Carbenes and the O–H Bond: Hydroxyalkyl-Substituted Arylcarbenes

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Received July 18, 1989

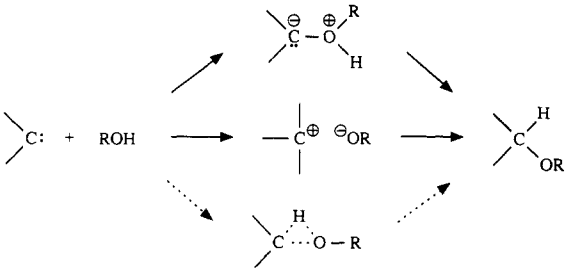
[2-(Hydroxymethyl)phenyl]carbene (**4**), [2-(hydroxymethyl)phenyl]phenylcarbene (**19**), and [2-(2-hydroxyethyl)phenyl]carbene (**30**) have been generated by photolysis of tosylhydrazone or diazo precursors in protic solvents. These carbenes give cyclic ethers (**7**, **18**, **33**) competitively with insertion into O–H bonds of the solvent. For comparison, the analogous benzyl cations (**9**, **17**, **31**) have been generated by solvolysis or dediazoniation. The cations are more sensitive to structural variation than their carbenic counterparts: **9** does not undergo intramolecular nucleophilic substitution, in contrast to **17** and **31**. These observations are explicable in terms of high barriers for rotation about aryl–cation bonds, as compared with low barriers for rotation about aryl–carbene bonds. Two major effects of the solvent (ROH) and of the base (RONa) on product formation may be distinguished: (i) protonation of the carbene (or of its precursors) in the more acidic media leads to predominantly cationic processes; (ii) deprotonation of the OH group under strongly basic conditions enhances the nucleophilicity of the oxygen, and also facilitates insertion into the α-C–H bonds of **30**.

The chemical properties of singlet and triplet carbenes are generally distinct and separable. For the most part, triplet carbenes behave as biradicals, and the singlets as electrophiles.[1] Some complexity in the assignment of spin-specific properties arises when the energy difference between the lowest states is small. Thus, the chemical behavior of phenylcarbene suggests that equilibration of spin states is faster than irreversible reaction.[2] In particular, direct and triplet-sensitized irradiations of (2-*n*-butylphenyl)diazomethane give exactly the same products.[3] A similar conclusion was reached from studies of α-naphthylcarbene.[4]

It has long been held that the reaction of carbenes with alcohols to give ethers is characteristic of the singlet state.[1] Triplet carbenes are believed to abstract H atoms from alcohols to form radical pairs that eventually go on to products. Recently, it was proposed that a single-step, spin-forbidden reaction of the triplet with alcohols may also occur.[5] Support for this proposal comes from the activation energies for the reaction of diphenylcarbene with methanol[5] and from the rate–product discrepancies in the scavenging of diphenylcarbene by amine/methanol mixtures.[6] In the analysis of the experimental results, a purely electrophilic reaction of diphenylcarbene with methanol has been assumed. Other mechanisms (see below) would lead to alternative interpretations of the data. In any event, the formation of ethers proceeds much faster from singlet than from triplet carbenes. The rates at which spin-equilibrated carbenes react with O–H bonds decrease sharply as ΔG_{ST} increases.[1e,7,8]

Three mechanistic sequences have been considered likely for the reaction of carbenes with alcohols. The first, more common, sequence involves attack by the carbene, behaving as an electrophile, on the oxygen atom of the alcohol. The dipolar intermediate (ylide) is then transformed into the product ether either by a proton shift or by intervention of a second molecule of the alcohol. The second route is initiated by protonation of the carbene to give a carbocation, which is subsequently captured by nucleophiles. Finally a concerted three-center interaction has been considered, by analogy with other insertion reactions of singlet carbenes, but there is no experimental support for this path (Scheme I).

Scheme I



The choice of either the ylide or the carbocation route appears to depend primarily on the electrophilic versus nucleophilic character of the carbene. We have demonstrated that (benzo)cycloheptatrienylidenes, typically nucleophilic carbenes, undergo protonation in alcohols with formation of the stable (benzo)tropylium ions.[9] Donor-substituted vinylcarbenes give rise to allylic cations.[10] "Foiled" carbenes also undergo protonation in alcohols to generate nonclassical homoallylic cations.[11] On the other hand, cyclopentadienylidene[9a] and acceptor-substituted vinylcarbenes[12] follow the ylide route. The substrates employed in these studies were chosen for their ability to delocalize the developing charge. The distribution of products and labels thus obtained identifies the polar intermediates unambiguously.

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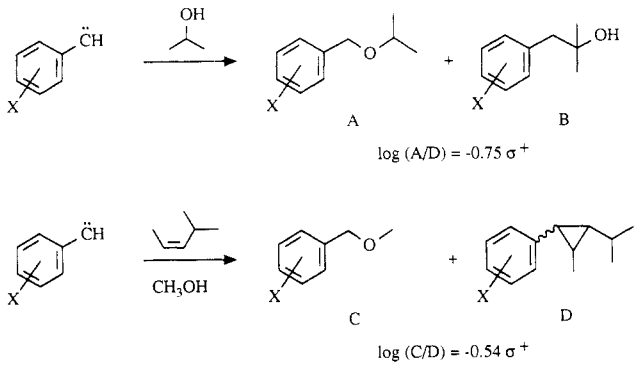
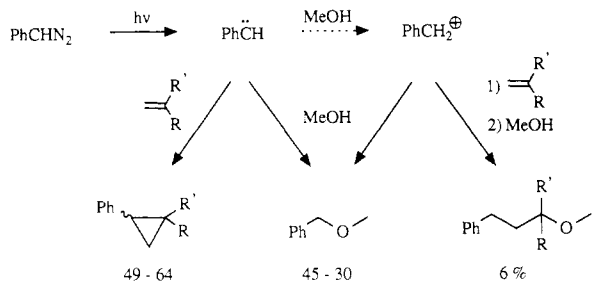
Scheme II

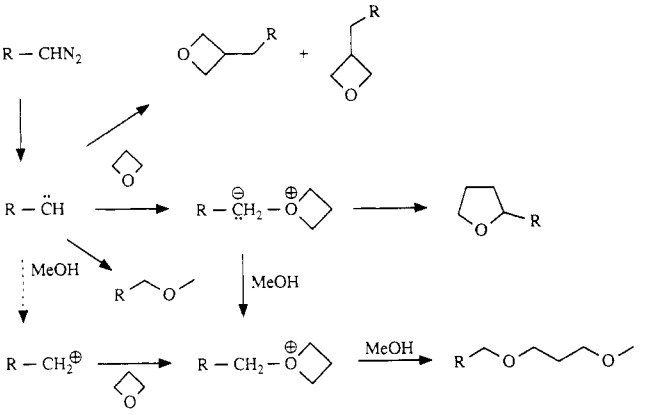


Scheme III

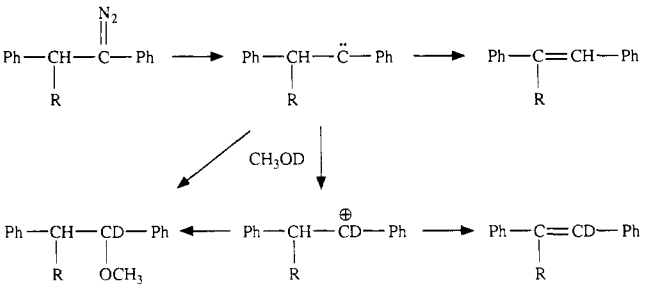


The mechanism for the addition of arylcarbenes to alcohols has been studied in some detail. It is generally agreed that the OH insertion of singlet arylcarbenes is very efficient and proceeds near the diffusion controlled limit.[1e,5-8,13-15] The relative rates of alcohol quenching of singlet diphenylcarbene can be correlated with the acidity of the O–H bond of the alcohol. These results, obtained by steady-state competitive quenching experiments[16,17] and confirmed by time-resolved laser flash photolysis measurements,[14b] support a protonation mechanism. However, the investigation of the isotope effect on these reactions led Bethell to favor the intervention of an ylide.[17b] There is a remarkable parallel between Bethell's findings and the isotope effects observed for fluorenylidene.[15b] (By analogy with cyclopentadienylidene,[9a] protonation of fluorenylidene appears unlikely.) When substituted aryldiazomethanes were photolyzed in isopropanol, the ratio of OH to CH insertion could be correlated with σ^+ (ρ = –0.75).[18] A similar correlation was found when binary mixtures of methanol and 4-methyl-2-pentene competed for arylcarbenes (ρ = –0.54).[18b,19] Donor substituents favor the formation of ethers over the competing insertion and addition reactions. The small negative ρ values suggest weakly nucleophilic behavior of arylcarbenes toward O–H bonds (Scheme II). Proton transfer to phenylcarbene in methanol–alkene mixtures should lead to electrophilic addition of benzyl cations to the alkene. Products indicative of electrophilic addition were indeed obtained with electron-rich alkenes, but cycloadducts of phenylcarbene predominated[20] (Scheme III). The intermediates arising from phenyldiazomethane were also examined in methanol–oxetane mixtures.[21] The fraction of products derived from attack at the oxygen of oxetane increased, relative to CH insertion, in the presence of methanol. It appears that protonation of phenylcarbene opens an independent route to oxonium ions, in addition to protonation of the ylide (Scheme IV). No analogous effect was observed with carbenes that are less amenable to protonation (methylene, ethoxycarbonylcarbene). When benzylphenylcarbenes (1,2-diphenylethylidenes) were generated in CH_3OD, the formation of stilbenes was found to proceed with incorporation of deuterium (0–15%).[22] Partial, although not exclusive, formation of the cation by protonation of the carbene provides a rationale for these observations (Scheme V).

Scheme IV



Scheme V



The experimental data summarized above suggest that arylcarbenes do not follow a single route in their reactions with alcohols. A wide variation in transition-state structure with changing structure of both the carbene and alcohol is indicated. In the present work we address the intramolecular insertion of arylcarbenes into O–H bonds. To that end, hydroxyalkyl groups were attached to the ortho position of arylcarbene precursors. Our studies uncovered dramatic differences in intramolecular reactivities of single arylcarbenes and benzyl cations which facilitate identification of the intermediates.[23] We also report on our efforts

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Scheme VI

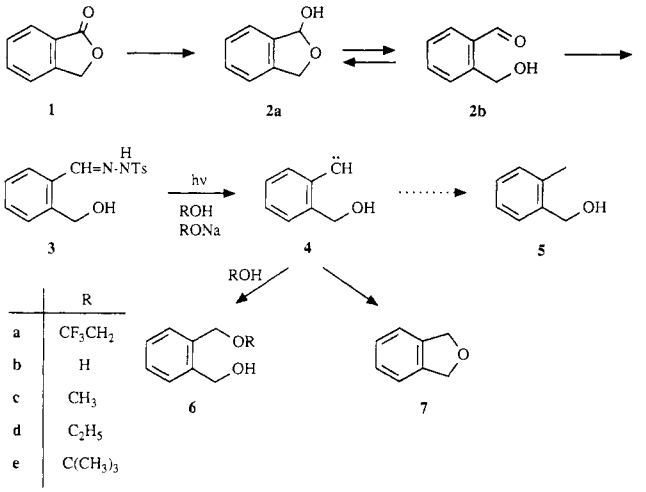


Table I. Photolyses of Tosylhydrazone 3 in ROH–0.2 M RONa (25 °C)

solvent	product ratio	yield,[a] %
CF_3CH_2OH	**6a**:**7** 98:2	53
H_2O	**6b**:**7** 90:10	84
H_2O–CH_3OH, 15:1	**6b**:**6c**:**7** 84:5:11	76
H_2O–CH_3OH, 7:1	74:10:16	67
H_2O–CH_3OH, 3:1	67:17:16	79
H_2O–CH_3OH, 1:1	39:37:24	76
H_2O–CH_3OH, 1:3	19:47:34	72
CH_3OH[b]	**6c**:**7** 62:38	84
CH_3CH_2OH[c]	**6d**:**7** 50:50	68
$(CH_3)_3COH$	**6e**:**7** 29:71	42

[a] Mass balance. Azine, **1**, and **2** were additional products. [b] The product ratio **6c**:**7** decreased by 25% when [NaOMe] was varied from 0.05 to 1.0 M. [c] The product ratio **6d**:**7** decreased by 16% when [NaOEt] was varied from 0.05 to 1.0 M.

to explore the origin of these differences through structural modification.

Results and Discussion

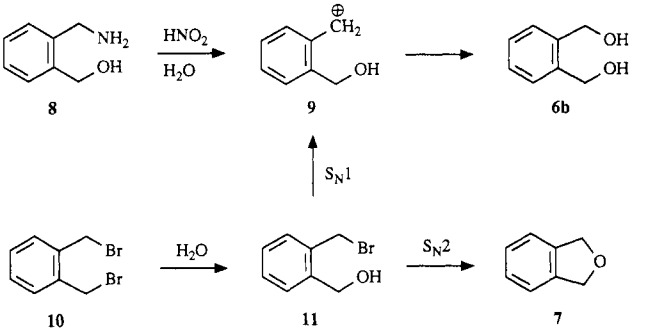
[2-(Hydroxymethyl)phenyl]carbene (4). Reduction of phthalide (**1**) with diisobutylaluminum hydride[24] gave a product mixture containing 1,3-dihydroisobenzofuran-1-ol (**2a**) in equilibrium with 2-(hydroxymethyl)benzaldehyde (**2b**) (**2a**:**2b** = 6.7 in H_2O[24b]), residual **1**, and diol **6b**. Treatment of the mixture with tosylhydrazine afforded the tosylhydrazone **3** of **2b** (28% from **1**). Photolyses of the tosylhydrazone **3** in 0.2 M RONa/ROH produced 2-(alkoxymethyl)benzyl alcohols (**6**) and 1,3-dihydroisobenzofuran (**7**) as the major products (Scheme VI). Minor products (<2% each) were **1** and **2**, arising from the carbene **4** and oxygen. The reaction of matrix-isolated phenylcarbene with oxygen was shown to give benzoic acid as well as benzaldehyde.[25] Small amounts (<3%) of 2-methylbenzyl alcohol (**5**), a typical product of hydrogen abstraction, were obtained from photolyses of **3** in methanol and ethanol.

The product ratios, **6**:**7**, were found to depend strongly on the nature of the solvent (Table I). In terms of competitive intramolecular and intermolecular capture of the carbene **4**, it might be expected that increasing solvent nucleophilicity should lead to more of the intermolecular trapping product, **6**. The opposite was found experimentally: as the solvent nucleophilicity increases, the fraction of dihydroisobenzofuran (**7**) increases. This parallels the decrease in solvent acidity, which should decrease the rate of protonation of the carbene **4**. The observed trend in products ratios led us to suspect that the 2-(hydroxymethyl)benzyl cation (**9**) does not undergo intramolecular nucleophilic substitution to give **7**, whereas the carbene **4** does.

Table II. Hydrolysis of *o*-Xylylene Bromide (10) at 80 °C

solvent, additives	**6b**:**7**	yield, %
dioxane–5 N NaOH (1:10)	0:100	58
dioxane–2.5 N NaOH (1:10)	19:81	59
dioxane–1 N NaOH (1:10)	26:74	62
dioxane–0.2 N NaOH (1:10)	45:55	70
dioxane–H_2O (5:1)	78:22	61
dioxane–H_2O (3:1)	87:13	63
dioxane–H_2O (1:1)	93:7	65
dioxane–H_2O (1:1), $AgBF_4$ (1 equiv)	97:3	67
dioxane–H_2O (1:1), $AgBF_4$ (2.5 equiv)	99.8:0.2	82

Scheme VII



In order to substantiate these ideas, the cation **9** was generated by nitrous acid deamination of 2-(aminomethyl)benzyl alcohol (**8**).[26] The cyclic ether **7** was not obtained; the only products were the diol **6b** and phthalide (**1**) (98:2). The formation of **1** is probably due to oxidation of **6b** by nitrous gases; the yield of **1** increased to 13% when a 4-fold excess of nitrous acid was employed. We also studied the hydrolysis of 1,2-bis(bromomethyl)benzene (**10**), proceeding by way of 2-(bromomethyl)benzyl alcohol (**11**). With decreasing concentration of base, and with increasing polarity of the solvent, the yield of diol **6b** increases at the expense of the cyclic ether **7** (Table II). Clearly, **7** is the preferred product under conditions which favor the S_N2 displacement. As we approach the S_N1 limit, in polar solvents and in the presence of excess silver ion, **6b** is formed almost exclusively (Scheme VII).

Our results with **8** and **10** exclude the cation **9** as a precursor to **7**. Therefore, the formation of **7** from the carbene **4** must be due to intramolecular electrophilic attack at the hydroxymethyl group. For the closely related [2-(alkoxymethyl)phenyl]carbenes the intervention of oxonium ylides has been implicated on the basis of characteristic reactions, e.g. the Stevens rearrangement.[27] By analogy, the intramolecular reactions of **4** to give **7** is thought to proceed by way of the ylide mechanism, rather than by direct OH insertion.

The product ratios in Table I indicate that the benzylic cation **9** is the predominant intermediate arising from **3** in more acidic media. The irradiation of tosylhydrazone sodium salts leads initially to diazo compounds which, in a second photochemical step, generate carbenes.[28] Thus

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the reaction sequence 3 → diazo compound → diazonium ion → 9 must be considered as a route to 9, as well as protonation of the carbene 4. Photolyses of 3 were complete within 1 h, the average lifetime of the diazo species under these conditions being much shorter. Phenyldiazomethane, a close analogy of the diazo compound involved here, proved to be stable for hours in most of our solvents. The only exception is trifluoroethanol (TFE), which decomposes phenyldiazomethane within several minutes. Therefore, protonation of the diazo compound is likely to contribute to the formation of 9 in TFE but not in the other solvents. We feel that protonation of the carbene 4 is a significant route to 9.

The difference in selectivity of 4 and 9 deserves comment. The carbene 4 undergoes intramolecular and intermolecular OH insertions at comparable rates whereas the cation 9 discriminates strongly in favor of the solvent. The rates of the reaction of aromatic carbenes with alcohols approach the diffusion-controlled limit (vide supra). The rate constant for the reaction of 1-(*p*-methylphenyl)ethyl cation in water is also estimated to be 10^{10} M^{-1} s^{-1}.[29] Reaction rates of benzylic cations in ethanol are known to be of the same order of magnitude.[30] These data suggest that the difference in selectivity of 4 and 9 does not arise from a higher reactivity of the cation than the carbene with alcoholic solvents. Instead, different intramolecular reaction rates of 4 and 9 must account for the observed products.

The electrophilic reactions of both singlet carbenes and carbocations are dictated by the vacant p orbital. The most stable conformers of 4 and 9, with the vacant p orbital perpendicular to the plane of the benzene ring, cannot interact with the oxygen of the 2-CH_2OH group. Rotation about the bond connecting the sp^2 carbon of the carbene or cation to the ring must occur in order for intramolecular OH insertions to take place. Arylcarbenes are expected to have considerably lower barriers to rotation than do the analogous benzylic cations. In the planar carbene, resonance donation from the phenyl group to the vacant p orbital occurs only with unfavorable charge separation. Consequently, the exocyclic bond largely retains single-bond character. In contrast, a large extent of conjugation is present in the planar form of the cation, due to significant delocalization of the positive charge. These views are fully supported by ab initio molecular orbital calculations, using the 3-21G basis set.[23,31] The rotational barrier calculated for the benzyl cation (45.4 kcal/mol) is about 4 times that for singlet phenylcarbene (11.2 kcal/mol).

[2-(Hydroxymethyl)phenyl]phenylcarbene (19). The preparation of 2-(hydroxymethyl)benzophenone (15) was patterned according to a reported synthesis of the 2′,4′-dimethoxy derivative.[32] α-Phenyl-1,2-benzenedimethanol (12), obtained by $LiAlH_4$ reduction of 2-benzoylbenzoic acid,[33] was selectively benzoylated at the primary OH group (92%), oxidized (MnO_2, 51%), and deprotected (NaOH/MeOH, 64%) (Scheme VIII). The formation and crystallization of the tosylhydrazone 16 (46%) proceeded reluctantly. Photolyses of 16 in ROH–RONa afforded mixtures of 1-phenyl-1,3-dihydroisobenzofuran (18).[33] and of the benzhydryl ethers 20. Authentic samples of 20a and 20b were prepared from the O-protected 2-bromobenzyl alcohol 21 by Grignard reaction with benzaldehyde to give 22, followed by O-alkylation (NaH, RI) and hydrolysis. The trifluoroethyl ether 20c was assigned only on the basis of GC retention times.

Scheme VIII

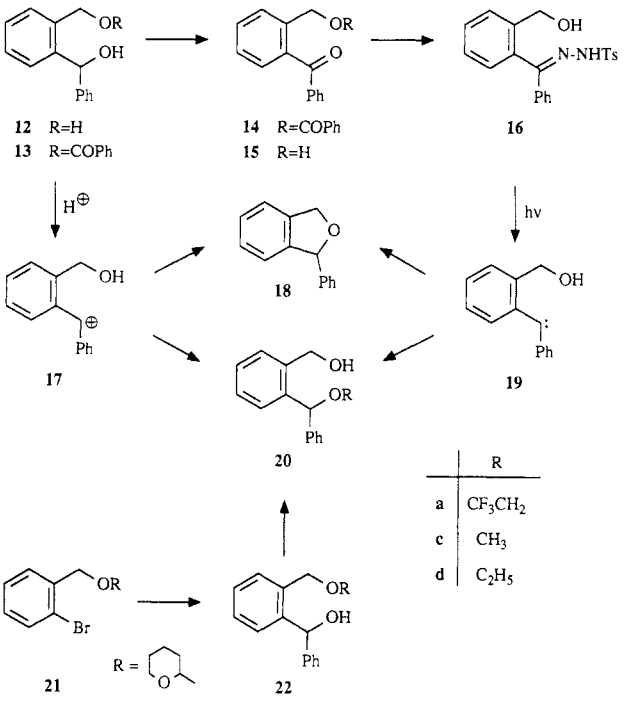

Table III. Photolyses of Tosylhydrazone 16 in ROH–RONa and Acidolyses of Diol 12 in ROH–TsOH (25 °C)

	products, %	
precursor, solvent	18	20
16, CH_3CH_2OH	57.6	42.4
16, CH_3OH	61.9	38.1
16, CF_3CH_2OH	90.3	9.7
12, CH_3CH_2OH	70.5	29.5
12, CH_3OH	70.7	29.3
12, CF_3CH_2OH	100	-

The carbene 19 gives rise to solvent-dependent ratios, 18:20 (Table III). The fraction of the intramolecular product 18 increases with decreasing nucleophilicity of the solvent. As compared with carbene 4 (Table I), the trend in product ratios is reversed. We conclude that the carbocation 17 does undergo intramolecular nucleophilic substitution, in contrast to 9. In fact, 18 has been prepared by acid-catalyzed dehydration of 12.[33] For additional insight into the mechanism, solutions of 12 in various alcohols were treated with *p*-toluenesulfonic acid. The formation of 20 as well as of 18 (Table III) and decreasing rates in the order TFE > MeOH > EtOH support the intervention of 17.

The divergent intramolecular reactivities of 9 and 17 are apparently directly related to the ease of rotation about the aryl–C^+ bond. As was pointed out above, rotation of 9 strongly reduces the benzylic conjugation and thus is slow. In contrast, rotation about one benzyl bond in 19 is facile because the positively charged carbon can remain conjugated with the second aryl ring. An analogous situation has been documented for cyclizations of benzyl and benzhydryl radicals, respectively.[34]

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Table IV. Photolyses of 26 and 27 in ROH–RONa and THF–ROH–RONa (25 °C)

precursor, conditions, concn of RONa, M		products,[a] % 29	33	35	yield, %
26, TFE, 0.2 M			39.6	60.4	50
26, TFE–THF (7:3),	0.025	1.2	52.1	45.9	33
	0.05	1.9	44.0	52.4	39
	0.1	2.4	34.8	61.6	50
	0.2	2.7	36.8	57.6	44
27, TFE–THF (7:3),	0.05	0.3	30.6	68.9	76
	0.1	1.3	33.3	64.4	59
26, TFE–THF (1:1),	0.025	2.2	70.8	26.0	25
	0.05	2.2	55.9	40.1	30
	0.1	2.7	41.6	54.2	44
	0.2	4.0	39.5	54.6	52
27, TFE–THF (1:1),	0.05	1.5	31.5	63.4	59
	0.1	3.1	38.2	58.8	56
26, H_2O, 0.2		1.0	57.0	41.2	61
26, H_2O–THF (7:3),	0.025	5.4	32.8	57.7	42
	0.05	5.6	40.5	50.6	44
	0.1	6.2	49.8	39.6	46
	0.2	7.8	55.0	32.7	42
27, H_2O–THF (7:3),	0.05	4.8	39.9	52.6	29
	0.1	4.3	40.6	51.9	26
26, H_2O–THF (1:1),	0.025	6.7	31.4	56.2	47
	0.05	6.2	45.9	41.5	52
	0.1	7.0	49.5	37.8	56
	0.2	8.4	53.4	32.5	59
27, H_2O–THF (1:1),	0.05	6.7	44.8	44.0	36
	0.1	6.9	50.5	37.3	38
26, MeOH, 0.2		4.7	22.4	67.9	39
26, MeOH–THF (7:3),	0.025	2.7	31.7	63.6	42
	0.05	5.0	29.8	60.9	51
	0.1	5.8	31.4	57.5	59
	0.2	7.6	35.8	50.1	53
27, MeOH–THF (7:3),	0.05	7.8	25.8	60.9	52
	0.1	8.0	31.6	54.0	43
26, MeOH–THF (1:1),	0.025	3.4	48.0	46.4	36
	0.05	4.8	36.1	55.9	44
	0.1	6.5	32.2	55.1	58
	0.2	7.1	41.5	44.3	61
27, MeOH–THF (1:1),	0.05	7.7	35.8	50.3	49
	0.1	7.7	41.5	44.0	44
26, EtOH, 0.2		12.8	24.6	55.4	42
26, EtOH–THF (7:3),	0.025	8.0	43.8	42.0	56
	0.05	10.9	47.8	34.5	51
	0.1	14.3	53.0	26.7	41
	0.2	19.4	53.3	20.7	26
27, EtOH–THF (7:3),	0.05	12.3	40.2	40.8	47
	0.1	13.8	39.9	38.6	44

[2-(2-Hydroxyethyl)phenyl]carbene (30). Reduction of 3,4-dihydro-1*H*-2-benzopyran-1-one (**23**) afforded **24**,[24] from which the tosylhydrazone **26** (44%) was obtained. When the sodium salt of **26** was warmed to 60 °C in THF, the diazo compound **27** formed with surprising ease. Solutions of **27** in THF were stable for hours at room temperature, but complete removal of the solvent led to decomposition. Therefore, **27** was photolyzed (to generate the carbene **30**) and acidolyzed (to generate the carbocation **31**) in THF–ROH mixtures (Tables IV and V). Photolyses of the sodium salt of **26** in neat ROH and in THF–ROH mixtures were also carried out, the results agreeing closely with those obtained from **27** (Table IV). As an additional source of the cation **31**, we studied the nitrous acid deamination of the benzylamine **28**, which was prepared from **24** by way of the oxime **25** (Scheme IX).

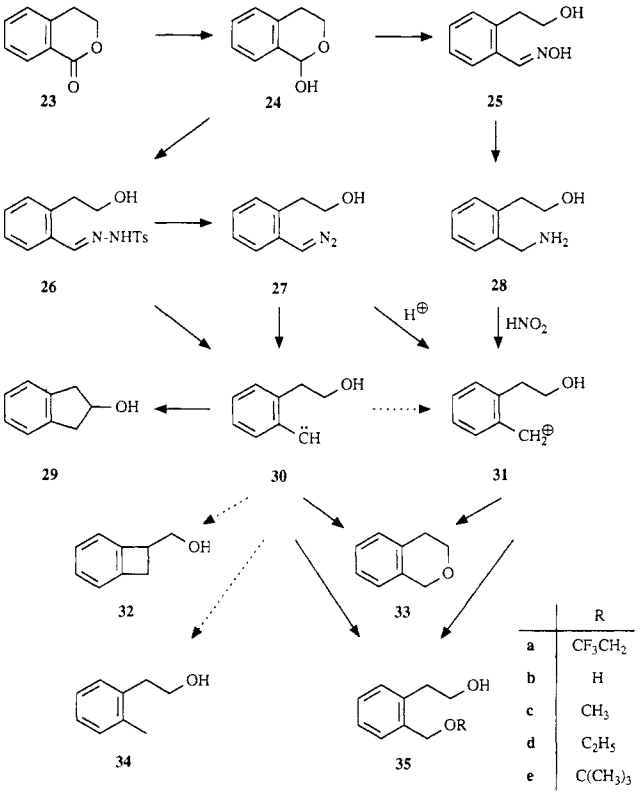
3,4-Dihydro-1*H*-2-benzopyran (**33**) and 2-(2-hydroxyethyl)benzyl derivatives (**35**) were the only products obtained from acidolyses of **27** and from nitrous acid deaminations of **28**. The formation of **33** demonstrates that the carbocation **31** undergoes intramolecular nucleophilic substitution, in contrast to the lower homologue **9**. As a consequence of the extended side chain, the cyclization of **31** does not require rotation about the aryl–C^+ bond. The

Table V. Acidolyses of 27 and Nitrous Acid Deamination of 28 (25 °C)

precursor, conditions	products, % 33	35	yield, %
27, TFE, TsOH[a]	32.8	67.2	60
27, TFE–THF (7:3), TsOH	37.2	62.8	71
27, TFE–THF (1:1), TsOH	45.6	54.4	51
28·HCl, $NaNO_2$, H_2O (pH 3.5)	14.4	85.6	25
27, H_2O, TsOH[a]	18.9	81.1	42
27, H_2O–THF (7:3), TsOH	21.0	79.0	45
27, H_2O–THF (1:1), TsOH	24.5	75.5	35
27, MeOH, TsOH[a]	15.2	84.8	55
27, MeOH–THF (7:3), TsOH	27.8	72.2	50
27, MeOH–THF (1:1), TsOH	29.6	70.4	56
27, EtOH, TsOH[a]	9.2	90.8	50
27, EtOH–THF (7:3), TsOH	27.9	72.1	52
27, EtOH–THF (1:1), TsOH	31.5	68.5	50
27, *t*-BuOH–THF (7:3), TsOH	46.1	53.9	37
27, *t*-BuOH–THF (1:1), TsOH	49.8	50.2	41

[a] Ca. 5% of THF was present in these experiments.

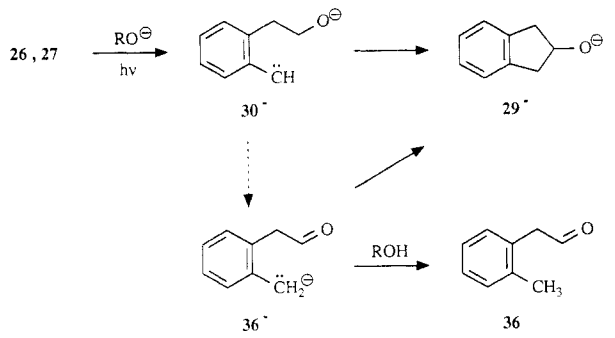
Scheme IX



ratios of **35**:**33** were similar in water, methanol, and ethanol, but decreased in both TFE and *tert*-butyl alcohol (Table V). Decreasing nucleophilicity and decreasing polarity of the solvent favor the formation of the intramolecular product **33**. The broad plateau observed with H_2O, MeOH, and EtOH is attributed to compensating effects of decreasing polarity and of increasing nucleophilicity. The addition of THF also lowers the **35**:**33** ratio, as the concentration of ROH and the polarity of the medium decrease.

Photolyses of **26** and of **27** afforded 2-indanol (**29**), **33**, and **35** as the major products (Table IV). Minor products (≤3%) were **24** (formed by oxidation), **32** (formed by insertion into the benzylic C–H bonds), and **34** (arising by hydrogen abstraction from the solvent). With regard to CH insertion, the carbene **30** conforms with previously studied (*o*-alkylphenyl)carbenes: the formation of indans

Scheme X



is strongly preferred to the formation of benzocyclobutenes.[3,35] While **33** and **35** originate from carbenic as well as from cationic processes, 2-indanol (**29**) and the minor products derive exclusively from the carbene **30**.

Photolyses of **26** and **27** in TFE give very minor amounts of **29** and **35**:**33** ratios similar to those recorded in Table V. Obviously, the carbocation **31** is the predominant intermediate in TFE. Enhanced yields of **29**, and **35**:**33** ratios lower than those recorded in Table V, point to intervention of the carbene **30** in less acidic solvents. Increasing concentrations of base and of THF favor the formation of **29** and of **33** even further. The effect of RONa is rather small in TFE, water, and methanol, moderate in ethanol, and strong in *tert*-butyl alcohol. Conversion of **26**, **27**, and **30** into the corresponding alkoxides accounts for these observations. In the most basic medium, *t*-BuONa–*t*-BuOH, a substantial fraction of **30** should be present as the alkoxide, thus promoting the intramolecular reactions at the expense of capture by the solvent (which is largely *t*-BuOH).

The facile and selective insertion of carbenes into the α-C–H bonds of alkoxides has been thoroughly studied by Oku and his group.[36] An intramolecular version, using (phenylthio)carbenes (carbenoids) has been reported by Cohen.[37] Depending on the substrate, two different mechanisms have been elucidated: (i) an oxyanion-facilitated, concerted CH insertion (leading to retention of configuration) and (ii) a hydride abstraction–recombination mechanism (proceeding without stereospecificity).[36] The present work appears to be the first account of oxyanion-facilitated insertions that take place in protic solvents. Intramolecular hydride abstraction in **30**$^-$ would generate the benzylic anion **36**$^-$ whose protonation by ROH to give **36** should compete with cyclization, **36**$^-$ → **29**$^-$ (Scheme X). Only traces of the aldehyde **36** were detected, never exceeding 2% of **29**. We feel, therefore, that the concerted mechanism of α-CH insertion is applicable, in accordance with Oku's results for primary alkoxides.

Conclusions

The insertion of arylcarbenes into O–H bonds of *o*-hydroxyalkyl side chains is not very sensitive to structural variations. Arylcarbenes (**4**) and diarylcarbenes (**19**) behave similarly; five-membered (**7**, **18**) and six-membered cyclic ethers (**33**) are readily formed. In contrast, the same structural changes have a profound influence on the intramolecular reactivity of benzylic cations. 2-(Hydroxymethyl)benzyl cations (**9**) do not yield dihydroisobenzofuran (**7**). Attachment of a second phenyl group (**17**) and extension of the side chain (**31**) restore the ability for intramolecular nucleophilic substitution. These findings are consistent with theory,[31] suggesting high barriers for rotation about aryl–cation bonds, as compared with low barriers for rotation about aryl–carbene bonds.

By means of the divergent intramolecular reactivities of phenylcarbenes and benzyl cations, protonation of the carbenes by ROH has been established as a significant reaction path. The more acidic media divert the carbenes to predominantly cationic processes. Under strongly basic conditions, on the other hand, deprotonation of the hydroxyalkyl group enhances the nucleophilicity of the oxygen and also facilitates insertion into the α-C–H bonds.[36] Thus, the influence exerted by the medium on the distribution of products is reasonably accounted for in terms of the acid–base properties of hydroxyalkyl-substituted arylcarbenes.

Experimental Section

2-(Hydroxymethyl)benzaldehyde Tosylhydrazone (3). To a stirred solution of phthalide (**1**) (2.68 g, 20 mmol) in toluene (50 mL) at −78 °C was added within 5 min diisobutylaluminum hydride (1 M solution in toluene, 60 mL, 60 mmol). After 5 min at −78 °C a saturated aqueous solution of potassium sodium tartrate (50 mL) was added, and the mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with saturated aqueous solutions of ammonium chloride and of sodium chloride, dried (Na_2SO_4), and concentrated in vacuo. The residue (2.7 g, 100%) consisted of **1** (7%), **2** (40%), and **6b** (53%) (GC). This mixture (1.56 g, containing 4.8 mmol of **2**) and five drops of a solution of hydrogen chloride (1%) in methanol were added to a hot solution of tosylhydrazine (2.2 g, 12 mmol) in methanol (10 mL). After refluxing for 1 h, the tosylhydrazone **3** was filtered with suction and recrystallized from methanol: 1.04 g (72% yield); mp 179–180 °C dec; ^{1}H NMR (CD_3SOCD_3) δ 2.36 (s, 3 H), 4.54 (d, J = 5.2 Hz, 2 H), 5.17 (t, J = 5.2 Hz, 1 H), 7.2–7.85 (m, 8 H), 8.20 (s, 1 H), 10.37 (br s, 1 H). Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 55.19; H, 5.30; N, 9.20. Found: C, 59.25; H, 5.33; N, 9.26.

Photolyses of 3. Solutions of **3** (30 mg, 1 mmol) in 0.2 M RONa–ROH (4 mL) were purged with nitrogen and then photolyzed (medium-pressure mercury arc, Pyrex vessel) for 1 h. 3,4-Dihydro-1*H*-2-benzopyran (**33**) was added as an internal standard. The mixture was diluted with ether (10 mL), washed with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), concentrated, and analyzed by GC. The minor products (**1**, **2**) and 1,3-dihydroisobenzofuran (**7**)[38] were identified by comparison with authentic samples. The hydroxy ethers **6** were isolated by HPLC (silica gel, Et_2O–pentane, 1:1). Anal. (**6a**) Calcd for $C_{10}H_{11}F_3O_2$: C, 54.55; H, 5.04. Found: C, 54.46; H, 4.94. ^{1}H NMR ($CDCl_3$): **6a** δ 2.15 (br s, 1 H), 3.84 (q, J = 8.4 Hz, 2 H), 4.73 (br s, 2 H), 4.78 (s, 2 H), 7.25–7.5 (m, 4 H); **6c**[39] δ 3.12 (br s, 1 H), 3.27 (s, 3 H), 4.38 (s, 2 H), 4.42 (s, 2 H), 7.1–7.25 (m, 4 H); **6d**[40] δ 1.23 (t, J = 7 Hz, 3 H), 2.95 (br s, 1 H), 3.58 (q, J = 7 Hz, 2 H), 4.57 (s, 2 H, 4.64 (s, 2 H), 7.2–7.4 (m, 4 H); **6e**[39] δ 1.32 (s, 9 H), 3.05 (br s, 1 H), 4.53 (s, 2 H), 4.62 (s, 2 H), 7.2–7.45 (m, 4 H).

2-(Aminomethyl)benzyl Alcohol (8). Crude **2** (1.0 g, containing 40% = 2.9 mmol of **2**), hydroxylamine hydrochloride (1.1 g, 15.8 mmol), and barium carbonate (1.6 g, 7.9 mmol) in ethanol (20 mL) were heated at reflux for 18 h. The hot solution was filtered and concentrated in vacuo. GC of the residue (1.0 g) indicated a new compound (45%), presumed to be the oxime of **2**, in addition to **1** (6%) and **6b** (49%) (contaminants of the

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starting material). The product mixture was dissolved in ether (20 mL) and added to lithium aluminium hydride (1.3 g, 34.3 mmol) in ether (50 mL). After heating at reflux for 2 h, water was added dropwise in order to obtain a flaky precipitate of aluminum hydroxide. The solution was filtered, dried over potassium carbonate, and concentrated to ca. 15 mL. Anhydrous hydrogen chloride was introduced, and the precipitate of **8**·HCl (0.5 g, 96%) was recrystallized from ethyl acetate–methanol, mp 222 °C. The preparation of **8**·HCl (mp 225 °C) by a different route has been reported.[26] ^{1}H NMR (CD_3SOCD_3): δ 3.28 (br s, 1 H), 4.06 (s, 2 H), 4.58 (s, 2 H), 7.25–7.6 (m, 4 H), 7.68 (br s, 3 H).

A solution of **8**·HCl (30 mg, 0.18 mmol) in water (1 mL) was adjusted to pH 3.8 (glass electrode) with dilute perchloric acid. Ether (2 mL) and sodium nitrate (13 mg, 0.19 mmol) in water (0.1 mL) were added, and the pH was readjusted. The mixture was stirred for 8 h at room temperature. Repeated extraction with ether, concentration of the extracts, and GC analysis indicated the formation of **6b** and **1** (98:2) in 48% yield.

Solvolysis of *o*-Xylylene Bromide (10). Samples of **10** (50 mg, 0.19 mmol) were dissolved in 0.1 mL of 1,4-dioxane, mixed with NaOH (1 mL), and heated at 80 °C for 10 h. Runs in dioxane–H_2O were carried out in the presence of 2,6-dimethylpyridine (0.1 g, 0.95 mmol). The reaction mixtures were diluted with a saturated aqueous solution of sodium chloride (8 mL). Repeated extraction with ether was followed by addition of a standard (**33**) and by GC analysis (Table II).

2-(Hydroxymethyl)benzophenone Tosylhydrazone (16). Reduction of 2-benzoylbenzoic acid with lithium aluminium hydride provided α-phenyl-1,2-benzenedimethanol (**12**)[33] in 65% yield: mp 73 °C; ^{1}H NMR ($CDCl_3$) δ 3.48 (br s, 2 H), 4.27 (d, J = 12.2 Hz, 1 H), 4.47 (d, J = 12.2 Hz, 1 H), 5.85 (s, 1 H), 7.15–7.25 (m, 4 H). Benzoyl chloride (16.9 g, 0.12 mol) was added dropwise at −5 °C within 1 h to a solution of **12** (21.9 g, 0.1 mol) in anhydrous pyridine (160 mL). The mixture was stirred at 0 °C for 20 h and then partitioned between water (100 mL) and ether. The combined extracts were dried ($MgSO_4$) and concentrated to give 30.0 g (92%) of the crude benzoate **13**. A small portion was purified by HPLC (silica gel, Et_2O–pentane 3:7) but was not obtained crystalline. ^{1}H NMR ($CDCl_3$): δ 2.43 (br s, 1 H), 5.40 (s, 2 H), 6.22 (s, 1 H), 7.2–7.65 (m, 12 H), 7.9–8.5 (m, 2 H).

A solution of crude **13** (15.0 g, 46 mmol) in ether (1 L) was stirred for 12 h at room temperature with powdered manganese dioxide (200 g). The solution was filtered and concentrated in vacuo. HPLC (silica gel, Et_2O–pentane, 2:8) of the residue gave 7.6 g (51%) of **14** as an oil: ^{1}H NMR ($CDCl_3$) δ 5.46 (s, 2 H), 7.15–7.65 (m, 9 H), 7.7–7.85 (m, 5 H). Anal. Calcd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.88; H, 5.17.

Hydrolysis of the benzoate was achieved by heating a solution of **13** (6.33 g, 20 mmol) in 5% NaOMe–MeOH (200 mL) at reflux for 10 h. After evaporation to dryness, the residue was partitioned between an aqueous solution of $NaHCO_3$ (5%, 200 mL) and ether. The combined extracts were dried (Na_2SO_4) and concentrated to give 2.7 g (64%) of **15** of 93% purity (GC): ^{1}H NMR (C_6D_6) δ 3.38 (br s, 1 H), 4.57 (s, 2 H), 6.75–7.25 (m, 6 H), 7.25–7.75 (m, 3 H).

The tosylhydrazone **16** was prepared by heating **15** (2.12 g, 10 mmol), tosylhydrazine (1.86 g, 10 mmol), methanol (15 mL), and five drops of methanolic HCl at reflux for 10 h. The methanol was evaporated in vacuo, and the residue was purified by flash chromatography (silica gel, ether) to give 1.74 g (46%) of **16**. Crystallization was induced by storing **16** with a few drops of methanol at −30 °C: mp 140–142 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (br s, 1 H), 2.42 (s, 3 H), 4.23 (s, 2 H), 6.95–7.95 (m, 13 H), 10.95 (br s, 1 H). Anal. Calcd for $C_{21}H_{20}N_2O_3S$: C, 66.30; H, 5.30; N, 7.36. Found: C, 66.44; H, 5.46; N, 7.48.

Photolyses of 16. The procedures described for **3** were followed. The concentration of RONa was varied between 0.05 and 0.4 M without significant effect on the distribution of products. Average values are given in Table III. Authentic samples for comparison were obtained as follows: The diol **12** (0.86 g, 4 mmol), concentrated aqueous HCl (10 mL), and ether (10 mL) were stirred for 12 h at room temperature. Partitioning between water and ether afforded 0.49 g (62%) of **18**:[33] mp 33–35 °C (after recrystallization from CCl_4–pentane) (lit. mp 35 °C); ^{1}H NMR ($CDCl_3$) δ 5.18 (dd, J = 12.0 and 2.0 Hz, 1 H), 5.38 (dd, J = 12.0 and 2.4 Hz, 1 H), 6.17 (dd, J = 2.4 and 2.0 Hz, 1 H), 6.95–7.45 (m, 9 H).

The tetrahydropyranol ether **21**[41] was obtained from 2-bromobenzyl alcohol by standard procedures (95% yield). To the Grignard reagent prepared from **21** (2.71 g, 10 mmol) and magnesium turnings (0.27 g, 11.1 mmol) in THF (20 mL) was added a solution of benzaldehyde (1.06 g, 10 mmol) in THF (5 mL). The mixture was stirred for 12 h at room temperature. Conventional workup and flash chromatography gave 2.9 g (97%) of **22**, purity 93% (GC): ^{1}H NMR ($CDCl_3$) δ 1.4–1.9 (m, 6 H), 3.20 (br s, 1 H), 3.25–4.05 (m, 2 H), 4.34 (d, J = 11.6 Hz, 0.5 Hz), 4.65 (d, J = 1.8 Hz, 2 H), 4.87 (d, J = 11.6 Hz, 0.5 H), 6.07 (br s, 1 H), 7.15–7.55 (m, 9 H).

A mixture of **22** (0.30 g, 1 mmol), sodium hydride (36 mg, 1.5 mmol), and THF (5 mL) was heated at reflux for 30 min. Methyl iodide (285 mg, 2 mmol) was then added, and reflux was maintained for 10 h. Partitioning between water and ether and concentration of the organic phase in vacuo yielded the tetrahydropyranol ether of **20c** (0.29 g, 92%), which was hydrolyzed (5 mL of 1 N methanolic HCl, room temperature, 12 h) to obtain **20c** (0.15 g, 82%). The sample was purified by HPLC (silica gel, Et_2O–hexane, 4:6): ^{1}H NMR ($CDCl_3$) δ 2.30 (br s, 1 H), 3.36 (s, 3 H), 4.48 (s, 2 H), 5.47 (s, 1 H), 7.15–7.35 (m, 9 H). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.77; H, 7.24.

The ethyl ether **20d** was prepared analogously, using ethyl iodide, with an overall yield of 80%: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3 H), 2.50 (br s, 1 H), 3.52 (q, J = 7.1 Hz, 2 H), 4.46 (s, 2 H), 5.56 (s, 1 H), 7.15–7.35 (m, 9 H). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.19; H, 7.47.

Acidolyses of 12. The acid-catalyzed reactions of **12** (0.025–0.1 M), induced by *p*-toluenesulfonic acid (10^{-4}–1 M), were followed by GC analysis. In TFE, >90% conversion into the cyclic ether **18** was achieved within 1 min, even at 10^{-4} M TsOH. The results of a representative run in MeOH, 0.2 M TsOH, 25 °C, follow (% conversion, **18**:**20c** ratio in brackets): 30 min, 1.3 (7.9); 1 h, 2.3 (10); 4 h, 6.6 (8.3); 8 h, 9.3 (5.3); 1 day, 28.9 (2.1); 2 days, 41.0 (2.4); 7 days, 66.5 (2.3); 14 days, 79.1 (2.4)). The high ratios of **18**:**20c** at low conversion are due to problems with the extraction and analysis of **20c**, rather than to an eventual instability of **18**. A 1:1 mixture of **18** and **20c** remained unchanged in MeOH, 0.2 M TsOH after 4 days. The reaction of **12** in EtOH proceeded slowly; only 4.4% conversion was achieved after 4 days at 25 °C in the presence of 1 M TsOH.

2-(2-Hydroxyethyl)benzaldehyde Tosylhydrazone (26). Reduction of 3,4-dihydro-1*H*-2-benzopyran-1-one (isochromanone, **23**) with DIBAL (toluene, −90 °C) according to the procedure for **1** furnished **24** (85%), **23** (2%), and **35b** (9%). A pure sample of **24**[24] (mp 73–75 °C, lit. mp 75 °C) was obtained by crystallization from ether–pentane at −15 °C. The crude material (2.0 g, 13 mmol), tosylhydrazine (2.5 g, 13 mmol), methanol (20 mL), and five drops of methanolic HCl were heated at reflux for 10 h. Evaporation of the methanol in vacuo, followed by flash chromatography (silica gel, ether), gave an oil which crystallized from ether–pentane at −15 °C within 14 days (2.0 g, 44% yield): mp 101–103 °C; ^{1}H NMR (CD_3SOCD_3) δ 2.36 (s, 3 H), 2.80 (t, J = 6.7 Hz, 2 H), 3.53 (t, J = 6.7 Hz, 2 H), 3.65 (br s, 1 H), 7.15–7.85 (m, 8 H), 8.22 (s, 1 H), 11.30 (br s, 1 H). Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.34; H, 5.84; N, 8.91.

[2-(2-Hydroxyethyl)phenyl]diazomethane (27). To a solution of **26** (0.64 g, 2 mmol) in THF (5 mL) was added at 0 °C sodium hydride (85 mg of a 60% dispersion in paraffin, 2.1 mmol). The mixture was stirred for 30 min at 0 °C, *n*-pentane (30 mL) was then added, and stirring was continued for additional 30 min. The sodium salt of **26** was filtered and dried in vacuo (0.65 g, 95% yield). A solution of the sodium salt (0.57 g, 1.7 mmol) in THF (20 mL) was warmed to 60 °C for 20 min. After cooling to room temperature, the precipitate of sodium *p*-toluenesulfinate was removed by filtration. Aliquots of the dark red solution were shaken with excess dimethyl maleate until the color had faded. GC analysis indicated that **27** was stable in THF for several hours at room temperature. However, 5–10% of **33** had formed during the preparation of **27**.

Photolyses of 26 and 27. The procedures described for **3** were applied to **26** and **27**, using **7** as an internal standard. The yields

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given in Table IV refer to **26**, i.e. complete conversion of **26** into **27** has been assumed. The product distributions obtained from **27** were corrected for the amount of **33**, which contaminated the solutions of **27** (see above). Consequently, the results obtained with **27** were less well reproducible than those from photolyses of **26**.

Authentic samples of **32**[42] and of **36**[43] were prepared according to published procedures; **29**, **33**, and **34** are commercially available (Aldrich). The hydroxy ethers **35** were isolated from the product mixtures by HPLC (silica gel, hexane–ether, 6:4) and/or prepared independently from 2-bromobenzyl ethers by reaction of the corresponding Grignard reagents with oxirane: ^{1}H NMR ($CDCl_3$) **35a** δ 1.60 (br s, 1 H), 2.94 (t, J = 6.5 Hz, 2 H), 3.83 (q, J = 8.7 Hz, 2 H), 3.86 (t, J = 6.5 Hz, 2 H), 4.72 (s, 2 H), 7.2–7.35 (m, 4 H); **35c**[44] δ 2.42 (br s, 1 H), 2.93 (t, J = 6.4 Hz, 2 H), 3.40 (s, 3 H), 3.85 (t, J = 6.4 Hz, 2 H), 4.48 (s, 2 H), 7.26 (br s, 4 H); **35d**[44] δ 1.25 (t J = 7.0 Hz, 3 H), 2.52 (br s, 1 H), 2.93 (t, J = 6.3 Hz, 2 H), 3.57 (q, J = 7.0 Hz, 2 H), 3.85 (t, J = 6.3 Hz, 2 H), 4.51 (s, 2 H), 7.2–7.35 (m, 4 H); **35e**[39] δ 1.33 (s, 9 H), 2.68 (br s, 1 H), 3.87 (t, J = 5.0 Hz, 2 H), 4.22 (t, J = 5.0 Hz, 2 H), 4.50 (s, 2 H), 6.8–7.4 (m, 4 H).

Acidolyses of 27. Solutions of *p*-toluenesulfonic acid in ROH and of **27** in ROH–THF were mixed at room temperature. The volumes were chosen to obtain solutions 0.025 M in **27** and 0.01 M in TsOH. For reaction in "neat" ROH, solutions of **27** in THF were concentrated in vacuo at 0 °C, and the residue was immediately dissolved in ROH. The formation of some **33** during this procedure cannot be excluded. The color of **27** faded within 5 min. The reaction mixture was shaken with powdered sodium carbonate, and the supernatant solution was analyzed directly by GC (Table V).

2-(2-Hydroxyethyl)benzylamine (28). The semiacetal **24** (1.35 g, 9 mmol), hydroxylamine hydrochloride (1.25 g, 18 mmol), barium carbonate (1.78 g, 9 mmol), and ethanol (20 mL) were heated at reflux for 8 h. The hot solution was filtered and concentrated in vacuo. The crude oxime (1.34 g, 90%, containing ca. 85% of **25**) was reduced with lithium aluminum hydride, as described for **8**, to give 0.67 g (44%) of **28**·HCl; mp 158–160 °C; ^{1}H NMR (CD_3SOCD_3) δ 1.82 (t, J = 6.2 Hz, 2 H), 2.63 (t, J = 6.2 Hz, 2 H), 3.07 (s, 2 H), 3.15 (br s, 1 H), 7.15–7.55 (m, 4 H), 8.50 (br s, 3 H). Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.73; H, 7.42; N, 7.53.

The nitrous acid deamination of **28** was carried out by the same procedure as described above for **8**. GC indicated the formation of **33** and **35b**[45] (15:85) in 25% yield.

Registry No. **2b**, 55479-94-2; **2b** (oxime), 125593-28-4; **3**, 125593-15-9; **6a**, 125593-16-0; **6b**, 612-14-6; **6c**, 62172-88-7; **6d**, 103386-05-6; **6e**, 125593-27-3; **7**, 496-14-0; **8**, 4152-92-5; **8**·HCl, 4152-84-5; **10**, 91-13-4; **12**, 1586-01-2; **13**, 125593-17-1; **14**, 125593-18-2; **15**, 100560-58-5; **16**, 125593-19-3; **18**, 7111-66-2; **20a**, 125593-20-6; **20c**, 125593-29-5; **20c** (tetrahydropyranol ether), 125593-31-9; **20d**, 125593-30-8; **21**, 17100-66-2; **22**, 125593-21-7; **23**, 4702-34-5; **24**, 95033-78-6; **25**, 125593-22-8; **26**, 125593-23-9; **26**·Na, 125593-35-3; **27**, 125593-24-0; **28**, 125593-25-1; **28**·HCl, 35050-30-7; **29**, 4254-29-9; **33**, 493-05-0; **35a**, 125593-26-2; **35b**, 6346-00-5; **35c**, 125593-32-0; **35d**, 125593-33-1; **35e**, 125593-34-2; *p*-$MeC_6H_4SO_2NHNH_2$, 1576-35-8; *o*-$PhCOC_6H_4CO_2H$, 85-52-9; phthalide, 87-41-2.

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Formation and Reactions of Diorganophosphinite Ions in Liquid Ammonia. Synthesis of Triorganophosphine Oxides by the $S_{RN}1$ Mechanism[1]

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Received August 16, 1989

The reaction of triphenyl- and tribenzylphosphine oxides with alkali metals in liquid ammonia gave diphenyl- and dibenzylphosphinite ions, respectively, in high yields and a small amount of deoxygenated products. These ions reacted under photostimulation with aryl halides by the $S_{RN}1$ mechanism to give aryldiphenyl- and aryldibenzylphosphine oxides in good yields. With tribenzylphosphine oxide, by consecutive debenzylation with alkali metals followed by photostimulated reaction with aryl halides, all the benzylic moieties could be replaced by aromatic moieties to finally obtain unsymmetrical triarylphosphine oxides.

The mechanism known as radical nucleophilic substitution or $S_{RN}1$ is well-known.[2] The three main steps of the propagation cycle are outlined in Scheme I. The addition of these three steps leads to eq 4, which is a nucleophilic substitution but with a radical and radical anions as intermediates. Many aromatic substrates react by this mechanism with different types of nucleophiles.

Scheme I

$$(RX)^{\bullet-} \rightarrow R^{\bullet} + X^- \quad (1)$$

$$R^{\bullet} + Nu^- \rightarrow (RNu)^{\bullet-} \quad (2)$$

$$(RNu)^{\bullet-} + RX \rightarrow RNu + (RX)^{\bullet-} \quad (3)$$

$$RX + Nu^- \rightarrow RNu + X^- \quad (4)$$

(1) Based on the Ph.D. Thesis of E. R. N. Bornancini, Universidad Nacional de Córdoba, 1988.
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0022-3263/90/1955-2332$02.50/0