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Involvement of alkoxyl radical intermediates in the photolysis of 1-alkylcycloalkanols in the presence of bis(pyridine) iodonium tetrafluoroborate Comparison with the (diacetoxyiodo)benzene/I_2 system

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Abstract

The product distributions observed after visible light irradiation of a series of 1-alkylcycloalkanols (**1**–**3**) and bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4), have been compared with those observed after irradiation of the same substrates in the presence of (diacetoxy)iodobenzene (DIB) and I_2, i.e. under bona fide conditions for alkoxyl radical generation. The observation of very similar product distributions with the two systems strongly supports the previous hypothesis that alkoxyl radical intermediates are formed after photolysis of substrates **1**–**3** in the presence of IPy_2BF_4.

Keywords: Photolysis; Bis(pyridine)iodonium tetrafluoroborate; (Diacetoxyiodo)benzene; Alkoxyl radical; β-Scission; Cycloalkanol

1. Introduction

Bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) is a mild iodinating and oxidizing reagent capable of selectively reacting with a wide variety of unsaturated substrates and, accordingly, this reagent is attracting increasing attention [1]. Among its applications, it has been recently shown that upon irradiation with visible light IPy_2BF_4 is able to promote a very efficient ring-opening reaction of cycloalkanols leading to ω-iodocarbonyl compounds, and a mechanism proceeding through an intermediate alkoxyl radical has been proposed as described in Scheme 1 for cyclopentanol [2,3].

The reaction proceeds through the initial formation of an oxonium ion, which undergoes deprotonation to give a iodane. Photolysis of the iodane forms $Py_2I^{\bullet}$ and an alkoxyl radical which in turn undergoes C–C β-scission to give a carbon centered radical, precursor of the observed reaction product. Quite interestingly, an efficient ring-opening reaction was observed with cyclobutanol and cyclopentanol, whereas the presence of a base such as Cs_2CO_3 was required in the reactions of cyclohexanol and cycloheptanol. This behavior reflects the reactivity towards fragmentation of the corresponding cycloalkoxyl radicals [4,5], and points towards a crucial role for the deprotonation step when the ring-opening of the intermediate cycloalkoxyl radical is not sufficiently fast.

C–C β-scission is one of the most important reactions of alkoxyl radicals, and accordingly this reaction has been thoroughly investigated [4–12], and has found increasing application in synthetically useful procedures [13–18]. In this context, in order to obtain information on the factors governing the fragmentation regioselectivity of tertiary alkoxyl radicals, we have recently carried out a product study on the C–C β-scission reactions of an extended series of 1-alkylcycloalkoxyl radicals, generated photochemically by visible light irradiation of CH_2Cl_2 solutions containing the parent 1-alkylcycloalkanols (diacetoxy)iodobenzene (DIB) and I_2 [19]. It is in fact well known that in the presence of visible light the DIB/I_2 reagent is able to convert alcohols into products deriving from intermediate alkoxyl radicals [14,15,20]. The 1-alkylcycloalkoxyl radicals thus formed, were observed to undergo competition

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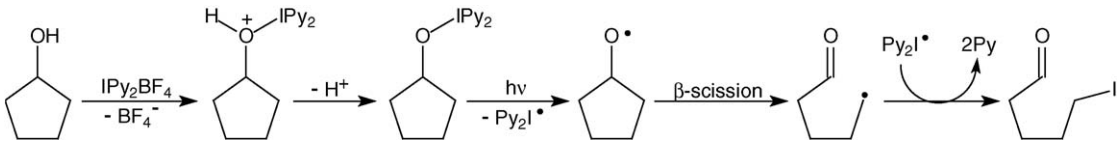
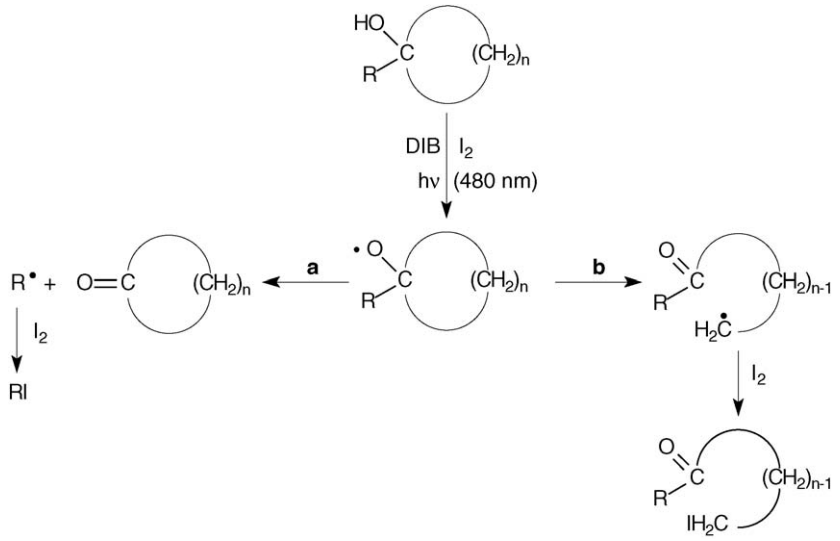


Scheme 1.



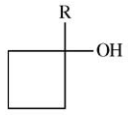
Scheme 2.

between C–alkyl bond cleavage (Scheme 2, path a) and ring opening (path b) as a function of ring size and nature of the alkyl substituent R.

On the basis of these results it was concluded that the fragmentation regioselectivity is essentially governed by the interplay between release of ring strain associated to ring opening and stability of the alkyl radical R• formed by C–R bond cleavage.

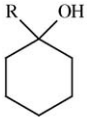
In order to provide support to the mechanism described in Scheme 1, in particular on the involvement of alkoxyl radical intermediates, and in view of the importance of cycloalkoxyl radical ring-opening reactions in synthetically useful procedures [14–18], we have carried out a detailed product study on the photolysis of a selected number of 1-alkylcycloalkanols (substrates **1**–**3** in Chart 1) in the presence of IPy_2BF_4.

The product distributions observed under these conditions have been compared with those observed previously for the same substrates after photolysis in the presence of DIB/I_2 [19], i.e. under bona fide conditions for alkoxyl radical generation. In other words, by comparing the product distributions obtained with the two systems, substrates **1**–**3** can be conveniently used as mechanistic probes in order to establish whether alkoxyl radical intermediates are also formed after irradiation of the same substrates in the presence of IPy_2BF_4.



1f: R = benzyl

2a: R = Me
2b: R = Et
2c: R = Pr
2d: R = *i*Pr
2e: R = *t*Bu
2f: R = benzyl



3a: R = Me
3c: R = Pr
3d: R = *i*Pr
3e: R = *t*Bu
3f: R = benzyl

Chart 1.

2. Experimental

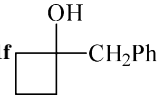
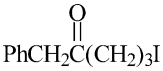
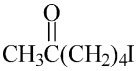
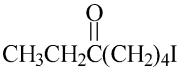
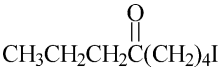
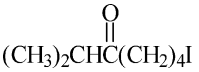
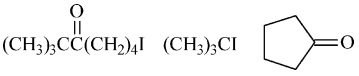
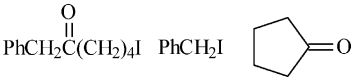
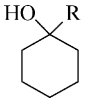
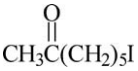
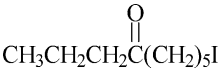
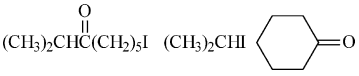
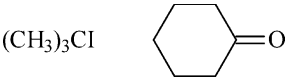
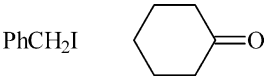
2.1. Reagents

Bis(pyridine)iodonium tetrafluoroborate and cesium carbonate were of the highest commercial quality available. Dichloromethane was purified prior to use through a basic alumina column. Commercial samples of 1-methylcyclopentanol (**2a**) and 1-methylcyclohexanol (**3a**) were used without further purification. 1-Alkylcycloalkanols **1f**, **2b**–**2f**, **3c**–**3f** were available from a previous work [19]. The purity of the 1-alkylcycloalkanols employed in the product studies was always ≥99%.

2.2. Product analysis

Argon saturated CH_2Cl_2 solutions (5 mL) containing the 1-alkylcycloalkanol (**1**–**3**) (10 mM) and IPy_2BF_4 (12.5 mM) were irradiated with visible light for 4 h (λ = 480 nm, 10× 15 W lamps) in a cylindrical flask equipped with a water cooling jacket thermostatted at 20 °C. Some experiments were carried out in the presence of 50 mM Cs_2CO_3. The irradiation time was chosen in such a way as to avoid complete substrate conversion. The reaction mixture was cooled in an ice-water bath and quenched with

Table 1
Product distributions observed after irradiation of argon saturated CH_2Cl_2 solutions ($T = 20\,^{\circ}C$) containing 1-alkylcycloalkanols (**1**–**3**) and DIB/I_2 or IPy_2BF_4

Substrate	Products	DIB/I_2[a,b]		IPy_2BF_4[c]	
		Conversion[d]	Q[e]	Conversion[d]	Q[e]
1f 		62	<0.01[f]	100[g]	<0.01[f]
				32[g,h]	
					
2a (R = CH_3)		56	<0.01[f]	17	<0.01[f]
2b (R = CH_2CH_3)		45	<0.01[f]	18	<0.01[f]
2c (R = $CH_2CH_2CH_3$)		55	<0.01[f]	25	<0.01[f]
2d (R = $CH(CH_3)_2$)		73	<0.01[f]	18	<0.01[f]
2e (R = $C(CH_3)_3$)		20	2.2	36	2.4
		39[i]			
2f (R = CH_2Ph)		49	1.0	14	0.9
				39[g]	
					
3a (R = CH_3)		47	<0.01[f]	4	<0.01[f]
				22[g]	
3c (R = $CH_2CH_2CH_3$)		63	0.06	27[g]	0.10
3d (R = $CH(CH_3)_2$)		52	15.9	50[g]	18.0
3e (R = $C(CH_3)_3$)		41	>200[j]	36[g]	>200[j]
3f (R = CH_2Ph)		72	>200[j]	43[g]	>200[j]

[a] [Substrate] = 10 mM; [DIB] = 11 mM; [I_2] = 10 mM; λ_{irr} = 480 nm; irradiation times: 2 min (**1f**), 5 min (**2a**–**2f**), 10 min (**3a**, **3c**–**3f**).
[b] From ref. [19].
[c] [Substrate] = 10 mM; [IPy_2BF_4] = 12.5 mM; λ_{irr} = 480 nm; irradiation time = 4 h.
[d] As compared to the starting 1-alkylcycloalkanol.
[e] Ratio between C—R bond cleavage and ring opening products.
[f] No C—R bond cleavage products detected.
[g] In the presence of 50 mM Cs_2CO_3.
[h] Irradiation time = 1 h.
[i] Irradiation time = 15 min.
[j] No ring opening products detected.

1 M H_2SO_4 (10 mL). The mixture was extracted with CH_2Cl_2 (2× 10 mL) and the combined organic layers were first washed with a saturated aqueous solution of sodium bicarbonate, then with a 10% aqueous solution of sodium thiosulfate (2× 30 mL) and finally with water (2× 30 mL), and dried over anhydrous sodium sulfate. Reaction products and unreacted substrate were identified by GC-MS and ^{1}H NMR and quantitatively determined by GC and ^{1}H NMR, using bibenzyl as internal standard. Good to excellent mass balances (≥85%) were obtained in all experiments. Reaction products were in all cases the same as those observed previously after photolysis of substrates **1**–**3** in the presence of DIB/I_2 (see ref. [19]). Accordingly, full details on their characterization (GC-MS and ^{1}H NMR data) can be found in ref. [19].

3. Results and discussion

Argon saturated CH_2Cl_2 solutions containing the 1-alkylcycloalkanol (**1**–**3**) and IPy_2BF_4 were irradiated with visible light ($\lambda_{max} \approx 480$ nm, 10× 15 W lamps) at 20 °C for 4 h. The reaction products are reported in Table 1, together with substrate conversions and ratios between C–R bond cleavage and ring opening products (Q). As a matter of comparison, in the same table are also displayed the corresponding data obtained after irradiation of the same substrates in the presence of DIB and I_2 [19].

In the presence of IPy_2BF_4, irradiation of 1-benzylcyclobutanol (**1f**) leads to the formation of 5-iodo-1-phenylpentan-2-one as the exclusive reaction product.

The results obtained for the 1-alkylcyclopentanol series show the exclusive formation of the corresponding ring-opened iodoketone in the reactions of substrates **2a**–**2d**. With 1-*tert*-butylcyclopentanol (**2e**), and 1-benzylcyclopentanol (**2f**) formation of comparable amounts of the corresponding ring-opened iodoketones (7-iodo-2,2-dimethylheptan-3-one and 6-iodo-1-phenylhexan-2-one, respectively), alkyl iodides (2-iodo-2-methylpropane and benzyl iodide, respectively) and cyclopentanone was instead observed.

In the 1-alkylcyclohexanol series, exclusive formation of the corresponding ring-opened iodoketone was observed in the reaction of substrate **3a**. With 1-*tert*-butylcyclohexanol (**3e**) and 1-benzylcyclohexanol (**3f**) exclusive formation of the corresponding alkyl iodide (2-iodo-2-methylpropane and benzyl iodide, respectively) and cyclohexanone was instead observed. The reaction of 1-propylcyclohexanol (**3c**) led to the formation of 9-iodononan-4-one as major product accompanied by smaller amounts of 1-iodopropane and cyclohexanone. The reaction of 1-isopropylcyclohexanol (**3d**) led to the formation of 2-iodopropane and cyclohexanone as major products accompanied by a smaller amount of 8-iodo-2-methyloctan-3-one.

Quite importantly, the results collected in Table 1 clearly show that the product distributions (expressed in terms of the Q ratios between C–R bond cleavage and ring opening products) obtained after irradiation of 1-alkylcycloalkanols **1**–**3** in the presence of IPy_2BF_4 are in all cases very similar to those observed after irradiation in the presence of DIB/I_2. This observation strongly supports the previous hypothesis that alkoxyl radical intermediates are also formed when cycloalkanols are irradiated in the presence of IPy_2BF_4 [2,3], and thus that also with this reagent the observed reaction products are formed as described in Scheme 2 (paths **a** and **b**). Accordingly, with both systems the exclusive fragmentation pathway of the 1-benzylcyclobutoxyl radical, generated from substrate **1f**, is cyclobutane ring opening ($Q < 0.01$), indicating that with this radical the fragmentation regioselectivity is governed by the relatively high ring strain associated to a four member ring [21]. Going to the 1-alkylcyclopentanol series, the exclusive fragmentation pathway of the alkoxyl radicals generated from substrates **2a**–**d** is cyclopentane ring opening ($Q < 0.01$), whereas competition between ring opening and C–R bond cleavage is observed for the alkoxyl radicals generated from substrates **2e** and **2f**. These results indicate that the importance of the C–R cleavage pathway increases with increasing the stability of the alkyl radical $R^\bullet$. However, as mentioned previously [19], the observation that the importance of the C–R cleavage pathway decreases on going from the 1-*tert*-butylcyclopentoxyl radical ($Q = 2.2$–2.4) to the 1-benzylcyclopentoxyl one ($Q = 0.9$–1.0), i.e. by increasing the stability of the alkyl radical $R^\bullet$ formed by C–R cleavage [22], suggests that in addition to the release of ring strain and alkyl radical stability the fragmentation regioselectivity is also governed by steric effects. In the 1-alkylcyclohexanol series, exclusive or predominant ring opening is observed for the alkoxyl radicals generated from substrates **3a** ($Q < 0.01$) and **3c** ($Q = 0.06$–0.10). With the alkoxyl radical derived from substrate **3d**, predominant C–R cleavage is observed ($Q = 15.9$–18.0). With substrates **3e** and **3f** exclusive C–R cleavage ($Q > 200$) is instead observed in the intermediate alkoxyl radicals. Clearly, in a strain free system the fragmentation regioselectivity is essentially governed by the stability of the radical formed.

Again, the comparison between the results obtained for the benzyl substituted cycloalkoxyl radicals **1f**, **2f** and **3f** clearly indicates that the ring opening reaction follows the order: cyclobutoxyl > cyclopentoxyl > cyclohexoxyl [19], in line with the ring strain associated to four, five and six member rings [21], and with the computed activation energies for the ring opening reactions of cycloalkoxyl radicals (7.7, 15.4 and 20.7 kcal/mol, for the cyclobutoxyl, cyclopentoxyl and cyclohexoxyl radical, respectively) [9].

Comparison between DIB/I_2 and IPy_2BF_4 also shows that in the photolysis of 1-alkylcycloalkanols the former system displays a greater efficiency than the latter one [23]. Accordingly, the substrate conversions observed after irradiation in the presence of DIB/I_2 are generally higher than those observed with IPy_2BF_4, even though much shorter irradiation times were employed with the former system. Moreover, as described previously [2,3], with the less reactive 1-alkylcyclohexanol derivatives, addition of a base such as Cs_2CO_3 (which has been suggested to promote alkoxyl radical formation) was necessary in order to increase substrate conversion.

4. Conclusions

In conclusion, very similar product distributions have been observed after photolysis of a series of 1-alkylcycloalkanols

(**1–3**) in the presence of IPy_2BF_4 or DIB/I_2. This similarity provides strong support to the previous hypothesis that intermediate alkoxyl radicals are also formed with the IPy_2BF_4 reagent. With both systems the fragmentation regioselectivity in the intermediate alkoxyl radicals is governed by the interplay between release of ring strain associated to ring opening and stability of the alkyl radical formed by C–R cleavage, even though in the presence of a *tert*-butyl group steric effects appear to play a role. The importance of the ring-opening pathway decreases by increasing ring size and by increasing the stability of $R^{\bullet}$. Accordingly, the rates of ring-opening follow the order: cyclobutoxyl > cyclopentoxyl > cyclohexoxyl, in line with the ring strain associated to four, five and six member rings.

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[23] It is however important to point out that with the secondary alcohol cyclohexanol photolysis in the presence of IPy_2BF_4 leads to the exclusive formation of 6-iodohexanal, whereas significant amounts of additional reaction products were observed when the DIB/I_2 system was employed (see ref. [3]).