Tetrahedron Letters 51 (2010) 720–723

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

On the curious oxidations of 2-furylethanols

Simon J. Hayes [a], David W. Knight [a,*], Andrew W. T. Smith [a], Mark J. O'Halloran [b]

[a] School of Chemistry, Cardiff University, Main College, Park Place, Cardiff CF10 3AT, UK
[b] Technical and Business Development, GlaxoSmithKline, Shewalton Road, Irvine KA11 5AP, UK

ARTICLE INFO

Article history:
Received 9 October 2009
Revised 17 November 2009
Accepted 27 November 2009
Available online 1 December 2009

Keywords:
Oxidation
2-Furyl ethanols
Jones
Furans
Ring opening

ABSTRACT

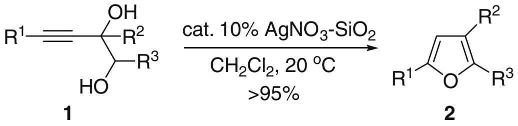
Rather than giving the corresponding aldehyde or carboxylic acid, Jones oxidation of 5-substituted-2-furylethanols gives rise to high yields of the corresponding dihydro-2-(2-oxoethyl)furan-3(2*H*)-ones, following Achmatowicz-type oxidative ring opening and subsequent reclosure by a 5-*exo* Michael addition of the pendant hydroxy group to the enedione function. Other oxidation methods such as a Swern reaction give lower yields of the same products while magnesium perphthalate tends to yield the intermediate enediones, and IBX tends to yield the furyl aldehydes.

The need for ever more efficient, mild and especially environmentally friendly synthetic processes continues to drive the development of heteroaromatic syntheses, despite the existence of many viable routes to these molecules. One of our recent contributions to this area has been the discovery that silver(I) nitrate absorbed on silica gel [10% $AgNO_3$–SiO_2], more often associated with a role as a stationary phase for the chromatographic separation of alkene stereoisomers, is a superbly efficient heterogeneous catalyst for the conversion of 3-alkyne-1,2-diols **1** into the corresponding furans **2** (Scheme 1), the only by-product being an equivalent of water.[1]

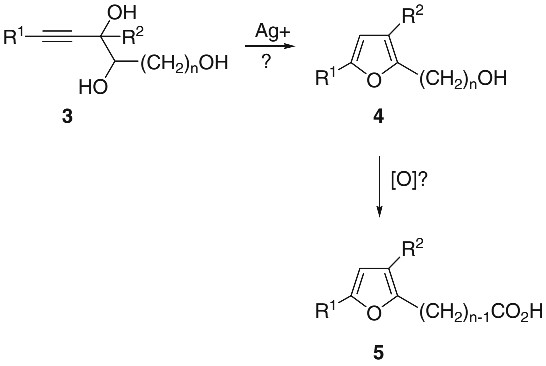
In one endeavour aimed at extending the utility of this methodology, we undertook a study of such cyclisations when applied to substrates **3** having unprotected hydroxyalkyl substituents in order to examine whether incorporation of these would result in the occurrence of any competing cyclisation modes. The motivation for this was to determine whether the need for protecting groups could be obviated; if such competing cyclisations did indeed occur, we hoped that protection methodology would provide a solution.

We also hoped that, given the successful outcome of such cyclisations, the resulting 2-furylalkanols **4** would act as precursors to additional derivatives such as the corresponding carboxylic acids **5** (Scheme 2).

It has been known for many years that oxidations of furylic alcohols (2-furylmethanols) do not always follow the expected pathway to the corresponding aldehydes or ketones, but rather can induce deep-seated rearrangements, one of the best known being the Achmatowicz oxidation, which originally used bromine in methanol to give pyranones,[2] while photo-oxygenation usually leads to 4-hydroxybutenolides.[3] Alternatively, exposure of these



Scheme 1.

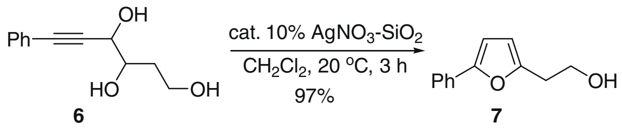


Scheme 2.

---

* Corresponding author.
E-mail address: knightdw@cf.ac.uk (D.W. Knight).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.119



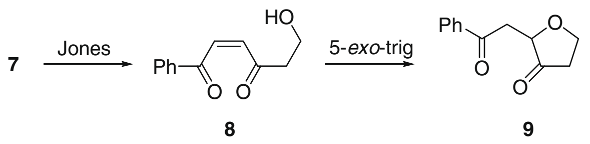
Scheme 3.

sensitive furyl alcohols to acidic conditions and by implication to acidic oxidising agents such as the Jones reagent results in the formation of a 4-hydroxy-2-cyclopentenone by alcohol protonation, water loss assisted by the furyl ring oxygen and the re-addition of water, but at the distal 5-position of the furan, followed by ring opening and finally aldol cyclisation.[4] We were therefore most unclear as to what would happen when we attempted to oxidise the 2-furylethanols **4**, especially as there appeared to be no references to any such transformations in the literature. However, a very recent report of the photo-oxidation chemistry of similar substrates[5] prompts us to report, in preliminary form, our own studies in this area.

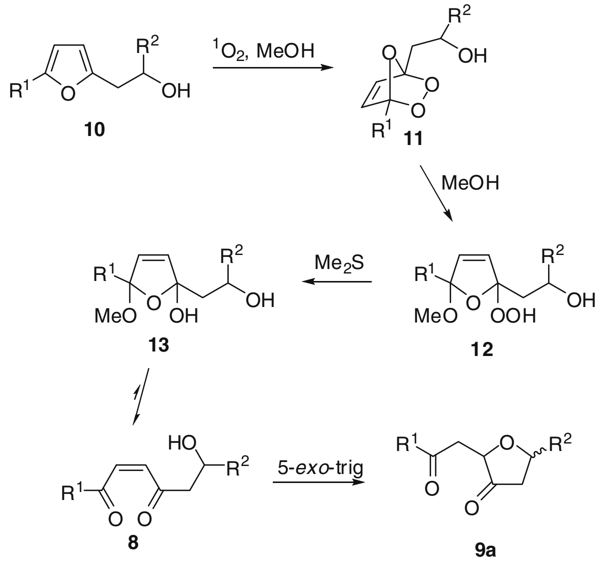
Our initial studies showed that a phenyl-substituted alkyne-1,2-diol **6** underwent very smooth silver-catalysed cyclisation to provide a virtually quantitative yield of the 2-furylethanol **7** without any interference from the unprotected primary hydroxy group (Scheme 3).[1,6]

When the 2-furylethanol **7** was exposed to the Jones reagent at 0 °C,[7] an oxidation clearly occurred as green chromium(III) salts became visible. However, quenching with aqueous carbonate followed by a simple solvent extraction gave an excellent yield of a product which clearly no longer contained a furan residue and equally clearly was not an aldehyde or a carboxylic acid. Further, to our surprise, its richly detailed ^{1}H NMR spectrum strongly suggested the formation of an aliphatic product as it showed the complete absence of alkenyl protons. Subsequent coupling constant and COSY analyses identified two separate groups of protons, a three-proton ABX system and a four-proton AA′BB′ pattern. Further, infrared, and especially ^{13}C NMR data, showed the presence of two ketone groups [δ_C 215.8 and 196.1], the latter likely to be due to the presence of a benzoyl group, PhCO. Further, the coupling constant values strongly indicated that most of the protons were attached to a cyclic system. That an oxidation had indeed occurred was confirmed by molecular weight determination: while the initial furylethanol **7** [$C_{12}H_{12}O_2$] had a molecular weight of 188, the new product showed $m/z = 227$ for $[M+Na]^+$, equivalent to a molecular weight of 204, and therefore contained an additional oxygen [$C_{12}H_{12}O_3$], a conclusion confirmed by high resolution measurements.

It therefore appeared that the furan ring had undergone an initial oxidative ring opening, perhaps related to the Achmatowicz reaction,[2] to give an intermediate enedione **8** (Scheme 4). This could then undergo ring closure by an intramolecular Michael addition of the pendant hydroxy group to the enedione acceptor, to give either a five- or a six-membered cyclic ether. In view of the Baldwin rule prediction that 5-*exo*-trig processes are generally preferred to 6-*endo*-trig competitors,[8] we favoured the keto-tetrahydrofuran structure **9** as being that of the unexpected product.[9]



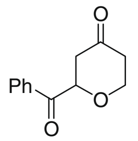
Scheme 4.



Scheme 5.

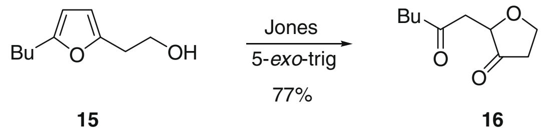
It was at this point that we became aware of the publication by Tofi et al.[5] in which they describe the formation of very similar keto-tetrahydrofurans but using a photo-oxidation method to generate the intermediate enediones [cf. **8**] (Scheme 5). This chemistry involves the Diels–Alder-like addition of photochemically generated singlet oxygen to the furan nucleus **10** to give an endoperoxide **11**, which is then opened by nucleophilic attack of the methanol used as the solvent. The resulting hydroperoxide **12** and presumably its positional isomer are then reduced in situ by the addition of dimethyl sulfide to give a hemiacetal **13** which is in equilibrium with the open chain enedione **8**, exactly the same type of species as we proposed as the intermediate in the Jones oxidation method (Scheme 4). A Michael addition then completes the sequence in the same way.

Comparisons of spectroscopic and analytical data reported from the foregoing Scheme 5 supported our structural assignments. The alternative pyranone structure **14** which could be formed by a less-favoured[8] 6-*endo*-trig cyclisation was ruled out mainly on the consideration of this mechanism and on the basis of comparative spectroscopic data.

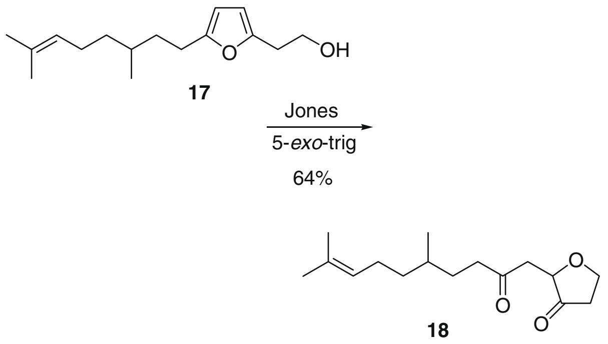


14

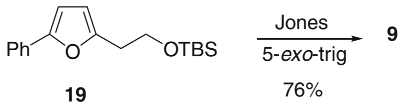
We then wondered whether the initial example **9** was a special case that perhaps, for instance, depended on the presence of the phenyl group. We therefore examined the behaviour of related 5-alkyl-substituted 2-furylethanols when exposed to Jones reagent, using exactly the same conditions which were used previously.[9] Thus the 5-butyl derivative **15** was converted into the keto-tetrahydrofuran **16** in 77% isolated yield.



The more sensitive citronellyl-derived furylethanol **17** similarly gave the keto-tetrahydrofuran **18** in 64% yield.

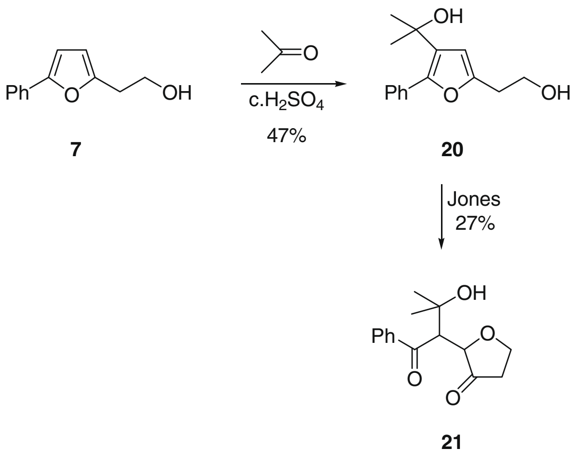


In much the same way as the Jones reagent can directly transform *O*-silyl ethers into the corresponding carbonyl compounds by sequential deprotection and oxidation,[10] exposure of the *t*-butyldimethylsilyl ether **19** to the Jones reagent led to a similar yield of the keto-tetrahydrofuran **9** as that obtained from the parent alcohol.



During attempts to probe the origins of the unexpected keto-tetrahydrofurans, we treated the initial 5-phenylfurylethanol **7** with acidic acetone, essentially Jones reagent[9] without the chromium salts, and were surprised to isolate a reasonable yield of the Friedel–Crafts product **20** (Scheme 6). When this was exposed to the 'normal' Jones reagent,[9] we were able to isolate, but in poor yield, the keto-tetrahydrofuran **21** as a 1.5:1 mixture of diastereoisomers. It seemed remarkable that such a sensitive product had survived the acidic conditions but, presumably, this is reflected in both the poor yield and the observation of the formation of a multitude of other, as yet unidentified products.

We also examined a number of alternative oxidation procedures in a continued effort to obtain 'simple' alcohol oxidation products from the model substrate **7**. Omitting the acidic component in a Jones oxidation mixture resulted in the formation of a ca. 1:1 mixture of the precursor **7** and the keto-tetrahydrofuran **9**. Pyridinium dichromate (PDC) in dimethylformamide (DMF) at ambient temperature[11] led to the very slow formation of the keto-tetrahydrofuran **9**, but formation of little else. Even the rather mild Swern oxidation method[12] delivered a similarly low yield of the keto-tetrahydrofuran **9**, while tetrapropyl perrhuthenate (TPAP)[13] and various methods using potassium permanganate[14] proved unsuccessful. By contrast, treatment of the alcohols **7**, **15** and **17** with magnesium monoperphthalate (MMPP)[15] in aqueous ethanol at ambient temperature for two hours gave a second product type, the (*Z*)-enediones **22a–c** (Scheme 7). This is a known transformation[16] but one which gave us a definitive insight into the mechanism of the present chemistry.

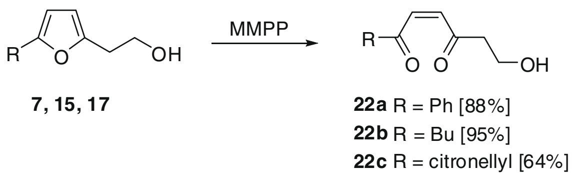


Scheme 6.

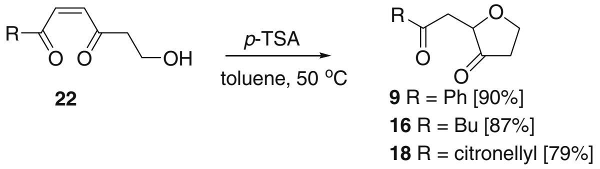
A second reaction of the products **22** strongly supported their intermediacy in the foregoing unexpected oxidation chemistry: exposure to catalytic *p*-toluenesulfonic acid,[5] as shown (Scheme 8), led to smooth formation of the corresponding keto-tetrahydrofurans by an acid-induced 5-*exo*-trig Michael addition.

A final contrast was shown by the use of IBX[17] which under typical conditions delivered excellent yields of the aldehydes **23** from the two representative 2-furylethanols **7** and **15** (Scheme 9).

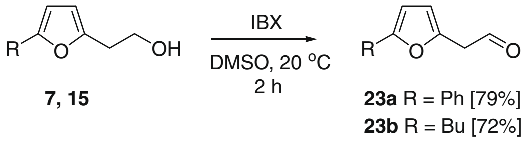
Therefore, despite our initial concerns, this chemistry has proven to be synthetically useful in the sense that, by a careful choice of oxidising reagent, three different product types can be obtained from 2-furylethanols. The 3-keto-tetrahydrofurans in particular may turn out to be especially useful as this is a structural type which is poorly represented in the current literature. Quite why the Jones chemistry and other oxidations follow this unexpected pathway remains unclear but, possibly, the β-hydroxy group in the 2-furylethanols could form complexes with the chromium-based or other activated oxidation moieties, thereby strongly encouraging such reactive species to interact directly with the furan ring, aided by the oxygen atom of the latter, leading to an intermediate enedione [cf. **22**]. This induced proximity could render such reactions faster than proton loss α-to the oxygen and aldehyde formation, as in a more usual oxidation. Under the acidic Jones conditions, such an intermediate would surely undergo rapid, acid-catalysed cyclisation to the observed keto-tetrahydrofurans. Efforts to further define and exploit this methodology are under way.



Scheme 7.



Scheme 8.



Scheme 9.

Acknowledgements

We are grateful to Professor Donald Craig (Imperial College) for a very enlightening discussion and to GSK and the EPSRC for financial support.

References and notes

1. Hayes, S. J.; Knight, D. W.; Menzies, M. D.; O'Halloran, M.; Tan, W.-F. *Tetrahedron Lett.* **2007**, *48*, 7709–7712.
2. Achmatowicz, O., Jr.; Bukowska, P.; Szachner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973–1996; Maier, M. In *Organic Synthesis Highlights II*; Waldermann, H., Ed.; VCH: Weinheim, 1995; pp 231–242; Singh, V.; Krishna, U. M.; Vikrant; Trivedi, G. K. *Tetrahedron* **2008**, *64*, 3405–3428. and references therein; For an alternative reagent [$PhI(OAc)_2$], see: De Mico, A.; Margarita, R.; Piancatelli, G. *Tetrahedron Lett.* **1995**, *36*, 3553–3556; But see: De Mico, A.; Margarita, R.; Partanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977. for examples of hypervalent iodine reagents which do not cause any such rearrangements.
3. Graziano, M. L.; Iesce, M. R.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2007–2112; Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057–2068; Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 7007–7014.
4. Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, 3555–3557; Piancatelli, G.; Scettri, A. *Tetrahedron Lett.* **1977**, 1131–1134; D'Auria, M.; D'Onofrio, F.; Piancatelli, G.; Scettri, A. *Gazz. Chim. Ital.* **1986**, *116*, 173–175; For the use of zinc chloride in place of a Brønsted acid, see: Csaky, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092–2094.
5. Tofi, M.; Koltsida, K.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 313–316.
6. Hayes, S. J.; Knight, D. W. unpublished observations.
7. Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39–43; Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548–2551; Chem.Rochester [Information Pages] [Online] http://chem.chem.rochester.edu/~nvd/jonesreagent.html.
8. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–735; Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736–737; Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738–739.
9. *A typical procedure is as follows: Dihydro-2-(2-phenyl-2-oxoethyl)furyl-3(2H)-one* (**9**): Jones reagent (3 ml, 6.38 mmol)[7] was added dropwise to a stirred, ice-cold solution of 5-phenylfuran-2-ethanol **7** (1.00 g, 5.32 mmol) in acetone (10 ml). After 0.5 h at this temperature, the mixture was made basic by the addition of saturated aqueous K_2CO_3 and the organic products were extracted into EtOAc (3 × 20 ml). The combined organic extracts were washed with H_2O (50 ml) and brine (50 ml), then dried ($MgSO_4$), filtered and evaporated. Crystallisation of the residue from aqueous MeOH gave the keto-tetrahydrofuran **9** (0.812 g, 81%) as pale orange prisms, mp 48–50 °C. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9. Found: C, 70.9; H, 6.0; R_f 0.56 (30:70 EtOAc/petrol); ν_{max}/cm^{-1} (CH_2Cl_2) 1756, 1686, 1597, 1449, 1370, 1268, 1219, 1150, 1092, 736, 689; δ_H (400 MHz, $CDCl_3$) 7.86 (2H, app. d, *J* 7.2 Hz, 2 × Ph), 7.51 (1H, app. t, *J* 7.2 Hz, Ph-H), 7.42–7.38 (2H, m, 2 × Ph-H), 4.34 (1H, app. dt, *J* 9.2 and 4.2 Hz, 5-H_a), 4.13–4.05 (2H, m, 2-H and 5-H_b), 3.55 (1H, dd, *J* 18.0 and 3.4 Hz, $1'$-H_a), 3.31 (1H, dd, *J* 18.0 and 5.5 Hz, $1'$-H_b), 2.82 (1H, dt, *J* 18.0 and 9.0 Hz, 4-H_a), 2.51 (1H, ddd, *J* 18.0, 7.5 and 4.2 Hz, 4-H_b); δ_C (125 MHz, $CDCl_3$) 215.8 (3-CO), 196.1 (PhCO), 136.2 (PhC), 133.6 (PhCH), 128.7 (2 × PhCH), 128.2 (2 × PhCH), 75.5 (2-CH), 65.3 (5-CH_2), 40.6 ($1'$-CH_2), 36.6 (4-CH_2); *m/z* (ES) 227 $[M+Na]^+$.
10. For a review, see: Muzart, J. *Synthesis* **1993**, 11–27; For a recent example, see: Zhang, S.; Xu, L.; Trudell, M. L. *Synthesis* **2005**, 1757–1760.
11. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402.
12. Mancuso, A. J.; Huang, S.-J.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
13. Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13–19; Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
14. Jefford, C. W.; Wang, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 634–635; Menger, F. M.; Lee, C. *J. Org. Chem.* **1979**, *44*, 3446–3448.
15. Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015–1017.
16. Dominguez, C.; Csáky, A. G.; Plumet, J. *Tetrahedron Lett.* **1990**, *31*, 7669–7670.
17. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276; Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538; Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022; De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272–9279; For recent reviews, see: Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111–124; Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812–2814; Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656–3665.