The β-(acyloxy)alkyl radical rearrangement revisited[1]

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Abstract: A β-(acyloxy)alkyl radical precursor, containing a carboxylate residue suitably placed for the trapping of any intermediate alkene radical cations, has been constructed. In nonpolar solutions the probe, in the form of either the free acid or its tetrabutylammonium salt, undergoes the typical rearrangement reaction with no evidence of trapping, leading to the conclusion that the reaction is either concerted or that collapse of any intermediate contact ion pair is so rapid as to preclude the possibility of trapping.

Key words: radical, rearrangement, contact ion pair.

Résumé : Un précurseur de transposition d'un radical β-(acyloxy)alkyle, equippé d'un résidu carboxylate convenablement placé pour piéger des intermediares alcene cation radicalaire, a été construit. En milieu apolaire la sonde, sous forme d'acide carboxylique ou sel de tetrabutylammonium quaternaire, subit la transposition typique et ne manifest aucune évidence de piègage, ce qui mène à la conclusion que la réaction est soit concertée, soit a lieu par l'intermédiaire d'une paire d'ions intime qui se réunit trop rapidement pour admettere la possibilité de piègage.

Mots clés : transposition radicalaire, paire d'ions intime.

Introduction

Initially thought to be concerted (1), the β-(phosphatoxy)alkyl radical rearrangement has recently been shown to involve a rate-determining radical ionic fragmentation to a contact radical ion pair with subsequent collapse to the product radical (Scheme 1, X = $P(OR)_2$) (2, 3). The jury is still out, however, in the case of the closely related β-(acyloxy)alkyl radical rearrangement (1), otherwise known as the Surzur–Tanner rearrangement (4). In this paper we describe attempts at trapping any intermediate contact ion pair, which attest, at the least, to the rapidity of its collapse to the product radical.

The evidence for the fragmentation mechanism in the rearrangement of β-(phosphatoxy)alkyl radicals is spectroscopic and kinetic (2, 3, 5) and is well supported by a range of trapping experiments (6–10). Thus, in more polar solvents, β-phenyl-β-(phosphatoxy)ethyl radicals fragment to give the styryl radical cation, which is readily detected in time-resolved laser flash photolytic experiments, and the phosphate anion. Kinetic experiments reveal the Arrhenius parameters for the fragmentation, with log(A) values typically in the vicinity of 10–12 (2, 3, 11). When the same experiments are conducted in nonpolar solvents only the rearranged radical is observed, but the Arrhenius parameters for these rearrangements closely resemble those for the fragmentations in more polar solvents (2, 3, 12, 13). The congruence between the two sets of Arrhenius parameters leads to the conclusion that both involve rate-determining fragmentation to a contact radical ionic pair, but that in nonpolar solvents rapid collapse to the product radical precludes the possibility of cage escape and spectroscopic detection of the radical cation. Note that, owing to the nanosecond timescale of the instrument used in the LFP experiments and the expected sub-nanosecond times anticipated for the escape of ions from contact ion pairs (14), only those radical cations that live long enough to escape the initial contact pair can be observed spectroscopically. Numerous trapping studies (6–10) have pointed to the ability of nucleophiles to intervene in this mechanism by trapping the alkene radical cation, and the stereochemical information retained in some of them (9) indicates that, with appropriate nucleophiles, trapping can take place at the level of the contact radical ion pair.

Significant effort has also been focused on the mechanism of the β-(acyloxy)alkyl radical rearrangement (15). A variety of stereochemical and isotopic labeling studies point to a reaction that is the formal equivalent of a 2,3-sigmatropic shift (Scheme 2) (1, 15). However, kinetic studies conducted by classical competition and (or) ESR spectroscopic methods (1, 15) and by time-resolved laser flash photolysis methods (13) have revealed Arrhenius parameters, especially typical log(A) values of 11.0–14.0, which closely parallel those of the β-(phosphatoxy)alkyl radical rearrangements, thereby strongly suggesting an analogous rate-determining fragmentation followed by an extremely rapid collapse to the product

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This paper is dedicated to Professor Ed Piers (UBC) in recognition of his many valuable contributions to organic chemistry.

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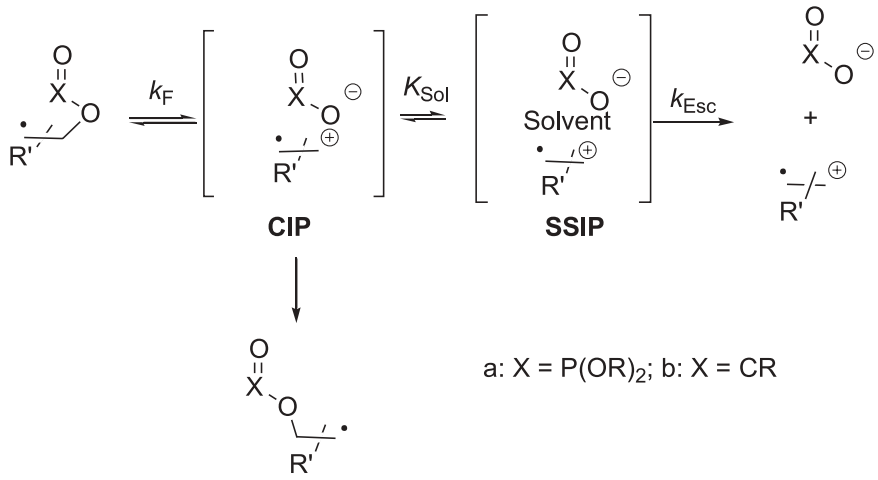
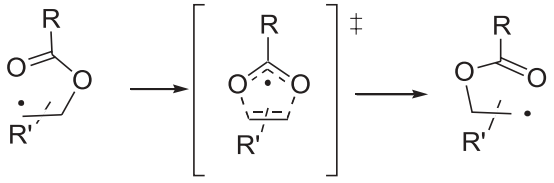
Scheme 1. The fragmentation–recombination mechanism for the rearrangement of ester-substituted radicals.



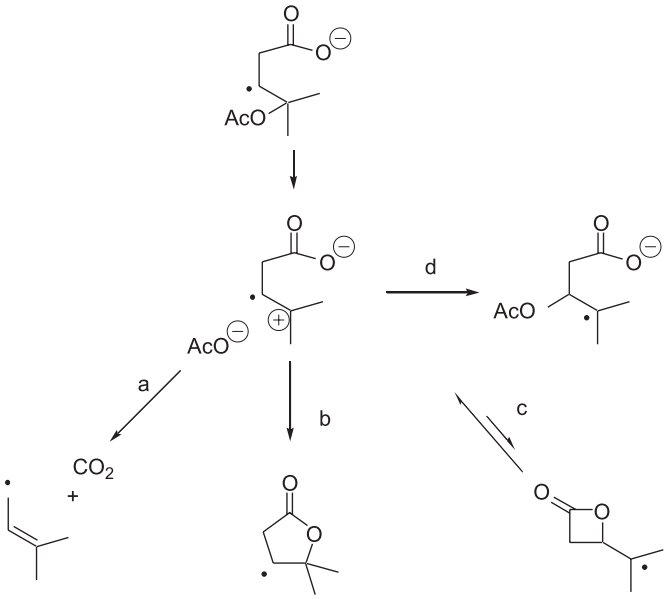
Scheme 2. A concerted mechanism for the [2,3]-rearrangement of β-(acyloxy)alkyl radicals.



radical (Scheme 1, X = CR). In contrast to the phosphates, though, is the failure of several trapping studies to subvert the rearrangement reaction and the lack of any direct observation of the intermediate alkene radical cation in such a mechanism. These apparent inconsistencies may be reconciled with the fragmentation mechanism if it is supposed that the carboxylate anion is much more basic than the diphenylphosphate anion, which leads to an even more rapid collapse of the contact ion pair, with which neither trapping nor cage escape can compete (16–18).[3]

The investigations reported in this paper were spurred by the possibility that carboxylates homoallylic to alkene radical cations might undergo facile decarboxylation (Scheme 3, path a) (19), analogous to the way in which glycine-based aminium radical cations suffer rapid decarboxylation (20, 21). Alternatively, it was considered possible that the radical cation might be trapped in a 5-endo-trig manner to yield γ-lactone-based products (Scheme 3, path b). There also exists the possibility that the alkene radical cation takes part in a 4-exo-cyclization to afford an azetidinone-substituted methyl radical (Scheme 3, path c), but, as these are known to fragment with rate constants of 10^5–10^6 s^{-1} at 80 °C (19), any equilibrium of this kind was expected to favor the open-chain product. Any or all of these processes could possibly divert the initial contact ion pair from collapse to the rearranged radical (Scheme 3, path d) and so potentially provide evidence for the intervention of alkene radical cations in the β-(acyloxy)alkyl radical rearrangement.

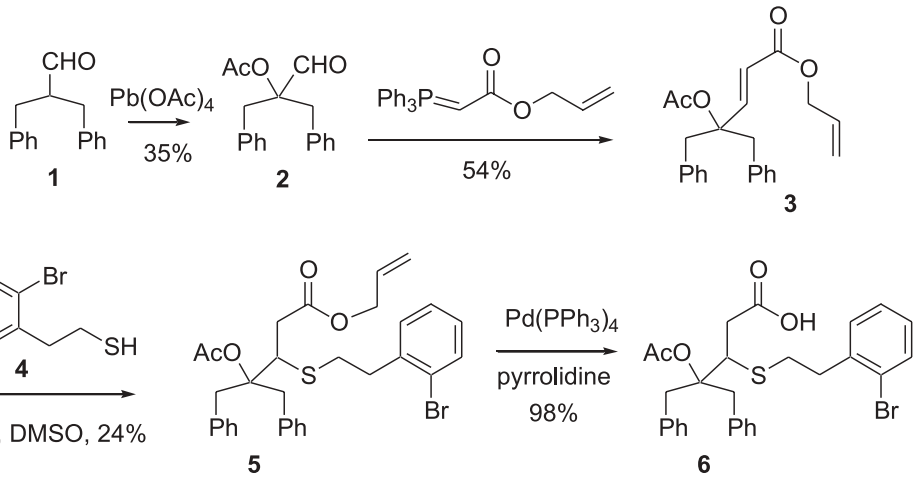
Scheme 3. Possible reaction pathways for carboxy-substituted β-(acyloxy)alkyl radicals.



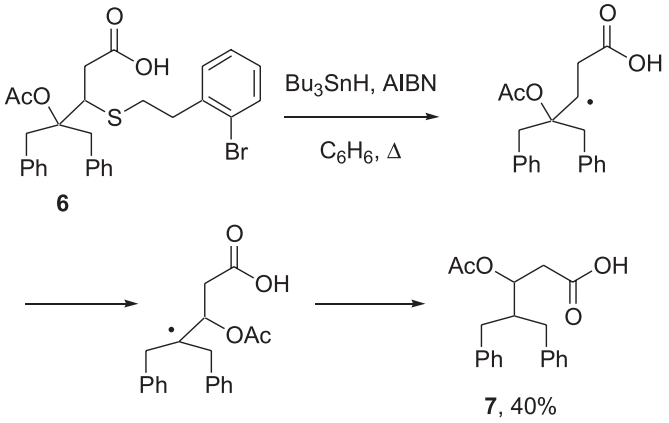
A suitable radical precursor was synthesized, as outlined in Scheme 4, with the main design feature being the use of the 2-(2-bromophenyl)ethanesulfenyl group (22) as a stable radical precursor β to the potentially enolizable carboxylate function. Thus, oxidation of 2-benzyl dihydrocinnamaldehyde **1** with lead tetraacetate afforded the acetoxyaldehyde **2**, which was immediately converted to the allyl ester **3** by Wittig olefination. Conjugate addition of 2-(2-bromophenyl)ethanethiol **4** (23) gave adduct **5** in poor but sufficient yield. Finally, removal of the allyl ester to give the product **6** was achieved with palladium(0) catalysis in the presence of pyrrolidine as nucleophile, the choice of ester and cleavage conditions being dictated by the desire to minimize elimination of the sulfide group.

[3] Against this background of experimental evidence it must be recognized that a series of computational investigations have supported the concerted mechanisms for rearrangement, although the more recent versions admit the possibility of a dissociative mechanism (16–18).

Scheme 4. Synthesis of the radical precursor **6**.



Scheme 5. Rearrangement of **6** to **7**.



Exposure of **6** to tributyltin hydride and benzene at reflux, with initiation by AIBN, afforded the rearrangement product **7** in 40% isolated yield, thereby establishing the viability of the rearrangement in question (Scheme 5, Table 1).

Similar results were obtained (Table 1) when **6** was first converted to its tetrabutylammonium salt before exposure to tributyltin hydride and AIBN in both benzene and THF at reflux. Careful inspection of the ^{1}H NMR spectra of the reaction mixtures in each case did not provide any evidence for the formation of products that may have been anticipated as arising from pathways a, b, and c of Scheme 3. In each case the only discernible products were **7**, arising from the rearrangement and the unreacted substrate **6**. Finally, neutralization of a methanolic solution of **6** with potassium hydroxide followed by azeotroping to dryness, then treatment with tributyltin hydride and AIBN in benzene at reflux also resulted only in the formation of the rearranged product **7** (Table 1). The relatively poor mass balances in some of these reactions are attributed to decomposition on silica gel chromatography, particularly the elimination of acetate from **7**. Under most conditions significant amounts of unreacted substrate **6** remained after prolonged treatment with tributyltin hydride and AIBN. While other explanations are possible, this is most likely symptomatic of the difficulty of sustaining good chain propagation under the dilute conditions employed to minimize the possibility of premature radical trapping by the hydride.

Table 1. Rearrangement of acid **6** and its salts.

Substrate	Solvent	Recovered **6** (%)[a]	Yield **7** (%)[a]
6	Benzene	9	40
6 Bu_4N^+ salt	Benzene	45	35
6 Bu_4N^+ salt	Tetrahydrofuran	49	20
6 K^+ salt	Benzene	0	63

[a]Yields refer to isolated material.

Overall we are driven to the conclusion that in nonpolar solvents the β-acyloxyalkyl rearrangement is either concerted or proceeds via a contact ion pair in which the rate of recombination to give the rearranged radical significantly exceeds that of trapping by intramolecular carboxylates. Given that the rate constant for intermolecular attack of acetate anion on the resonance-stabilized, photochemically generated 4-methoxystyrene radical cation in acetonitrile solution is 4×10^{10} (mol $L^{-1})^{-1}$ s^{-1} (24), it is perhaps not surprising that collapse of the acetate onto the alkene radical cation, within the confines of the putative contact ion pair, out-competes other modes of trapping, even intramolecular.

Experimental part

2-Acetoxy-2-benzyldihydrocinnamaldehyde (2)

To a solution of 2-benzyldihydrocinnamaldehyde **1** (27.1 g, 0.12 mol) and $Pb(OAc)_4$ (58.9 g, 0.13 mol) in benzene (250 mL) was added BF_3OEt_2 (15.3 mL, 0.12 mol) (25). After stirring overnight at room temperature, the reaction mixture was washed with Na_2CO_3 solution and the washings back extracted with Et_2O (100 mL). The combined organic layer was washed with brine and then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure followed by column chromatography on silica gel (eluent: hexane → hexane–EtOAc, 20:1) gave the title product (11.9 g, 35%), which was used immediately in the next step. ^{1}H NMR ($CDCl_3$) δ: 2.11 (s, 3H), 3.16 (d, 2H, J = 8.6 Hz), 3.23 (d, 2H, J = 8.6 Hz), 7.13–7.31 (m, 10H), 9.26 (s, 1H).

^{13}C NMR ($CDCl_3$) δ: 21.5, 40.3, 86.4, 127.5, 128.8, 131.0, 134.8, 171.3, 201.6.

Allyl 4-acetoxy-4-benzyl-5-phenyl-2*E*-pentenoate (3)

To a solution of **2** (12.9 g, 45.7 mmol) in benzene (200 mL) was added (allyloxycarbonylmethylidene)triphenylphosphorane (16.5 g, 45.7 mmol) (26). The mixture was heated to reflux overnight, then cooled to room temperature, diluted with EtOAc, and washed with water and brine, then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure followed by column chromatography on silica gel (eluent: hexane) gave the target product **3** (9.1 g, 54%). ^{1}H NMR ($CDCl_3$) δ: 1.95 (s, 3H), 3.20 (d, 2H, J = 8.3 Hz), 3.63 (d, 2H, J = 8.3 Hz), 4.62–4.64 (m, 2H), 5.23–5.31 (m, 2H), 5.64 (d, 1H, J = 9.5 Hz), 5.86–5.94 (m, 1H), 6.90 (d, 1H, J = 9.5 Hz), 7.10–7.27 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 22.5, 43.4, 65.4, 84.8, 118.4, 120.9, 127.3, 128.5, 131.0, 132.5, 135.7, 150.1, 165.9, 170.7. Anal. calcd. for $C_{23}H_{24}O_4$: C 75.80, H 6.64; found: C 75.96, H 6.69.

Allyl 4-acetoxy-4-benzyl-3-[2-(2-bromophenyl)ethylsulfanyl]-5-phenylpentanoate (5)

To an ice-cooled solution of **3** (4.5 g, 12.3 mmol) and 2-(2-bromophenyl)ethylthiol **4** (23) (2.7 g, 12.3 mmol) in DMSO (20 mL) was added NaH (50 mg, 1.2 mmol). The reaction mixture was stirred overnight at room temperature before it was diluted with CH_2Cl_2, then washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure followed by column chromatography on silica gel (eluent: hexane → hexane–EtOAc, 10:1) gave the thioether **5** (1.7 g, 24% based on 0.52 g recovered starting material). ^{1}H NMR ($CDCl_3$) δ: 1.81–1.87 (m, 1H), 2.05 (s, 3H), 2.21–2.25 (m, 1H), 2.92–3.07 (m, 4H), 3.22 (s, 2H), 3.57(d, 1H, J = 8.5 Hz), 3.71 (d, 1H J = 8.5 Hz), 4.08–4.10 (m, 1H), 4.44–4.49 (m, 2H), 5.14–5.23 (m, 2H), 5.77–5.83 (m, 1H), 7.05–7.54 (m, 14H). ^{13}C NMR ($CDCl_3$) δ: 22.9, 35.3, 37.0, 38.4, 41.1, 41.7, 49.8, 65.6, 89.0, 118.5, 124.8, 127.2, 127.3, 127.9, 128.55, 128.61, 128.67, 131.2 131.4, 132.5, 133.3, 136.9, 137.2, 140.0 171.1, 171.8. Anal. calcd. for $C_{31}H_{33}BrO_4S$: C 64.02, H 5.72; found: C 64.44, H 5.69.

4-Acetoxy-4-benzyl-3-[2-(2-bromophenyl)ethylsulfanyl]-5-phenylpentanoic acid (6)

To an ice-cooled solution of **5** (1.1 g, 1.9 mmol), $Pd(PPh_3)_4$ (55 mg, 0.05 mmol), and PPh_3 (25 mg, 0.1 mmol) in CH_2Cl_2 (50 mL) was added pyrrolidine (1.6 mL). After stirring for 1.5 h at room temperature, the reaction mixture was washed with 1 N HCl, water, and brine, then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure followed by column chromatography on silica gel (eluent: hexane–EtOAc, 5:1 → 1:3) gave the title acid **6** (1.0 g, 98%). ^{1}H NMR ($CDCl_3$) δ: 1.72–1.78 (m, 1H), 2.04 (s, 3H), 2.15–2.20 (m, 1H), 2.96–3.01 (m, 4H), 3.18 (s, 2H), 3.54 (d, 1H, J = 8.5Hz), 3.69 (d, 1H, J = 8.5Hz), 4.01–4.04 (m, 1H), 7.05–7.51 (m, 14H). ^{13}C NMR ($CDCl_3$) δ: 22.9, 35.5, 36.9, 37.9, 41.1, 41.7, 49.5, 89.1, 124.8, 127.3, 127.4, 127.9, 128.6, 128.7, 131.1, 131.4, 133.3, 136.8, 137.1, 139.9, 171.2, 176.7. Anal. calcd. for $C_{28}H_{29}BrO_4S$: C 62.11, H 5.40; found: C 62.33, H 5.40.

3-Acetoxy-4-benzyl-5-phenylpentanoic acid (7)

A solution of Bu_3SnH (59.6 μL, 0.22 mmol) and AIBN (1.5 mg, 9.2 μmol) in benzene (3.1 mL) was added dropwise over 3 h with the aid of a syringe pump to a solution of **6** (100 mg, 0.18 mmol) in benzene (3.1 mL) at reflux under Ar. After heating to reflux for a further 1 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in MeCN (1 mL) and extracted with hexanes (3 × 3 mL). The acetonitrile layer was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: hexane–EtOAc, 2:1) to afford **7** (24.1 mg, 40%) ^{1}H NMR ($CDCl_3$) δ: 1.96 (s, 3H), 2.42–2.46 (m, 1H), 2.55–2.71 (m, 6H), 5.23–5.26 (m, 1H), 7.07–7.30 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 21.3, 36.3, 36.6, 45.4, 71.8, 126.6, 126.7, 128.8, 128.9, 129.33, 129.39, 140.1, 140.3, 170.8, 175.6: ESI-HR-MS calcd. for $C_{20}H_{22}NaO_4$: 349.1416; found: 349.1428 ($[M + Na]^+$).

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