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ARTICLE TYPE

## Room temperature sonochemical initiation of thiol-ene reactions

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**5 Thiol-ene ‘click’ reactions have been initiated for a range of primary alkenes using ultrasound in both toluene and water. The method is particularly effective in aqueous solutions in the presence of air.**

While efficient coupling between sterically unhindered thiols and  
10 electron rich alkenes has been known since the early 1900's<sup>1-3</sup>, there has been renewed interest in ‘thiol-ene’ reactions as part of the development of ‘click’ chemistry.<sup>4</sup> Thiol-ene reactions, discussed in recent reviews,<sup>5-7</sup> typically display high rates with near quantitative, regioselective yields, tolerance of water and  
15 oxygen and orthogonality across a wide range of commercially available thiols and alkenes.<sup>5</sup> As a result thiol-ene reactions have found wide ranging applications in materials chemistry.<sup>7-9</sup> These reactions can proceed either by a Michael addition or *via* a free radical mechanism, initiated thermally or by UV irradiation, and  
20 often employ an added initiator. UV initiation gives a cleaner reaction profile and faster reaction rates<sup>10,11</sup> and has been the predominant method used in, for example, crosslinking applications<sup>5</sup>.

Sonochemistry offers a potentially attractive, alternative  
25 method of promoting radically initiated thiol-ene reactions.<sup>12, 13</sup> High concentrations of radicals can be formed<sup>14, 15</sup> by thermolysis of the solvent or by accelerated breakdown of added initiators and sonochemistry has been used to generate radicals for synthesis<sup>16</sup>, for degradation of surfactants<sup>17</sup> or pollutants in water<sup>18</sup> and for  
30 radical polymerisation.<sup>19,20</sup> Hence it was of interest to determine whether ultrasound could be used to initiate this class of click reaction. The rate of production of radicals was measured by radical trapping under conditions typically used for thiol-ene reactions to determine conditions where ultrasound can produce  
35 comparable rates. Coupling reactions between 1-butanethiol (in toluene) or cysteamine hydrochloride (in water) with a number of alkenes were then used as model systems to explore the potential usefulness of sonochemical initiation.

Considering first the toluene system, radical dosimetry  
40 employing 2,2-diphenyl-1-picrylhydrazyl (DPPH)<sup>14,19</sup> was used to quantify radical production in the thermal and sonochemical systems. The change in absorbance at 520 nm, due to radical trapping by the purple DPPH and its conversion to orange DPPH<sub>2</sub>, allows measurement of the rate of radical production.  
45 Zero order kinetics with respect to DPPH were observed indicating that radical production is the rate limiting step rather than reaction between the radicals and DPPH.

Rate constants, *k*, were measured with the aim of determining

conditions where the rate of radical production in a sonochemical  
50 system around room temperature matched that from thermally initiated reactions at the temperatures typically used. As shown in Table 1 using an ultrasound horn at an intensity of 17 W cm<sup>-2</sup> with a 10 - 20 mM solution of 2,2'-azobis(2-methylpropionitrile) (AIBN) at 24 °C produces radicals with a rate constant that is  
55 comparable with heating a 5 mM solution of AIBN at 50 °C. In the thermal and ultrasound reactions, increasing the concentration of AIBN results in a corresponding increase in *k* (see ESI<sup>†</sup>). In the absence of ultrasound, the rate of decomposition of AIBN at room temperature is too slow to be conveniently measured by  
60 trapping. Extrapolation from higher temperatures<sup>21</sup> suggests the rate constant to be ~ 2 × 10<sup>-8</sup> s<sup>-1</sup> so ultrasound accelerates the breakdown of AIBN at 24 °C. Hence, it might be expected that thiol-ene reactions should be initiated under ultrasound irradiation around room temperature. In addition, the  
65 sonochemical radical production observed in the absence of AIBN offers the possibility of reactions without added initiator, albeit at markedly reduced rates.

Table 1: Rate constants for DPPH radical trapping in 0.08 mM toluene solutions.

Initiation	[AIBN] mM	Temperature (°C)	<i>k</i> (× 10 <sup>-4</sup> mol dm <sup>-3</sup> s <sup>-1</sup> )
Thermal	20	50 ± 2	15 ± 2.6
	10		6.8 ± 0.4
	5		3.3 ± 0.4
	0		0
20 kHz ultrasound, 17 W cm <sup>-2</sup>	20	24 ± 2	3.8 ± 0.4
	10		3.0 ± 0.4
	5		2.2 ± 0.2
	0		0.62 ± 0.03

70 Table 2(a) shows illustrative results for the reaction of a range of alkenes with 1-butanethiol. Good conversions were obtained in the low temperature sonochemical coupling, with AIBN, norbornene or N-isopropyl acrylamide (NIPAm). Previous  
75 studies<sup>6</sup> indicate that the alkene reactivity in thiol-ene coupling decreases as the electron density in the double bond decreases. The reactivity of the alkenes follows this trend in both the sonochemical and the thermal systems suggesting that the reaction mechanism is essentially similar in each reaction.

80 Despite the comparable rates of radical production demonstrated by the DPPH dosimetry, higher conversions were

observed in most thermally initiated reactions compared with those initiated using ultrasound. A possible explanation for this discrepancy is competing side reactions in the latter. GC-MS analysis did not indicate the formation of significant concentrations of particular side products but did confirm the identity of the expected major product in each case. Previous reports<sup>22</sup> have indicated that thioether bonds are relatively labile to sonolysis so some product may be lost. The resulting radical species could form a range of compounds but also act as a radical trap, reducing the radical concentration available for initiating the desired thiol-ene reaction.

Table 2: Percentage conversions for reaction of (a) 1-butanethiol with alkenes using AIBN, (b) cysteamine hydrochloride with alkenes using potassium persulfate.

Alkene	))))* 24 °C	)))) 24 °C	Δ* 50 °C	Δ 50 °C
<b>(a) <i>N</i><sub>2</sub> saturated toluene</b>				
<b>% conversion at 2 h</b>				
norbornene	63	14	99	0
N-isopropyl acrylamide	42	0	100	0
butyl vinyl ether	30	2	8	0
1-heptene	15	0	24	0
1-pentene	0.3	0.5	0	0
allyl butyl ether	0	0	0	0
allyl amine	0	0	0	0
Alkene	))))* 24 °C	)))) 24 °C	Δ* 45 °C	Δ 45 °C
<b>(b) <i>Air</i> equilibrated water</b>				
<b>% conversion at 1 h</b>				
4-pentenoic acid	100	100	100	0
3-allyloxy-2-hydroxy-1-propanesulfonic acid	100	5	100	0
N-isopropyl acrylamide	69	0	62	0
allyl alcohol	100	30	77	0
acrylamide	35	12	41	28
allyl amine	33	8	14	0

\*with initiator; (a) 20 mM AIBN in the ultrasound reaction and 5 mM AIBN in the thermal reaction (b) 1.75 mM K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in both cases. )))) ultrasound at 17 W cm<sup>-2</sup>.

The conversion achieved in the sonochemical reactions can be improved by extending the reaction time, by raising the ultrasound power and by increasing the concentration of AIBN or number of thiol equivalents. For example, for butyl vinyl ether, 88% conversion was achieved after 4 h by using 60 mM AIBN and 5 equivalents of thiol with an ultrasound intensity of 21 W cm<sup>-2</sup> (simply extending the reaction time to 4 h with other conditions remaining as in Table 2 increased the conversion to 45%). However such conditions are unlikely to be adopted on a larger scale.

No reaction occurred with either initiation for the electron deficient alkenes, allyl amine and allyl butyl ether, or for thermal

initiation with 1-pentene; the sonochemical conversion with the latter was negligible. Much higher concentrations of radicals and/or thiol would seemingly be required for significant conversion. As predicted, no reaction was observed with heated reactions without AIBN. However, in the sonochemical system, the more reactive alkenes did show some reactivity even without AIBN leading to low conversions. This demonstrates a potentially favourable feature of the sonochemical approach in, for example, polymer cross-linking where residues from an added initiator may lead to problems with discolouration of the product or to biocompatibility issues. Here, quantitative conversions are not required in order to achieve effective cross linking.

Having investigated sonochemical thiol-ene reactions in an organic system, it was of interest to investigate their use in aqueous solution under ambient conditions. Cysteamine hydrochloride was chosen as a model water soluble thiol to react with six alkenes using potassium persulfate as an initiator. The reactions were conducted in an analogous manner to those detailed above except that they were carried out in air and the number of thiol equivalents was increased from 1.5 to 5 to suppress potentially competing polymerisation reactions<sup>24</sup> for some alkenes. Terephthalic acid dosimetry<sup>23</sup> was used to measure radical (specifically the hydroxyl radical) production in the aqueous system (see ESI<sup>†</sup>) to determine conditions under which the same concentration of initiator could be used in the thermal and sonochemical systems to achieve comparable rates of radical production.

For alkenes that do not polymerise, Table 2(b) shows that quantitative conversions can be achieved in both sonochemical and thermal systems. Whilst sonolysis of thiols has been reported in aqueous systems<sup>25</sup> it appears that there is less retardation of sonochemical reaction than observed when using toluene as solvent. For NIPAm and acrylamide, some polymerisation was observed resulting in reduced conversion to thioether (16% and 50% conversion to polymer was observed in the sonochemical case for NIPAm and acrylamide respectively). Acrylamide also showed significant conversion when heated in the absence of initiator, indicating that thermal decomposition alone at 45 °C produces a sufficiently high concentration of radicals to initiate a reaction.

Figure 1 shows conversion as a function of time during the early stages of reaction for the four most reactive alkenes in each system. In toluene, the sonochemical results show a steady decrease in reactivity as more electron deficient alkenes are used although there are much wider differences in the thermal reactions. The short inhibition period observed in the thermal reactions is likely to be caused by residual oxygen, a problem which is alleviated in the sonochemical system by the degassing effect of ultrasound.

For the aqueous reactions, Figure 1 shows that, for the more reactive alkenes, quantitative conversions can be achieved in 10-30 min and while the thermal reactions are generally faster the slightly longer times needed for the sonochemical reaction are not significant. As expected, some reaction was achieved in the sonochemical system in the absence of initiator, facilitated by the production of hydroxyl radicals upon sonication of water. In the case of pentenoic acid quantitative conversion could be rapidly achieved even with no added initiator. It is not clear why this

compound is exceptional but opens up the possibility of using sonochemical thiol-ene coupling in aqueous systems where thermal lability and/or added initiators cause problems. In addition, sonochemical thiol-ene coupling offers a genuine alternative to initiator driven thiol-ene reactions in wider applications such as cross linking where quantitative conversion is not crucial for efficacy.

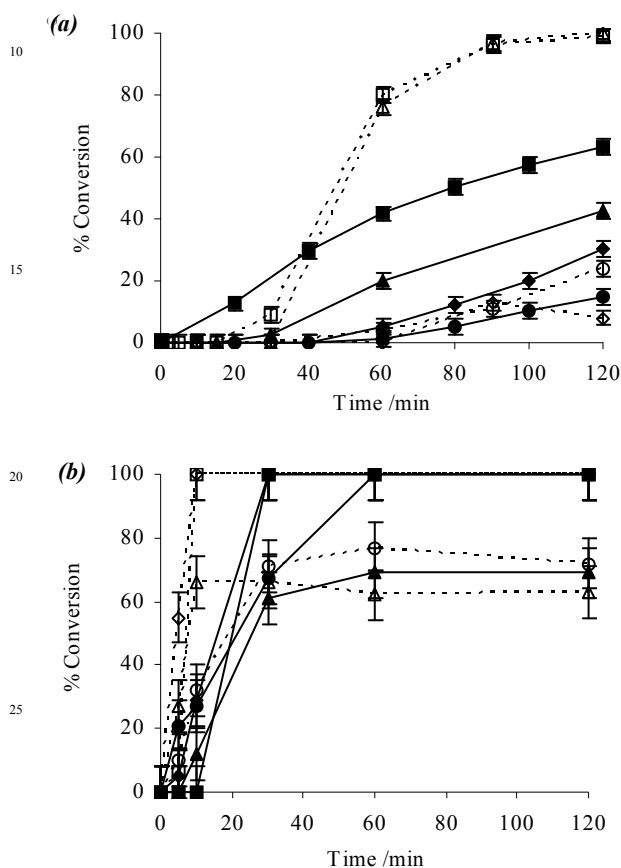


Figure 1: Reaction profiles for sonochemically (closed shapes, —) and thermally (open shapes, - - -) initiated thiol-ene coupling (a) 1-butanethiol with AIBN in toluene: ■, □ norbornene; ▲, △ NIPAm; ◆, ◇ butyl vinyl ether; ●, ○ 1-heptene (b) cysteamine hydrochloride with  $K_2S_2O_8$  in water: ◆, ◇ pentenoic acid; ■, □ 3-allyloxy-2-hydroxy-1-propanesulfonic acid; ▲, △ NIPAm; ●, ○ allyl alcohol.

The use of ultrasound as an effective method of initiation for thiol-ene reactions in toluene or water has been demonstrated for a range of alkenes. Reactions conducted in toluene are not greatly advantageous over conventional conditions but there exists the possibility of using other solvents more conducive to sonochemical radical production. High conversions were observed for sonochemical initiation of thiol-ene couplings in air equilibrated water. Whilst ultrasound initiation of thiol-ene couplings does not fulfil all of the attributes of a 'click' reaction it can be presented as an effective and useful method of conducting thiol-ene coupling reactions around room temperature with potential for use in cross linking applications. Of particular note is the effectiveness of this strategy in the presence of air for aqueous systems. We foresee this to be of particular use in sonochemical cross linking for biomedical applications. Beyond the small molecule couplings discussed here this method of

initiation offers potential applications in interfacial thiol-ene chemistry, utilising emulsions that are readily formed in ultrasound systems.

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<sup>†</sup> Electronic Supplementary Information (ESI) available: [Full experimental together with plots relevant to the dosimetry reported]. See DOI: 10.1039/b000000x/