A New Class of Stable Enol Based on the 2,2,6,6-Tetramethylheptane-3,5-diol Framework

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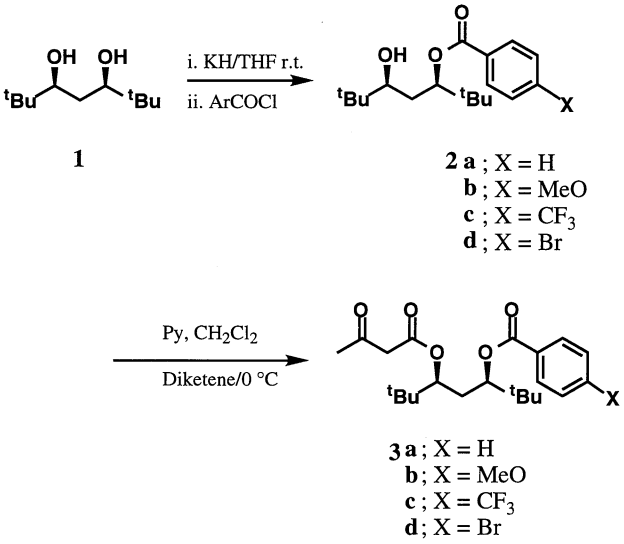
The enol content of 3-[(p-trifluoromethylphenyl)oxy]-2,2,6,6-tetramethyl-5-heptyl 3-oxobutanoate **3c** in $CDCl_3$ at room temperature is about 98 %, although that of ordinary 3-oxobutanoates such as ethyl acetoacetate is around 10 %.

It is generally believed that the keto form of ordinary carbonyl compounds is more stable than the enol form, although existence of stable enols is known in certain cases.[1] The stability of these enols arises in one of a number of ways: a) the presence of several bulky substituents which hinder proton transfer from the enol and also destabilise the resulting keto form, b) severe structural constraints which disfavour ketonisation, c) the presence of multiple, powerfully electron-withdrawing groups which retard protonation of the enol and destabilise the corresponding keto tautomer, and d) coordination to a transition metal fragment.[2] We herein report what we believe to be the first example of a stable enol system which derives its stability from *conformational* sources.

Our discovery arose as an extension of investigations into the chemistry of *meso*-2,2,6,6-tetramethylheptane-3,5-diol (TMHDiol) **1** which has already been shown to act as a rigid, acyclic template for highly stereoselective Diels-Alder reactions and conjugate additions of lithium *N*-benzyl-*N*-(trimethylsilyl) amide (LSA) and organocuprates to acrylates.[3] Initially, three acetoacetate derivatives (X=H, MeO, CF_3) were prepared in good yield by reacting the mono potassium salt of TMHDiol in THF with an aroyl chloride to give the alcohols **2a-c**, which were converted to the required β-keto esters **3a-c** by treatment with pyridine and diketene in CH_2Cl_2 as shown in Scheme 1.

Examination of the ^1H NMR spectra ($CDCl_3$) of **3a** and **3b** showed the presence of both the keto and enol forms in the ratio of 87 : 13. This observation was not too surprising viewed in the light of the fact that the keto/enol ratio of the parent compound ethyl acetoacetate is 92 : 8.[4] However, inspection of the ^1H NMR spectrum ($CDCl_3$) of **3c** (X=CF_3) showed that in this case the enol form was present almost *exclusively* (> 98%) whilst the keto form was present in < 2% (Fig 1). The keto and enol forms of **3c**



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2a; X = H
b; X = MeO
c; X = CF_3
d; X = Br

3a; X = H
b; X = MeO
c; X = CF_3
d; X = Br

Scheme 1.

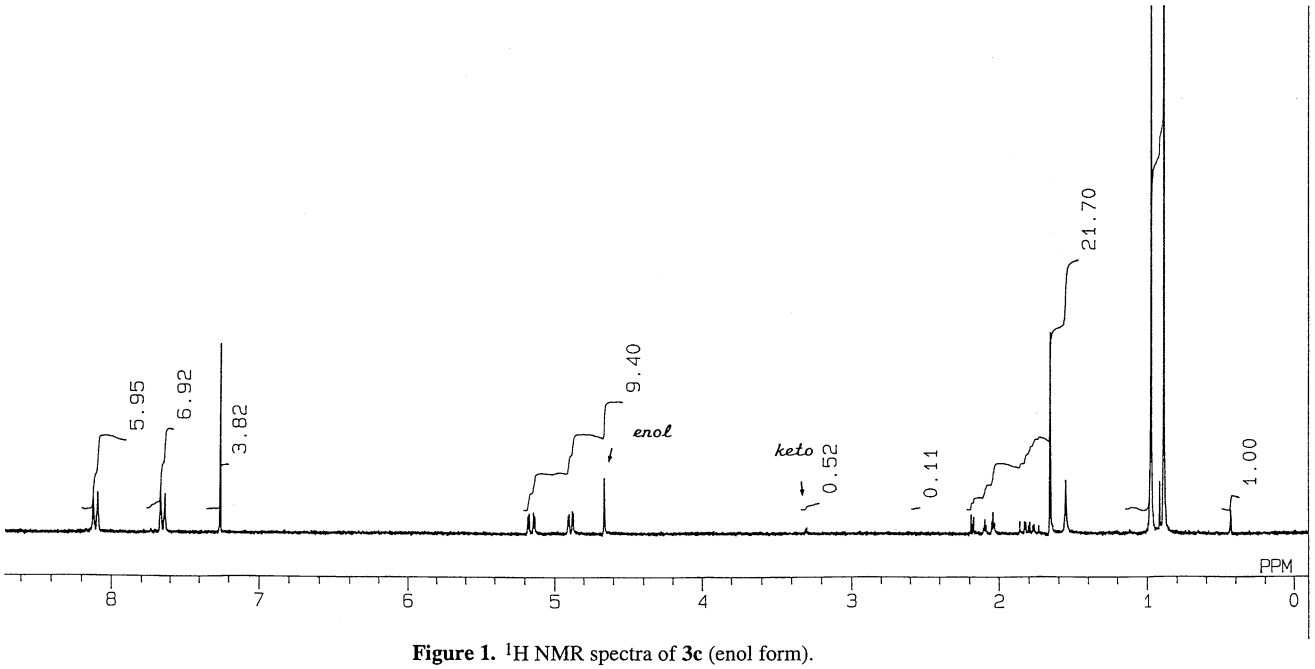
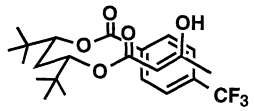


Figure 1. ^1H NMR spectra of **3c** (enol form).

may be readily distinguished in the ^{1}H NMR. The principle diagnostic peaks are the peak due to the acetoacetate methyl group which occurs at around δ_{Henol} 1.65 ppm in the enol form and at δ_{Hketo} 2.20 ppm in the keto form and the AX doublets of the aromatic protons which occur at around δ_{Henol} 7.64 ppm and δ_{Henol} 8.10 ppm, and δ_{Hketo} 7.72 ppm and δ_{Hketo} 8.15 ppm for the enol/keto forms, respectively. The resonances due to the acetoacetate methylene group of the keto form and the vinylic proton in the corresponding enol form occur at approximately δ_{Hketo} 3.30 ppm and δ_{Henol} 4.65 ppm, respectively.

Thus at first sight it would appear that electron-donating substituents favour the keto form whereas electron-withdrawing substituents the enol form. With these intriguing results in hand it was decided to synthesise a range of compounds of this type in order to investigate further the effect of aromatic substituents on the keto/enol ratio [X=F, Cl, CN, Ph, CO_2Me, ...]. Unfortunately, none of the new systems synthesised had keto/enol ratios that were comparable with **3c**. It is worth noting that in those systems with very strongly electron-withdrawing substituents on the aryl ring [e.g., pentafluoro or bis(trifluoromethyl)] the keto/enol ratios for these systems are essentially no higher than for those systems having less strongly electron-withdrawing substituents (e.g., Ph, or CO_2Me). Thus it began to appear that the keto/enol ratios for these types of systems are not dependent solely on the electronics of the aryl ring.[5]

One possible explanation for this phenomenon is that the enol form of the acetoacetate portion is stabilised *via* interactions between the enol double bond and the π-system of the aryl ring. This interaction would only be possible if the two unsaturated systems are so arranged in space that they lie *parallel* to one another. It is known that suitably substituted TMHDiol-based systems readily adopt just such a conformation and this phenomenon has been utilised synthetically.[3]



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Unforunately, all our attempts to grow crystals of **3c** suitable for X-ray crystallography met with failure Therefore we were unable conclusively to establish its solid-state conformation and thus verify this postulate directly. However, it is interesting to note that the *p*-bromo analogue **3d**, whose solid-state structure was determined unambiguously by X-ray crystallography and whose keto/enol ratio is only 64 : 36, adopts a conformation in which the enol and aryl π-systems are skewed well out of parallel and therefore no such stabilising interaction is possible. Further, a support for the above parallel conformation came from n.O.e experiments although it was not conclusive. Irradiation of the aryl protons of the enol form of **3c** led to enhancement of the vinylic enol proton and *vice-versa*. However, no such enhancement was observed in the case of **3d**, suggesting that the enol and aryl π-systems of **3c** are held more closely in space than those of **3d**.

The stability of the enol form is believed to arise from stablising interactions between the π-systems of the enol portion and the aryl substituent facilitated by a parallel alignment of these two groups. Although further studies are needed to establish the origin of the stability of the enol form, the present findings seem to provide a new class of stable enol which is not stabilized simply by steric or electronic effects.

References and Notes

1 For a comprehensive disscusion of enols, see: "*The Chemistry of Enols*", ed Z. Rappoport, Wiley, New York (1990).

2 For an excellent review of simple stable enols, see: a) H. Hart, *Chem. Rev.*, **79**, 515(1979); b) H. Hart and M. Sasaoka, *J. Chem. Educ.*, **57**, 685(1980).

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5 The lifetime of the enol form was found to be longest-lived and the highest equilibrium concentration in $CDCl_3$, taking almost one-and a-half days to reach an equilibrium containing 80-82% enol. The ketonization process in C_6D_6 and d8-THF was faster, and an equilibrium was reached in around 60-80 min. The enol content of *o*-CF_3 and *m*-CF_3 substituted derivatives of **3a** was low (~10-15%).