A NEW VERSATILE SYNTHESIS OF 4-ACYL-5-METHYL-4-ISOXAZOLIN-3-ONES[1)]

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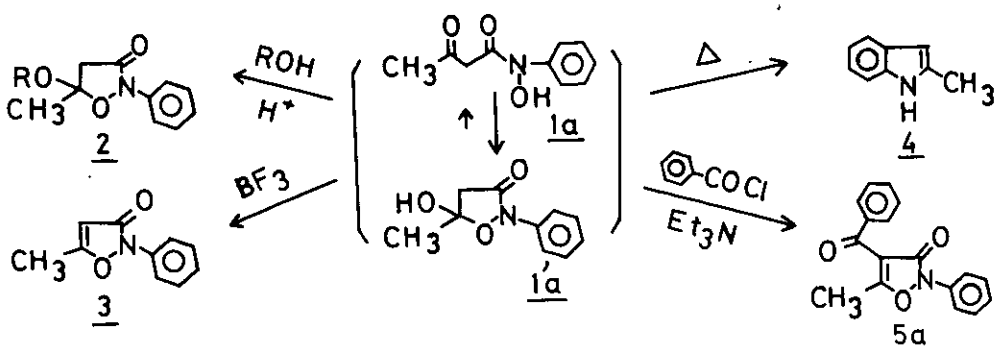
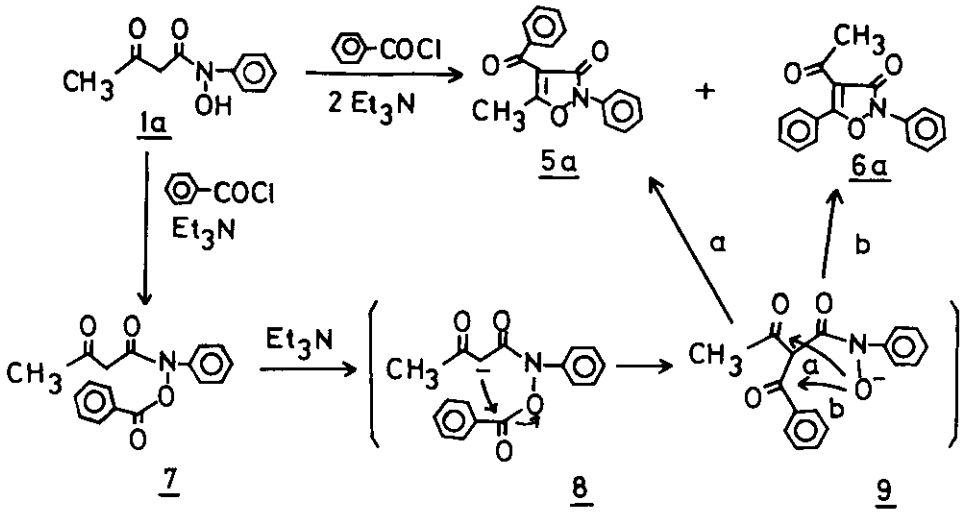
Abstract: Treatment of N-substituted N-hydroxyacetoacetamides 1 with acyl chlorides in the presence of two equivalents of triethylamine gave 4-acyl-5-methyl-4-isoxazolin-3-ones 5. The reaction was thought to proceed via acyl rearrangement as shown in 8 and 9.

It has been reported[2)] that N-hydroxyacetoacetanilide 1a exists mainly as a cyclic form, 5-hydroxy-5-methyl-2-phenylisoxazolin-3-one 1a' and the alkylation of 1a in acidic media gives the 5-alkoxy compound 2. Under acidic conditions 1a cyclizes into 2-phenyl-5-methyl-4-isoxazolin-3-one.[3)] On the other hand, the neutral thermal rearrangement of 1a gives 2-methyindole 4.[4)] To our best knowlege no work was documented on the reactivity of 1a under basic conditions. So our interest was directed towards the investigation of the reaction mode of N-substituted N-hydroxyacetoacetamides 1 in basic conditions. In this report, we wish to describe a new reaction of 1 with acyl chlorides in the presence of triethylamine, affording the new 4-acyl-5-methyl-4-isoxazolin-3-ones 5. Various 4-isoxazolin-3-ones have been synthesized[5)] except 4-acyl-4-isoxazolin-3-ones 5.



N-Hydroxyacetoacetanilide 1a was easily prepared from N-phenylhydroxylamine

and diketene.[4a] In the presence of two equivalents of triethylamine 1a was treated with benzoyl chloride in dry benzene at r.t. for 12 hr. The column

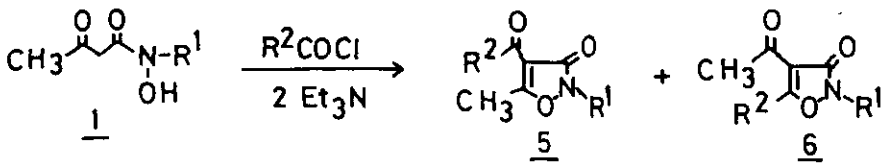


chromatography on silica gel of the reaction mixture gave two regio isomeric products: 4-benzoyl-5-methyl-2-phenyl-4-isoxazolin-3-one 5a (65% yield)[6] and 4-acetyl-2,5-diphenyl-4-isoxazolin-3-one 6a (12% yield).[7] The similarity of their spectroscopies except ^{13}C-NMR annoyed us on the occasion of the structural assignment. On ^{13}C-NMR spectra the methyl group of 5a shows a singlet at 13.8ppm, which is different from that of 6a at 30.5ppm.

With the reaction of a variety of benzoyl chlorides, 1a gave various 4-benzoyl-5-methyl-2-phenyl-4-isoxazolin-3-ones 5b-i as a sole product (Table 1). The reaction of 1a with acetyl chloride smoothly proceeded to afford 4-acetyl derivative 5j. In a series of the reaction of 1k-p with benzoyl chloride, the corresponding 4-benzoyl-4-isoxazolin-3-ones 5k-p were obtained in good yields along with a small quantity of 4-acetyl-4-isoxazolin-3-ones 6k-p. Under the same conditions N-methyl-N-hydroxyacetoacetamide 1 (R^1=Me) reacted with benzoyl chloride or 2,6-dichlorobenzoyl chloride to give 4-isoxazolin-3-one 5q or 5r in moderate yield, respectively. N-Hydroxyacetoacetamide 1 (R^1=H), however, did not afford the corresponding 4-benzoyl derivative but 5-methyl-4-oxazolin-2-one in nearly quantitative yield. The scope of this new reaction is, therefore, limited to N-substituted N-hydroxyacetoacetamides.

In order to clarify the reaction mechanism, N-hydroxyacetoacetanilide 1a was treated with benzoyl chloride in the presence of one equivalent of triethylamine. An oily product, $C_{17}H_{15}NO_4$ was obtained in 81% yield. Perronnet[2] describes that in ^{1}H-NMR spectra both 5-hydroxyisoxazolin-3-one 1a' and its 5-alkoxy derivatives 2

Table 1. Yields of 4-Acyl-4-isoxazolin-3-ones



1 → 5 + 6

	R^1	R^2	5 Yield %	5 mp °C	6 Yield %	6 mp °C
a	Ph	Ph	66	93-94.5	12	72-79
b	Ph	2-ClC_6H_4	57	123-124	0	
c	Ph	2,4-$Cl_2C_6H_3$	89	141.5-143	0	
d	Ph	3-MeC_6H_4	50	80-82	0	
e	Ph	4-MeC_6H_4	56	135-138	0	
f	Ph	4-BrC_6H_4	83	117-118	0	
g	Ph	2-$MeOC_6H_4$	56	100-106	0	
h	Ph	3,5-$(NO_2)_2C_6H_3$	74	201-203	0	
i	Ph	3,4,5-$(MeO)_3C_6H_2$	61	178.5-179.5	0	
j	Ph	Me	64	92-93	0	
k	3-ClC_6H_4	Ph	80	97-98	3.6	Oil
l	4-ClC_6H_4	Ph	73	139-140	5.1	170-171
m	4-BrC_6H_4	Ph	62	140-141	3.8	164-166
n	3-MeC_6H_4	Ph	80	112-113	3.5	Oil
o	4-MeC_6H_4	Ph	72	106-107	2.1	100-102
p	3,5-$Cl_2C_6H_3$	Ph	80	149-150	0.8	129-130
q	Me	Ph	29	40-42	0	
r	Me	2,4-$Cl_2C_6H_3$	40	99-100	0	

All reactions were carried by the standard procedure described in this paper. All new compounds exhibit the correct elemental analysis and satisfactory spectral data.

possess AB type signal ascriable to the methylene protones at the C_4-position. The methylene group of the oily product shows singlet at 3.55ppm. Therefore, the product is assumed to N-benzoyloxyacetoacetanilide 7,[8] not the benzoate of 1a. Further treatment of this unstable oily compound 7 with another one equivalent of triethylamine for 24 hr at r.t. afforded 4-benzoyl derivative 5a (87% yield) together with 4-acetyl derivative 6a (6% yield). These results show that the reaction proceeds via benzoate 7, which undergoes a base-catalyzed acyl

rearrangement into N-oxide anion 9. The resulting oxygen anion attacks the acetyl carbonyl (path a) or the benzoyl carbonyl (path b), affording 4-benzoyl isomer 5a or 4-acetyl isomer 6a, respectively. The product ratio of 5a (87%) and 6a (6%) is ascribable to the higher population of the ketone form of acetyl than benzoyl part in intermediate 9, i.e., path a is more effective than path b in the anionic attack reaction. The unexpected formation of 5-methyl-4-oxazolin-2-one from N-hydroxyacetoacetamide 1 (R^1=H) has been interpreted[9] by Lossen rearrangement of the benzoyloxyacetoacetamide formed intermediately.

In conclusion new hereto described reaction enables us to synthesize 4-acyl-5-methyl-4-isoxazolin-3-ones 5 from N-substituted N-hydroxyacetoacetamides 1.

References and Footnotes

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2. J. Perronnet, P. Girault, and J-P. Demoute, J. Heterocyclic Chem., 17, 727 (1980).
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5. K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, Chem. Pham. Bull., 27, 2398 (1979), and references cited therein.
6. 5a: mp 93-94°C. IR(nujol): 1685, 1660cm^{-1}. NMR[10] δ: 2.52(s,3H), 7.3-8.2(m, 10H)ppm. Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.19; N, 5.02. Found: C, 73.35; H, 4.85; N, 5.13%.
7. 6a: mp 77-78°C. IR(nujol): 1685, 1680cm^{-1}. NMR[10] δ: 2.69(s,3H), 7.3-8.2(m, 10H)ppm. Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.19; N, 5.02. Found: C, 72.85; H, 4.49; N, 5.17%.
8. 7: IR(film): 3100, 1765, 1720, 1680cm^{-1}. NMR[10] δ: 2.28(s,3H), 3.55(s,2H), 7.2-7.8(m,8H), 8.0-8.3(m,2H)ppm. Mass m/e: 297(M^+).
9. H. Fukumi, K. Oohata, and K. Takada, Heterocycles, 12, 1297 (1979).
10. The NMR (60MHz) spectra were measured in $CDCl_3$ solution with TMS as an internal standard.

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