A Study of the Microwave-Accelerated Condensation of Substituted Benzaldehydes with 3-Substituted Hydantoins and the Unexpected Interception of Alcohol Products

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Abstract

A systematic study of the effect of microwave irradiation on the condensation of substituted benzaldehydes with 3-substituted hydantoins (imidazolidine-2,4-diones) led to the isolation of benzylhydantoin alcohols as major products, as well as of benzalhydantoins. The alcohol products had characteristic HPLC retention times with respect to aldehyde and benzalhydantoin traces, and were identifiable through mass spectrometric analysis at detection as all gave molecular ions. The alcohols were isolated on preparative scale in one example and studied by two-dimensional NMR experiments such as COSY, HSQC, and HMBC. Their study in the solid state by X-ray single crystal crystallographic analysis revealed them to form as two racemic diastereoisomers that crystallized together in racemic pairs.

Keywords: crystallography, hydantoins, microwave-acceleration, substituted benzaldehydes.

1. Introduction.

Many methods rely on condensation of aldehydes with active methylene compounds, including commercially available, hydantoin 1 and its N-(3)-substituted derivatives. Wheeler and Hoffmann described the condensation of aromatic aldehydes with hydantoin 1 itself a little over a century ago. Their synthesis proceeded in glacial acetic acid, in the presence of a little acetic anhydride and fused sodium acetate. The products were isolated by filtration directly from the cooled reaction mixtures.

Boyd and Robson (1935) later observed that the condensation of hydantoin 1 and aromatic aldehydes occurred in pyridine in the presence of piperidine or diethylamine as a catalyst. These Knoevenagel conditions afforded the desired products in 14-100% yields with the piperidine catalyst and 65-94% yields with diethylamine as catalyst.
across six examples of condensation reaction of benzaldehyde, anisaldehyde, \( p \)-hydroxybenzaldehyde with hydantoin 1 and acetylthiohydantoin.

More recently, a group at Lilly Industrial Limited patented a process involving the condensation reaction of hydantoins with aromatic aldehydes in water/ethanol. The reaction was promoted using ethanolamine and proceeded under reflux for 3 h \(^1\). Hosztafi et al.\(^4\), used this method to synthesis \( N \)-unsubstituted benzalhydantoins and benzal-2-thiohydantoins as antifungal agents. They found that in the first step of the reaction, arylideneimine Schiff bases were formed. The Schiff bases were reactive species in this reaction and played an important role in the arylidene transfer.

Even more recently, the Wheeler and Hoffmann procedure reemerged when it was employed in the condensation of related piperizinediones with aldehydes\(^4\) and with \( N \)-(3)-substituted hydantoins with aldehydes\(^5\) as part of an efficient synthesis of 2-substituted indoles. This route attracted us as a candidate for automation. However in it, and in all previous cases above, the methods involved relatively long reaction times and sometimes unexpectedly low yields, dependent it seemed on reactant substituents.

In this study, it was decided to investigate microwave acceleration\(^6\),\(^7\),\(^8\) as a means of improving the efficiency of the condensation process. This rapid form of heating had been beneficial in accelerating the progress of the allylation of benzalhydantoins in previous research, where it had also given reaction products with fewer byproducts. The aim in this study was therefore to reinvestigate the condensation of aldehydes with hydantoins. Ultimately, the study also generated a series of alcohol products and one set of these was examined by single crystal X-ray crystallography.

2. Experimental

2.1. General

Melting points were measured on a Reichert hot-stage microscope and are uncorrected. Microanalyses were performed by Dr R. Bergman and Dr V. Withers, Microanalytical Unit, Australian National University. Ultraviolet spectra were measured on a Hitachi U-3200 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 298 IR spectrophotometer. The samples were prepared as neat thin films for liquids and KBr disks for solids. \(^1\)H NMR spectra were recorded in designated solvents on a Bruker DPX300F or DMX500 instrument. Spectra were recorded at 300 MHz or 500 MHz and data were reported as chemical shift (\( \delta \)) in parts per million (ppm) downfield from tetramethylsilane (TMS), multiplicity, observed coupling constant (\( J \)) in Hertz (Hz), and proton assignment. Multiplicities were reported as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), or multiplet (m). Broad signals were reported as br. \(^1\)C NMR spectra were recorded at 75 MHz or 125 MHz. Chemical shifts (\( \delta \)) were reported in ppm downfield from TMS. \(^1\)H and \(^1\)C NMR assignments were determined with the aid of COSY, NOESY, HSQC, HMBC, DEPT 90 and DEPT 135 experiments.

HPLC analyses were performed on a Waters LC-MS instrument with a Waters reagent manager, a Waters 2767 sample manager, LC-Waters 600 controller, Waters-2996 photodiode array detector, and a Waters Micromass ZQ2000 detector using ESI multi-mode ionization. Masslynx 4.0 software was used for system control and data processing.

The X-ray crystallographic data collection and analysis were performed by MB in the Solid State and Elemental Analysis Unit at Mark Wainwright Analytical Centre, University of New South Wales, and by Dr. Tom Caradoc-Davies in the Micro Materials Characterisation beamline at the Australian Synchrotron Facility, Melbourne.

2.2. Reaction Monitoring to Understand the Role of Aldehyde Substitution and Role of Hydantoin Substitution under Microwave-Accelerated Conditions.

Individual 10 mL glass microwave reaction vessels containing a stirrer bar were charged in turn with combinations of aldehydes \( 5-8 \) (0.55 mmol), hydantoin \( 1-4 \) (0.50 mmol), KOAc (125 mg, 1.276 mmol) in AcOH (2.5 mL), and \( \text{Ac}_2\text{O} \) (25 \( \mu \)L, 0.265 mmol). The vessels were sealed and placed in the automated handling rack of a CEM Discover Microwave Reactor, from where they were treated for a total of 1 h at 120 °C, 200 psi pressure, and
250 watt power. At the end of each intermediate time cycle (see following), the vessel was cooled to below 50 °C, opened and aliquots (20 µL) withdrawn by Eppendorf pipettes. The vessel was then resealed and subjected to further reaction. Monitoring of the condensation reaction was continued at 10 min intervals over 60 min. Samples were made up to 1 mL with CH$_3$CN and the mixtures briefly sonicated to ensure total solubility of the species. Aliquots of the solutions (5 µL) were analysed by HPLC on a Synergy Max-RP column with 5 µm particle size using a gradient elution 5-95% CH$_3$CN-water over 15 min and then 95% CH$_3$CN-MilliQ water (0.1% formic acid) for 5 min with 1 mL/min flow, with UV detection at 254 nm and ESI/APCI mass spectrometric detection. The ratios of peak areas, based on UV absorption at 254 nm, were used to determine percentage composition.

2.3. Preparative Scale Reaction of Hydantoin 1 with 4-Chlorobenzaldehyde (6)

4-Chlorobenzaldehyde, 6 (643.5 mg, 5 mmol), hydantoin, 1 (500 mg, 5 mmol), KOAc (490 mg, 5 mmol), HOAc (2.5 mL) and Ac$_2$O (50 µL, 0.49 µmol) were added in sequence and dissolved together in a microwave reaction vessel (10 mL). The vessel was then heated in a microwave vessel (sized, 10 mL). The vessel was then resealed and subjected to further microwave irradiation (250 watt) for 60 min. Upon rapid cooling, the mixture was diluted with water (2 mL) to give a pale yellow precipitate. The solid was collected and recrystallized from MeOH to give (Z)-5-(4-chlorobenzylidene)imidazolidine-2,4-dione, 13 as pale yellow needles (434 mg, 39%) m.p. 294-296 °C. $^1$H NMR (DMSO-$d_6$): δ 6.4, s, H-1; 7.42, d, J = 9 Hz, H-3" and H-5"; 7.65, d, J = 9 Hz, H-2" and H-6"; 10.0, br s, N(1)H; 10.96, N(3)H. $^{13}$C NMR (DMSO-$d_6$ 75 MHz): δ 165.8, C-4; 156.1, C-2; 133.2, C-1"; 132.1, C-4"; 131.1, C-6"; 131.4, C-2"; 129.1, C-3"; 128.1, C-5", 107.1, C-1'. Mass spectrum (ES-MS): m/z 225 ([M(35Cl)]$,^+$, 37%), 223 ([M(37Cl)]$,^+$, 100).

Further, the initial aqueous filtrate deposited a flaky white precipitate. It was collected and recrystallized from aqueous EtOH to give a 50:50 mixture of diastereoisomeric 5-((4-chlorophenyl)(hydroxy)methyl)-imidazolidine-2,4-dione, 20 (20A and 20B) as elongated plates (176.8 mg, 16 %) m.p. 112-114 °C. Isomeric NMR signals were observed and assigned to isomer 20A and isomer 20B according to COSY, HSQC, HMBC and NOESY experiments. These labels may not coincide with the stereochemical assignments of 20 (5R, rel-1’R) and 20 (5S, rel-1’R). $^1$H NMR (DMSO-$d_6$): δ 4.23, dd, J =2.1, 1.6 Hz, H-5 (A); 4.35, dd, J =2.9, 1.0 Hz, H-5 (B); 4.90, d, J =2.4 Hz, H-1’ (A); 4.92, d, J =2.1 Hz, H-1’ (B); 5.84, d, J =5.5 Hz, OH (A); 5.95, d, J =3.9 Hz, OH (B); 7.30, br d, J =8.5 Hz, H-6’ and H-2” (B); 7.37, br d, J =8.5 Hz, H-5” and H-3” (B); 7.39, d, J =7.5 Hz, H-6” and H-2” (A); 7.41, d, J =7.5 Hz, H-5” and H-3” (A); 7.55, br s, H-1 (A); 8.09, br s, H-1 (B); 10.34, br s, H-3 (B); 10.55, br s, H-3 (A). $^{13}$C NMR. (DMSO-$d_6$ 75 MHz): δ 64.27, C5 (A); 64.31, C5 (B); 70.5, C1’ (A); 72.0, C1’ (B); 128.3, C3” (A); 127.9 C3” (B); 128.5, C-2” (A); 129.2, C-2” (B); 132.1, C-4" (A); 132.4, C-4" (B); 141.0, C-1” (A); 138.8, C-1” (B); 158.4, C-2 (A); 156.7, C-2 (B); 174.3 C-4 (B); 173.4, C-4 (B). Mass spectrum (ES-MS): m/z 265 ([M(37Cl)+Na]$^+$, 37%), 263 ([M(35Cl)+Na]$^+$, 100), 241 (7), 169 (43).

The sample was suitable for single crystal, X-ray crystallographic analysis.

3. Results and Discussion

Since much information had been assembled in previous studies$^{1,3,4}$ on the method used by Wheeler and Hoffman with conventional heating, it was thought best to adapt this set of conditions. The Wheeler and Hoffman conditions already had attractive features for microwave acceleration, including the use of a salt, sodium or potassium acetate, as a base, and polar protic solvent and dehydrating additive, acetic acid and acetic anhydride. Moreover, these conditions were more suited to microwave irradiation than alternative triethylamine/dimethylformamide conditions developed by Yang et al. (2003).$^9$ They were therefore adapted with the replacement only of their conventional heating by microwave heating.

3.1. Monitoring the Microwave-Assisted Condensation Process

In the long term, the complete matrix of reactions of hydantoin 1-4 with benzaldehydes 5-8, as show in Scheme 1, was of interest. However, initially, the reactions of only two axes of this matrix, all four aldehydes with 3-phenylhydantoin 2, the previously most reactive hydantoin$^{3,4}$, and then reactions of 4-chlorobenzaldehyde 6, the aldehyde of most moderate and generally useful reactivity$^{3,4}$, with all four hydantoins, were examined.
The reactions were performed for comparative purposes under identical conditions in sealed reaction vessels under microwave irradiation using a commercial, automated reactor (see Experimental). In each case the reaction was repeated several times over. On each occasion the reaction time was fixed so that data were collected after one minute and then at 10 minute intervals. Reactions were quenched by dilution with CH₃CN and product mixtures analysed by HPLC using the chromatographic conditions described in the Experimental Section. Percentage component compositions for each series were recorded in Table 1, along with HPLC retention times (Rt) and respective mass spectrometric (m/z) data.

Table 1. Timecourse study of percentage component composition of reactions between 3-phenylhydantoin 2 and aldehydes 5-8, and aldehyde 6 and hydantoins 1-4, under microwave conditions.

| RCHO | Hydantion | Components | Rt (min) | m/z  | Composition (%) | Reaction time (min) |
|------|-----------|------------|----------|------|-----------------|---------------------|
| 1    | 10        | 100;105    | 54       | 48   | 48              | 48                  | 49                  | 50                  | 51                  |
| 10   | 2         | 284;283    | 30       | 47   | 48              | 48                  | 46                  | 47                  | 46                  |
| 9    | 8.6       | 265;264    | 6        | 5    | 4               | 4                   | 5                   | 3                   | 3                   |
| 8    | 11        | 311;310    | 0        | 0    | 0               | 0                   | 2                   | 4                   | 5                   |
| 7    | 2         | 152;151    | 90       | 90   | 90              | 90                  | 87                  | 84                  | 81                  |
| 17   | 6.9       | 327        | 10       | 10   | 10              | 10                  | 11                  | 12                  | 14                  |
| 10   | 8.7       | 311;316    | 0        | 0    | 0               | 0                   | 0                   | 0                   | 0                   |
| 18   | 6.3       | 137;136    | 93       | 91   | 67              | 65                  | 57                  | 51                  | 54                  |
| 11   | 8.5       | 295;294    | 0        | 0    | 0               | 0                   | 0                   | 0                   | 0                   |
| 6    | 1         | 143;141    | 56       | 34   | 39              | 33                  | 28                  | 24                  | 24                  |
| 20   | 7.5       | 265;263    | 36       | 60   | 59              | 67                  | 72                  | 76                  | 79                  |
| 13   | 9.5       | 223;225    | 8        | 6    | 2               | 0                   | 0                   | 0                   | 0                   |
| 6    | 2         | 143;141    | 69       | 62   | 60              | 64                  | 65                  | 65                  | 69                  |
| 19   | 7.5       | 319;317    | 29       | 36   | 38              | 35                  | 34                  | 34                  | 36                  |
| 12   | 9.4       | 301;299    | 2        | 2    | 2               | 2                   | 1                   | 1                   | 1                   |
| 6    | 3         | 143;141    | 98       | 98   | 97              | 95                  | 94                  | 92                  | 90                  |
| 21   | 7.5       | 283;281    | 2        | 2    | 3               | 4                   | 6                   | 7                   | 9                   |
| 14   | 9.5       | 265;263    | 0        | 0    | 0               | 0                   | 0                   | 0                   | 0                   |
| 6    | 4         | 143;141    | 99       | 96   | 94              | 91                  | 88                  | 85                  | 82                  |
| 22   | 7.5       | 299;297    | 1        | 3    | 5               | 8                   | 10                  | 13                  | 16                  |
| 15   | 9.7       | 281;279    | 0        | 1    | 1               | 2                   | 2                   | 2                   | 2                   |

$^{a/b}$ Experiments (and analyses) marked a and b were performed two days apart, which accounts for differences in absolute Rt values. $^[M+Na]$

In all cases, absolute percentage composition values were not important because each set of aldehyde and aldehyde-derived product had different UV-absorption and therefore detection characteristics. Hence the analysis focussed on relative percentage compositions. In addition to the expected and desired (mostly Z-) benzalhydantoin derivatives 9-15, analysis showed formation of alcohols 16-22.
The alcohols 16-22 all chromatographed in reverse-phase HPLC with retention times consistently less than the aldehyde and benzalhydantoin components, supportive of their polar nature. They were identified by respective mass spectrometric detection analysis using positive ion electrospray ionisation; all gave molecular or sodiated molecular ions. This was consistent with an earlier report\(^4\) in which a related alcohol had been isolated from a similar reaction, in only one example, when a sub-stoichiometric quantity of acetic anhydride had been used. In this case the alcohol was reportedly isolated in 67% yield as a single, unspecified diastereomer. Unfortunately, the relative stereochemistries of each alcohol product in the present study could not be determined because the compounds were not isolated, although they gave only single peaks in the HPLC traces. This meant that they were generated either as single diastereoisomers or as two diastereoisomers that had effectively the same retention times. Related and, in some cases, identical alcohols have also been reported as sole products from base catalysed hydantoin/aldehyde condensations\(^10,11,12\) but in these cases they were generated as unspecified mixtures of diastereoisomers and under different reaction conditions. They serve as intermediates to $\beta$-hydroxy-$\alpha$-amino acids\(^11\) and bioactive compounds\(^12\) in their own rights. Returning to our original objective, the following presents a discussion of the time course study for the two sets of reactions.

### 3.2. Effect of Substituents on the Aldehydes under Microwave-Assisted Conditions

The first set of four reactions made use of aldehydes 5-8 with different substituents of electron withdrawing and donating ability, in reaction with 3-phenylhydantoin 2. Substituted hydantoin 2 had previously given the highest yields of all the hydantoins in condensation under conventional heating\(^1,4\). It also was unique amongst them in having significant absorption at 254 nm so its concentration could be monitored. Plots of percent component composition are given in Fig. 1 in which component types are coloured consistently. Regrettably, all the reactions in this series gave significant recovery of the aldehyde component and very little (< 5 %) of the desired benzalhydantoin component.
In the two extremes, the reaction with benzaldehyde 5 gave very rapid changes within the first minute after combining the reactants. There was significant loss of aldehyde 5 and 3-phenylhydantoin 2 with concomitant formation of alcohol 16 and only a very minor amount of the desired benzalhydantoin 9 [Figure 1(a)]. In contrast, 4-nitrobenzaldehyde 7 showed little reaction and only gradual decline, from 94% to 84% concentration, with almost complete loss of the hydantoin 2 and very minor formation of alcohol 17 and of benzalhydantoin 10 [Figure 1(c)]. The other aldehydes, gave moderate to good formation of the alcohols, at different rates, and again almost complete loss of hydantoin 2, but with very little benzalhydantoin formation [Figure 1(b) and 1(d)]. The relative rate of loss of aldehyde was 4-nitrobenzaldehyde 7 < 4-methoxybenzaldehyde 8 < 4-chlorobenzaldehyde 6 < benzaldehyde 5. Meanwhile, little could be defined about ratios of formation of the desired benzalhydantoin products although the relative rates of formation of the alcohols followed the same order as the order of reactivity of aldehydes. Neither of these orders of reactivity made sense mechanistically from an electronic standpoint, nor were they consistent with a previous brief study by others of alcohol formation under aqueous triethylamine conditions and so additional information was sought.

3.3. Effect of Substituents on the Hydantoin in Microwave-Assisted Reactions

The second set of time course reactions summarized in Table 1 utilized a single aldehyde, namely 4-chlorobenzaldehyde 6, and the full range of four hydantoins 1-4, to assess the effect of substituents that were in the hydantoin.
Fig. 2. Percent composition of reactants, aldehydes (Ald) and hydantoins (Hyd), and products, benzalhydantoin (Benz) and alcohols (Alc) in the microwave accelerated reactions of aldehyde 6 with hydantoin (a) 1, (b) 2, (c) 3 and (d) 4.

Analysis of percentage composition charts (Figure 2) again revealed very little formation if any, of the desired benzalhydantoins 12-15, but significant formation of most of the now familiar alcohols, 19-22. The reaction with 3-allylhydantoin 3 [Figure 2(c)] appeared to be an exception. The level of 4-chlorobenzaldehyde 6 and of 3-allylhydantoin 3 remained constant, within experimental error, for up to 60 min. Notably, 3-phenylhydantoin 2 appeared to give rapid formation of alcohol 19, which rose to become only about 35% of the reaction mixture but then remained constant [Figure 2(b) and Figure 1(b)]. In contrast, the reactions with hydantoins 1 and 4 gave near linear, gradual formation of alcohols 20 and 21, respectively [Figure 2(a) and 2(d)].

The rate of consumption of aldehydes 4-chlorobenzaldehyde 6, with four hydantoins 1-4 indicated that under microwave irradiation, these results supported the following order of reactivity in the hydantoins: hydantoin 1 > 3-phenylhydantoin 2 > 3-n-butyldantoin 4 > 3-allylhydantoin 3. The order could possibly be explained by a decrease in the rate of condensation caused by the electron donating effect of the alkyl group on the hydantoin. In contrast, in 3-phenylhydantoin 2 the aryl group is electronegative and might provide an activating effect. This does not explain the success when hydantoin 1 was used. In this case, the mild acidity of the imide nitrogen might assist the condensation through an acid catalysed or buffering process.

Correlation between formation of alcohols 19-22 and the decline in the proportion of aldehydes, influenced by the substitution of the hydantoins 1-4, indicated that the initial C–C bond formation was influenced by the hydantoin. Direct comparison of benzalhydantoin formation influenced by hydantoin substitution showed that only the reaction with hydantoin 1 gave any appreciable benzalhydantoin formation. Moreover, it showed that in this case there was a minor but measurable level of formation of benzalhydantoin 13 within the first few minutes of reaction but then consumption of the substance.

These studies had therefore shed light on the factors influencing the initial condensation process, but had not yielded a satisfactory experimental method for providing optimal yields of benzalhydantoins. It appeared that the alcohols that had been detected might provide the key, as they were readily formed under microwave conditions. However, in this situation they might serve as either intermediates or products of a competing reaction pathway.

3.4. Isolation and Characterization of Alcohol (20)

In order to better understand the process, a study of the nature of the alcohols was undertaken. The reaction that had proceeded to give the highest yield of this class of substance, namely the reaction between hydantoin 1 and 4-chlorobenzaldehyde 6, was repeated on ten-fold larger scale and with proportionately less solvent. After reaction, the mixture was rapidly cooled, quenched with water, and the solid, yellow precipitate collected and recrystallized from methanol to give the sought after and known benzalhydantoin 13 in 39% yield. Meanwhile, the aqueous filtrate was chilled, whereupon it deposited a white flakes that were recrystallized from aqueous ethanol to afford the anticipated, and again known, alcohol 20 as elongated white plates, m.p. 112-114 °C, in 16% yield. Duplication of signals in the \(^1\)H and \(^13\)C NMR spectra revealed that the substance comprised an equimolar mixture of diastereoisomers, arbitrarily assigned as 20A and 20B. Electrospray ionisation mass spectrometry of the mixture showed supportive isotopic ions at \(m/z\) 265 [M(\(^{37}\)Cl)+Na\(^+\); 37%] and 263 [M(\(^{35}\)Cl)+Na\(^+\); 100%].
The $^1$H and $^{13}$C NMR signals were relatively well dispersed and all relatively easily assigned with the assistance of two-dimensional COSY, HSQC, and HMBC experiments. Also a NOESY experiment was able to be used to confirm the linkage between the nuclei in the imidazolidine (hydantoin) rings from each isomer and the respective nuclei associated with the adjacent, covalently bound aromatic rings. In particular, the H-5 signal at δ 4.23 showed a distinct correlation with the two proton aromatic signal at δ 7.39 (H-2" and H-6"). Regrettably, the spectroscopic data did not allow the particular assignment of spin systems to either of the possible diastereoisomers.

Fortunately the sample was suitable for study by single crystal X-ray crystallographic analysis. The unit cell comprised four molecules, two enantiomers from each diastereoisomer $20\,(5R,\,\text{rel-1'\,R})$ and $20\,(5S,\,\text{rel-1'\,R})$ and each was paired through H-bond interactions between the hydroxyl group of one enantiomer with the N(3)-H and C(2)=O group of the imidazolidinedione ring of its partner.13

The two diastereoisomeric molecular structures showed very similar conformations about the C(5)H and 5-CH(OH) bond [Figure 4 (a)(b)]. Further, an overlaid representation of the two [Figure 4(c)], showed almost perfect overlap of the imidazolidinedione ring system and the C5 substituent, except that the imidazolidinedione ring was twisted through 180 degrees. The next most major difference was the twist of the 4-chlorophenyl ring from coplanarity and a slightly smaller bond angle between the aryl ring and the imidazolidinedione ring at the benzylic carbon in isomer $20\,(5S,\,\text{rel-1'\,R})$; this was possibly brought about by attractive electronic forces between the C(4) carbonyl oxygen atom and the electron deficient region above the face of the aryl ring.
Conclusion

In summarizing the outcome of the condensation reactions under microwave conditions, a number of general observations could be made. Firstly, in all the reactions, alcohols were detected, and in all cases these were observed as the major products, rather than the expected benzalhydantoins. Analysis of progressive percentage reaction mixture compositions showed that formation of the alcohol component, as well as the expected benzalhydantoin derivatives, was consistent with the observed rates of consumption of aldehyde in previous results for conventional heating. This did not translate into comparable rates of formation of the desired benzalhydantoin products, and indicated that microwave irradiation dramatically accelerated the initial C-C bond formation in the overall process, without necessarily accelerating the dehydration step of the process. Satisfactory conversion to the benzalhydantoins therefore requires attention at the dehydration step.

It was observed that alcohols 16-22 were generated either as single diastereomers or as diastereomers that had effectively the same HPLC retention time as each other. Alcohol 20 was characterised by two-dimensional COSY, NOESY, HSQC and HMBC experiments, and also studied by single crystal X-ray crystallographic analysis. It was found to crystallize as a stable, equimolar mixture of diastereoisomers 20(5R, rel-1'R) and 20(5S, rel-1'R). Important in contemplating strategies to improve the dehydration step, in both diastereomeric alcohols, the hydroxyl group was oriented antiperiplanar to the vicinal hydrogen on the imidazolidinedione ring through which dehydration must take place. A two-step, E1 process is therefore most likely to be successful.

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