



Advances in bridged 1,2,4-trioxane-based chemistry. A divergent approach to oxa-heterocycles based on ambident reactivity

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ABSTRACT

Heterogeneous catalytic hydrogenation of unsaturated 1,2,4-trioxanes derived from β -ionone-type dienones has been investigated. Our studies revealed a versatile reactivity of trioxanic substrates that led to the development of reaction methodology for the selective manipulation of the alkene and peroxide functionalities. Depending on the catalytic system used, divergent reaction pathways can be controlled to afford either the corresponding saturated 1,2,4-trioxanes or furan structures. A mechanistic rationalisation, which accounts for the reductive behaviour of these heterocycles, is proposed.

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Compounds with a peroxide linkage constitute a broad class of organic molecules that have attracted a great deal of interest in a variety of scientific fields. Due to their structural diversity and multiple reactivity profile they have become useful entities in organic chemistry having diverse applications, which range from oxidants and radical initiators to valuable organic intermediates.¹

Particularly based on their rich and varied chemistry, endoperoxides are well-established intermediates that offer versatility in organic synthesis as precursors of heterocycles and diverse arrays of oxygenated functions such as 1,4-diols and the intricate bis-diepoxy moiety, difficult to obtain under conventional procedures.² Recently, additional chemistry has been realised for 1,2-dioxines, considered masked forms of *cis*- γ -hydroxy enones which in turn are highly flexible systems that can be utilised in a wide range of synthetic transformations.^{3–5}

While 1,2,4-trioxane systems might be expected to display similar reactivity possessing the weak peroxide bond as latent functionality, the knowledge of their fundamental chemistry is a far less developed subject and much remains to be explored about their synthetic utility. A marked structural feature of these highly oxygenated heterocycles, which distinguishes them from the related six-membered 1,2-dioxacycles, is that an extra oxygen atom and the peroxide group are linked to a single carbon becoming an acetal site, significant to impart specific and unusual chemical behaviour.

We previously reported that the photooxidation of $\alpha,\beta,\gamma,\delta$ -dienone compounds derived from β -ionone (**1**) produced the bridged 1,2,4-trioxanes **2** (Scheme 1).^{6,7} In the course of our programme intended to study their basic reactivity we have uncovered their ability of participating in specific chemical reactions selectively yielding different oxygenated heterocycles and polyfunctionalised

structures for synthetic application.^{8,9} By exploiting the intrinsic reactivity of their particular oxygenated rigid core, we have developed an unconventional route to dioxabicyclic ketal containing targets (**3**) and disclosed the first use of the trioxane functional group in the synthesis of natural products.¹⁰ The key step of our approach involves the reduction of the carbon–carbon double bond and the deoxygenative ring contraction using catalytic hydrogenation conditions in an efficient and simple one-pot sequence.

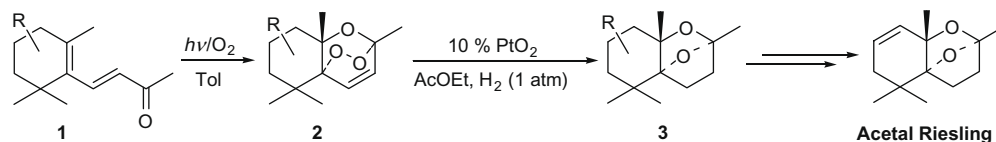
To further define the scope of the reductive process we took interest in examining the chemistry underlying this process addressing the question of its selectivity. Associated to this central methodological issue, we intended to explore the potential of heterogeneous catalytic hydrogenation for performing the controlled manipulation of each of the reducible functional groups present in the template structure **2** aimed at developing the reaction methodology for chemoselective control.

Herein, we would like to report our recent findings concerning the versatile reactivity of substrates **2** under different catalytic hydrogenation conditions leading to the development of chemodivergent routes towards functionalised oxa-heterocycles.

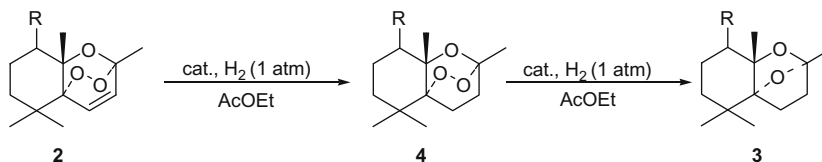
Currently, great interest has been attracted to the behaviour of O–O bonds as its chemistry is related to the antimalarial activity of artemisinin and analogues.^{11–14} Being one of the most fragile covalent bonds in organic compounds and very sensitive to reductive reactions,¹⁵ the selective saturation of an olefin in the presence of a peroxy function is a demanding task. Although the diimide protocol is the established method for hydrogenolysis-free hydrogenation of unsaturated peroxides,^{16,17} it suffers from well-known drawbacks such as the difficulties of generating the reducing agent, the tedious procedure it involves and the concerns with the potential acid sensitivity of the substrates in the presence of the required amount of acetic acid when potassium azodicarboxylate is to be used. These problems, in addition to the lack of experimental

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Scheme 1. Oxidative cyclisation/reductive ring contraction strategy for the synthesis of 2,7-dioxabicyclo[2.2.1]heptane structures.



Scheme 2. Stepwise hydrogenation of unsaturated 1,2,4-trioxanes derived from β -Ionone.

reports in the area, prompted us to examine peroxy bond compatibility with heterogeneous hydrogenation conditions which offer advantages with respect to handling, easy recovery as well as minimisation of undesired toxic wastes.

After a series of trials it was clarified that saturated trioxanes **4** are intermediates in the reduction of **2** to **3** and that these can be isolated if the reaction is stopped before completion (Scheme 2). Taking into account the reaction conditions previously employed in obtaining epoxy-bridged tetrahydropyran compounds **3** (10 wt % PtO₂ under atmospheric pressure of hydrogen in ethyl acetate), attempts to control selectivity were explored by adjusting variables such as amount of catalyst, solvent, time and temperature.

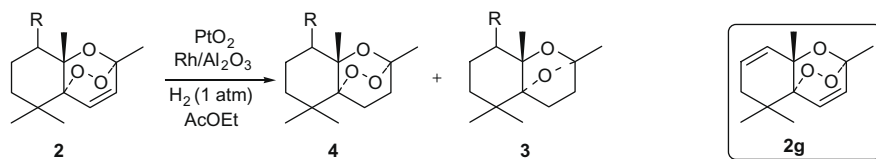
While changing the solvent or lowering the temperature gave no significant improvement, some chemoselective control could be achieved by reducing the catalyst loading and time of reaction. Unfortunately, this only proved to be useful for the unsubstituted substrate **2a** (R = H) which upon treatment with 6 wt % of PtO₂ under atmospheric pressure of hydrogen gave after 1 h the desired saturated trioxane **4a** (R = H) in decent yield (70%). In all other cases, mixtures of both trioxanes **4** and dioxolanes **3** were always obtained implying inevitable over-hydrogenation. At this point, we turned our attention to the use of rhodium over alumina, reported to prevent hydrogenolysis in certain reduction reactions. Since it was found that by using this catalyst hydrogenation of the O–O bond was markedly reduced, albeit obtaining a low conver-

sion to **4** even at prolonged reaction times, we believed Rh could serve as an appropriate cocatalyst to minimise hydrogenolysis and decided to explore the use of mixed catalyst of Rh and Pt as a suitable system for partial hydrogenation.^{18,19}

In the event, we found that by applying the combined use of Rh/Al₂O₃ (5 wt %) and PtO₂ the reaction was greatly improved by obtaining a good chemoselectivity for the hydrogenation of the double bond, indicating that the nature and stereochemistry of the substituent present in **2** had little influence on the time required for the process. In a typical experimental procedure, a mixture of substrate, Rh/Al₂O₃ (5 wt %) and platinum oxide was hydrogenated under atmospheric pressure in ethyl acetate (ca. 15 mM) at room temperature and the results are summarised in Table 1. The reduction of compounds **2a–f** using this protocol afforded the corresponding saturated trioxabicyclo[2.2.2]octane derivatives **4a–f** in moderate to good yields. Reaction of substrate **2g** which carries an extra olefin moiety was of particular interest demonstrating again tolerance of the peroxide linkage towards hydrogenolysis, yet no selectivity among both unsaturations could be achieved (Table 1, entry 7).

Next, we explored the influence that palladium catalysts could have on the outcome of the hydrogenation reaction considering the higher oxophilicity of this metal relative to platinum.²⁰ During the course of this study aimed at developing a selective method for the reduction of the O–O bond while retaining the olefin function,

Table 1
Selective olefin hydrogenation of unsaturated 1,2,4-trioxanes^a



Entry	Substrate	PtO ₂ (wt %)	Rh/Al ₂ O ₃ (wt %)	Reaction time (min)	Product (yield) ^b
1	2a	2.5	2.5	30	4a (70%)
2	2b	2.5	2.5	30	4b (70%)
3	2c	2.0	2.0	70	4c (60%) 3c (10%)
4	2d	5.0	5.0	40	4d (90%)
5	2e	2.5	2.5	80	4e (80%)
6	2f	2.5	2.5	80	4f (65%) 3f (15%)
7	2g	2.5	2.5	50	4g (15%) 4a (55%)

^a Substrate **2**: R = (a) H; (b) OH_{ax}; (c) OH_{eq}; (d) OAc_{ax}; (e) OAc_{eq}; (f) O.

^b Isolated yield.

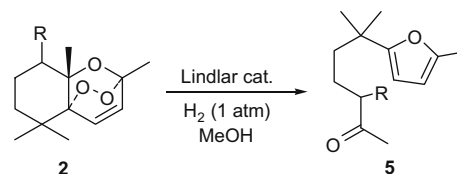
we determined that Pd/C is an active but non-selective catalyst promoting different reaction pathways to afford complex mixtures of products. When compound **2a** was treated with Pd/C, a mixture of ketal **3a** and peroxyketal **4a** was obtained along with a small amount of a product identified as furan **5a** (Table 2, entry 1).

The formation of **5a** as a reduction product derived from **2a** was not totally unexpected and indeed interesting from a mechanistic point of view. These data in addition to previous results related to deoxygenation reactions of **2a** led us to suggest possible reaction pathways to account for the formation of each individual class of products. We postulated two competitive scenarios comprising both, initial saturation of the double bond or hydrogenolysis (Scheme 3). If the first step in the process involves the saturation of the double bond (path I), saturated trioxanes **4** are formed as stable intermediates that could be isolated in good yields. Then, hydrogenolysis of the O–O bond followed by intramolecular ketalisation would afford 2,7-dioxabicyclo[2.2.1]heptane frameworks **3** previously reported. On the other hand, when the O–O bond is cleaved first (path II), unsaturated species **B** thus formed may have a different outcome compared to their saturated analogues **A**. We propose that intermediate **B** would be subsequently transformed into a new hemiketal **C**, presumably via its *cis*- γ -hydroxyenone open form, which could be prone to rearrangement to afford furan structure **5**, derived formally from a vinylogous retro-aldol or Grob type fragmentation.

The point of interest here is that the selective reduction of the O–O bond in **2** would result in the formation of furan compounds

instead of unsaturated dioxo-bicyclo frameworks. Focused on testing the generality of the observed trend, different reaction conditions were examined. After considerable experimentation, we found that manipulation of experimental parameters such as catalyst loading, reaction time and solvent failed to achieve good selectivity for furanic compounds (Table 2, entries 1–3). We therefore

Table 3
Synthesis of 2,5-disubstituted furans **5**^a

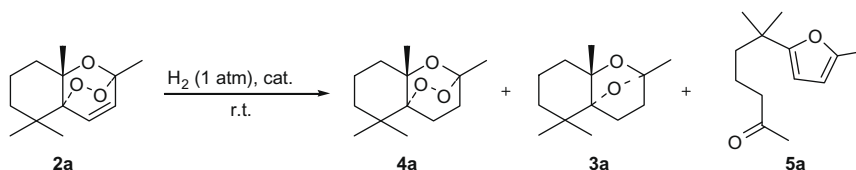


Entry	Substrate	Lindlar cat. (wt %)	Reaction time (h)	Product (yield) ^b
1	2a	10	24	5a (70%)
2	2b	5	4	5b (80%)
3	2c	5	1	5b (70%)
4	2d	20	100	N.R.
5	2e	10	20	5c (70%)
6	2f	5	2	5d (55%)

^a Substrate **2**: R = (a) H; (b) OH_{ax}; (c) OH_{eq}; (d) OAc_{ax}; (e) OAc_{eq}; (f) O. Substrate **5**: R = (a) H; (b) OH; (c) OAc; (d) O.

^b Isolated yield.

Table 2
Hydrogenation of **2a**



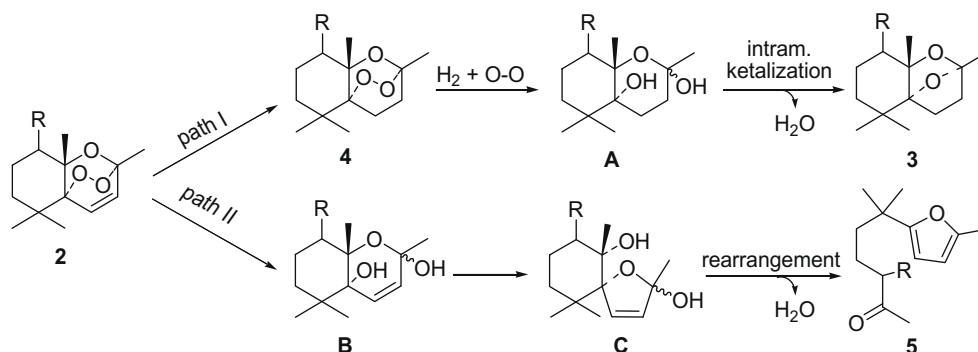
Entry	Solvent ^b	Cat. (wt %)	Reaction time (h)	Product distribution (%) ^a		
				4a	3a	5a
1	AcOEt	Pd/C (5%)	3	43	31	26
2	AcOEt	Pd/C (10%)	1	—	86	14
3	MeOH	Pd/C (5%)	1	—	96	4
4	MeOH	Pd/BaSO ₄ (10%)	24	57	14	29
5	MeOH	Pd/C (10%) + NEt ₃ ^c	2	22	—	78
6	MeOH	Lindlar (10%)	24	7	7	86

Effects of additives.

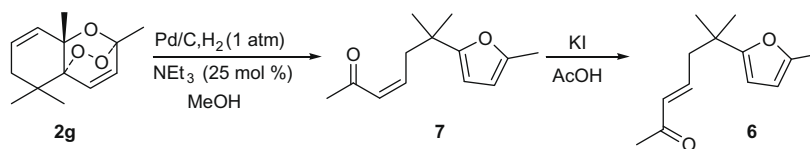
^a Spectroscopic ratio (¹H NMR) after depletion of starting material.

^b Conc'n ca. 40 mM.

^c NEt₃ 25 mol %.



Scheme 3. Competitive scenarios for the heterogeneous hydrogenation of **2** over Pd catalysts.



Scheme 4. Hydrogenation of diene **2g**.

became interested in the utilisation of poisoned palladium catalysts since certain additives are known to reduce the activity of the catalyst towards the olefin moiety, expecting that the O–O bond could compete efficiently for the active catalytic sites. During this study we found that the hydrogenation of **2a** over Pd/BaSO₄ proceeded slowly and with no significant improvement in selectivity (entry 4). The effect of nitrogen-containing bases, as weak catalyst poisons,²¹ was tested by the addition of triethylamine to previously used Pd/C system resulting in an enhanced inhibition of the hydrogenolysis of the O–O bond (entry 5). Best results were obtained when Lindlar catalyst was assayed affording **5a** in good yield^{22,23} (entry 6).

Accordingly, reduction of substrates **2b–f** was examined using Lindlar catalyst under atmospheric pressure of hydrogen at room temperature. Under these conditions, methanol was found to be the solvent of choice. As summarised in Table 3, reactions exhibited improved chemoselectivity for compounds **5** compared to that found previously, showing strong substrate dependence. Ring substituents have such an effect on the reduction process that for instance compound **2e** was totally unaffected using this protocol (Table 3, entry 5). Furan **5c** could nevertheless be obtained from the latter by using Pd/C as a catalyst though the yield of the product was 40% due to the unselective nature of the catalytic system.

As an extension of this work, we also examined the catalytic hydrogenation of trioxane **2g** under these conditions since the expected furan **6** has been recently isolated from natural sources and attracted attention due to its remarkable olfactory properties²⁴ (Scheme 4). Although compound **2g** turned out to be unstable under the reaction conditions, hydrogenolysis took place obtaining furan **7** and its over-reduction compound **5a** as the only isolable products albeit with low yield. Best results were obtained using Pd/C poisoned with triethylamine (yield of **7**, 50%). Although unexpected, the absence of **6** in the product mixtures indicates tolerance of the enone moiety to suffering isomerisation in the reaction media.

While the patterns of chemical shifts for compounds **6** and **7** are similar, a comparative analysis of the coupling constants for the vinyl protons established the *cis*-configured exocyclic alkene moiety of synthetic compound **7** ($J_{3-4} = 12$ Hz vs $J_{3-4} = 16$ Hz). As expected, treatment of **7** with acetic acid-potassium iodide led to isomerisation to the *trans*-isomer **6** thus corroborating its structure as the non-natural diastereoisomer.

In summary, conditions for the chemo-differentiation between alkene and peroxy functionalities under catalytic hydrogenation conditions have been explored and identified. Based on a distinctly different property of platinum and poisoned palladium (Lindlar) catalysts, competitive reduction pathways available from unsaturated 1,2,4-trioxane precursors could be efficiently controlled. During our work, we have uncovered unusual reactivities for substrates **2**, reinforcing their utility as important synthetic precursors. Our find-

ings resulted in a direct access to a series of either saturated trioxanes or furan compounds from a common substrate representing a new example of 'divergent catalysis'²⁵ type process for the generation of skeletal diversity.

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Supplementary data

Supplementary data (detailed experimental procedures, compound characterisation data, and copies of ¹H and ¹³C NMR spectra of all new structures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.135.

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