3,5-Disubstituted Isoxazoles as a Latent Aldol Moiety: Application to the Synthesis of (±)-[6]-Gingerol

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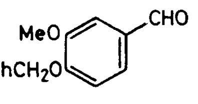
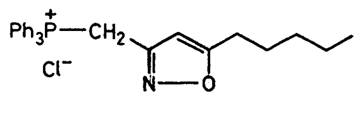
Summary (±)-[6]-Gingerol (**9**) has been synthesized by a route involving the use of a 3,5-disubstituted isoxazole derivative as an equivalent of the sensitive β-hydroxyketone unit.

3,5-DISUBSTITUTED isoxazoles are useful in synthetic chemistry for at least three reasons: (a) they are easily available; (b) they are unaffected by many transformations of other parts of the molecule; (c) they are easily reconverted into many functional groups by reductive fission of the N–O bond under appropriate conditions. From this point of view they can be considered as protected 1,3-diketones,[1] β-enamino-ketones,[1] α,β-unsaturated ketones,[2,3] and β-keto-amides.[4]



(1)



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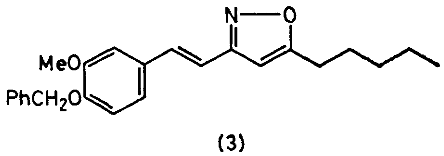

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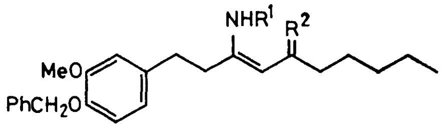
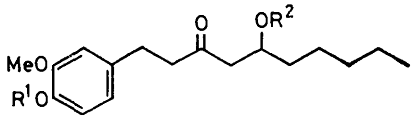
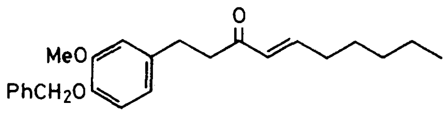


(4) R^1= H ; R^2= O
(5) R^1= COPh ; R^2= O
(6) R^1= COPh ; R^2= <$^{OH}_{H}$



(7) R^1= CH_2Ph ; R^2= H
(8) R^1= CH_2Ph ; R^2= Me
(9) R^1= R^2 = H



(10)

Moreover, as we have recently reported,[5] the regiospecific cycloaddition of nitrile oxides to terminal alkynes to give 3,5-disubstituted isoxazoles, in conjunction with a specific reduction–elimination sequence, allows them to be considered as an aldol or stabilized Wittig condensation equivalent. However, despite the extensive studies on isoxazole chemistry, we are unaware of any previous attempts to utilize 3,5-disubstituted isoxazoles as a masked form of a β-hydroxy-ketone moiety.

We have examined this possibility, since the presence of a rather sensitive aldol grouping in a molecule severely limits the manipulations which can be performed at other points, since it is susceptible to reverse aldol reaction or to dehydration to give α,β-unsaturated carbonyl compounds. Reported herein is a successful attempt to use 3,5-disubstituted isoxazoles in this way, in the synthesis of (±)-[6]-gingerol (**9**), the major component of pungent principle from rhizome of *Zingiber officinale* Roscoe.[6–8]

The key isoxazole (**3**), m.p. 80—81 °C,† incorporating the complete carbon atom skeleton of the target compound (**9**) was prepared in 85% yield by Wittig reaction between the commercially available 4-benzyloxy-3-methoxybenzaldehyde (**1**) and the ylide produced from the phosphonium salt (**2**),‡ m.p. 153—154 °C, with KOBu^t in Me_2SO.

Hydrogenation of (**3**) in the presence of pre-reduced PtO_2-in methanol under atmospheric pressure (2 equiv. of H_2 were smoothly taken up) gave the vinylogous amide (**4**) as an oil in quantitative yield.

Treatment of (**4**) with benzoyl chloride in pyridine at room temperature for 12 h afforded the vinylogous imide (**5**), m.p. 81—82 °C, in 77% yield, which was transformed in high yield into the alcohol (**6**) by means of $NaBH_4$ in methanol.

Exposure of crude (**6**) to 90% aqueous acetic acid§ for 2 h at 0 °C followed by silica gel chromatography of the crude reaction mixture (diethyl ether–light petroleum ether, 6:4, as eluant) produced (**7**) as a white solid, m.p. 53—54 °C (from n-hexane) or 58—59 °C (from MeOH–H_2O, 1:1) lit.,[6] 67 °C (unspecified solvent), whose spectroscopic properties fully agreed with the literature data.[6,7]

Debenzylation of (**7**) to give (**9**) occurred smoothly by hydrogenolytic cleavage in the presence of 10% Pd/C in methanol.

(*Received*, 23*rd March* 1981; *Com.* 329.)

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† Satisfactory analytical and spectral data were obtained for all new compounds.

‡ Prepared by refluxing a benzene solution of equimolar quantities of triphenylphosphine and 3-chloromethyl-5-n-pentylisoxazole, in turn obtained from ethyl 5-n-pentylisoxazole-3-carboxylate (T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, 1961, **26**, 1514) by $NaBH_4$ reduction in ethanol followed by treatment with thionyl chloride.

§ Treatment of (**6**) with dilute mineral acids gave the expected[3] α,β-unsaturated ketone (**9**), while the action of 10% aqueous methanolic KOH afforded the β-methoxy-ketone (**8**), probably arising from nucleophilic addition of methanol to the α,β-unsaturated compound (**9**).

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