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Selective C^{α}–O Bond Cleavage of α,β-Epoxy Ketones to Aldols induced by Free Radical Processes

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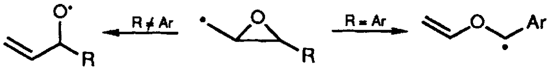
Several α,β-epoxy ketones were converted to aldols in good yields upon irradiation or heating with azoisobutyronitrile in the presence of tributyltin hydride in benzene; the reactions involve selective C^{α}–O bond cleavage of the oxiranylmethyl radicals derived from these substances.

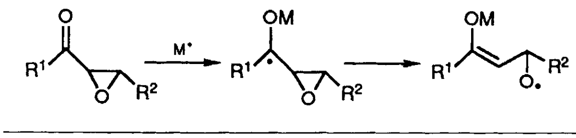
Free-radical reactions of organic molecules have been of major interest in mechanistic[1] and synthetic[2] organic chemistry. The cyclopropylmethyl-allylmethyl radical rearrangement is a well known process that forms the basis of a radical clock.[3] The regiochemical outcome of the ring opening of substituted cyclopropylmethyl radicals is governed by substitution pattern and reaction conditions.[4] Analogous rearrangements of heteroatom-containing three-membered rings, such as oxiranes[5] or aziridines,[6] can also occur. Recent studies concerning oxirane ring-opening reactions *via* free-radical processes have demonstrated that both C^2–O and C^2–C^3 bond cleavage occurs [equation (1)].[7,8] Murphy and co-workers pointed out that regioselective C^2–C^3 bond cleavage reactions were due to the presence of radical-stabilizing 3-aryl groups.[8a] We report herein that selective C^{α}–O bond cleavage reactions of α,β-epoxy ketones induced by free-radical processes occurs even when aryl groups are present at C^{β} [equation (2)]. This chemical process could provide a convenient conversion of α,β-epoxy ketones into aldols.[9]†

The α,β-epoxy ketones reported here can be grouped into four classes: (i) aroyl–aryl–oxirane (**1**); (ii) aroyl– or aroyl–alkyl–oxirane (**3**), (**5**); (iii) acyl–aryl–oxirane (**7**); (iv) acyl–alkyl–oxirane (**9**). Ring-opening reactions of these substances were performed using tributyltin hydride under photochemical and thermal conditions. The results are shown in Table 1.‡

Irradiation of a benzene solution of *trans*-chalcone epoxide (**1a**) with Bu_3SnH afforded the corresponding aldol (**2a**) in



(1)



(2)

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† Although Rahm and co-workers subjected some α,β-epoxy ketones to Bu_3SnH reduction under high pressure, aldols were obtained only as byproducts (M. D. Castaing, A. Rahm, and N. Dahan, *J. Org. Chem.*, 1986, **51**, 1672).

‡ Although β-hydroxy stannyl enol ethers would have been the expected products, column and subsequent TLC separations gave pure aldols as major products. The aldols obtained were identified by direct comparison of their spectroscopic data with those of aldols independently prepared by Yoshikoshi's method (ref. 9a).

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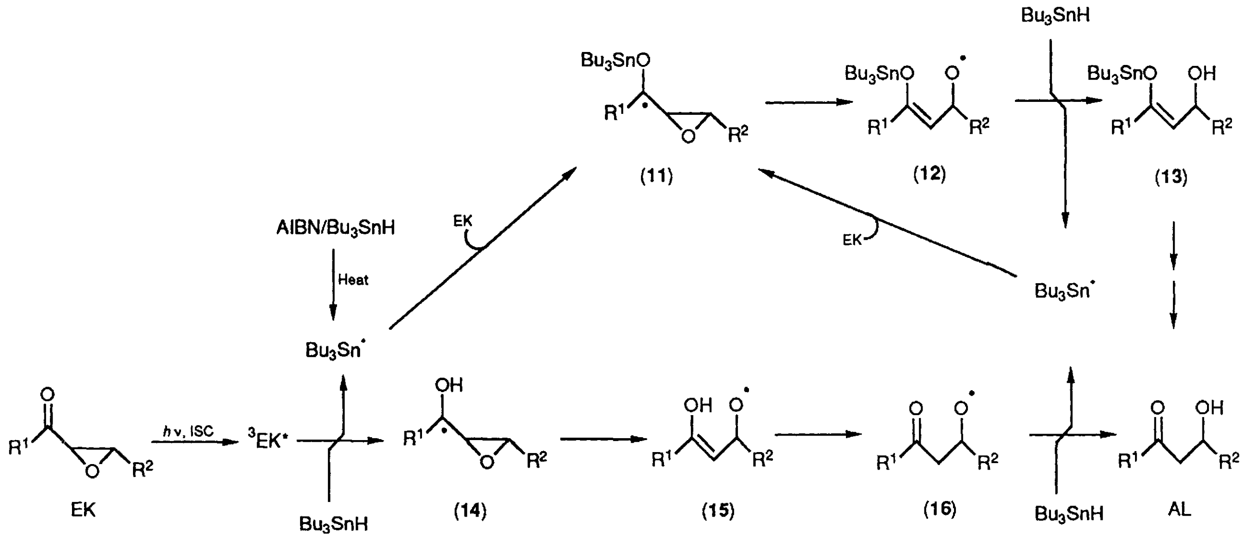
Table 1. Conversion of α,β-epoxy ketones to aldols by photochemical and thermal reactions with Bu_3SnH in benzene.

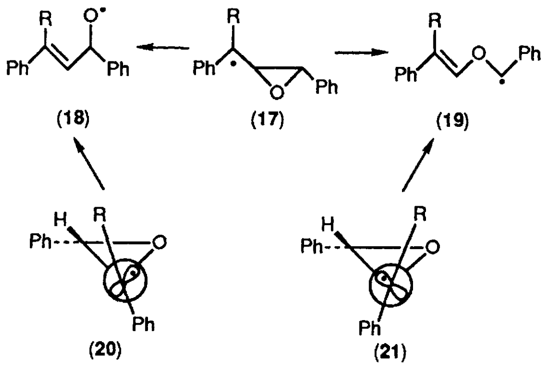
α,β-Epoxy ketone (EK)				Photoreaction[a]			Thermal reaction[b]		
	R^1	R^2	Aldol (AL)	% Yield	% Conv.	*t*/min	% Yield	% Conv.	*t*/min
(1a)	Ph	Ph	**(2a)**	93	100	30	83	100	60
				96[c]	100	30			
				54[d]	57	30			
(1b)	Ph	*p*-Tol[j]	**(2b)**	85	100	30	84	100	60
(3)	Ph	H	**(4)**	84	100	30	89[f]	100	60
(5)	Ph	Pr^i	**(6)**	81	100	30	75[f]	97	60
(7)	Me	Ph	**(8)**	5	17	120	91[g]	98	60
				24[e]	30	120			
(9)	Me	Pen^n	**(10)**	2	11	120	81[h]	95	60
				40[e]	54	120			

[a] [EK] = 0.049 M, [Bu_3SnH] = 0.101 M; 400 W Hg-lamp/Pyrex/N_2. [b] [EK] = 0.040 M, [Bu_3SnH] = 0.048 M, [AIBN] = 0.0048 M; reflux/N_2. [c] [Bu_3SnH] = 0.054 M. [d] [Bu_3SnH] = 0.025 M. [e] [AIBN] = 0.010 M. [f] [Bu_3SnH] = 0.061 M, [AIBN] = 0.0061 M. [g] [Bu_3SnH] = 0.088 M, [AIBN] = 0.0088 M. [h] [Bu_3SnH] = 0.090 M, [AIBN] = 0.0090 M. [j] *p*-Tol = *p*-MeC_6H_4.



Scheme 1. ISC = intersystem crossing.

93% yield. Similarly, aldols **(2b)**, **(4)**, and **(6)** were obtained in good yields upon irradiation of **(1b)**, **(3)**, and **(5)** with Bu_3SnH. Varying the amount of Bu_3SnH [2.06, 1.10, or 0.51 equiv. with respect to **(1a)**] yielding **(2a)** (93, 96, and 54%) indicates that an equivalent of Bu_3SnH is needed for a complete conversion of **(1a)** to **(2a)**. The low conversions of **(7)** and **(9)** under photochemical conditions which could be due to inefficient excitation of the acyl chromophore by the incident light imply that hydrogen abstraction from Bu_3SnH by the nπ* triplet state of the carbonyl group initiates the reactions. Based on the above observations, the mechanism in Scheme 1 involving two different oxiranylmethyl radicals **(11)** and **(14)** is proposed.§ The sequence of transformations from $^3EK^*$ to AL which requires two equivalents of Bu_3SnH would operate only at an initial stage of the reaction. Radical **(11)** which must also participate in the thermal reaction can undergo ring opening at ambient temperature, and this is supported by the observation that addition of azoisobutyronitrile (AIBN) to solutions of **(7)** and **(9)** increased the aldol yields in the photochemical reactions.



Scheme 2. R = H, OH, $OSnBu_3$.

Upon heating of **(1a)** and Bu_3SnH with AIBN in benzene, **(2a)** was obtained in 83% yield. In the absence of AIBN, 95% of **(1a)** was recovered along with 4% of **(2a)**. The reaction mechanism shown in Scheme 1 would operate in analogy with known free-radical reactions of cyclopropyl ketones with Bu_3SnH and AIBN.[4] Similar treatment of **(1b)**, **(3)**, and **(5)**

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§ A referee indicated the possibility of intramolecular Bu_3Sn transfer in **(12)**, and such a type of process has been observed (A. G. Davies and M. W. Tse, *J. Organomet. Chem.*, 1978, **155**, 25). However, we feel that this may not happen in the presence of Bu_3SnH.

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with Bu_3SnH produced the corresponding aldols in good yields. The thermal reaction was particularly useful for (**7**) and (**9**) affording 91% of (**8**) and 81% of (**10**) respectively, since these substances showed relatively low photochemical reactivities under the conditions employed.

Especially noteworthy is the exclusive formation of the aldol product from (**1**) and (**7**) since oxiranylmethyl radicals (**11**) and (**14**) are probably responsible for these reactions. Murphy and co-workers observed that 3-aryloxiranylmethyl radicals underwent regioselective C^2–C^3 bond cleavage to yield vinyl ethers,[8a] whereas we did not isolate such vinyl or keto ether products in any of the cases reported here. Our qualitative rationalization for these observations based on stereoelectronic considerations[10] is in Scheme 2. Ring opening of the oxiranylmethyl radical (**17**) must require maximum overlap between the relevant semioccupied p-orbital and σ-orbital. Conformer (**20**) would yield the oxyl radical (**18**) while conformer (**21**) would yield the benzyl radical (**19**). When there was no large difference in the stability of (**20**) and (**21**) (R = H), formation of the thermodynamically more stable radical (**19**) would predominate over formation of the less stable radical (**18**). However, if the side chain α-carbon atom is O-substituted (R = OH or $OSnBu_3$), electron pair–electron pair repulsion between the two oxygen lone pairs would raise the relative energy of (**21**), and formation of (**20**) would be favoured leading to (**18**).

In conclusion, we have found that several α,β-epoxy ketones were converted to aldols in good yields *via* free-radical processes. That the reactions of the substances possessing a β-aryl substituent produced the products *via* less stable radical intermediates is particularly notable. A full explanation of these unexpected observations must await further work.

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