



Reaction of a triazolinedione with simple alkenes. Isolation and characterization of hydration products

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ABSTRACT

The reaction of *N*-phenyltriazolinedione with three simple alkyl-substituted alkenes in water/alcohol or water/acetone solution was found to give a mixture of the corresponding ene and water addition products. The new hydration products were characterized by spectroscopy, and in one case, also by X-ray diffraction analysis. Thermodynamic parameters were determined for the reactions involving 2-methylbut-2-ene, TriME, and 2,3-dimethylbut-2-ene, TetraMe, in accordance with an 'S_N2-like', nucleophilic attack on a closed aziridinium imide (AI) intermediate by water.

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The 'ene' reaction of triazolinediones (TADs)¹ with an alkene-bearing allylic hydrogens is of current interest from both synthetic² and mechanistic^{3–6} points of view. Stereoisotopic studies have supported the involvement of a 'closed' diaziridinium imide intermediate (AI).⁴ However, this view has recently been challenged by the proposal of an alternative mechanism involving an 'open' diradical,⁵ albeit one with restricted structural characteristics.⁶

In protic nucleophilic solvents, the reaction affords, in addition to the 'ene' adduct, a product that is derived from nucleophilic addition of the solvent to a 'closed' AI intermediate, a suggestion supported by both stereochemical studies,⁷ thermodynamic data⁸ and solvent isotope effects.⁹ Very recently, an argument has been made for the existence of open dipolar intermediates in the ene reaction.¹⁰ In protic solvents such as water or MeOH, formation of the open intermediate is thought to be the rate-determining step, and the ene product is subsequently formed without the intervention of an AI intermediate. However, in polar aprotic solvents, such as DMSO or MeCN, the open dipolar species equilibrates to an AI intermediate which is the precursor of the ene adduct. This argument¹⁰ has inspired further mechanistic studies of the ene reaction of PhTAD by ourselves and others.¹¹

We decided to see whether water, despite its weakness as a nucleophile, adds to the AI intermediate. At the beginning of the study, we chose to study the reaction of a simple alkyl-substituted alkene, 2-methyl-2-butene (trimethylethylene, TriME), which is known to give a regiospecific Markovnikov 'ene' adduct in the reaction with PhTAD, and also regio- and stereospecific nucleophilic protic solvent adducts, attributed to some positive charge separation at the tertiary carbon in the AI intermediate.^{4a,7} Initially, we chose to work with the protic solvent *t*-butanol since it gives exclusively the 'ene' product, presumably because steric hindrance prevents its nucleophilic addition to the AI intermediate. It is also homogeneously miscible with large quantities of water at room temperature.

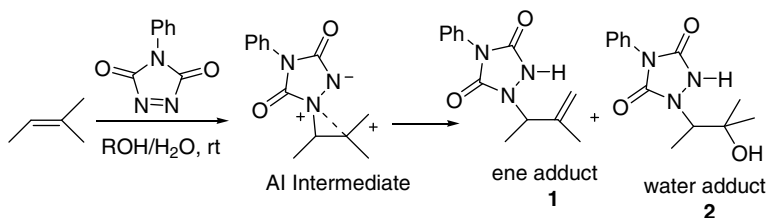
The reaction was carried out by the rapid addition of solid PhTAD (0.1 mmol, 18 mg) to a solution of TriME (0.11 mmol, 10% excess, 12.5 μ L) in *t*-butanol/water mixtures of varied v/v ratios (total volume 1 mL) at room temperature. The solution lost its red colour, and became brownish. It was then dried with MgSO₄, and the solvent was removed on a rotary evaporator. Remaining traces of solvent were finally removed with a high-vacuum pump. Immediately thereafter, ¹H NMR showed the existence of two products: the 'ene' adduct, **1**, and a new compound which proved to be the alcohol, **2**.¹² Scheme 1.

By integration of the appropriate quartets of the two reaction products (methine hydrogen atoms at 4.75 ppm for **1** and at 4.18 ppm for **2**), we were able to estimate their molar ratio in different alcohol/water mixtures, Table 1. Appreciable amounts of the hydration product **2** are only obtained when the water content of

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Scheme 1. Reaction of PhTAD with TriME in t -BuOH/ H_2O mixtures.

Table 1

Molar ratio of reaction products in different t -butanol/water mixtures^a

t -BuOH/ H_2O , v/v	Molar ratio, [1]:[2]
94/6	74/26
88/12	55/45
76/24	48/52
70/30	44/56
65/35	45/55
60/40	46/54

^a Reactions were carried out at room temperature in 1 mL total volume.

the solvent is more than 10% by volume. The minimum molar ratio [1]:[2] of 44:56 occurs when the t -butanol/water v/v ratio is 70/30. Further increase in water content has virtually no effect on the [1]:[2] molar ratio.

A preparative experiment in 70/30 v/v t -butanol/water solution (after column chromatography on a short column of SiO_2 , with EtOAc/ n -hexane 1/1 v/v, as eluent) afforded the pure new product **2** in 35% yield, separated from the ene product **1** which was eluted first and isolated in 34% yield.¹³ Product **2** was crystallized from $CHCl_3/n$ -hexane as white prisms, and characterized by 1H , ^{13}C NMR, FT IR and ESI MS spectroscopy and by X-ray analysis.¹⁵

It is worth noting that the presence of an intramolecular N–H...O hydrogen bond in **2**, evident from the X-ray analysis, Figure 1, was confirmed by the observation of a strong absorption at 3417 cm^{-1} in the FT IR spectra. In addition, small differences in the 1H NMR spectra of **2** before and after crystallization were observed: the signals corresponding to the three methyl groups in **2** were shifted downfield by 0.02–0.05 ppm on going from the oil to the crystalline product.

We also isolated the corresponding alcohols from the reactions of 2-methylpropene (isobutylene), **3**,¹⁶ and 2,3-dimethylbut-2-ene (TetraME), **4**,¹⁷ under comparable conditions, Figure 2. The respective yields of **3** and **4** were 32% and 30% relative to PhTAD.

We also considered the formation of the alcohol **2** when the reaction was carried out in aqueous iso -propanol or trifluoroethanol (TFE) at room temperature. For the iso -propanol/water reaction, 1H NMR of the crude product mixture indicated that the

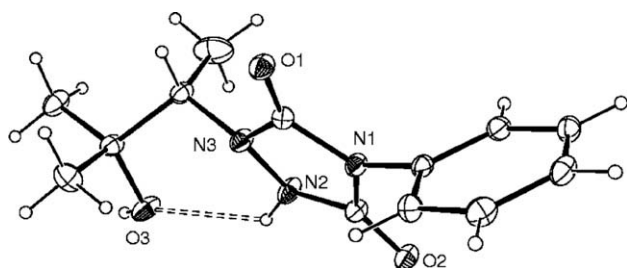


Figure 1. A view of a molecule of **2** (50% ellipsoids). Minor disorder (0.19 site occupancy) of the $Me_2C(OH)CHMe$ substituent is not shown. Dimensions of the intramolecular hydrogen bond (Å and °): N2–H 0.85(3), H...O3 2.16(4), N2...O3 2.713(4) and N2–H...O3 123(3).

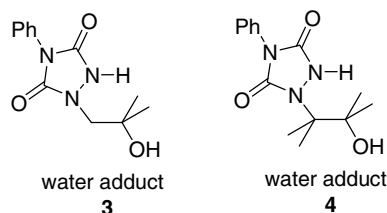


Figure 2. Alcohols isolated from the reaction of PhTAD with alkenes in water mixtures: water adduct **3** from 2-methylpropene, and adduct **4** from 2,3-dimethylbut-2-ene.

maximum formation of **2** occurred in the 80/20 v/v mixture, with a molar ratio [1]:[2] equal to 38/62. In contrast, with TFE/water the best mixture for forming **2** was 60/40 v/v, with the ratio [1]:[2] = 48/52. Small amounts of products arising from addition of the solvent alcohol were encountered with both iso -propanol and TFE solvent mixtures.

From these experiments, we conclude that appreciable amounts of the alcohol **2** will form only when the water content is high enough for the AI intermediate to form a hydrogen bond via its negatively charged nitrogen atom mainly to water rather than to the protic solvent. With t -butanol and iso -propanol, the water content needs only to be 30% and 20% v/v, respectively, for optimum yield of the alcohol **2**, whereas this rises to 40% v/v with the more effective proton donor TFE. In addition, higher water content will be more effective in preventing the approach and nucleophilic addition of the alcoholic solvent to the AI intermediate.

Following our recent determination of thermodynamic parameters for the addition of nucleophilic-alcohol solvent to the AI intermediate,^{8,9} we decided to perform a similar experiment with water mixtures. t -Butanol, though an effective medium for the formation of **2** in that it gives a satisfactory [1]/[2] molar ratio, has a high-freezing point. Furthermore, in order to simplify the integration of the NMR spectra, we wished to avoid the formation of alcohol addition products. These considerations led us to use acetone as the second component of the solvent mixture. No acetone addition adducts were formed, and the water mixture remained liquid down to $-33\text{ }^\circ\text{C}$.

Accordingly, we reacted PhTAD with 2-methylbut-2-ene (TriME) and 2,3-dimethylbut-2-ene (TetraME) at four different temperatures ranging from $+21$ to $-33\text{ }^\circ\text{C}$ in acetone/ H_2O mixtures (70/30, v/v). Only the ene and the water addition products were detected in the 1H NMR spectra of the crude reaction mixtures. Relative integration of appropriate signals gave molar ratios of the two products at different temperatures. From these, the thermodynamic parameters listed in Table 2 are derived by standard transition-state theory. Values for the reaction in MeOH as solvent are included for comparison.

Table 2 clearly shows how similar are the thermodynamic parameters obtained for both reaction media and for the two alkenes. The great difference in nucleophilicity between methanol and water is not reflected by the activation parameters. These

Table 2

Thermodynamic parameters calculated for the reaction of PhTAD with alkenes in MeOH and mixtures of acetone/water as solvents

Alkene	MeOH		Acetone/H ₂ O	
	$\Delta\Delta H^\ddagger$ (kcal/mol)	$\Delta\Delta S^\ddagger$ (e.u.)	$\Delta\Delta H^\ddagger$ (kcal/mol)	$\Delta\Delta S^\ddagger$ (e.u.)
TriME	6.8 $\pm$ 0.1	22 $\pm$ 1	4.3 $\pm$ 0.1	16 $\pm$ 1
TetraME	5.3 $\pm$ 0.1	18 $\pm$ 1	4.5 $\pm$ 0.1	18 $\pm$ 1

results may be taken as qualitative evidence for a similar 'S_N2-like' transition state for the solvent addition process. The latter conclusion, though qualitative in nature, witnesses, in our opinion, for the intervention of the AI intermediate in water and alcohol environments, when used as protic nucleophilic solvents.

As discussed above, the solvated AI intermediate may reach a transition state by adding one water molecule to the tertiary carbon atom (in the case of TriME reaction, see Scheme 2), and a second one approaching the negatively charged nitrogen atom of the PhTAD moiety, in analogy with the reports on *anti*-addition of nucleophilic solvents to AI intermediates.^{7,8} Alternatively, a single water molecule could be added in a concerted fashion, donating a proton to the negatively charged nitrogen atom and a hydroxide anion to the tertiary carbon in a *syn* addition, Scheme 2.

This alternative has the advantage that the reactive nucleophile (a partially formed hydroxide anion) is formed in situ, thereby explaining the very low yields of *iso*-propanol, and TFE solvent adducts. Moreover, this transition state is consistent with the solid-state structure of alcohol **2**, which is stabilized by an intramolecular N–H...O hydrogen bond (see Fig. 1). Further stereochemical studies are needed to clarify the nature of this reaction and, in particular, to discriminate between *syn* and *anti* water addition to the AI intermediate. *Syn* addition, though, of MeOH or EtOH as nucleophilic solvent to a 'closed' AI intermediate has been ruled out.⁷

In summary, we have reported here for the first time the formation of a product derived from hydration of the AI intermediate in the reaction of PhTAD with simple alkenes, such as trimethylethylene. This new aspect of the reactivity of TADs opens the way for reactions in aqueous environments, for example, with lipid substrates, which may model biological processes. It may also serve as a useful, new, synthetic transformation of unfunctionalized alkenes: for example, it could be used to synthesize amino alcohols since it is known that the PhTAD moiety can be transformed into an amino functionality,^{2b,18} and also to form enamines by dehydration. In addition, the present work emphasizes that, in the reaction

of PhTAD to alkenes in aqueous environments, the potential formation of water addition products should always be borne in mind. Further work with different alkenes is in progress to clarify the nature of the transition state of the reaction.

Acknowledgements

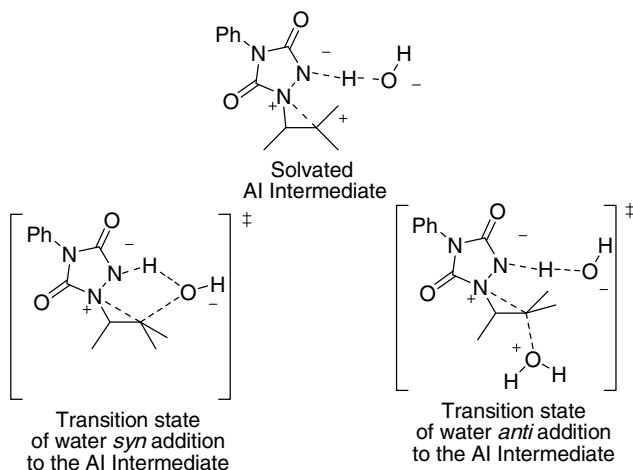
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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.150.

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- ¹H NMR (250 MHz, CDCl₃) of alcohol **2**: δ (ppm) 7.87 (br s, 1H, –NH), 7.33–7.55 (m, 5H, aromatic), 4.18 (q, 1H, methine, *J* = 7.0 Hz), 1.93 (br s, 1H, –OH), 1.38 (s, 3H), 1.35 (d, 3H, *J* = 7.0 Hz), 1.32 (s, 3H). ¹³C NMR (60 MHz, CDCl₃): δ (ppm) 152.7 (carbonyl), 151.9 (carbonyl), 131.4 (aromatic), 129.1 (aromatic), 128.1 (aromatic), 125.6 (aromatic), 74.1 (C–N), 58.2 (C–O), 28.4 (Me₂C–OH), 27.5 (Me₂C–OH), 12.2 (Me–C–N). ESI MS spectra showed the [M+H]⁺ signal at 264.36 *m/z* (100% intensity), and also the [M+H–H₂O]⁺ signal at 246.36 *m/z* (50% intensity). FT IR spectra (KBr) showed strong absorptions at 3417 (coupled NH + OH), 3306 (shoulder), 2980 (C–H), 1763 (carbonyl), 1704 (carbonyl), 1435, 1127, 768, 704 cm^{–1}. Elemental Anal. Calcd for C₁₃H₁₇N₃O₃: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.53; H, 6.53; N, 16.02.
- Triazolinediones were reported to react with alcohols by decomposition to afford a variety of characterized products depending on the reaction media.¹⁴ We also noticed that a stirred PhTAD/water mixture lost the red colour at room temperature after 15 min, and gave products that are unidentified for the moment. For the above-mentioned reasons, the isolated yield of alcohol **2** is expected to be lower than that estimated from the ¹H NMR spectra of the crude reaction mixture.
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- Crystal data for **2**: C₁₃H₁₇N₃O₃, *M* = 263.30, monoclinic, *a* = 9.1677(7), *b* = 13.7222(13), *c* = 11.3050(11) Å, β = 109.50(1)°, *U* = 1340.6(2) Å³, *T* = 120 K, space group *P*2₁/*c*, *Z* = 4, μ (Mo K α) = 0.094 mm^{–1}, 8117 reflections measured, 1995 unique (*R*_{int} = 0.11). The final *R*(*F*) and *wR*(*F*²) values were 0.063 [*I* > 2(*I*)].



Scheme 2. Solvated AI intermediate and transition states for the *syn* and *anti* addition of water to the AI intermediate.

and 0.147 (all data). $|\Delta\rho| < 0.28 \text{ e}/\text{\AA}^3$. The structure of this Letter has been deposited with the Cambridge Structural Database with deposition number CCDC 245941.

16. ^1H NMR (250 MHz, CDCl_3) of alcohol **3**: δ (ppm) 7.32–7.55 (m, 5H, aromatics), 3.60 (s, 2H, CH_2), 1.33 (s, 6H, 2 CH_3). ^{13}C NMR (60 MHz, CDCl_3): δ (ppm) 154.8 (carbonyl), 153.5 (carbonyl), 131.5 (aromatic), 129.1 (aromatic), 128.0 (aromatic), 125.6 (aromatic), 77.2 (C–N), 52.8 (C–O), 20.0 (2Me). ESI MS calculated for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_3$: $[\text{M}] = 249$, found: $[\text{M}+\text{H}]^+ = 250$.
17. ^1H NMR (250 MHz, CDCl_3) of alcohol **4**: δ (ppm) 7.32–7.55 (m, 5H, aromatics), 1.55 (s, 6H, $\text{Me}_2\text{–C–N}$), 1.27 (s, 6H, $\text{Me}_2\text{–C–O}$). ^{13}C NMR (60 MHz, CDCl_3): δ (ppm) 154.4 (carbonyl), 153.4 (carbonyl), 129.2 (aromatic), 129.1 (aromatic), 128.2 (aromatic), 76.9 (C–N), 64.9 (C–O), 22.2 ($\text{Me}_2\text{–C–N}$), 19.0 ($\text{Me}_2\text{–C–O}$). ESI MS calculated for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_3$: $[\text{M}] = 277$, found: $[\text{M}+\text{H}]^+ = 278$.
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