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# Malonic Acid Half Oxyesters and Thioesters: Solvent-Free Synthesis and DFT Analysis of Their Enols

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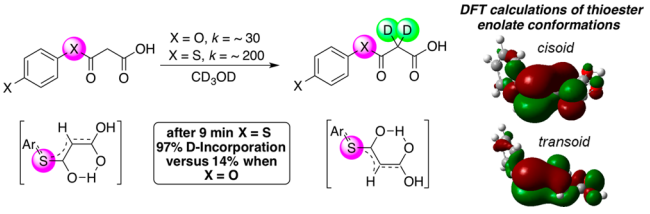
## ABSTRACT




**A much improved synthetic route to malonic acid half thioesters (MAHTs) and oxyesters (MAHOs), the easy incorporation of deuterium labeling expecially in MAHTs, and an unexpectedly large difference in enolization chemistry between MAHTs and MAHOs are reported. Density functional theory calculations explore the origins of this difference and identify an additional MAHT molecular orbital which increases delocalization between sulfur and the enol in both *cisoid* and *transoid* forms.**

Malonic acid half thioesters (MAHTs) and oxyesters (MAHOs) are common starting materials in Claisen couplings,[1] aldol condensations,[2] and Mannich[3] and Michael[4] reactions, with their utility in both synthetic and biological chemistry residing in the $\beta$-carbonyl carboxylic acid group.

With MAHTs and MAHOs, basic or metal-catalyzed[5] bond formation with electrophiles such as aldehydes, imines, azodicarboxylates, and ketones seems to proceed *via* an 'addition−decarboxylation' process[6] whereas it is the opposite with the enzymes that perform polyketide synthesis.[7] We report in this *Letter* important data to help evaluate the apptitude of these substrates in their ability to undergo efficient enolization.

Recent burgeoning interest in MAHTs and MAHOs can be attributed to their exploitation in organocatalysis. For this reason, aryl thioester enolates with lower p$K_a$ values, *i.e.* ~16−17 [dimethyl sulfoxide (DMSO)],[3c] have found favor. A difficulty in using MAHOs as phenol oxyester

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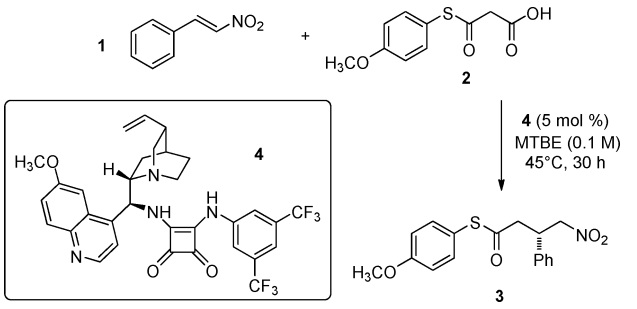
enolate precursors, however, is their relatively high p$K_a$ values, *i.e.* ~18 (DMSO).[8] By way of example, Song et al. utilized squaramide-derived **4** to mediate the enantioselective Michael addition of **2** to *trans*-$\beta$-nitrostyrene (**1**) generating $\gamma$-amino acid precursors, based on **3** (up to 88−99% *e.e.* and 15−96% yields, Scheme 1).[4d]

**Scheme 1.** Application of MAHT **2** in the Asymmetric Organocatalytic Synthesis of Aryl Thioester **3**

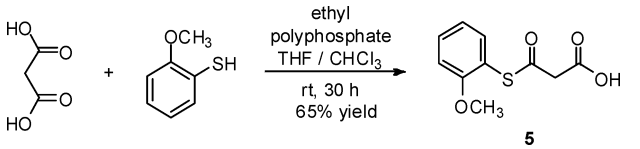



Despite their importance, very few synthetic methods are avaliable for the convenient preparation of MAHTs. A search for *aryl*thioester MAHTs generated 32 references containing only 10 individual MAHTs, and in fact, only two distinct approaches[9] had been utilized for their synthesis. Kee et al.[9a] generated **12** in a poor 24% yield using Meldrums acid with, unfortunately, an unwanted dithiophenylmalonic ester byproduct formed in 21% yield. Imamoto et al.[9b] reported the synthesis of MAHTs from thiophenol and 2-methoxythiophenol. A potential problem here was the use of excess, noncommerical ethyl polyphosphate (Scheme 2). Similar synthetic issues are apparent in the ester series. For example, Mase et al. generated a MAHO from *para*-methoxybenzyl alcohol and malonic acid using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as the coupling agent.[10] Although not commented on by Mase et al.,[10] the difficulty of efficiently removing trace amounts of polar dicyclohexylurea from (polar) products generated using DCC is a well-known disadvantage of the method.

We describe here a much improved synthetic route to MAHTs and MAHOs, the easy incorporation of deuterium labeling, expecially in MAHTs, an unexpectedly large difference in enolization chemistry between MAHTs and MAHOs, and data from density functional theory (DFT) calculations to explore the origins of this difference.

A key advantage of our synthetic approach is that we can employ simple chemistry on a large scale, using well-known reactions that so far have been overlooked from the standpoint of their importance in MAHT and MAHO synthesis. First, we established a simple multigram preparation of our key starting material malonyl monochloride, using commerical, cheap

**Scheme 2.** Synthesis of Malonic Acid Half Thioester **5**




'off the shelf' reagents. By direct reaction of malonic acid and thionyl chloride, 50 g batches of malonyl monochloride were easily produced as a pale yellow solid in 2 h, with an estimated purity of >90%. Storage at ambient temperature for at least 3 months showed no signs of decomposition.

Next we turned to straightforward esterification reactions, focusing initially on preparing phenoxy ester derived MAHOs. By simply mixing malonyl monochloride with phenol at ambient temperature, a slow coalescence toward homogeneity was observed. Warming the mixture to 100 °C quickly produced a clear, pale yellow, homogeneous solution. After 30 min, dichloromethane (DCM) was added to precipitate the product which was collected by filtration as a white solid, dried, and redissolved in $CDCl_3$. $^1$H-nuclear magnetic resonance ($^1$H NMR) analysis showed that **8** had formed, with minimal decomposition, in a 75% yield. In fact, this simple and convenient esterification reaction is surprisingly fast. Under solvent-free conditions, utilizing phenol and malonyl monochloride, the formation of **8** after 2, 5, 10, and 20 min was investigated. $^1$H NMR analysis showed complete consumption of phenol and, in all cases, efficient formation of **8**. Indeed after only 2 min, **8** was generated in a 77% yield. An important advantage of this fast, efficient, and high yielding procedure is that it is easy to scale up. Reacting **6** (20 g) with **7** at 100 °C for 2 min afforded 13 g of **8** in a 77% yield (Scheme 3). The method is also generally applicable. Incorporating electron-rich 4-methoxyphenol and halogen-containing 4-chlorophenol and 4-bromophenol into our standard reaction conditions (Scheme 3) afforded **9**−**11** in unoptimized 61%, 64%, and 69% yields, respectively.

In contrast, however, utilizing the same reaction protocol with thiophenol afforded **12** in only 25% yield. This problem was solved by employing a longer reaction time. Heating at 65 °C for 2 h gave **12** (59% yield), and similarly, **2**, **13**, and **14** were synthesized in unoptimized 61%, 50%, and 41% yields, respectively. The results reported in this *Letter* provide a simple preparation of both MAHTs and MAHOs that we required to underpin future work in which they are to be applied in mechanistic studies of organocatalysis and polyketide synthesis/biosynthesis. Athough the procedure is slower in the MAHT series, both MAHTs and MAHOs are now easily obtained by robust, straightforward chemistry on a substantial scale.

For our intended applications, we need stable-isotope labeled MAHOs and MAHTs as NMR and mass spectrometric mechanistic probes. In view of their importance, it is surprising that only two deuterated MAHTs have been

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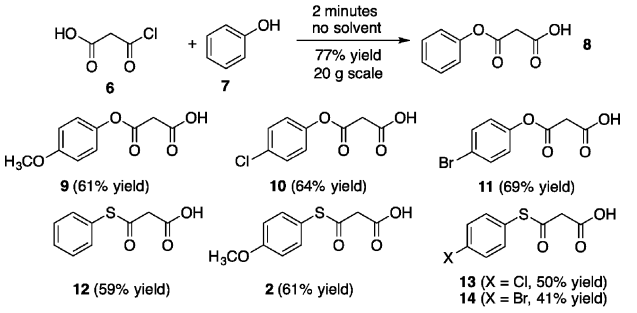
**Scheme 3.** Synthesis of Malonic Acid Half Oxyester **8** and Alternative MAHOs and MAHTs Generated in This Study




previously reported, *i.e.* 2-methyl-3-oxo-3-(phenylthio)-propanoic-$d_2$ acid and 2-(methyl-$d_3$)-3-oxo-3-(phenylthio)-propanoic acid.[11] Because the unlabeled starting materials were now readily available, we have been able to take advantage of the relatively acidic methylene protons to introduce deuterium labels directly by exploiting the keto–enol tautomerization properties of the esters and thioesters. The method is very straightforward and easy to perform. We began work with the parent phenyl compounds **8** and **12** which were simply dissolved in $d_4$-methanol and monitored by $^1$H NMR, recording spectra after 4, 9, 19, and 29 min. As seen from Figure 1 (blue traces: crosses, esters; dots, thioesters) both compounds incorporated the deuterium label. The data, however, reveal an important and unexpected difference between oxy-**8** and thio-**12**. The thioester showed significantly higher levels of $^2$H-incorporation in the early stages of the experiment. Thus after only 4 min, the H/D exchange for thioester **12** was far more advanced than for oxyester **8**, *i.e.* 72% and 18% respectively (Figure 1). Indeed after 9 min, **12** had incorporated 52% more deuterium than **8**. The substituted aryl esters and thioesters from our synthetic work were examined in comparable NMR experiments, which showed (Figure 1; green, magenta, pink and brown traces) that more rapid H/D exchange was consistently observed with MAHTs. Indeed after only 9 min, MAHTs **2**, **13**, and **14** had undergone

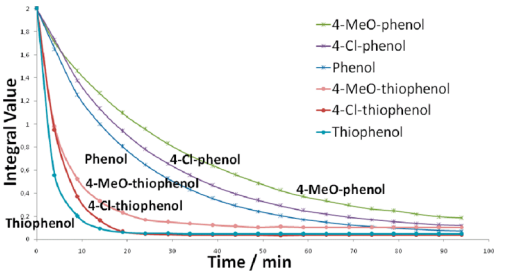



**Figure 1.** Rates of H/D exchange for MAHOs and MAHTs.

extensive, *i.e.* 74–97%, deuteration, whereas MAHOs **9**–**11** exhibited much lower levels of H/D exchange, *i.e.* 14–38%.

The NMR data and comparisons of ease of deuterium incorporations between MAHTs and MAHOs will be significant when these compounds are employed as mechanistic probes. The ease of enolization in the MAHT series was explored by DFT calculations. Using B3LYP[12]/6-31G(d)[13] with Gaussian 09,[14] we first explored a series of 30 ester and 30 thioester conformations (e.g. *transoid*/*cisoid*) and configurations (e.g. *E*/*Z*) in the parent phenol and thiophenol esters. Using the B3LYP/6-31G(d) minima as starting points the optimizations were repeated with the M06-2X functional which has performed well in a benchmarking study of 52 melatonin conformers.[15] The geometries and molecular orbitals of the MAHOs and MAHTs are generally very similar. The main difference between the MAHO and MAHT series is the presence of the additional sulfur-centered orbital in the MAHTs which increases delocalization of electron density from the sulfur atom into the enol. Similar results were obtained when the study was extended to a selection of representative solvents (acetonitrile, dichloromethane, and methanol) and alternative functionals.

Both MAHOs and MAHTs are easily prepared by the method described here, and the rapid enolization of the MAHT series measured by H/D exchange has important mechanistic consequences in synthetic and bioorganic chemistry. DFT calculations have examined this effect, and it is ascribed to the presence of an additional sulfur-centered frontier orbital which increases $\pi$-delocalization between the heteroatom and the enol.

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**Supporting Information Available.** Experimental details, spectral and analytical data for all reaction products, and details of the DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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