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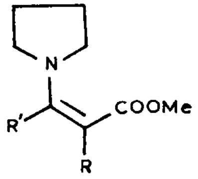
ALKYLATION OF CARBANIONS FROM ISOXAZOLIN-5-ONES

Samuel A. Tischler and Larry Weiler*
Department of Chemistry, University of British Columbia
Vancouver, British Columbia, Canada, V6T 1W5

Summary: Methyl acetoacetate and other β-keto esters can be converted into the corresponding isoxazolin-5-ones which can be metalated α to C-3. These anions are trapped by a range of electrophiles to produce 3-substituted isoxazolin-5-ones.

Recently we required various β-amino α,β-unsaturated esters as intermediates in the synthesis of natural products,[1] and we were interested in extending the utility of β-keto esters which we have been studying recently.[2] There was no difficulty in preparing β-amino α,β-unsaturated esters which have a hydrogen on the α carbon as in 1 (R=H)[1b] [3,4] or in the synthesis of enamines of tetronic acids including α-substituted derivatives of these β-keto lactones.[5] However, we were frustrated in our attempts to prepare acyclic tetrasubstituted enamines of type 1 (R=alkyl) from the corresponding β-keto ester. Using some of the more drastic conditions reported for enamine formation,[6] occasionally we were able to obtain low (ca. 20%) yields of the desired enamines;[1b] but, we have been unable to effect these reactions in synthetically useful yields. It is well known that tetrasubstituted enamines are difficult to form due to steric interactions. In the isoxazolin-5-ones of type 2, this steric interaction is now replaced by a chemical bond.



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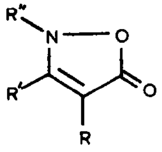

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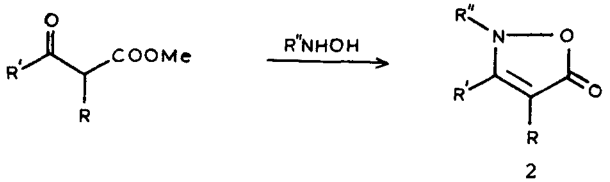
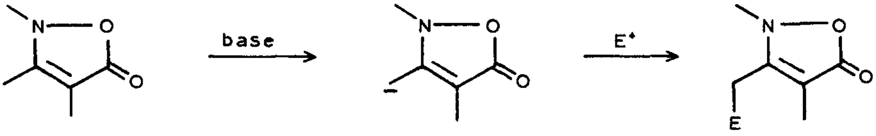
In this note we report the synthesis and some chemistry of the isoxazolin-5-ones 2. These heterocycles are readily available by treating a β-keto ester with an N-substituted hydroxylamine (equation 1).[7] Acyclic and cyclic β-keto esters undergo this condensation to give the isoxazolin-5-ones 2 in 70-100% yield for R"=Me.[8] The ease and high yield in the formation of 3,4-disubstituted isoxazolin-5-ones is contrasted with our inability to prepare enamines of the same starting β-keto esters.



2

(1)

A number of reactions involving the heterocyclic ring of 2 are known; however we were interested in studying the generation and reactivity of an α-carbanion on the R' chain of 2. This report concentrates on the 2,3,4,-trimethylisoxazolin-5-one (2,R=R'=R"=Me); however we have obtained similiar results with the bicyclic system 2 [R,R'=$(CH_2)_4$ and R"=Me]. The anion 3 was generated when 2 was treated with a number of strong bases e.g., lithium diisopropylamide, potassium bistrimethylsilylamide,[9] n-butyllithium, or potassium diphenyl-2-pyridylmethide.[10] The resulting anion was reacted with a range of electrophilic traps to produce 4 (equation 2 and Table).



2 3 4

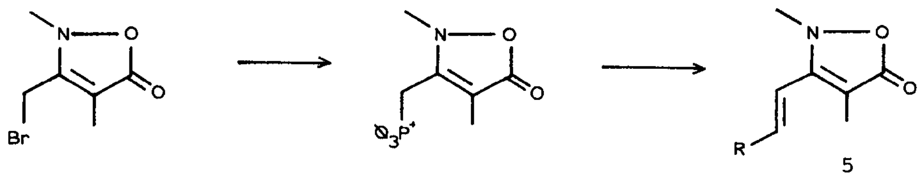
(2)

A number of interesting features can be noted from this data. Anion 3 reacts at the exocyclic carbon with all of these electrophiles. In this sense the reaction of 3 is similiar to the anions of enamines of type 1 which trap electrophiles at the γ-carbon.[3-5] The isoxazolin-5-one can therefore be regarded as a latent β-keto ester. However, there are some important differences between the reactivity of β-keto ester dianions and the anion 3 which should prove useful. Dianions of β-keto esters do not react cleanly with trimethylchorosilane or phenylselenyl chloride, whereas

TABLE: Reaction of Carbanion 3 from 2,3,4-Trimethylisoxazolin-5-one with Electrophiles.

Electrophile	Isolated Yield of 4
MeI	81%
EtI	67%
n-BuBr	80%
$CH=CHCH_2Br$	75%
$Me_2C=CHCH_2Br$	75%
ϕCH_2Cl	52%
ϕCHO	71%
$\phi SeCl$	61%
Me_3SiCl	64%
Br_2	41%
$\phi COOMe$	57%

anion 3 does react with these electrophiles to give 4 (E = TMS or ϕSe) in moderate yield. Bromination of β-keto ester dianions yields a plethora of products which are not synthetically useful, but bromination of 3 gives 4 (E=Br) in only fair yield. However, direct bromination of 2 with N-bromosuccinimide gives 4 (E=Br) in good yield (ca. 70%). This bromide has been converted into the triphenylphosphonium salt 4 ($E=\phi_3P^+$), which on treatment with base and an aldehyde gave the alkene 5 ($R=\phi$ or $n\text{-}C_5H_{11}$) in 60-65% yield (equation 3).



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(3)

These isoxazolin-5-ones can be cleaved by catalytic hydrogenation to the saturated amine or ketone depending on the experimental conditions.[7a] They may also be converted into pyrazolin-5-ones with hydrazine, or cleaved to amides with aqueous sodium hydroxide.[11] Finally, we have found that diisobutylaluminum hydride will reduce the carbonyl of the isoxazolin-5-ones to the corresponding lactol. We are currently investigating these cleavage reactions and the application of the carbanions from isoxazolin-5-ones in the synthesis of more complex molecules where the use of dianions from β-keto esters is precluded.

Experimental conditions for the generation and reaction of 3 with electrophiles are all similar. The anion is generated by adding a THF solution of the isoxazolin-5-one to 1.0 equivalent of lithium diisopropylamide in THF. After stirring for an additional 45 minutes, the electrophile is added, and stirring is continued for 15-30 minutes. This entire sequence is carried out at 0°C. Finally the reaction is worked up to yield 4.[12]

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