MELDRUM'S ACID IN ORGANIC SYNTHESIS 4. SYNTHESIS OF 5-SUBSTITUTED 2-PHENYLISOXAZOLIN-3-ONES FROM N-ACYLACETYLPHENYLHYDROXYLAMINES

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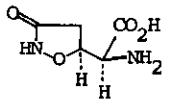
Abstract ——— When N-acylacetylphenylhydroxylamines, readily prepared from phenylhydroxylamine and acyl Meldrum's acids (5-acyl-2,2-dimethyl-1,3-dioxane-4,6-diones) were refluxed in benzene in the presence of a catalytic amount of p-toluenesulfonic acid, an acid-catalyzed dehydrative cyclization occurred smoothly to afford 5-substituted 2-phenylisoxazolin-3-ones in high yields.

Since flycidal tricholomic acid (1)[1] and ibotenic acid (2)[2] were isolated by Takemoto et al. from Tricholoma and Amanita species, numerous biologically active isoxazoles have been synthesized, most of them reported in patents,[3] and 3-hydroxy-5-methylisoxazole (3) synthesized by the Sankyo group is one of practically useful representatives.[4] Many naturally occurring biologically active isoxazole derivatives were also reported, e. g., an anti-tumor antibiotic, AT-125(4), was isolated from Streptomyces sviceus[5] and recently synthesized.[6]



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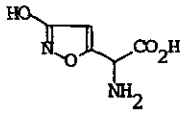

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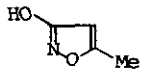

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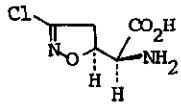

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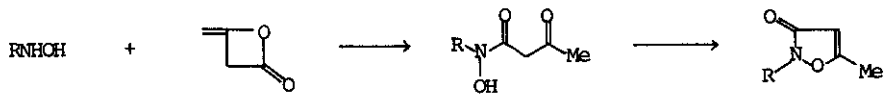
Because of such a biological importance, much of the synthetic effort have been concentrated on 5-substituted 3-hydroxyisoxazoles (isoxazolin-3-ones) and their derivatives.[4,7] The β-keto ester (involving diketene) method[8] seems to be very useful, but is usually limited to 5-methyl and 5-phenyl derivatives, because starting materials for other derivatives are not so easily available. As a preliminary application of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) to the isoxazole synthesis, we report here a simple synthesis of 5-substituted 2-phenylisoxazolin-3-ones, which will be extended to a convenient synthesis of isoxazolin-3-ones having various 2- and/or 5-substituents.

Almost twenty years ago, Matter et al.[8d] reported that phenylhydroxylamine (5a; R=C_6H_5) was

treated with diketene (6) to give N-acetoacetylphenylhydroxylamine (7), which was then converted to 5-methyl-2-phenylisoxazolin-3-one (8a; R=C_6H_5) in a moderate yield by the treatment with a relatively large amount of boron trifluoride etherate or with a large excess of anhydrous zinc chloride in acetic acid, and recently this reaction was extended to the synthesis of several 2-substituted isoxazolin-3-ones (8) using a large amount of sulfuric acid as a dehydrating agent, though also in moderate yields.[8g] *This method seems to be simple and convenient*, but the 5-substituents are naturally limited to the methyl group. 2-Substituted isoxazolin-3-ones (8), more generally 10, were also synthesized from 9 with alkyl halides under basic conditions, but the concomitant formation of 3-O-substituted isoxazoles (11), which were sometimes major products, was unavoidable.[9]



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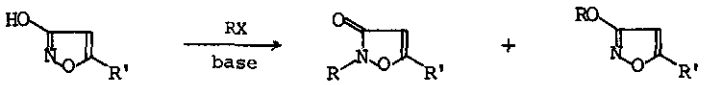
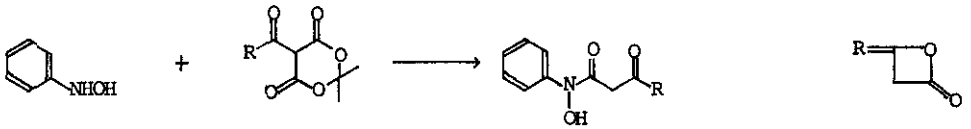
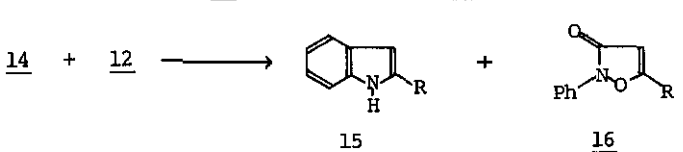


9 10 11

Meldrum's acid is one of malonic esters having an unusually high acidity and nucleophilic reactivity, and hence acyl Meldrum's acids (12) were easily synthesized.[10] An acyl Meldrum's acid (12) is a synthetic equivalent for a mixed diketene (13), which is not available, and a strong acylacetylation agent. When equimolar mixtures of various 12 and phenylhydroxylamine (5a) were heated in acetonitrile, the corresponding N-acylacetylphenylhydroxylamines (14) were obtained in high yields.[11] Further treatment of 14 with another 12 gave 2-substituted indoles (15), frequently accompanied by 5-substituted isoxazolin-3-ones (16) as reported in the preceding report.[11] The formation of 16 is probably explained in terms of the acid-catalyzed dehydration of 14 with 12.

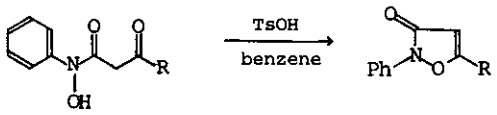


5a 12 14 13



15 16

When a benzene solution of N-acetoacetylphenylhydroxylamine (14a) was refluxed in the presence of a catalytic amount (0.05 equivalent) of anhydrous p-toluenesulfonic acid for 2-3 hr under argon atmosphere, 16 was isolated in 96% yield. Similarly, several 5-substituted 2-phenylisoxazolin-3-ones (16) were synthesized from the corresponding 14 (Table I).



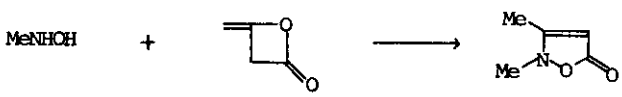
14 16

Table I. Synthesis of 5-Substituted 2-Phenylisoxazolin-3-ones (16) from N-Acylacetylphenylhydroxylamines (14).

16	R	yield,%	mp°C(solvent)	ir,cm^{-1}(solvent)
a	CH_3	96	39-40(hexane)	1675,1640,1595($CHCl_3$)
b	CH_3CH_2	97	oil	1670,1630,1590($CHCl_3$)
c	$(CH_3)_2CH$	87	oil	1660,1625,1595($CHCl_3$)
d	$CH_3O_2C(CH_2)_2$	26	72-73(benzene-hexane)	1730,1660,1590(Nujol)
		53[a]	120-122(benzene)	3130,1725,1635,1590(Nujol)
e	$CH_3CH_2O(CH_2)_2$	80	oil	1670,1630,1590($CHCl_3$)
f	C_6H_5	83	85-86(benzene-hexane)	1675,1630,1590(Nujol)
g	$C_6H_5CH_2$	76	117-118(benzene-hexane)	1665,1640,1595(Nujol)

[a] The corresponding carboxylic acid. In the reaction of 14d, a mixture of the expected methyl ester (16d) and its carboxylic acid, which was probably formed by the hydrolysis of the methyl ester group during the reaction, and could be converted to 16d by the treatment with diazomethane, was obtained.

When N-methylhydroxylamine (5b) was treated with diketene (6), followed by acid-treatment, 3-methylisoxazolin-5-one (17) instead of 5-methylisoxazolin-3-one (8; R=Me) was isolated.[12] β-Keto esters with hydroxylamine also usually gave isoxazolin-5-ones, but sometimes especially 2-substituted β-keto esters gave isoxazolin-3-ones.[8b] Therefore, special attention should be given to the structural determination of the products. Nevertheless, the carbonyl absorption at 1660-1675 cm^{-1} in the ir spectra clearly shows that all the products are 16, and not the corresponding 3-substituted isoxazolin-5-ones, whose carbonyl absorption usually appears at not less than 1700 cm^{-1}.[12]



5b 6 17

Extension of this simple and efficient method to the synthesis of general isoxazolin-3-ones with various 2- and/or 5-substituents which involve hydrogen and functionalized groups, and to the natural product synthesis is now in progress.

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