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On-Column Solvent-Free Oxidative Cleavage Reactions of Vicinal Diols by Silica Gel and Paraperiodic Acid: Application to In-Situ Sequential Oxidation and Knoevenagel Reactions

Saada C. Dakdouki,[a] Didier Villemin,*[a] and Nathalie Bar[a]

Keywords: Reactive chromatography / Cleavage reactions / Oxidation / Solid-phase synthesis / Domino reactions

An on-column solvent-free oxidative cleavage reaction of vicinal diols by paraperiodic acid supported on silica gel at room temperature is described. The resulting pure carbonyl compounds are prepared in good to excellent yields with short reaction times. The cleavage reactions proceed under mild conditions, which avoids further cyclization reactions of the product dialdehydes. This method is also used for sequential oxidation and Knoevenagel reactions to prepare condensation products in good yields by using paraperiodic acid on a mixed bed of alumina and silica gel.

Introduction

The development and invention of new synthetic strategies and technologies represent major challenges for organic chemists, and different innovative methodologies have been developed to increase synthetic efficiency. One such approach is the on-column strategy.[1] In our ongoing research into reactive chromatography, we are interested in extending the application of our methodology to various chemical reactions (Horner–Emmons, Wittig, oxidative cleavage reaction of vicinal diols) as well as to new reaction sequences.[2]

The oxidative carbon–carbon bond cleavage of 1,2-diols has been extensively investigated. Various reagents have been used for this transformation;[3] periodic acid (H_5IO_6) and its salts were first employed by Malaprade in 1928.[4] Oxidative cleavage reactions with H_5IO_6 can be performed in either water or aprotic organic solvents such as diethyl ether or tetrahydrofuran.[5] Although H_5IO_6 is a strong oxidant and one of the classical oxidants for the cleavage reactions of vicinal diols, few examples of its use as a supported reagent have been reported. Villemin and co-workers employed alumina-supported H_5IO_6 in the presence of transition metal complexes or salts to oxidize α-phenyl olefins to aldehydes in carbon tetrachloride.[6] Previously, we described the efficient on-column oxidative cleavage reaction of vicinal diols by using alumina-supported KIO_4 under microwave irradiation in the absence of solvent.[2b] These experimental conditions led to intramolecular aldol cyclizations of the resulting dialdehydes, but this could be avoided by carrying out the scission reactions under milder conditions, at room temperature, and in the presence of minimal volumes of solvent. Here we report a new on-column oxidation of vicinal diols by using silica gel supported H_5IO_6 at room temperature under solvent-free conditions.

Results and Discussion

Choice of Inorganic Support

Three different inorganic supports – montmorillonite K10, alumina, and silica gel – along with solid H_5IO_6 as an oxidant, were tested for the on-column oxidative cleavage reaction of *cis*-1,2-diphenylethane-1,2-diol (**1**). The diol, inorganic support, and H_5IO_6 were ground together. The resulting fine powder was packed in a solid-phase extraction (SPE) column in which the oxidation reaction was allowed to proceed at room temperature (Figure 1).

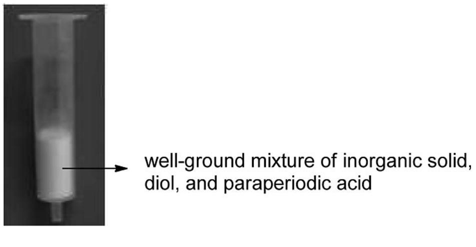

Figure 1. On-column oxidative cleavage reaction of vicinal diols by H_5IO_6 and various inorganic supports.

Surprisingly, the use of montmorillonite K10 as the inorganic support with H_5IO_6 led to a violent and exothermic reaction that gave off characteristic violet fumes of iodine within a few seconds. Alumina underwent acidic/basic interactions with H_5IO_6 that resulted in the break down of

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[a] Laboratoire de Chimie Moléculaire et Thioorganique,
UMR CNRS 6507, INC3M, FR 3038,
ENSICAEN & Université de Caen,
14050 Caen, France
Fax: +33-2-31452877
E-mail: didier.villemin@ensicaen.fr

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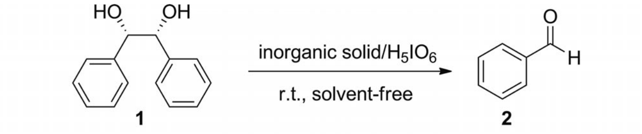
Table 1. Optimization of the on-column oxidative cleavage reaction of vicinal diols by H_5IO_6 for various inorganic supports.



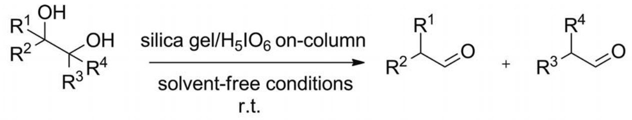
Inorganic solid	Experimental observations	Yield [%]
Montmorillonite K10	violent exothermic reaction with liberation of violet fumes	–
Neutral alumina	acidic/basic interactions with formation of water	–
Silica gel	no visible changes	99

the solid support and liberation of water. Pleasingly, the oxidation reaction of *cis*-1,2-diphenylethane-1,2-diol by silica gel and H_5IO_6 occurred smoothly to afford benzaldehyde (**2**) in 99% yield (Table 1). On the basis of these results, silica gel was chosen as the inorganic support for the cleavage reactions.

On-Column Oxidative Cleavage by Silica Gel and H_5IO_6

We used a supported-reagent on-column approach to investigate the oxidation of several vicinal diols. A finely ground mixture of diol, silica gel, and H_5IO_6 was loaded onto a SPE column and afforded pure aldehydes in 15–

Table 2. On-column oxidative cleavage reaction of vicinal diols by silica gel supported H_5IO_6 under solvent-free conditions.



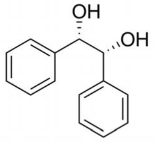
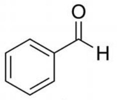
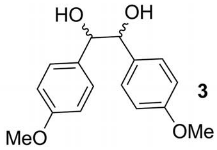
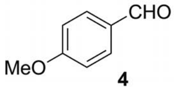
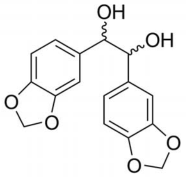
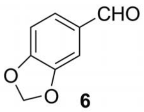
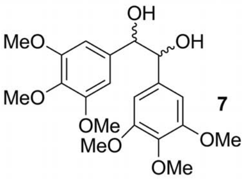
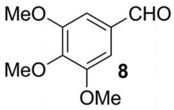
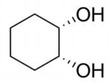
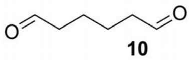
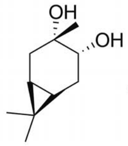
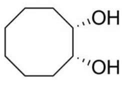
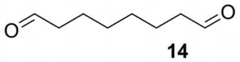
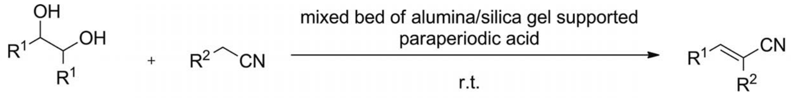
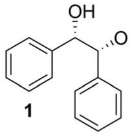
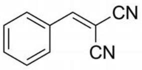
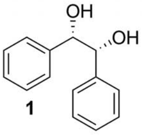
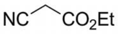
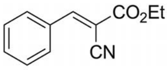
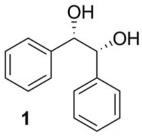
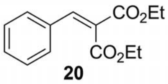
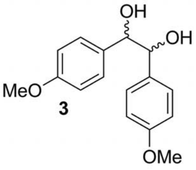
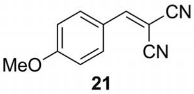
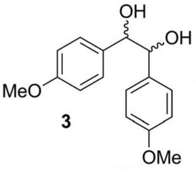
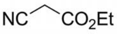
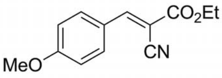
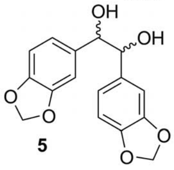
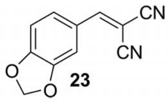
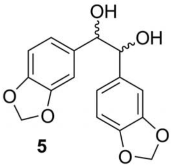
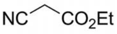
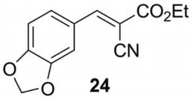
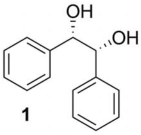
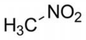
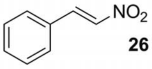
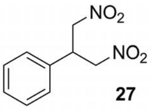
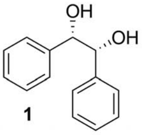
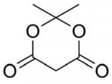
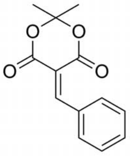
Entry	Diol	Time [h]	Product	Conversion [%]	Yield [%]	Ref.
1	 **1**	0.25	 **2**	100	99	–
2	 **3**	0.25	 **4**	100	99	–
3	 **5**	0.25	 **6**	100	70	–
4	 **7**	0.25	 **8**	100	91	–
5	 **9**	1	 **10**	100	77	[7]
6	 **11**	1	 **12**	100	96	[8]
7	 **13**	1	 **14**	100	83	[9]

Table 3. On-column sequential oxidative cleavage and Knoevenagel reactions by using a mixed bed of alumina and silica gel supported H_5IO_6.



Entry	Diol	Methylene compound	Product	Time [min]	Yield [%][a]	Ref.
1	 1	 15	 16	30	67	[12]
2	 1	 17	 18	60	70	[13]
3	 1	 19	 20	180	0	–
4	 3	 15	 21	180	75	[14]
5	 3	 17	 22	180	78	[15]
6	 5	 15	 23	180	40	[16]
7	 5	 17	 24	180	47	[17]
8	 1	 25	 26  27	180	44[b] 27	[18] [19]
9	 1	 28	 29	30	28	[20]

[a] Yield determined by ^1H NMR spectroscopy. [b] Yield determined by GC–MS.

60 min at room temperature in good to excellent yields. No solvent was required. This approach permitted efficient and smooth cleavage of both substituted α,α′-diphenylethane-1,2-diols and cycloalkane-1,2-diols. The oxidative cleavage reaction of various diols is summarized in Table 2. For example, 1,2-bis(4-methoxyphenyl)ethane-1,2-diol (**3**), 1,2-bis(3,4-dioxymethyleneyphenyl)ethane-1,2-diol (**5**), and 1,2-bis(3,4,5-trimethoxyphenyl)ethane-1,2-diol (**7**) gave 4-methoxybenzaldehyde (**4**), piperonal (**6**), and 3,4,5-trimethoxybenzaldehyde (**8**) in 99, 70, and 91% yield, respectively (Table 2, Entries 2–4). Similarly, *cis*-cyclohexane-1,2-diol (**9**), 3,7,7-trimethylbicyclo[4.1.0]heptane-3,4-diol (**11**), and *cis*-cyclooctane-1,2-diol (**13**) yielded adipaldehyde (**10**), 2-(2,2-dimethyl)-3-(2-oxopropyl)acetaldehyde (**12**), and octanedial (**14**) in 77, 96, and 83% yield, respectively (Table 2, Entries 5–7). Interestingly, this system enables easy oxidative cleavage of α,α′-diphenylethane-1,2-diols (i.e., **1**, **3**, **5**, and **7**) at room temperature, unlike the cleavage reactions with alumina and KIO_4 that necessitate the use of microwave irradiation.[2b] Furthermore, the silica gel/H_5IO_6 system permitted smooth cleavage of cycloalkane-1,2-diols, in the absence of solvent, to give the corresponding dialdehydes without further intramolecular aldol cyclization reaction.

Sequential Oxidative Cleavage and Knoevenagel Reaction by using Supported H_5IO_6 over a Mixed Bed of Alumina and Silica Gel

The on-column oxidation and Knoevenagel reaction sequence was studied by using a mixed bed of alumina and silica gel with H_5IO_6. The SPE columns were loaded with a mixture of alumina and silica gel with H_5IO_6 (prepared as described previously, Figure 1). A solution of the diol and acidic methylene compound was then adsorbed on the mixed bed and the cleavage reactions were allowed to proceed at room temperature. The reaction products were collected by simple elution with dichloromethane. The choice of the eluent was important because H_5IO_6 is soluble in more polar solvents such as tetrahydrofuran. We note that no interaction between the alumina and the silica gel/H_5IO_6 mixture was observed.

The oxidation and Knoevenagel reaction sequence was investigated with several diols and acidic methylene compounds. The oxidative cleavage reactions occurred smoothly with complete conversion of the starting diols. The Knoevenagel step took place with 80–95% conversion. Thus, the mixed bed of alumina and silica gel mixed with H_5IO_6 permitted the preparation of a number of Knoevenagel products in 30–180 min in moderate to good yields, as shown in Table 3. Malononitrile (**15**) and diethyl cyanoacetate (**17**) reacted efficiently with the formed aldehydes affording the condensation products in good yields (Table 3, Entries 1, 2, 4–7). Diethylmalonate (**19**) did not react at all with benzaldehyde (**2**) under these conditions. Such non-reactivity of diethylmalonate with aldehydes in the presence of alumina at room temperature has been reported by Texier-Boullet and co-workers.[10] The Knoevenagel condensation with Meldrum's acid (**28**) gave desired product **29** in 30 min in only 28% yield (Table 3, Entry 9). The reaction of **28** with **15** and **17** was reported by Villemin with the use of neutral alumina at room temperature in 5 h.[11]

The Henry reaction was also investigated by using nitromethane (**25**) as the acidic compound (Table 3, Entry 8). In this case, *cis*-1,2-diphenylethane-1,2-diol (**1**) is cleaved to form benzaldehyde (**2**), which immediately condenses with nitromethane to yield nitrostyrene derivative **26**. This compound then undergoes a Michael reaction with another nitromethane molecule to give the corresponding Michael adduct **27**. After 3 h, 88% of the formed aldehyde is converted affording a mixture of β-nitrostyrene (**26**) and Michael adduct **27** in 44 and 27% yield, respectively (determined by GC–MS).

Conclusions

We have developed a rapid, simple, and efficient procedure for the on-column oxidative cleavage reaction of vicinal diols in the solid state by using silica gel and H_5IO_6. This protocol does not require pre-preparation of the supported oxidant or dissolution of H_5IO_6 or the diol. The scission reactions proceed without the need for toxic, volatile organic solvents or aqueous workups. This method allows easy cleavage of substituted 1,2-diphenylethane-1,2-diols and cycloalkane-1,2-diols with short reaction times under mild conditions. This methodology can also be employed for on-column sequential oxidation and Knoevenagel reactions by using a mixed bed of alumina and silica gel and H_5IO_6 permitting the successful formation of the condensation products at room temperature and in good yields. These results open the door for investigation of other reaction sequences.

Experimental Section

General Methods: All commercial reagents were purchased from Acros, Aldrich, and Sigma and were used as received. Reaction times were monitored by using TLC until no starting material remained. TLC was performed by using Silica gel 60 F_{254} precoated aluminum sheets. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 250 or Bruker AC 400 spectrometer. Chemical shifts (δ) were referenced to the internal deuterated solvents with tetramethylsilane as the internal standard. Mass spectra were recorded with a QTOF Micro (Waters) spectrometer with electrospray ionization (ESI, positive mode), lockspray orthophosphoric acid, infusion introduction at 10 µL/min, a source temperature of 80 °C and desolvation temperature of 120 °C. All the compounds synthesized in this work are known and their spectroscopic data are in agreement with those reported in the literature. References are cited either in the text or in the tables.

Preparation of Substituted 1,2-Diphenylethan-1,2-diols 3, 5, and 7: These diols were prepared as mixtures of *cis* and *trans* isomers through a pinacol coupling described by Zhang and Li.[21] The mixtures of isomers were subjected to glycolic cleavage without separation.

General Procedure for the On-Column Oxidative Cleavage Reaction of Vicinal Diols by using Silica Gel Supported H_5IO_6 Acid: A mixture of diol (1 mmol), silica gel (1 g), and H_5IO_6 (1.5 g) was ground together before being loaded onto a commercially available SPE column (Varian Bond Elut, 6 mL). The column was allowed to stand at room temperature for 15–60 min. The reaction products were then eluted with dichloromethane (≈15 mL). Evaporation of the solvent in vacuo afforded the corresponding scission products. In most cases, the cleavage products were pure.

General Procedure for the On-Column Sequential Oxidation and Knoevenagel Reactions by using a Mixed Bed of Alumina, and Silica gel, and H_5IO_6: A mixture of H_5IO_6 (0.75 g) and silica gel (0.5 g) was ground together before being mixed well with alumina (3.0 g) and loaded onto a SPE column (Varian Bond Elut, 6 mL) equipped with a frit at the lower end. A solution of the diol (0.5 mmol) and the acidic methylene compound (1 mmol) in dichloromethane (0.2 mL) was adsorbed on the support in the SPE column. The reaction was allowed to proceed at room temperature for 30–180 min. The reaction product was then eluted from the column with dichloromethane (≈15 mL).

Supporting Information (see footnote on the first page of this article): Characterization of the prepared compounds.

Acknowledgments

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