Scheme 2.

nism, probably by oxygen molecules under a strong acidic condition, we examined products formed in the reaction mixture at certain time intervals after treatment of sulfuric acid. The reaction was stopped by diluting the reaction mixture with water followed by extraction with ethyl acetate to give phenolic compounds. The aqueous layer was neutralized with $Ba(OH)_2$, filtered and evaporated to give compound 9[7] as a major intermediate. From this experiment, we found that isophorone was oxidized very fast to 7 and 8, and further to 9. Phenols and intermediate 9 were isolated by column chromatography in 40% and 56% yields, respectively after the reaction was stopped in 1 min and in this reaction mixture no isophorone was left at all. Also, all the aromatization processes were found to occur almost spontaneously under the strong acidic condition except the rearrangement of 9 to 11, which might be slowed down due to the formation of an intramolecular hydrogen bond of the hydroxyl groups. This transformation was proceeded slowly but terminated completely by addition of water. Also, oxidative rearrangement of 4-hydroxyisophorone (7) was very fast to produce 10, or 13 and 14. Product 10 was rearranged immediately to 12. Oxidation of silyl enol ether of isophorone to 6-hydroxyisophorone was reported[4c]. The multiple oxidation of 6 or 7 under a strong acidic condition has not been reported to our knowledge and it is interesting to observe the oxidative aromatization of isophorone and 4-hydroxyisophorone.

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7. Phenols 2, 3, 4, 5, 13 and 14 were identified by comparison with authentic samples; **12**: mp. 110-114℃, ¹H-NMR (CDCl₃), δ, 2.09 (s, 3H), 2.21 (s, 6H), 6.51 (s, 1H); **11**: mp. 210℃ (dec.), ¹H-NMR (CDCl₃): δ, 2.21 (s, 3H), 2.23(s, 3H), 4.08(s, 2H), 6.55 (d, J=3.2 Hz), 6.71 (d, J=3.2 Hz); M⁺: m/z 152; **9**: mp. 258℃ (dec.), ¹H-NMR, δ, 1.05 (s, 3H), 1.37 (s, 3H), 2.35 (d, 1H, J=17 Hz), 3.26 (dd, 1H, J=17 & 2 Hz), 3.30 (s, 1H), 3.68 (s, 2H), 6.89 (d, 1H, J=2 Hz).

Formation of Deoxybenzoins and β-Keto Sulfides by the Reaction of α-Stabilized Anion of Phosphonates with Nitriles

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In the course of our research program toward the preparation of various β-keto phosphonates using nitriles as an acyl cation equivalent[1], we have partly found that the reaction of α-lithio anion of phosphonate bearing a phenyl or thiophenyl substituent on a carbon to the phosphorus function with nitriles gives deoxybenzoins or β-keto sulfides as by-products during hydrolysis. From this observation, we report here the nucleophilic addition of an α-stabilized anion of phosphonates to nitriles and subsequent basic hydrolysis to afford deoxybenzoins[2] or β-keto sulfides in good yield.

A general reaction procedure is as follows: To a stirred solution of phosphonate (1 mmol) in dry THF (5 m*l*) is added *n*-butyllithium (1.1 mmol, 1.6 M in hexane) at −78℃ under nitrogen atmosphere. After being stirred for 1 h at same temperature, nitrile (1 mmol) is added and the reaction mixture is warmed to room temperature. After being stirred for additional 2 h, the mixture is added 5 N-NaOH solution (1 m*l*) and stirred for 2 h at room temperature. Normal work up gives the deoxybenzoin or β-keto sulfide, which is purified by Kugelrohr distillation or recrystallization (ethyl acetate).

Scheme 1.

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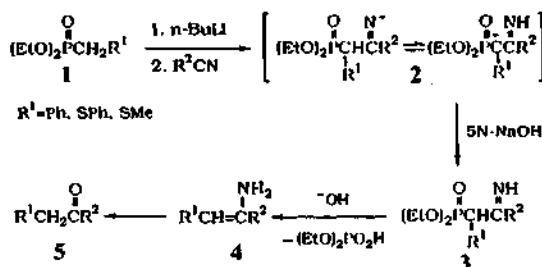
Table 1. Formation of Deoxybenzoins and β-keto Sulfides (5)[a]

Run	R^1	R^2	Isolated yields, %[a]	Mp. or bp. °C/torr Found	Mp. or bp. °C/torr Lit.
1	Ph	Ph	92	54-55	55-56.5[2]
2	Ph	4-MeC₆H₄	83	108-110	108.5-110[2]
3	Ph	2-MeC₆H₄	32	153-156/0.5	150-155/0.5[7]
4	Ph	4-ClC₆H₄	85	106-107	105-107[2]
5	PhS	Ph	50	53-54	53-54[8]
6	PhS	4-MeC₆H₄	60	58-60	59-60[8]
7	PhS	Ph	90	103-108/2	100-104/2[9]
8	MeS	4-MeC₆H₄	85	122-125/2	120-125/2[9]
9	Me	Ph	–	–	–

[a]The hydrolysis was normally completed within 2 h at room temperature. [b]The numbers indicate purified yield after crystallization or distillation (Kugelrohr) and all products had identical spectral properties with reported data.

As shown in Scheme 1. phosphonate 1 is deprotonated by n-butyllithium to form an α-lithio anion of phosphonate within 1 h at −78°C, which reacts with aromatic nitrile to form a ketimine intermediate 2. The direct treatment of a ketimine intermediate 2 with 5 N-NaOH solution gives the deoxybenzoin or β-keto sulfide 5 in good yield within 2 h. The present reaction is assumed to proceed through the enamine intermediate 4 which is formed by attack of hydroxide anion on the phosphoryl P-atom of 3.

There is also other possibility of the mechanism involving attack of the hydroxide ion on the imino carbon atom of the ketimine intermediate, the hydrated intermediate then undergoing an intramolecular Horner-Emmons type reaction.

As shown in Table 1, the reaction works well with aromatic nitriles. In the case of nitriles bearing an α-hydrogen dimerized products (α-cyano ketones) were obtained as a major product, as previously reported by Sumrell[3].

α-Lithio anion of phosphonates derived from benzyl-, thiophenyl-, and thiomethyl phosphonates react with aromatic nitriles to give ketones, generally, in good yield. However, under identical conditions, α-lithio anion derived from ethyl phosphonate is able to bring about little conversion of nitrile to ketone (Run 9). Instead corresponding β-keto phosphonate is obtained. Thus it appears to be of fundamental importance that the only anion of phosphonate stabilized at the α-position reacts with nitrile to give ketone, which is in accord with the fact that efficient Wittig elimination can only be brought about if the intermediate is activated at the α-position to the phosphorus atom by an electron-withdrawing group[4]. On the other hand, the hydrolysis is carried out with 5 N-NaOH solution within 2 h. The hydrolysis using H₂SO₄ solution also can be carried out, but requires longer reaction time for completion (12 h with 5 N-H₂SO₄).

Deoxybenzoins[5] and β-keto sulfides[6] are well recognized in organic synthesis as a versatile precursors of a large number of interesting organic compounds.

In conclusion, the present method, which uses phosphonates, is mechanistically interesting and practical in terms of increased reactivity, easy separation of products, and readily available starting materials.

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Stereochemistry of Substitution in the Reaction of 1-Phenylethyl Benzenesulfonates with Anilines

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In our studies on the nucleophilic substitution reactions of 1-phenylethyl benzenesulfonates (1-PEB) with anilines,[1] we proposed involvement of a four-center transition state (TS), TS_f in Scheme 1, based on the unusually large cross interaction between substituents X in the nucleophile and Z in the leaving group (LG) with a large magnitude of ρ_{XZ},[1]
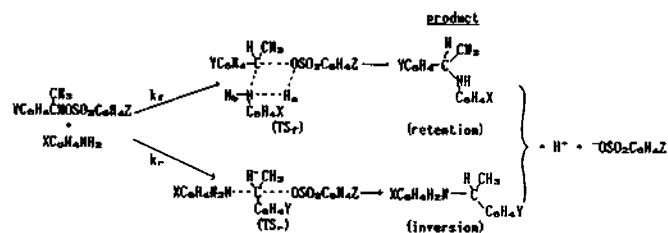
Scheme 1.

defined in equation (1).[3]

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \tag{1}$$

In the four-center TS (TS_f) substituents X and Z can interact via two routes, an extra interaction route being provided by hydrogen bonding of an amine hydrogen (H_a) toward the oxygen atom in the LG. We report here the results of our stereochemical studies providing direct evidence for the in-