

Ozone-mediated Reaction of Aromatic Acetals and Acylal with Nitrogen Dioxide: a Novel Methodology for the Nuclear Nitration of Acid-sensitive Aromatic Compounds under Neutral Conditions

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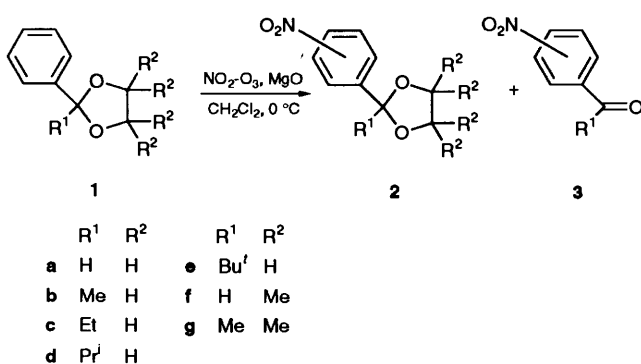
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Cyclic acetals **1c–e** and **1g** can be nitrated smoothly with nitrogen dioxide in ice-cooled dichloromethane in the presence of ozone and magnesium oxide to give mainly *ortho*- and *para*-nitro derivatives in good combined yields, the acetal protective group remaining almost intact; acylal **6** is similarly nitrated on the aromatic ring to give a mixture of isomeric nitro derivatives **7**, in which the *ortho* and *meta* isomers predominate.

Acetals are widely employed as a masked carbonyl function in organic synthesis, since they are easily hydrolysed by the action of weak acid to generate the original aldehyde or ketone.¹ It is quite understandable, therefore, that we find no reports of the successful nitration of aromatic acetals in the literature, because electrophilic nitrating agents would prefer the acetal oxygen atoms to the less basic aromatic ring carbons at initial stage,² thus facilitating the subsequent nucleophilic cleavage of the C–O bond; also the generation of nitronium ion itself should, of course, require strong acid conditions.

Recently we have found that nitrogen dioxide is activated in the presence of ozone to act as a powerful nitrating agent for aromatic systems.³ The results so far obtained from the reactions with some electron-rich arenes are highly suggestive of a non-classical mechanistic pathway, in which nitrogen trioxide is involved as the initial electrophile.^{4,5} When aromatic acetals were subjected to this novel type of nitration (kyodai nitration †), we were pleased to see that some cyclic acetals **1c–e** and **1g** could be successfully nitrated on the aromatic ring to give products **2c–e** and **2g** in good yields, the acetal protecting function remaining almost intact (Scheme 1).



Scheme 1

† The nitration of arenes with the lower oxides of nitrogen using a combination of ozonized air and some third substance as the promoter is now subject to industrially based research to circumvent the problems arising from the classical methodologies based on the use of nitric acid–sulfuric acid. The ozone generators (WOH-A series; Toshiba Co. Ltd., Tokyo) with the output of ozone in 1–30 kg h⁻¹ from air are now available. The process is referred to as the kyodai nitration, where the prefix kyodai is short for Kyoto University.

Table 1 Nitration of the cyclic acetals **1** in dichloromethane at 0 °C

Acetal	Product 2 Yield (%) ^a	Isomer proportion (%) ^b <i>ortho</i> : <i>meta</i> : <i>para</i>
1a	0 ^c	—:—:—
1b	4 ^{c,d}	31:19:50
1c	95 ^e	14:31:55
1d	88	18:20:62
1e	93	6:25:69
1f	0 ^f	—:—:—
1g	90	8:13:79

^a The yields refer to isomeric mixtures isolated and were not optimized.

^b Product compositions were determined by GLC. ^c Deacetalization preceded the nuclear nitration. ^d Accompanied by small amounts of the nitrate ester **5**, in addition to the unmasked ketone and its nitration product **3**. ^e Acetonitrile was employed as the solvent, in which the ring opening could be mostly avoided. In dichloromethane, the yield was ca. 60%. ^f Readily cleaved to yield 3-benzoyloxy-2,3-dimethylbutan-2-ol as the main product. Such facile ozonolytic cleavage of the acetal ring may be interpreted in terms of the stereoelectronic orbital interaction.¹⁴

The general procedure is as follows. A mixture of acetal **1** (5–10 mmol), magnesium oxide (7.5–15 mmol) and dichloromethane (50 cm³) was stirred vigorously at 0 °C, while ozonized oxygen and nitrogen dioxide mixed immediately before were bubbled slowly into the chalky suspension. The progress of the reaction was monitored by GLC. After 1–2 h the reaction was quenched with aqueous sodium hydrogen carbonate and the organic phase was extracted with dichloromethane. The combined extracts were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure to leave a mixture of isomeric nitro compounds **2**. The results are summarized in Table 1.

'Crowdedness' around the acetal carbon is crucial for the successful nitration of cyclic acetals **1**. When the 'non-crowded' cyclic acetal **1a** was allowed to react under similar conditions, cleavage of the acetal ring occurred in preference to nuclear nitration, to give a mixture of the original aldehyde, its nitration product **3a** and some unidentified products, the ratio of which depended on the conditions employed. With the moderately 'crowded' acetals **1b, c**, small amounts of a nitrate ester **5** were obtained in addition to the parent ketone and expected nitration products **2b, c/3b, c**, showing the complex nature of the reaction. Compound **5** was isolated by chromatography on silica gel and confirmed by direct comparison with the authentic specimen prepared by an independent route. Although the mechanistic pathway leading to the ester **5** is not clear at

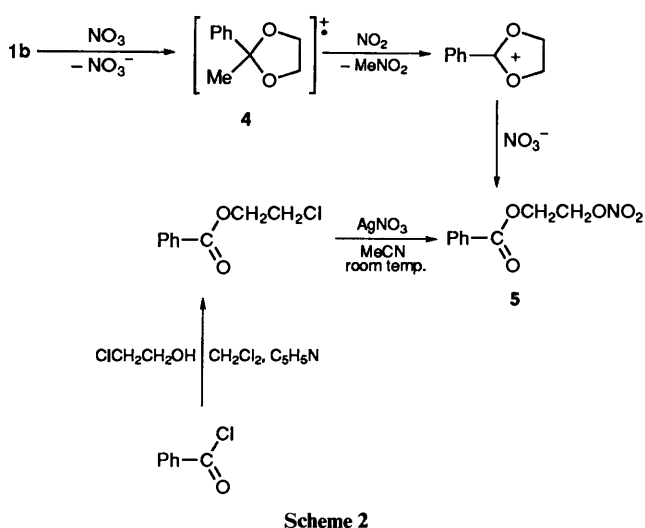


Table 2 Partial rate factors of cyclic acetals 1^a

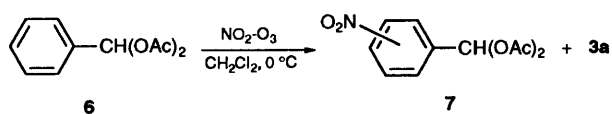
Acetal	k_R/k_B	f_o	f_m	f_p
1c	0.42	0.31	0.25	1.4
1d	0.69	0.35	0.44	2.6
1e	0.81	0.20	0.62	3.2

^a At 15% conversion.

present, the cation radical **4** is a possible intermediate for the ester formation, as tentatively depicted in Scheme 2.⁶ Attempted nitration of acetals **1d**, **e** and **1g** by the conventional procedure based on the use of nitric acid–sulfuric acid always led to the nitration products **3** of the original carbonyl compounds, as expected.*

Acyclic acetals such as benzaldehyde diethyl acetal and acetophenone dimethyl acetal were rapidly cleaved under our conditions to afford the expected nitration product of the original aldehyde or ketone. The isomer proportions of the products were almost the same as those obtained from the kyodai nitration of the respective carbonyl compounds.⁷

Acylal is another type of masked carbonyl function, which tolerates mild acidic conditions. Compound **6** was smoothly



nitration with the present nitrating system to give product **7** in a satisfactory yield. The isomer distribution of the product **7** was *ortho* 55, *meta* 28 and *para* 17%, reflecting the increased electron-attracting nature of the acylal group, CH(OCOMe)₂, as compared with the acetal function, CH(OR)₂. Some interaction between the ester oxygen atoms and attacking species maybe responsible for the high *ortho*–*para* isomer ratio.² The attempted nitration of the acylal **6** using the classical procedure resulted only in the production of nitrobenzaldehydes **3a**, mainly composed of the *meta* isomer.

* Cyclic acetals were similarly nitrated with dinitrogen pentaoxide, prepared by distilling fuming nitric acid from an excess of phosphorus pentaoxide under a stream of ozonized oxygen. Reaction with nitric acid in acetic anhydride, however, led to a complex mixture of products probably arising from acid-catalysed acetal–acylal exchange and subsequent reactions.

No information is available to date on the directing properties of the acetal group as a ring substituent for the nitration of arenes. As shown above, although the acetal function directs an entering electrophile mainly at the *ortho* and *para* positions, substitution at the *meta* position is also appreciable, probably due to the joint electron-withdrawal by two geminal alkoxy groups. The partial rate factors of compound **1e** were determined by the competition method to be $f_o = 0.20$, $f_m = 0.62$ and $f_p = 3.2$ (Table 2). The values showed that the acetal group is comparable in its electronic influence with the chloromethyl group ($f_o = 0.72$, $f_m = 0.30$ and $f_p = 2.24$).⁸ The low f_o value is attributable to the bulky *tert*-butyl group in compound **1e**. Stepwise substitution of one, two or three chlorine atoms into the methyl group in toluene is known to bring a gradual changeover of the directing effect from mainly *ortho/para* to mainly *meta*. Thus, on nitration with nitric acid–sulfuric acid, benzyl chloride gives an isomeric mixture in which the *ortho*–*para* nitro derivatives predominate (*o*:*m*:*p* = 34:14:53);⁸ in contrast, α,α,α -trichlorotoluene affords the *m*-nitro derivative as the major product (*o*:*m*:*p* = 7:65:29).⁹ As far as can be judged from the proportion of the *meta* isomer, the acetal group may be regarded to be less electronegative than the dichloromethyl and bis(acetoxy)methyl groups, their respective electron-withdrawing abilities being in the order CH(OR)₂ < CH(OCOMe)₂ < CHCl₂.

Conventional nitration of benzaldehyde and alkyl phenyl ketones by nitric acid–sulfuric acid leads mainly to the *meta*-isomers, the *ortho* isomer being the next major product. In contrast, kyodai nitration of these carbonyl compounds gives mainly the *ortho* isomer, the *meta* isomer being the second important product.⁷ In both cases, formation of the *para* isomer is insignificant. The *para*-nitro derivatives of these carbonyl compounds are usually prepared by way of multi-step routes involving the acetoacetic ester synthesis,¹⁰ malonic ester synthesis,¹¹ oxidation of *p*-nitroalkylarenes,¹² or nitration of α -phenylalkyl acetates.¹³ Since further structural elaboration of the acetal portion would improve the product yields, the nitration of cyclic acetals according to the present procedure provides a novel route to this class of compounds, noteworthy for its manipulative simplicity and easy access to starting materials of major industrial importance.

In conclusion, by a proper choice of the nitration methodology (conventional or kyodai) and carbonyl substrate (unmasked or masked), we are now able to obtain either one of the desired isomers as the major product from the nitration of aromatic ketones.

Acknowledgements

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