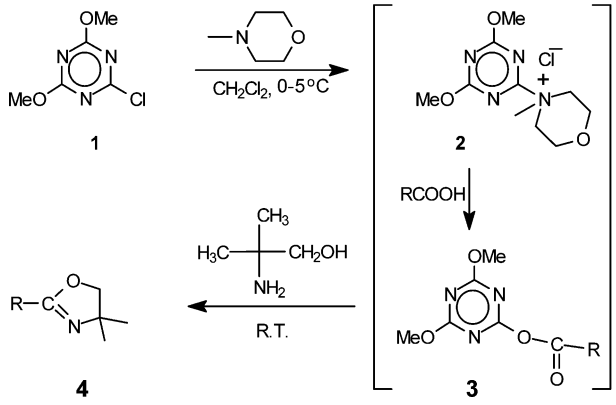
Abstract—2-Acyloxy-4,6-dimethoxy-1,3,5-triazines obtained from carboxylic acids and 2-chloro-4,6-dimethoxy-1,3,5-triazine were subsequently treated with 2-amino-2-methyl-1-propanol to afford the corresponding 2-oxazolines in excellent yield at room temperature. © 2003 Published by Elsevier Science Ltd.

Many classes of drugs such as non-steroidal anti-inflammatory drugs (NSAID) aspirin and naproxen, the diuretics furosemide and bumetanide or the biologically active natural eicosanoids prostaglandin $F_{2\alpha}$ and prostacyclins, contain carboxylic groups, which determine their pharmacokinetic properties and biological action. Since it was anticipated that modification of the carboxylic groups would change the resorption characteristics and pharmacokinetic properties of these drugs and furthermore might, as in the case of NSAIDs, diminish their erosive action on the mucosa of stomach and intestine, it is interesting to convert the carboxyl moieties of the NSAIDs, diuretics and eicosanoids into their corresponding 2-oxazolines as potential prodrugs.[1] These derivatives are expected to hydrolyze gradually under physiological conditions to the corresponding free or protonated ω-amino esters which would subsequently be saponified in vivo to the starting NSAIDs, diuretics or eicosanoids[2] or rearrange via their cyclols to ω-functionalized amides. 2-Oxazolines have been described as important structural entities in natural products,[3] useful synthetic intermediates,[4] protecting groups[5] for carboxylic acids and valuable auxiliaries in asymmetric synthesis.[6,7]

Numerous methods have been developed for the preparation of 2-substituted oxazolines from carboxylic acids,[8] carboxylic esters,[9] nitriles,[10] aldehydes[11] and amido alcohols.[12] Most methods utilize complex reagents, strongly acidic conditions, long reaction times and hence stringent reaction parameters occasionally giving low yields of products. The hitherto described methods for the direct conversion of carboxylic acids into the corresponding 2-oxazolines[2,4e] require either heating to temperatures up to 200–220°C or the repeated use of aggressive reagents such as $SOCl_2$[13] to convert the carboxylic acids via the acid chloride to the corresponding amides followed by cyclization of the ω-hydroxy amides with $SOCl_2$ to give the desired 2-oxazolines. However, some of these reactions are sluggish and yields are generally low. Hence, these procedures did not appear to be applicable to sensitive NSAIDs. Therefore, it is still necessary to develop a general, efficient and mild method for the direct synthesis of 2-oxazolines from carboxylic acids. In this communication we now report the use of 2-chloro-4,6-dimethoxy-1,3,5-triazine for the direct conversion of carboxylic acids into the corresponding 2-oxazolines under mild conditions (Scheme 1).



Scheme 1.

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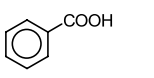
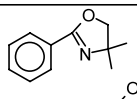
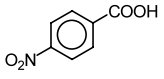
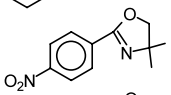
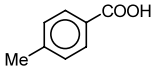
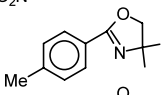
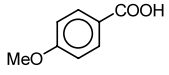
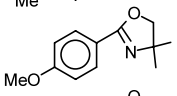
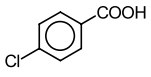
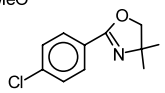
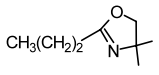
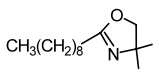
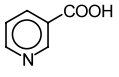
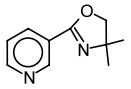
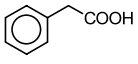
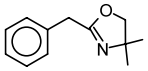
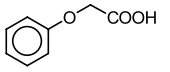
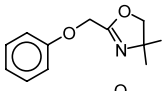
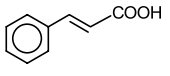
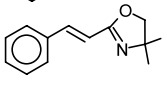
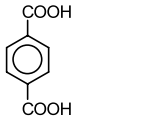
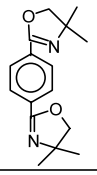
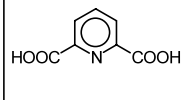
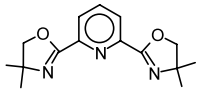
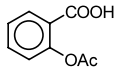
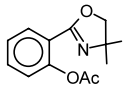
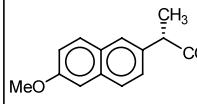
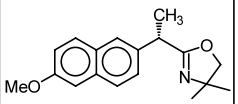
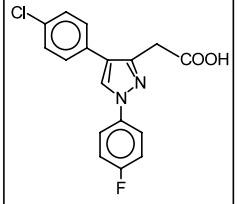
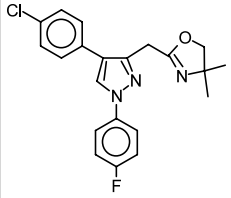
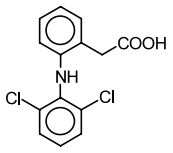
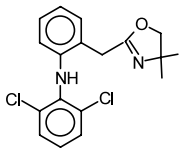
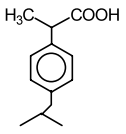
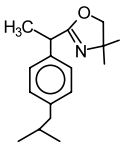
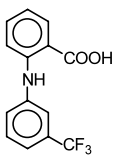
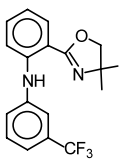
The procedure is based on the reaction of complex **2** formed from the very inexpensive reagent 2,4,6-trichloro-1,3,5-triazine (TCT) and *N*-methylmorpholine. Complex **2** was subsequently treated with a carboxylic acid to furnish a 2-acyloxy-4,6-dimethoxy-1,3,5-triazine **3**. The 2-acyloxy derivative **3** was reacted with 2-amino-2-methyl-1-propanol to yield 2-oxazoline **4**. The reactions are rapid and reaction conditions are mild as compared to reported procedures.[2,4a] The present protocol appears to be general as aliphatic, aromatic, heterocyclic and dicarboxylic acids are converted to the corresponding 2-oxazolines in high yields (Table 1). This method has been successfully applied to the transformation of the carboxyl groups of sensitive NSAIDs into their corresponding 2-oxazolines in order to change their pharmacokinetic properties and therefore the topical toxicity of these NSAIDs. Thus aspirin (entry n), *S* (+) naproxen (entry o), pyrazolac (entry p), diclofenac (entry q), ibuprofen (entry r) and flufenamic acid (entry s) are transformed into the corresponding oxazolines in good yields. Moreover, this method can be successfully applied to large scale synthesis of oxazolines directly from carboxylic acids.

Table 1. Synthesis of 2-oxazolines from carboxylic acids using the 4,6-dimethoxy derivative of cyanuric chloride

Entry	Acid	2-Oxazoline	Time (h)	Yield[a,b] (%)
a			3	78
b			10	81
c			8	89
d			6	89
e			6	85
f	$CH_3(CH_2)_2COOH$		12	87
g	$CH_3(CH_2)_8COOH$		11	82
h			4	68
i			3	73
j			8	51
k			12	79
l			4	80
m			5	71
n			7	75
o			5	82
p			8	77
q			12	70
r			11	84
s			10	83

[a] Yield of isolated pure product [b] Products were characterized by IR, ^{1}H NMR, elemental analysis and by comparison with authentic samples.

In conclusion, the procedure reported here is operationally simple and allows a rapid and high yielding synthesis of 2-oxazolines from carboxylic acids using an inexpensive and readily available reagent under mild conditions.

Typical procedure: To a solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (5 mmol) in dichloromethane (20 ml), *N*-methylmorpholine (5 mmol) was added at 0–5°C with continuous stirring. A white suspension was formed after 30–40 min and to this reaction mixture 4-chlorobenzoic acid (5 mmol) in CH_2Cl_2 (10 ml) was added which resulted in the formation of clear solution. After stirring the mixture for 1 h, 2-amino-2-methyl-1-propanol (15 mmol) was added followed by constant stirring at room temperature for 6 h. After completion of the reaction (TLC), aqueous solution of sodium bicarbonate (10%, 10 ml) was added in the mixture.

The organic layer was separated, washed with water (2×10 ml) and dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude product which was further purified by column chromatography (pet. ether:ethylacetate = 9:1). **4e**: mp = 79°C; IR (KBr): $\nu = 720$, 950, 1470, 1510, 1600 cm^{-1}, ^1H NMR: $\delta = 1.42$ (s, 6H, 2×CH_3), 4.1 (s, 2H, OCH_2), 7.6 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.8 (d, $J = 8.5$ Hz, 2H, Ar-H); mass: m/z (%) = 209.5 (M^+, 100). Anal. calcd for $C_{11}H_{12}ONCl$: C, 63.01; H, 5.72; N, 6.68; Cl, 16.95. Found: C, 62.97; H, 5.81; N, 6.59; Cl, 17.02%.

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