The solvent was evaporated to yield (*Z*)-2,3-diphenyl-1-butenal (**7a**) (^{1}H NMR). No *E* isomer **7b** was found. A quantitative experiment performed in CH_3OD in the ^{1}H NMR spectrometer showed an 80% conversion to the *Z* isomer.

Photolysis of 4,5-Epoxy-3,5-diphenyl-3-methyl-1-pyrazoline (1b) in PhH. A 132.3-mg portion of (0.529 mmol) of epoxide **1b** was dissolved in 2 mL of benzene. Six 300-μL portions were placed in individual NMR tubes. One of the tubes was kept in the refrigerator while the other five tubes were photolyzed at 5 °C using a sunlamp. One tube was removed every hour and kept in the refrigerator. ^{1}H NMR analysis of each tube showed two products appearing in a 2:1 ratio. In ppm downfield from the epoxide CH_3 (which occurs 0.30-ppm downfield from cyclohexane), the two products appeared at 0.37 (3 H), 8.83 (1 H), and 0.20 (3 H), 8.23 (1 H), respectively. The contents of each tube were evaporated, dissolved in CCl_4, and analyzed by ^{1}H NMR. In ppm downfield from the epoxide CH_3 (δ 1.83 ppm), the two products appear at 0.60 (3 H), 8.70 (1 H), and 0.46 (3 H), 7.95 (1 H), respectively. The integrals showed a 90% conversion to these two products.

The tubes were combined and the solution was heated at 85 °C for 1 h. ^{1}H NMR showed a small amount of the thermolysis products (see above). In addition, about half of the major photolysis product had disappeared with a corresponding increase in the minor photoproduct.

The PhH was evaporated, the residue was dissolved in 5:1 hexane–CCl_4, and the solution was put in the freezer. A yellow impure precipitate was formed: mp 95–96 °C; UV (hexane) 268 nm (ϵ 16 600); IR (CCl_4) 2820, 1710, 1650, 1450, 1370, 1250, 870 cm^{-1}: ^{1}H NMR (CCl_4) δ 2.30 (s, 3), 7.2–7.5 (m, 9), 7.6–7.8 (m, 2), 9.80 (s, 1); MS (70 eV) *m/e* 250 (p, 2), 221 (4), 119 (100), 104 (100), 77 (100), 51 (47). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.63; N, 11.20. Found: C, 77.42; H, 5.85; N, 10.74.

Irradiations in CD_3CN showed similar results with formation of the same two photoproducts. In all cases, comparison of the ^{1}H NMR's of the irradiated solutions with ^{1}H NMR's of aldehydes **6a,b** and dypnones **7a,b** showed the latter four compounds were not present (<10%). Control experiments showed that both the aldehydes and dypnones were stable to the reaction conditions.

Registry No.—**1a**, 54541-36-5; **1b**, 63904-61-0; **2**, 22675-60-1; **3**, 63904-62-1; **4a**, 63904-63-2; **6a**, 22573-24-6; **6a** *anti*-hydrazine, 63904-64-3; **6a** *syn*-hydrazone, 63904-65-4; **6b**, 54435-79-9; **7a**, 63904-66-5; **7b**, 63904-67-6; **8a**, 60728-10-1; **8b**, 60728-09-8; **10a**, 63904-68-7; **10b**, 63904-69-8; acetophenone, 98-86-2; tosylhydrazide, 1576-35-8; 1,2-diphenylpropan-2-ol, 5342-87-0; (*E*)-1,2-diphenylpropene, 833-81-8; (*R,*R**)-1,2-diphenyl-1,2-dibromopropane, 63904-70-1; (*R*S*)-1,2-diphenyl-1,2-dibromopropane, 63904-71-2; bromine, 7726-95-6; (*E*)-1-bromo-1,2-diphenyl-1-propene, 63904-72-3; (*Z*)-1-bromo-1,2-diphenyl-1-propene, 63904-73-4; (*E*)-2,3-diphenyl-2-buten-1-ol, 63904-74-5; (*Z*)-2,3-diphenyl-2-buten-1-ol, 22641-64-1.

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Phenylacetone Dianion: Alkylation with Iodomethane[1]

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The alkylation products of the phenylacetone dianion have been examined. It has been shown that the alkylation is nonregioselective, carbon–carbon bond formation taking place at either the α or α′ position. Both the ease of formation of the dianion and the monoalkylation product ratio are affected by the metal ions present. Methylation at the terminal position does not predominate in any case examined.

In recent years carbon–carbon bond formation by means of dianion alkylation has become an increasingly important synthetic tool.[3] Although such reactions have most frequently involved β-dicarbonyl compounds,[3a] carboxylic acids,[3b] β-keto sulfones[3c] and imides[3d] have also proven useful. With each of these precursors the dianion alkylation is normally regioselective, carbon–carbon bond formation taking place at the position from which the second proton has been removed. This observation has been succinctly summarized in the generalization that "the more basic (and less stable) enolates usually react more readily with alkylating agents".[4] Versatility is thus available, since regioselective alkylation can be accomplished in a predictable fashion using either monoanion or dianion alkylation procedures; the position of alkylation is normally well defined and different with each method.

Of course it is well known that many factors contribute to the relative rates and regioselectivity of alkylation of enolate anions. Among these considerations are charge densities,[5] steric interactions in the transition state, solvent, metal ion effects,[6] and the principle of least motion.[7] All of these contribute to the relative nucleophilicity observed for separate enolate anions or for differing positions on the same dianion. Despite these other factors, however, dianion alkylation regioselectivity has generally been successfully predicted simply on the basis of relative pK_a values.

In 1967 Hauser reported[8] that the combination of a phenyl

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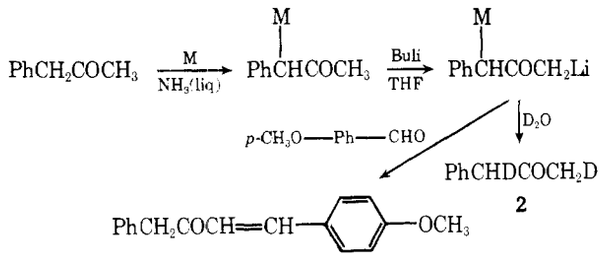
Table I. Product Distribution for the Reaction:[a]

$$C_6H_5CH_2COCH_3 \xrightarrow[3.\ MeI]{1.\ Base\ A;\ 2.\ Base\ B;\ 4.\ H_3O^+}$$

Rxn	Reactants: Base A	Base B	MeI, equiv	Yield, %[b]	Product Distribution, %: Phenylacetone	3-phenyl-2-butanone (8)	1-phenyl-2-butanone (9)	2-phenyl-3-pentanone (10)
1	NaH	BuLi	1	80	22	40	31	7
2	NaH	LDIPA	1	84	92	3	4	
3	NaH	LDIPA + BuLi	1	70	45	25	27	
4	KH	BuLi	Excess	91		3	4	93
5	KH	BuLi	1	91	1	43	56	1

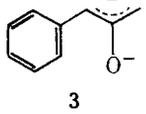
[a] All reactions utilized anhydrous THF as solvent. [b] The cited yield includes all products and recovered starting material ($PhCH_2COCH_3$ + 8 + 9 + 10).

Scheme I



group and a ketone provides sufficient activation for dianion formation, the specific example being phenylacetone (Scheme I). Evidence cited for the intermediacy of the dianion was the condensation reaction with anisaldehyde to give the linearly conjugated unsaturated ketone **1** and deuteration with D_2O to give the 1,3-dideuteriophenylacetone (**2**). This report came to our attention since, in connection with another synthetic problem, it became necessary to make compounds which are derived, in principle, by alkylation at the terminal positions of phenylacetone and its derivatives.

The difference in acidity for protons at the two positions flanking the carbonyl in phenylacetone has recently been reported to be 7.2 pK units.[9] Based on this rather substantial difference, it would seem reasonable to predict regioselective alkylation at the more basic terminal position, analogous to the dianions derived from β-dicarbonyls. On the other hand, to the extent that the dianion can be formulated as **3**, it might



3

be more appropriate to take the kinetically controlled protonation of the cinnamyl anion as the analogy,[10] in which case a nonregioselective alkylation would be predicted.

The work reported by Hauser (Scheme I) does not shed light on the problem, suffering from three major criticisms. First, the condensation product **1** is identical to that obtained from the equilibrium-controlled condensations of the enolate.[11] In contrast, the kinetically controlled alkylation of the enolate occurs almost exclusively at the methylene position.[12] Although it has been shown that enolate condensation occurs exclusively and steroselectively at the methylene position under conditions in which the kinetically controlled product is trapped by zinc ion,[13] condensation product **1** would probably be formed from the enolate under the reported reaction conditions and therefore its isolation does not unambiguously demonstrate the intermediacy of the dianion, nor does it speak unequivocally to the question of dianion reaction regioselectivity.

The second criticism involves the irreproducability of the deuteration experiment in our hands. Instead of the regioselective incorporation of two deuteriums to give **2**, we routinely observe polydeuteration. This proton exchange is not surprising in light of the reported alkylation of phenylacetone in the presence of aqueous base.[12c]

Finally, Hauser reports that the dianion derived from the sodium enolate (M = Na in Scheme I) is bright red, while that derived from the lithium enolate is yellow. Although, as we shall demonstrate, the counterion greatly affects the ease of dianion formation and its reactivity, it is surprising that the absorbance maximum is so dramatically shifted. Although this may appear to be a trival point, we believe it to indicate, based upon our results, that the dilithio dianion was not formed as reported. This observation makes the condensation and deuteration results all the more ambiguous.

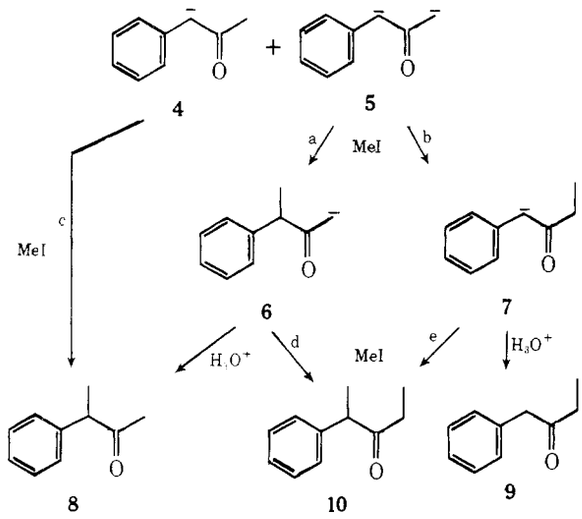
For all of these reasons, we have embarked on a study of the phenylacetone dianion. We have initially chosen to examine the alkylation reaction of the dianion, both because this was ultimately our synthetic goal and because alkylation is not an equilibrium-controlled process, thus avoiding the ambiguities described above.

Results and Discussion

The principle results of this study are summarized in Table I. We have chosen to form the enolates in anhydrous THF rather than in liquid ammonia as previously described (Scheme I). These enolates have then been deprotonated in THF using a slight excess of n-butyllithium. Iodomethane (MeI) has been used as the alkylating agent in all cases. Product analysis has involved a combination of two gas chromatographic systems[14] and NMR spectral analysis of both crude reaction mixtures and preparatively purified products.

Treatment of the sodium enolate of phenylacetone—formed by reaction of the ketone with excess sodium hydride—with a slight excess of n-butyllithium gives the bright, rust-red solution reported by Hauser. Upon alkylation with 1 equiv of MeI, followed by protonation of the resulting enolates, the mixture of products shown as reaction 1 in Table I is obtained. Although 71% of the volatile product mixture is

Scheme II



monoalkylated, both dialkylated [2-phenyl-3-pentanone (**10**)] (7%) and unalkylated (22%) material are present. Furthermore, there are two monoalkylated products, alkylation having occurred at either the methylene position of the original phenylacetone to give 3-phenyl-2-butanone (**8**) (40%) or at the methyl position to give 1-phenyl-2-butanone (**9**) (31%).

These observations can be interpreted in several ways, as illustrated in Scheme II. The fact that starting material is recovered from the reaction leads us to believe that the conversion from enolate **4** to dianion **5** is not complete; that is, that there is enolate present in the dianionic solution. Intuitively one would predict that the dianion **5** would be more reactive than the enolate **4** toward methyl iodide, an expectation which is experimentally demonstrable, as we shall discuss presently. Thus, it would be anticipated that, upon addition of 1 equiv of MeI, the dianion would react regioselectively by pathway a or b, or nonregioselectively by pathways a and b to initially give monoanions **6** and/or **7**. Competition between these enolates (**4**, **6**, and/or **7**) for the residual MeI leads directly to monoalkylated product **8** and dialkylated product **10**. Since there is not sufficient MeI present in the reaction mixture, alkylation will not be complete and protonation of the mixture with water will give rise to monoalkylated products **8** and **9** (from **6** and **7**, respectively) and the recovery of starting material (by protonation of **4**). The relative amounts of the various products will, of course, reflect the relative rates of the alkylation processes. Clearly, because of the assumptions required for the interpretation of the data, this experiment does not elucidate the chemistry of the phenylacetone dianion.

Clarification of the situation requires either that a method be found for distinguishing between reactions of the mono- and dianion, or, alternatively, that a technique be found for assuring total conversion of the enolate to the dianion. Reactions 2–5 (Table I) demonstrate solutions involving both of these alternatives.

The recovery of starting material from reaction 2, in which lithium diisopropylamide (LDIPA) was used as the second base, demonstrates two points crucial to the following discussion: (1) that LDIPA is not a sufficiently strong base to deprotonate the sodium enolate of phenylacetone to give the dianion, and (2) that LDIPA is a much better nucleophile than the sodium enolate, effectively scavenging the alkylating agent. The first point is not surprising since House has routinely used excess LDIPA for the stereoselective formation of the *cis*-enolate of phenylacetone.[15] In no instance has he reported reactions which suggest a dianion intermediate. The second point is confirmed by the presence of methyldiisopropylamine in an acid extract of the reaction mixture.[16] Thus, an order of relative nucleophilicities has been established which potentially allows the masking of enolate reactions in the presence of LDIPA. The technique is illustrated in the following experiment.

In reaction 3 (Table I) the sodium enolate is deprotonated by *n*-butyllithium in the presence of LDIPA. Upon alkylation with MeI, the LDIPA effectively scavenges excess alkylating agent thereby eliminating the ambiguities introduced by enolate competition in reaction 1 (pathways c, d, and e of Scheme I). The result is a simplified product mixture in which there is no dialkylated phenylacetone (**10**) and both monoalkylated products **8** and **9** must be derived from the dianion.

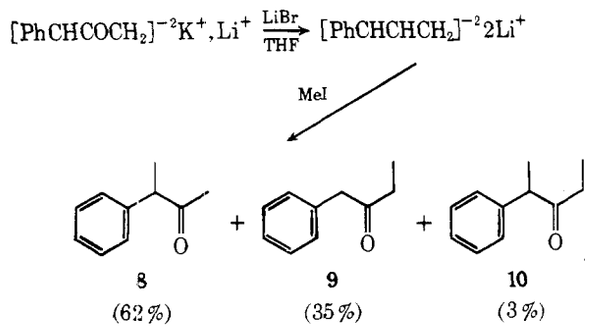
The product mixture demonstrates that the alkylation is totally nonregioselective, giving rise to equal amounts of α and α' alkylation (**8** and **9**, respectively). We have examined this reaction many times under a variety of conditions. Although the ratio of nonalkylated to alkylated products may vary depending upon the reaction conditions, the ratio of the two monoalkylated products is always 1:1. It is, in fact, possible to simply titrate the solution of the dianion with MeI, using as an indicator the disappearance of the red color; even in this crude experiment a 1:1 ratio of monalkylated products (**8**:**9**) is observed. No products have been isolated from any of our experiments which suggest ring alkylation. Furthermore, when starting from the sodium enolate, we have never observed alkylation to exceed 65–70%, at least 30% of the product mixture constituting recovered starting material. Our conclusions are that the sodium enolate is not totally deprotonated by *n*-butyllithium and that the dianion, when formed, is equally reactive at both positions flanking the carbonyl.

The situation is somewhat different in the case of the potassium enolate, formed by reaction of the ketone with potassium hydride. As illustrated in reactions 4 and 5 (Table I), the enolate is rapidly, and apparently completely, converted to the dianion by *n*-butyllithium even at 0 °C. Upon treatment with excess MeI (reaction 4) this dianion is alkylated at both the terminal and the methylene positions to give **10** in high yield. With 1 equiv of MeI, the reaction is again nonregioselective (reaction 5), although there is a slight, reproducible preference for terminal alkylation (1.3:1).

Clearly, when the dianion is formed by alkyllithium deprotonation of either the sodium or potassium enolate, there are two different associated counterions. It has been well established[17] that the counterion is an important factor, affecting both the reactivity and regioselectivity of enolate alkylations. This has been attributed to the degree of association of the ion pair; whereas lithium associates relatively tightly, particularly with the oxygen of the enolate, the potassium–enolate ion-pair association is relatively weak. These considerations lead to some uncertainty in the interpretation of our results, since it is not clear how the two different counterions are associated with the dianion. This could be resolved if the dianion were formed under conditions such that the two counterions were identical.

To date, all efforts to achieve the direct formation of the dilithio dianion of phenylacetone have failed. These attempts have included: (1) reaction of the ketone with 2–3 equiv of LDIPA, (2) *n*-butyllithium deprotonation of the lithium enolate, formed by reaction of the ketone with LDIPA, and (3) *n*-butyllithium or *tert*-butyllithium deprotonation of the lithium enolate, formed by methyllithium displacement of the trimethylsilyl enol ether.[15] In all cases, the expected deep-red color was faint or absent, and upon alkylation with limited MeI only phenylacetone was recovered. Apparently, in each case the dianion was not formed and the residual strong base effectively scavenged the alkylating reagent. These observations contradict the results reported by Hauser (Scheme I) and

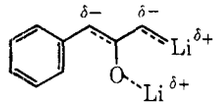
Scheme III



it is our belief that he did not form the dilithio dianion from the lithium enolate. Condensation product **1** probably arises from the enolate rather than from the dianion in that system.

Since the direct route to the dilithio dianion seemed fruitless, we have taken an indirect approach. This is outlined in Scheme III and is based upon the observation[18] that potassium enolates are rapidly and quantitatively transmetalated to give lithium enolates in the presence of anhydrous lithium bromide in THF. Thus, the potassiolithio dianion, formed as described in reactions 4 and 5 (Table I), was treated with 2–10 equiv of anhydrous lithium bromide prior to addition of the alkylating agent. This resulted in rapid formation of a precipitate, presumably potassium bromide. Upon alkylation, the ratio of monoalkylated products was dramatically affected, preference being shown for alkylation at the methylene position (**8**:**9** = 1.5–1.8:1).

This result can be rationalized by considering the dianion to be tightly associated with its counterions, perhaps as in **11**.



11

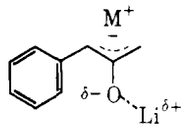
This species would be expected to alkylate preferentially at the methylene position, on the basis of analogy with the lithium enolates.[17] However, it is not clear that the transmetallation has gone to completion; the presence of residual potassiolithio dianion in the mixture will skew the results in favor of terminal alkylation. It does seem reasonable to say, on the basis of these observations, that the alkylation preference is at the methylene position for the dilithio dianion.

Conclusions

In contrast to the dianions derived from β-dicarbonyls, the phenylacetone dianion is not alkylated regioselectively. This observation is also counter to predictions based solely upon pK_a considerations, demonstrating once again that the generalized relationship between pK_a and nucleophilicity, sometimes promolgated to and amongst our students, is highly imperfect. We are presently in the process of investigating the steric and electronic effects on this system and those results will be reported at a later date.

We are also in the process of investigating the rather puzzling order of enolate reactivity toward *n*-butyllithium deprotonation. We have shown that, whereas the lithium enolate is unreactive, the potassium enolate is rapidly and completely deprotonated at 0 °C to form the dianion. The sodium enolate exhibits intermediate reactivity, being deprotonated sluggishly and negligibly at 0 °C, but to the extent of about 65% in 15 min at room temperature.[19] One possible rationale for these observations is based on the report that *n*-butyllithium is transmetalated by sodium or potassium *tert*-butoxide to form lithium *tert*-butoxide and *n*-butylsodium or *n*-butylpotassium.[20] In our system the enolate salt may serve as the transmetalating agent, producing the lithium enolate and the strongly basic metal alkyl. These bases are apparently sufficiently strong to deprotonate the highly coordinated lithium enolate, though the deprotonation does not go to completion in the sodium system as evidenced by the alkylation results. On the other hand, with the lithium enolate, no transmetalation can take place to give a stronger base, and apparently *n*-butyllithium itself does not deprotonate the monoanion. Although this is an attractive rationalization for the observed phenomena, experimental substantiation is presently unavailable.

It is clear that the counterions have a significant effect on the alkylation process. If one pictures the dianion as shown in **12**, these observations can be rationalized in terms of the



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degree of association of the dianion with its counterions. Based upon a mechanism of formation involving the previously postulated transmetalation, we have proposed that the lithium ion is coordinated with the oxygen. The other counterion may then be associated with the second negative charge which is delocalized in the carbon side chain. When this counterion is potassium, that portion of the molecule is most "naked", in agreement with the recently reported ^{13}C NMR analysis of the enolates.[21] In this relatively bare state, there is a slight preference for alkylation at the terminal position. On the other hand, when the second counterion is lithium, the ion pair is expected to be highly associated, perhaps as shown in **11**. This leads to alkylation preference at the methylene. The intermediate associative capacity of the sodium ion is reflected in the totally nonregioselective alkylation of the sodiolithio dianion.

Experimental Section

All syringes and reaction vessels were carefully washed and oven dried prior to use. Reaction flasks were equipped with rubber septums and cooled under a nitrogen atmosphere which was maintained throughout the course of the reaction. The solvent used in each reaction was THF which had been freshly distilled from $LiAlH_4$ under a nitrogen atmosphere. Unless otherwise specified, all solvent and reagent additions and solution transfers were performed by means of syringes. Alkyllithium reagents (*n*-butyllithium in hexane, ca. 2.25 M; methyllithium in ether, ca. 1.8 M; and *tert*-butyllithium in pentane, ca. 1.8 M) were obtained from Alpha Inorganics and were standardized by titration[22] prior to use. Phenylacetone and 1-phenyl-2-butanone (**9**) were obtained from Aldrich Chemical Co. Authentic samples of the alkylated products **8** and **10** were prepared by iodomethane alkylation of the sodium enolates of phenylacetone and **9**, respectively.[12b,23]

Product analyses were carried out using NMR spectra and GLC. We have found it necessary to utilize two GLC systems.[14] Both columns have been calibrated with standard mixtures of dodecane (internal standard) and ketones. For the DC-710 column, which was used for overall yield determinations, the detector response ratio was found to be 1.2 (dodecane/ketone). The data from both columns were used to determine product distributions. For example, whereas the dialkylated product **10** is not separable from the monoalkylated product **9** on the DC-710 silicone oil column, it is cleanly separated on the Carbowax column. On the other hand, **10** and phenylacetone have the same retention time on the Carbowax column.[24] It has therefore been necessary to examine retention times and relative peak areas for all product mixtures on both chromatographic systems and to analyze the preparatively purified products on both columns as well as spectrally (NMR). In all cases product structural assignments have been confirmed both by GLC retention times and by the characteristic NMR spectra. For some relatively simple, two or three component mixtures, it has been possible to assign product distributions on the basis of NMR spectra and GLC analysis of the mixture. In representative cases these assignments have been completely confirmed by preparative separation.

Following are the NMR spectral data for each of the four major reaction products: phenylacetone ($CDCl_3$) δ 2.09 (s, 3), 3.64 (s, 2), 7.28 (s, 5); 3-phenyl-2-butanone (**8**) ($CDCl_3$) δ 1.39 (d, 3), 2.01 (s, 3), 3.74 (q, 1), 7.29 (s, 5); 1-phenyl-2-butanone (**9**) ($CDCl_3$) δ 1.00 (t, 3), 2.44 (q, 2), 3.65 (s, 2), 7.26 (s, 5); 2-phenyl-3-pentanone (**10**) ($CDCl_3$) δ 0.95 (t, 3), 1.38 (d, 3), 2.35 (q, 2), 3.75 (q, 1), 7.27 (s, 5).

The Potassiolithio Dianion. (A) Monoalkylation. A large excess of KH (5 g, 18 mM) as a 22% dispersion in oil was weighed into a 50-mL three-necked flask. The KH was washed three times with pentane to remove the mineral oil. It was then suspended by stirring in 10 mL of anhydrous THF, and a mixture of 2.008 g of phenylacetone (15.0 mM) and 1.0100 g of dodecane (internal GLC standard) in 5 mL of THF was slowly added from a pressure-equalized addition funnel. When hydrogen evolution had ceased (20–30 min) the mixture was allowed to stand until the excess KH had settled, and the resulting enolate solution was transferred to a 100-mL three-necked flask. The residual KH was washed with two 5-mL portions of THF and these washes were combined with the enolate solution. Standardized *n*-butyllithium solution in hexane (16.9 mM) (7.5 mL) was added at room temperature and the resulting rust-red dianion solution was allowed to stir for 15 min.

The mixture was cooled in an ice bath and 0.95 mL of MeI (15.3 mM) in 10 mL of THF was added from a pressure-equalized addition funnel with vigorous stirring. After 5–10 min, the resulting yellow mixture was acidified with dilute acid and diluted with ether. The ether phase was extracted with two portions of dilute acid and the resulting aqueous phase was back-extracted with two portions of ether. The combined organic extract was dried (Na_2SO_4) and the solvent removed in vacuo at 25 °C. The residue was dissolved in 10.0 mL of $CHCl_3$ for gas chromatographic analysis.

Based on dodecane as the internal standard a 91% yield was obtained (phenylacetone + alkylated products). The product distribution was: phenylacetone (<1%), 1-phenyl-2-butanone (**9**) (56%), and 3-phenyl-2-butanone (**8**) (43%). (See reaction 5, Table I.)

(B) Dialkylation. The cooled rust-red solution of the dianion, prepared as described above, was transferred to a cooled flask containing 5 mL of MeI (81 mM) in 15 mL of THF. After 5–10 min, the resulting solution was diluted with water and ether. The ether phase was washed twice with dilute acid, the combined aqueous extracts were back-extracted with two portions of ether, and the combined organic phase was dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was dissolved in 10.0 mL of $CHCl_3$ for gas chromatographic analysis.

The product yield was 91% (phenylacetone + alkylated products). The mixture contained: 2-phenyl-3-pentanone (**10**) (93%), 3-phenyl-2-butanone (**8**) (3%), and 1-phenyl-2-butanone (**9**) (4%). (See reaction 4, Table I.)

The Sodiolithio Dianion. (A) Unmasked Reaction. An excess of NaH (2.0 g, 42 mM) as a 50% dispersion in oil was weighed into a 100-mL three-necked flask. The NaH was washed two times with pentane to remove the mineral oil and was then suspended in 5 mL of THF. To this suspension was slowly added 5.001 g of phenylacetone (37.3 mM) and 1.510 g of dodecane (GLC internal standard) in 15 mL of THF from a pressure-equalized addition funnel. In order to maintain reasonable hydrogen evolution, the addition was carried out slowly and the reaction was cooled in an ice bath. When addition was complete, the reaction mixture was stirred at room temperature for 15 min or until hydrogen evolution had ceased. It was then allowed to stand at room temperature until the excess NaH had settled; this usually required 1–2 h, although it was sometimes left overnight. The resulting enolate solution was transferred to a clean dry flask and the NaH washed with two portions of THF.

To the yellow enolate solution was added 38 mM (16.8 mL) *n*-butyllithium solution in hexane. This mixture was allowed to stir for 15 min after which it was cooled in an ice bath and 2.3 mL (37 mM) of MeI in 10 mL of THF was added with vigorous stirring. After 5–10 min, the reaction was acidified and extracted as previously described for the potassiolithio system.

Based on dodecane, the yield was 80%. The following product distribution was obtained: phenylacetone (22%), 3-phenyl-2-butanone (**8**) (40%), 1-phenyl-2-butanone (**9**) (31%), and 2-phenyl-3-pentanone (**10**) (7%). (See reaction I, Table I.)

(B) Masking of the Enolate with LDIPA. The sodium enolate was prepared as described above using 5.016 g of phenylacetone (37.4 mM), 2.016 g of dodecane, and 2.0 g of NaH (42 mM). Prior to separation of the enolate solution from residual NaH, 6.0 mL (42.6 mM) of diisopropylamine (DIPA) was added. When the NaH had settled this solution was transferred to another flask and the NaH washed with two portions of THF. To this enolate solution was added 40 mM (17.8 mL) *n*-butyllithium in hexane; the mixture was allowed to stir for 15 min at room temperature, and was then cooled in an ice bath. Iodomethane (2.3 mL, 37 mM) in 10 mL of THF was added to the vigorously stirred solution. After 5–10 min, the reaction was acidified, extracted, and analyzed as previously described.

Based on internal standard, the yield was 84%, with the following product distribution: phenylacetone (92%), 3-phenyl-2-butanone (**8**) (3%), and 1-phenyl-2-butanone (**9**) (4%). (See reaction 2, Table I.)

The acidic aqueous phase from the extractions of this reaction was made basic with sodium hydroxide and extracted three times with ether. After drying (Na_2SO_4), the organic solvent was partially removed and the residue subjected to GLC analysis and preparative separation.[16] The predominant product was methyldiisopropylamine,[25] present as 60–70% of the acid-soluble material. The structure assignment is based on the characteristic NMR spectrum and upon comparison of the GLC retention time (4 min) with that of an authentic sample, synthesized by methylation of DIPA with MeI: NMR ($CDCl_3$) δ 1.01 (d, 12), 2.13 (s, 3), 2.91 (septet, 2).

(C) Masking of the Enolate with LDIPA in the Presence of Dianion. The enolate was formed as described above using 5.0220 g of phenylacetone (37.5 mM), 1.0130 g of dodecane, and 2.1 g of NaH (44 mM). After hydrogen evolution had ceased, 5.3 mL (37.5 mM) of DIPA was added and the mixture was allowed to stand at room temperature until the residual NaH had settled. After transfer of the enolate–DIPA solution to a clean flask with the usual washing of the residual NaH, 78 mM (34.7 mL) *n*-butyllithium in hexane was added at room temperature. After stirring for 15 min, the mixture was cooled in an ice bath and 2.4 mL of MeI (38.6 mM) in 10 mL of THF was added with vigorous stirring. This was followed after 5 to 10 min by acidification and extraction in the usual fashion.

Based on dodecane, a product yield of 60% was realized. The following products were present: phenylacetone (45%), 2-phenyl-3-butanone (**8**) (25%), 1-phenyl-2-butanone (**9**) (27%), and unidentified products (3%). (See reaction 3, Table I.)

Dilithio Dianion. (A) Direct Method. Into a clean, dry 100-mL three-necked flask was placed 3.009 g (14.6 mM) of the *trans*-trimethylsilyl enol ether of phenylacetone,[15] 1.020 g of dodecane (internal GLC standard), and a few milligrams of bipyridyl which serves as an alkyllithium indicator. To this solution was added 15 mM (8.4 mL) methyllithium in ether. The resulting mixture was allowed to stir at room temperature for 15 min, and additional methyllithium was added as necessary to maintain an excess, as judged by the purple color of the indicator. To this solution was added 16 mM (7.2 mL) *n*-butyllithium and the mixture was stirred for an additional 15 min at room temperature. It was then cooled in an ice bath and 0.91 mL (14.7 mM) of MeI was added in 5.0 mL of THF with vigorous stirring. After 5–10 min, the resulting reaction mixture was acidified and extracted in the previously described manner. GLC analysis showed only one volatile product, phenylacetone, isolated in 93% yield.

Identical results were obtained using *tert*-butyllithium as the second base, or with 2 equiv of LDIPA. In none of these instances was alkylation of the phenylacetone observed.

(B) Indirect Method. The potassiolithio dianion was formed as previously described using 4.1 g of KH (22.5 mM), 2.047 g of phenylacetone (15.3 mM), 1.012 g of dodecane (internal GLC standard), and 15.75 mM (7 mL) *n*-butyllithium. To this solution was added 2.5 g (29 mM) of anhydrous LiBr (Alpha Inorganics) in 15 mL of THF. (The LiBr solution had been previously treated with *n*-butyllithium using bipyridyl as indicator to assure that no water was present.) Immediately a precipitate formed. The mixture was stirred for 15 min at room temperature and then cooled in an ice bath. To the cold, vigorously stirred solution was added 0.95 mL of MeI (15.2 mM) (1 equiv). A portion (15 mL) of the resulting reaction mixture was transferred to 3 mL of MeI (48 mM) in 15 mL of THF. After 5–10 min, both reactions were acidified and extracted as previously described.

For the portion of the reaction treated with excess MeI, analysis of the mixture demonstrated the following product distribution (80% yield): 3-phenyl-2-butanone (**8**) (4%), 1-phenyl-2-butanone (**9**) (11%), and 2-phenyl-3-pentanone (**10**) (85%).

For that portion of the reaction treated with only 1 equiv of MeI, the product analysis was as follows (70% yield): 2-phenyl-3-butanone (**10**) (3%), 3-phenyl-2-butanone (**8**) (62%), 1-phenyl-2-butanone (**9**) (35%).

For a reaction utilizing 10 equiv of lithium bromide, the product analysis was essentially the same, with the ratio of **8**:**9** decreasing from 1.8:1 to 1.5:1.

Registry No.—Iodomethane, 74-88-4; potassiolithio phenylacetone, 63866-06-8; sodiolithio phenylacetone, 63866-07-9; sodium phenylacetone enolate, 61674-95-1; dilithio phenylacetone, 63866-04-6.

Reference and Notes

(1) (a) This research has been supported by Grant GM20368 from the National Institutes of Health. (b) This work was presented in preliminary form at the 173rd National Meeting of the American Chemical Society in New Orleans, March 22, 1977.
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Perfluoroacetylenic Ethers[1]

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The first examples of perfluoroacetylenic ethers, $CF_3C{\equiv}COCF_3$ and $CF_3C{\equiv}COCF_2CF_2CF_3$, were synthesized via several routes starting with $CF_3CCl{=}CCl_2$. They homopolymerize at room temperature and have been copolymerized with other perfluoro monomers.

In the course of our work on fluorocarbon polymers the need arose to investigate perfluoroalkoxyacetylenes, a hitherto unknown class of compounds. As a starting point for their synthesis we chose $CF_3CCl{=}CCl_2$, a commercially available material,[2] which can be readily converted to $CF_3C{\equiv}CZnCl$ by zinc dust in dimethylacetamide.[3] Halogenation of this species[4] yielded $CF_3C{\equiv}CCl$ (**1**) and $CF_3C{\equiv}CBr$ (**2**), respectively, which have been made before less conveniently or in lower yields[5–7] by other routes. The IR and Raman spectra of both **1** and **2** have been reported,[8,9] as has the microwave spectrum of **1**.[10]

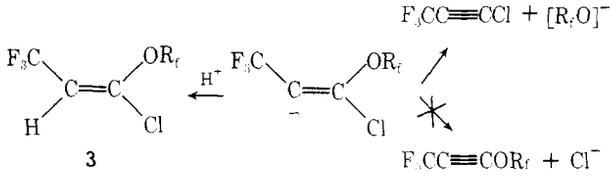
$$F_3CCCl{=}CCl_2 \xrightarrow[DMAC]{Zn} F_3CC{\equiv}CZnCl \xrightarrow{X_2} F_3CC{\equiv}CX$$

1, X = Cl
2, X = Br

Despite the reported high-yield replacement of Cl^- in **1** by $(F_3C)_3C^-$,[11] the direct halide replacement by R_fO^- in **1** or **2** did not appear very promising because of the known poor nucleophilicity of R_fO^- and the equilibrium[12]

$$R_fCF_2O^- \rightleftharpoons R_fCFO + F^-$$

Furthermore, in view of the established mode of trans addition to acetylenes[13,14] and, hence, also of trans elimination, the intermediate vinylic carbanion would be expected to eliminate R_fO^- rather than Cl^-. On the other hand, conducting the reaction in the presence of a proton source should trap the carbanion and give rise to the perfluoroalkoxy vinyl ether (**3**).



3

Indeed, when I was treated with "$AgOCF_3$", made in situ from AgF, COF_2, and HF in adiponitrile, compound **3**, bp 49–50 °C, was obtained in about 45% yield. There was no evidence for CF_3O^- addition to the 2 position. Compound **3** was a single isomer, identified as trans (H, OCF_3) by NMR spectroscopy. Treatment with strong base under drastic conditions converted it only to **1** (Scheme I). Irradiation in the presence of a trace of bromine converted **3** to a 50:50 cis/trans mixture. This mixture, upon being passed through soda lime at 210 °C, yielded both **1** and $CF_3C{\equiv}COCF_3$ (**4**), although in low yields and conversions thus confirming the trans elimination mechanism, though not providing a convenient synthetic path to **4**.

Compound **3** was readily converted to the dibromo derivative **5**, which evolved bromine during distillation at atmospheric pressure, but which could be distilled undecomposed in vacuo. Triethylamine converted **5** cleanly to a cis/trans mixture of **6**. No dehydrochlorination was observed.

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