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ETHYL 5-SUBSTITUTED-3-ISOXAZOLECARBOXYLATES AS STARTING MATERIALS FOR A CONVENIENT ROUTE TO 3(2H)FURANONES AND 3(2H)IMINOFURANES.

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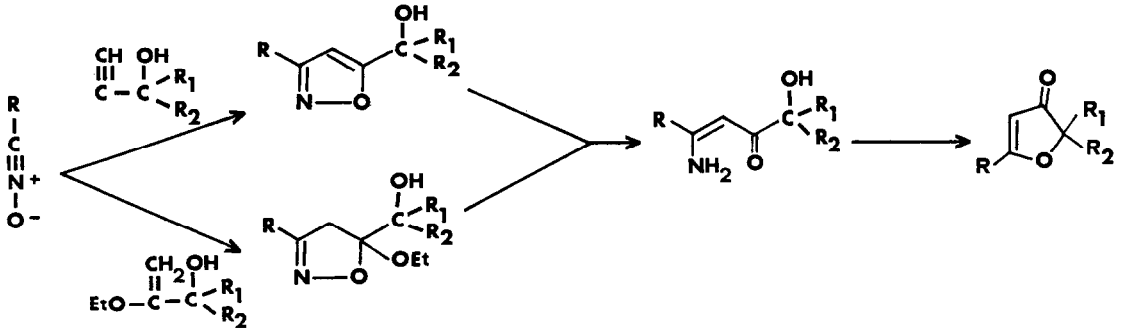
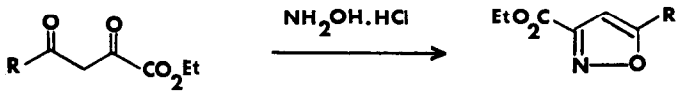
Summary: Cyclodehydration of γ-hydroxy-β-enaminoketones derived from 5--substituted-3-isoxazolemethanols leads to 3(2H)furanones or 3(2H)iminofuranes depending on the substitution pattern and on the reaction conditions.

Since the establishment of the structure of bullatenone and its synthesis by Raphael et al. in 1958[1], the discovery of a growing number of natural product antitumoral agents (like jatrophone and geiparvarin), which have as a central structural element the 3(2H)-furanone ring system, led to the development of efficient synthetic approaches to a variety of simple 3(2H)-furanones[2].
The most general strategy involves the acid catalyzed cyclization-dehydration of an α'-hydroxy-1,3-diketone precursor, thus reducing the synthetic protocol to the elaboration of an appropriately substituted 1,3-dicarbonyl or its equivalent.
Both 3,5-disubstituted isoxazoles[3] and 4,5-diidroisoxazoles[4], in turn obtained by cycloaddition of nitrile oxides to acetylenic alcohols or hydroxyenol-ethers respectively, have been utilized as logical functional equivalents of 1,3--dicarbonyl compounds, through well-established procedures based on the hydrogenolitic lability of the N-O bond, as summarized in the Scheme:

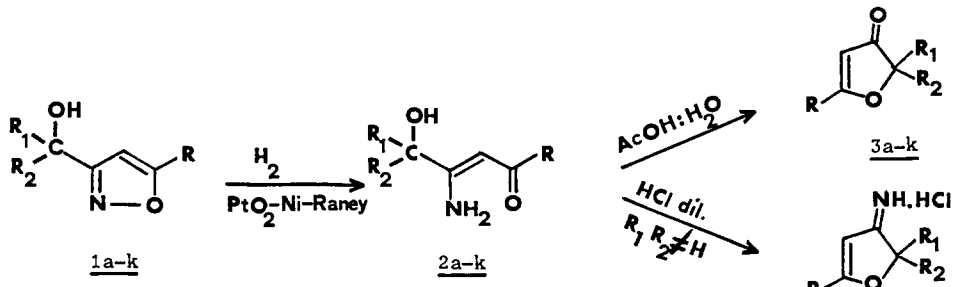


We have recently demonstrated[5] that ethyl 2,4-dioxoalkanoates, the ethoxyoxalyl derivatives of methyl ketones, react regiospecifically with an excess of hydroxylamine hydrochloride in ethanol to afford good yields of ethyl 5-substituted--3-isoxazole carboxylates.



This offered us the opportunity to examine these readily available building blocks as a starting point for a new synthesis of 3(2H)-furanones. We anticipated that the carboxylic ester group attached to the 3-position could be a convenient source of primary, secondary and tertiary alcoholic functions in the α'-position of a masked 1,3-diketone moiety. Simple operations like i) reduction with $NaBH_4$; ii) reaction with methyl magnesium iodide in the presence of triethylamine[6] to give an intermediate methyl ketone, which can be alternatively reduced with $NaBH_4$ or newly treated with a Grignard reagent; iii) direct reaction with an excess of Grignard reagent; can give rise to an array of different alcohols. Thus the isoxazole alcohols 1a-k prepared through these standard operations, suffer easy fission of the labile N-O bond by hydrogenolysis in the presence of PtO_2/Ni-Raney mixture[7] of catalysts in methanol to give essentially quantitative yields of the corresponding vinylogous amides 2a-k. Their structure differs from those described in previous approaches[3,4], the alcoholic appendage being located at the carbon atom adjacent to the carbon-nitrogen bond rather than to the carbonyl group of the enaminone moiety. We found that the substitution pattern at this position determines their behaviour towards mineral acids usually utilized in the following cyclization-dehydration step.

Thus treatment of the vinylogous amides 2a-f bearing at least one hydrogen atom at the γ-position under both previously reported acid conditions (H_2SO_4 dil., reflux, 1 hr)[3] or (THF, H_2O, HCl, RT)[2,4] led to the expected formation of substituted 3(2H)-furanones 3a-f. In contrast vinylogous amides 3h-k bearing a tertiary alcoholic function at the γ-position gave only traces of the corresponding 3(2H)furanones, the main products being the rather unprecedented[8] 3(2H)iminofuranes, which can be isolated in high yield, as nicely crystalline hydrochlorides 4g-k stable in boiling hydrochloric acid. However we found that all vinylogous amides 2a-k on exposure to AcOH:H_2O 2:1 mixture at room temperature are easily transformed to 3(2H)furanones 3a-k in good yields.



1a-k 2a-k 3a-k 4g-k

Our results are summarized in the following Table:

		2[a]	3[b]	4
a	R_1=R_2=H; R=Ph	mp 124°-126°C	mp 86°-88°C[3a]	-
b	R_1=R_2=H; R=isobut	mp 50°- 52°C	oil[3b]	-
c	R_1=R_2=H; R=n-C_5H_{11}	oil	oil[3b]	-
d	R_1=H; R_2=Me; R=Ph	mp 107°-109°C	mp 60°-62°C[4]	-
e	R_1=H; R_2=Me; R=isobut	oil	oil	-
f	R_1=H; R_2=Me; R=n-C_5H_{11}	mp 92°- 94°C	oil[9]	-
g	R_1=R_2=Me; R=Ph	mp 114°C	mp 66°C[1]	mp 255-256°C
h	R_1=R_2=Me; R=isobut	oil	oil	mp 157°-158°C
i	R_1=R_2=Me; R=n-C_5H_{11}	oil	oil[10]	mp 148°C
k	R_1=R_2=Me; R=Et	mp 80°- 82°C	oil[11]	mp 186°-187°C

[a] All new compounds were fully characterized by spectral and analytical data.
[b] All known compounds were characterized by comparison with literature data.

Among the methods for the construction of these important compounds, the reported sequence presents several merits, namely: a) it employs very accessible and convenient starting materials; b) it is readily applicable to large scale operations; c) it allows the preparation of many different 3(2H)furanone derivatives from each starting material through trivial manipulations; d) the reactions give crude products suitable for the next process or products easy to purify by crystallization or distillation. For instance the synthesis of bullatenone 3g was realized in 45% overall yield starting from ethyl benzoylpyruvate. Similarly the 3(2H)furanone 3k, already converted to geiparvarin[11] was obtained in 46% yield.

References and Notes

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