# Reactions of Substituted 5,5-Di(R)(Ar)-2-cyclohexenones. I. SN2 and SN2′ Reactions of 4-Bromoisophorone

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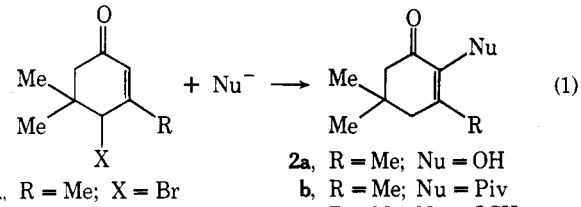
The reactions of 4-bromoisophorone (**1a**) with pivalate (Piv) salts in various solvents were studied. With AgPiv in HPiv, the nonconjugated SN2′ product, 2-pivaloxy-3,5,5-trimethyl-3-cyclohexenone, was obtained (25%). With KPiv in HPiv, 25% of **1a** reacted to give the reconjugated SN2′ product, 2-pivaloxyisophorone (**2b**). In DMF a 29% yield of **2b** and a 71% yield of the direct SN2 product, 4-pivaloxyisophorone (**1b**), were obtained; phenols were not formed. This was the first unequivocal instance of an uncatalyzed SN2 reaction of **1a**. A qualitative kinetic study with added triethylamine negated the intermediacy of a carbanion for the formation of this mixture of **1b** and **2b**. The absence of solvolysis products in the presence of a trace of base precludes a role for a solvent-separated ion pair. A negative salt effect opens to question the need to invoke a tight ion pair. The formation of **2b** may be consistent with a classical SN2′ mechanism. It is suggested that reactions of **1a** with strong bases such as $HO^-$, $RO^-$, and $ArO^-$ which give $C_2$ substitution products and phenols may proceed through a carbanion intermediate. Under these conditions no $C_4$ substitution is observed. Furthermore, reactions of **1a** with soft bases such as $I^-$, $ArS^-$, and $ArSO_2^-$ may proceed initially by displacement on Br to give the $C_4$ carbanion.

Recently[1,2] 4-bromoisophorone (**1a**) was reported to react with nucleophiles to give 2-substituted 2-cyclohexenones (eq 1). It was asserted that these products were



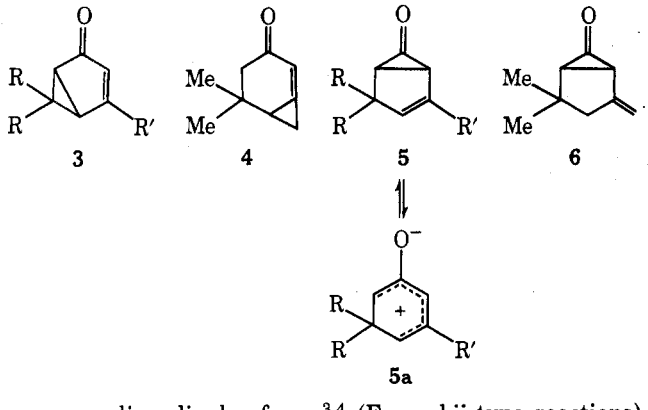
(1)

**1a**, R = Me; X = Br
b. R = Me; X = $OCOC(CH_3)_3$(Piv)
c. R = Me; X = OH
d. R = Ph; X = Br

**2a**, R = Me; Nu = OH
**b**, R = Me; Nu = Piv
**c**, R = Me; Nu = $OCH_3$
**d**, R = Ph; Nu = Piv

$Nu^-$ = $OH^-$, $I^-$, 3,4,5- and 2,3,5-trimethylphenoxide, $ArS^{2-}$, $ArSO_2^{2-}$

formed by an SN2′ mechanism. However, this conclusion is equivocal because other mechanisms were overlooked. For example, a strong base such as $OH^-$ could abstract a proton from $C_6$ or $C_3$ $CH_3$ and the resulting carbanion could then undergo an intramolecular displacement of $Br^-$ to give any of several cyclopropyl intermediates (**3–5**) or their



**3** **4** **5** **6**

**5a**

corresponding dipolar forms[3,4] (Favorskii-type reactions). These intermediates could aromatize to phenols and/or bond with nucleophiles at $C_2$ to give SN2′-like products such as **2a**. Nucleophilic attack is more likely at $C_2$ than at the more sterically hindered $C_4$ and $C_6$ positions. Intermediate **3** (R = R′ = $CH_3$) was postulated by Kosower and Wu[3] for the formation of phenols from the reaction of 6-chloroisophorone with $N(CH_3)_3$ and $Ag^+$. Zimmerman and Epling[4] implicated **5a** (R = Ph; R′ = H) in the formation of phenols during the reaction of 6-bromo-5,5-diphenyl-2-cyclohexenone with KO-*t*-Bu in *t*-BuOH. It is noteworthy that in neither case was $C_2$ substitution observed, possibly because sterically hindered bases were used. Structure **4** was postulated as an intermediate in the formation of 3,4,5-trimethylphenol from the reaction of 3-chloromethyl-5,5-dimethyl-2-cyclohexenone with triethylamine.[3] A cyclopropanone intermediate **6** similar to **5**, was suggested by Fort[5] in the reaction of 6-tosyloxyisophorone with methoxide ion. In this case, **2c**, 6-methoxyisophorone, and methyl trimethylcyclopentenecarboxylate were identified.

The aforementioned base-induced carbanion mechanisms are precluded in the reaction of **1a** with $I^-$. However **1a** has all of the structural requirements suggested by Jarvis and Saukaites[6] for a soft base[7] to displace on bromine, namely, a sterically hindered carbon and an ability to form a stabilized carbanion. The carbanion could react with the resulting IBr or $I_2$ at $C_2$ to give the observed product. $\alpha,\beta$-Unsaturated enolates react with electrophiles such as $H^+$ and RX[8] at the $\alpha$ carbon, giving an unconjugated product isomerizable to the more stable conjugated isomer. This same type of reaction could account for the formation of $C_2$ substituted products when the soft nucleophiles $ArS^-$ and $ArSO_2^-$ reacted with **1a**.[2b]

In an attempt to look for an unambiguous SN2′ reaction, we chose the pivalate (Piv) anion as the nucleophile because it is (a) not soft and therefore will not displace on Br, (b) a weak Brønsted base and therefore less likely to form carbanions easily, and (c) bulky and less likely to undergo direct SN2 attack at $C_4$.

## Results and Discussion

When **1a** was treated with potassium pivalate (KPiv) in pivalic acid (HPiv), the only product isolated was 2-pivaloxyisophorone (**2b**) in 25% yield (Table I, expt 1); 75% of **1a** was unreacted. However, in the aprotic solvent dimethylformamide (DMF), a 29% yield of **2b** was obtained along with a 71% yield of 4-pivaloxyisophorone (**1b**), the direct substitution product (Table I, expt 2). In hexamethylphosphoramide (HMPA) only **1b** was detected (Table I, expt 3). *These are the first substantiated instances of an uncatalyzed formation of a $C_4$ substitution product from* **1a**. With silver pivalate (AgPiv) in pivalic acid a 10% yield of

† Taken from the Ph.D. Thesis of S. J. Jasne, City University of New York, 1973.

Table I
Reactions of 4-Bromoisophorone with Nucleophiles[a]

| Expt | Reactants (equiv) | Solvent | Product(s) (yield, %) |
|---|---|---|---|
| 1 | KPiv (1.3) | $Me_3CCOOH$ | 2-Pivaloxyisophorone (2b, 25) |
| 2 | KPiv (1.3) | DMF | 2b (29), 4-pivaloxyisophorone (1b, 71) |
| 3 | KPiv | HMPA | 1b (95) |
| 4 | AgPiv | $Me_3CCOOH$ | 2b (10), 1a (65), 2-pivaloxy-3,5,5-trimethylcyclohex-3-enone (7a, 25) |
| 5[b] | KPiv | DMF | 5,5-Dimethyl-3-phenyl-2-pivaloxycyclohex-2-enone (>90) |
| 6 | KPiv (1.3), $Et_3N$ (1.3) | DMF | 2b (29), 1b (71) |
| 7[c] | AgPiv (1.3), AgPiv (1.3) | $Me_3CCOOH$ | No reaction |
| 8[c] | KPiv (1.3), KBr (1.3) | DMF | No reaction |
| 9 | KPiv (1.3), $KClO_4$ (1.3) | HMPA | 2b (20), 1b (80) |
| 10 | KPiv (1.3) | Dioxane–$H_2O$ (1:1) | 2b (8), 1a (92) |

[a] 45°, 40.5 hr. [b] Substrate was 5,5-dimethyl-3-phenyl-4-bromocyclohex-2-enone. [c] Substrate was 1b.

2b and a 25% yield of the nonconjugated isomer 2-pivaloxy-3,5,5-trimethyl-3-cyclohexenone (7a) were obtained (Table I, expt 4). It is noteworthy that in none of these four reactions of 1a were phenols formed. The structure of 2b was proven by direct synthesis from 2-hydroxyisophorone (2a), pivalic acid, and trifluoroacetic anhydride. Compound 1b was similarly prepared from the corresponding alcohol 1c. Although 7a was not isolated as an analytically pure sample, its spectral data were consistent with the assigned structure, and in addition it rearranges exclusively to 2b in the presence of base and with KPiv in DMF.

Since pivalate anion may be sufficiently basic to form carbanions, it was necessary to examine whether intermediates 3–5 could be precursors for the $C_2$ substitution products, the so-called SN2′ products. The formation of 4 requires the removal of a proton from the $C_3$ $CH_3$ group of 1a. Since 1d, with a phenyl group instead of a $CH_3$ group at $C_3$, also afforded the SN2′-type product, 2d (Table I, expt 5), 4 is *not* a required intermediate for the formation of 2b.

Elimination of mechanisms initiated by carbanion formation at $C_6$ was more circuitous. Experiment 1 (Table I) is complicated by the possibility that the enol of 1a, formed from the $C_6$ carbanion, could be the substrate undergoing the displacement reaction, possibly by pivalolysis, to give 2b. We studied deuterium exchange of 1a using NaPiv in pivalic acid-*O*-*d*. NMR and mass spectral analysis showed that no more than a 5–6% exchange of deuterium in recovered 1a occurred at $C_4$, $C_6$, $C_2$, and $C_3$ $CH_3$. The percentage of exchange at each position was much less than the percent yield of 2b (25%). However, these data do not permit the drawing of an unequivocal conclusion about the intermediacy of a carbanion in the formation of 2b under these conditions. The data are consistent with a carbanion *not* being an intermediate; the mechanism of deuterium exchange could be independent of the mechanism for formation of 2b. Yet a carbanion could be a common intermediate for the H–D exchange and displacement reactions, if its return to deuterated 1a is slower than the steps leading to the formation of 2b. Although Bordwell[9a] ruled out this latter possibility in the Favorskii reaction of $ArCH_2COCH_2Cl$ and $ArCHClCOCH_3$ with $CH_3O^-$ in $CH_3OH$ because of the low concentration of enol in the strongly basic medium, it could be significant in our system because pivalate is a weaker base than methoxide and pivalic acid is a stronger acid than methanol. However, the observation of some deuterium exchange definitely mitigates against a concerted loss of H and Br[9a] during the displacement reactions.

The enol should not be a significant intermediate in expt 2 (Table I) because DMF is an aprotic solvent. This reaction is therefore better for studying whether the formation of 2b proceeds by a concerted SN2′ reaction or whether it requires the initial formation of a carbanion. Our premise was that the rate of any reaction initiated by carbanion formation should be increased by the addition of a supplementary base. Reactions not proceeding through a carbanion should be insensitive to the added base. In expt 2 (Table I) the added base should have no affect on the formation of 1b, which likely arises by direct SN2 displacement at $C_4$. If 2b arose via a carbanion, its rate of formation should be augmented by added base. If the foregoing situation prevails, the addition of triethylamine should alter the product distribution of 1b and 2b. Even if 1b and 2b were to arise from a common carbanion intermediate, the rates of their formation should increase on the addition of triethylamine.

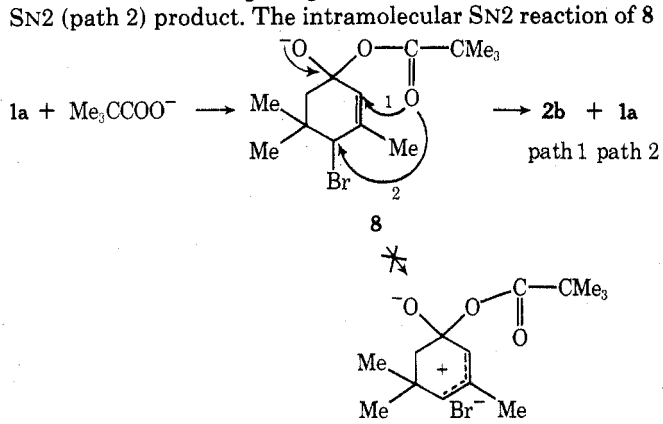
Identical reactions were run, treating 1a with KPiv, in DMF, except that 1.3 equiv of triethylamine was added to one of the reactions (Table I, expt 2 and 6). NMR analysis of aliquots taken periodically from the reaction mixture revealed that added base had no effect on either the product distribution or the rate of formation of these products. The relative amounts of 1b and unreacted 1a were determined by comparing the ratio of the areas of the $C_2$ vinylic (ca. $\delta$ 5.8 ppm) and the $C_4$ CHX protons of 1b (X = Piv, $\delta$ 5.48 ppm) and 1a (X = Br, $\delta$ 4.43 ppm). The relative yields of $C_2$ substitution products were usually determined by the differences in the expected as compared to the observed integration of the $C_3$ methyl, $C_4$ and $C_6$ methylene groups ($\delta$ 1.8–2.8), and the *gem*-dimethyl region ($\delta$ 0.8–1.3). Similar types of NMR analyses were done for all reactions in Table I. Apparently 1b and 2b do not arise from a C-6 carbanion. This conclusion is reinforced by the observation that the reaction of KPiv with 1a in HMPA, which gave only $C_4$ substitution product, also showed no product or rate change with added triethylamine.

Since Bordwell[9b] has criticized earlier assignments of SN2′ mechanisms because they did not consider one or more of the following pathways, (1) SN1, (2) SN2 followed by an SNi′, (3) SNi′ followed by an SN2, we addressed ourselves to these possibilities. Attempted ethanolysis of 1a afforded only 3,4,5-trimethylphenol. However, this is an auto-acid-catalyzed reaction, since with a trace of 2,6-lutidine no reaction occurs even at ten times the normal reaction time. In addition, no reaction occurs in dioxane–water

(1:1 v/v) or in HPiv. The lack of solvolysis rules out an SN1 mechanism and any mechanism proceeding through an intermediate solvent-separated ion pair. In typical allylic systems such as α- and γ-methylallyl chloride, SNi′ reactions proceed through tight ion pairs and are always accompanied by solvolysis.[10] Hence the absence of solvolysis products also precludes the SNi′–SN2 pathway for rearrangement of **1a** to 2-bromo-3,5,5-trimethylcyclohex-3-enone (**7b**). It should be noted that a $C_4$ carbonium ion is a vinylog of one α to a carbonyl group and would have a high energy.[11a,b] The SN2–SNi′ pathway involves initial formation of the $C_4$ direct substitution product followed by an internal allylic rearrangement. This pathway is untenable because **1b** is stable under the reaction conditions (Table I, expt 7 and 8).

To determine whether a tight ion pair precedes nucleophilic attack on $C_2$ and $C_4$, we looked for a positive salt effect as observed by Bordwell.[12] Whereas **1a** with KPiv in HMPA (Table I, expt 3) gave only **1b**, the addition of 1.3 equiv of $KClO_4$ gave 80% **1b** and 20% **2b** (Table I, expt 9) but at an overall *decrease* in rate of disappearance of **1a**. In the absence of $KClO_4$ the reaction was complete in 2.5 hr. With the salt in the same period of time 50% of **1a** was unreacted. This negative salt effect for the rate of formation of **1b** is expected for an SN2 reaction *not* proceeding through an ion pair.[12] Sneen[10] showed that competitive SN2 and SN2′ reactions follow from equilibrating intermediate tight ion pairs. Our system would be exceptional if the SN2 reaction proceeds from an un-ionized substrate while the SN2′ reaction occurs through a tight ion pair. It is more likely that *neither the SN2 nor SN2′ products arise from the intermediate tight ion pair of* **1a**. The yield of **2b** could increase on adding $KClO_4$ if the rate of formation of **1b** is decreased more than is the rate of formation of **2b**.

Since $C_4$ is adjacent to a quaternary carbon ($C_5$) the facile nucleophilic displacement leading to **1b** (in HMPA, 2.5 hr at 45°) is extraordinary. Rather than the displacements occurring directly on **1a**, it is possible that **8**, formed by attack of Piv on the carbonyl carbon, may be an intermediate.[13] **8** could rearrange to give either the SN2′ (path 1) or SN2 (path 2) product. The intramolecular SN2 reaction of **8**




would not be sterically hindered by the $C_5$ *gem*-dimethyl groups as would an intermolecular SN2 reaction. The intermediate **8** would not undergo an SN1-type reaction because no solvolysis products, e.g., Table I, expt 10, or phenols are obtained.

However, one argument against **8** being a *common* intermediate for **1b** and **2b** is the variation in product distribution on changing the solvent or on adding $KClO_4$ (Table I, expt 2, 3, 9). The validity of the intermediacy **8** is being tested by reacting **1a** with hard weakly basic anions which are incapable of bridging to $C_4$ from the carbonyl carbon.

In our hands the reaction of **1a** with $I^-$ in $Me_2SO$ gave, in addition to iodinated products, about 25% of isophorone recovered by preparative thick layer chromatography. This substantiates our suggestion that **1a** can react with soft nucleophiles by displacement on bromine. Markley[2] isolated only isophorone and ethyl disulfide when **1a** was treated with sodium ethylthiolate.

## Conclusion

The several routes whereby **1a** can react with nucleophiles can be sorted out in terms of the distribution of products. Hard, moderate to strong bases such as $OH^-$, $RO^-$, and $R_3N$ can initiate carbanion formation and displacement can then proceed through intermediates **3**, **4**, and/or **5**. Phenol formation always accompanies these pathways. We have not ruled out the possibility that some of these bases also react with **1a** directly at $C_2$. No $C_4$ substitution products occur from these intermediates. The absence of phenols in our reactions with pivalate anion argues against these pathways. With soft nucleophiles such as $I^-$ displacement could occur initially at Br, giving only substitution at $C_2$, no phenolic products, and isophorone as a possible side product. With a hard, weakly basic nucleophile such as Piv in aprotic solvents, both direct SN2 and SN2′ reactions can occur giving $C_4$ and $C_2$ substituted products, respectively. In protic solvents only attack at $C_2$ occurs. In these cases phenols and isophorone do not form. The directly formed SN2′ product does not arise from a solvent separated ion pair because no solvolysis products are obtained.[10] The observance of a negative salt effect opens to question whether even a tight ion pair must be invoked. This reaction may indeed be of the concerted SN2′ type. More work is underway to test this hypothesis.

## Experimental Section

Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York, N.Y. Melting points were determined using a Thomas-Hoover apparatus, in open capillary tubes, and are corrected; boiling points are uncorrected. Mass spectra were determined using a Varian CH5 mass spectrometer at 70 eV under direct sample inlet conditions and logarithmic mass scan. Infrared spectra were determined using a Perkin-Elmer 137 spectrophotometer and a Beckman IR 20A spectrophotometer. Absorption maxima are expressed in reciprocal centimeters. Proton magnetic resonance spectra were determined using a Varian A-60 spectrometer and a Jeolco C-60HL spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane (δ 0).

**Preparation of 4-Bromoisophorone (1a).**[14] Methylene chloride was substituted for carbon tetrachloride as the solvent. **1a** had mp 49.5–50.2° (lit.[14] mp 48–49.5°); NMR ($CDCl_3$) δ 5.66 (t, $J$ = 1 Hz, 1 H, C=CH), 4.40 (d, $J$ = 1 Hz, 1 H, CHBr), 2.37 (AB pattern, 2 H, $CH_2$), 2.13 (d, $J$ = 1 Hz, 3 H, C=$CCH_3$), 1.30 (s, 3 H, $CH_3$), 1.22 (s, 3 H, $CH_3$); ir ($CHCl_3$ solution) 1675 (s, ketone).

**Preparation of 3,5,5-Trimethylcyclohex-3-enone (7c).** 4-Bromoisophorone (**1a**, 32.5 g, 0.15 mol) was added to 300 ml of 95% ethanol in a 500-ml flask fitted with a reflux condenser, drying tube, and mechanical stirrer. Zinc dust (65 g, 1 mol) was added and the reaction mixture was stirred rapidly for 14.5 hr at 41–45°. The reaction mixture was suction filtered and the solid was washed with 100 ml of diethyl ether which was combined with the filtrate and concentrated under reduced pressure at room temperature. The resulting solution was placed under a nitrogen atmosphere and stored in the freezer (4°). Fractional vacuum distillation gave cut 1, bp 34–37° (1.8 Torr); cut 2, bp >40° (2 Torr). A rough NMR analysis indicated that cut 1 contained the desired product contaminated with isophorone. There appeared to be a significant amount of liquid collected in the Dry Ice–acetone vacuum trap. Analysis of this material by NMR showed it to be mainly **7c** contaminated with ethanol. Diethyl ether (200 ml) was added to the material collected from the trap and this solution was extracted with three 200-ml portions of water, dried over $MgSO_4$, and concentrated at reduced pressure at room temperature. The resulting liquid was added to the material from cut 1 to yield a total of 4.78 g (23.1%) of **7c** [lit.[15] bp ca 70° (10 Torr)]; NMR ($CDCl_3$) δ 5.42 (broad, 1 H, C=CH), 2.65 (s, 2 H, C=$CCH_2$), 2.23 (s, 2 H, $CH_2$), 1.68 (d, $J$ = 1 Hz, 3 H, C=$CCH_3$), 1.00 (s, 6 H, 2-$CH_3$); ir (neat) 1735 $cm^{-1}$ (s, ketone).

**Preparation of 3-Oxido-3,5,5-trimethylcyclohexanone.** 3.5.5-Trimethylcyclohex-3-enone (**7c**, 0.50 g, 3.56 mmol) was dissolved in chloroform (10 ml) and placed in a three-neck 25-ml flask fitted with a condenser, drying tube, and magnetic stirrer. Solid *m*-chloroperbenzoic acid (0.77 g, 3.8 mmol) was added in small portions to the stirred solution over an 8-min period. Chloroform (2 ml) was used to wash some solid from the side of the flask into the solution. The reaction mixture was stirred for 15 min and then allowed to stand for 70 min. The white solid, *m*-chlorobenzoic acid, was suction filtered. The filtrate was concentrated under reduced pressure at room temperature, yielding a white solid which was partially dissolved upon the addition of 10 ml of petroleum ether (bp 30–60°). The resulting solid was suction filtered and a second crop of crystals was suction filtered from the solution. The solution was concentrated under reduced pressure at room temperature to yield a colorless liquid which was used as is, immediately, for the following reaction: NMR ($CDCl_3$) $\delta$ 2.88 (s, 1 H, epoxy H), 2.67 (s, 1 H, epoxy CH), 2.60 (s, 1 H, epoxy CH), 2.13 (AB pattern, 2 H, $H_2C$–C=O), 1.38 (s, 3 H, epoxy $CH_3$), 1.17 (s, 3 H, $CH_3$), 1.03 (s, 3 H, $CH_3$); ir (neat) 1740 $cm^{-1}$ (s, ketone).

**Preparation of 4-Hydroxyisophorone (1c).** The 3-oxido-3,5,5-trimethylcyclohexanone obtained from the above reaction was dissolved in 2 ml of diethyl ether and 2 ml of distilled water in a 10-ml flask fitted with a condenser, magnetic stirrer, and drying tube. The pH of the solution was brought to between 11 and 12 by the dropwise addition of 10% sodium hydroxide. The mixture was stirred at this pH, at room temperature, for 5.7 hr and diethyl ether was added when necessary to maintain a constant volume. The layers were separated and the ethereal solution was washed with two 10-ml portions of a saturated sodium chloride solution and dried over $MgSO_4$. The sodium hydroxide layer was extracted with two 15-ml portions of ether which were dried over $MgSO_4$, added to the previously recovered ethereal solution, and concentrated under reduced pressure at room temperature to yield 0.272 g (48%) of **1c**: NMR ($CDCl_3$) $\delta$ 5.87 (broad, 1 H, C=CH), 4.37 (broad, 1 H, OH), 4.03 (broad, 1 H, HCO), 2.32 (AB pattern, 2 H, $H_2C$–), 2.06 (broad s, 3 H, C=$CCH_3$), 1.08 (s, 3 H, $CH_3$), 1.03 (s, 3 H, $CH_3$); ir (neat) 3400 (m, hydroxy group), 1670 (s, conjugated ketone).

**Preparation of 4-Pivaloxyisophorone (1b). Method A.** Crude 4-hydroxyisophorone (**1c**, 1.0 g, 6.6 mmol) and 10 ml of trifluoroacetic anhydride were placed in a 25-ml flask fitted with a condenser and magnetic stirrer. Pivalic acid (0.663 g, 6.6 mmol) was added and the reaction flask was stoppered lightly. After being stirred for 4 hr at room temperature the reaction mixture was diluted with 20 ml of benzene. The organic layer was then extracted with three 20-ml portions of 10% sodium hydroxide and two 20-ml portions of a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature to yield 0.928 g of a yellow oil. This oil was divided into two parts and placed on two 20 × 20 cm thick layer silica gel chromatography plates, activated for ca. 15 min at 100°. After development in 1,2-dichloroethane three bands were observed. The silica gel between $R_f$ 0.28 and 0.31 was scraped from the plates and the organic material was extracted from the adsorbent by addition of two 50-ml portions of acetone. The combined acetone solutions were concentrated under reduced pressure at room temperature to yield 0.472 g (27.8%) of **1b**: NMR ($CDCl_3$) $\delta$ 5.75 (broad, 1 H, C=CH), 5.48 (broad, 1 H, HCO), 2.33 (s, 2 H, $CH_2$), 1.87 (t, $J$ = 1 Hz, 3 H, C=$CCH_3$), 1.27 [s, 9 H, $C(CH_3)_3$], 1.02 (s, 6 H, 2-$CH_3$); ir (neat) 1740 (s, ester), 1680 (s, conjugated ketone); mass spectrum *m/e* (rel intensity) 239 (7.4), 238 (47), 192 (15), 164 (56), 149 (15), 147 (16), 146 (16), 122 (14), 118 (12), 108 (73), 103 (24), 94 (95), 91 (16), 88 (11), 76 (14), 67 (14), 66 (100, base peak), 64 (12), 50 (78), 48 (22). A DNP derivative of this liquid was prepared (mp 146–147°). Anal. Calcd for $C_{20}H_{26}N_4O_6$: C, 57.40; H, 6.26; N, 13.38. Found: C, 57.81; H, 6.30; N, 13.19.

**Preparation of 4-Pivaloxyisophorone (1b). Method B.** 4-Bromoisophorone (**1a**, 15.19 g, 0.07 mol), silver pivalate (14.56 g, 0.07 mol), and 56 ml of pivalic acid were placed in a 250-ml flask fitted with a condenser, magnetic stirrer, and drying tube. The entire apparatus was covered with aluminum foil to prevent light-catalyzed decomposition of the silver salt. The reactants were heated at ca. 90–95° for 355 min. The precipitated silver bromide was suction filtered and triturated with 350 ml of diethyl ether. The ethereal layer was washed with 10% sodium bicarbonate until the washings were no longer acidic (1800 ml) and then dried over $MgSO_4$ and concentrated under reduced pressure at room temperature to yield 11.89 g of an orange oil.

The crude product was prepared for wet column chromatography. A column, 3.4 cm diameter, using Davidson silica gel (ca. 900 g), activity grade III, 100–200 mesh, was used. A slurry of silica gel to a height of 114 cm, in benzene, including 1 cm of glass wool packing and 2 cm of sand below the absorbant, was used. The entire quantity of orange oil was placed on the column using a minimal amount of benzene. Cuts of 100 ml were generally taken: solvent system for cuts 1–15, benzene; cuts 16–20, 2% ethyl acetate, 98% benzene; cuts 21–27, 5% ethyl acetate, 95% benzene; cuts 28–35, 8% ethyl acetate, 92% benzene; cuts 36–40, 10% ethyl acetate, 90% benzene; cuts 41–46, 33% ethyl acetate, 67% benzene; cuts 47–53, ethyl acetate. Cuts 1–33 were combined based on TLC analysis but were not fully analyzed because they contained less than 10% of the weight of the material placed on the column. Based on rough NMR analysis cuts 34–40 were combined to yield 6.39 g of an orange oil which appears to contain mainly, based on spectral analysis, 2-pivaloxy-3,5,5-trimethyl-3-cyclohexenone (**7a**). Cuts 43–50 were combined based on rough NMR analysis and were proved to be **1b** by comparison with a sample obtained using method A. A light yellow oil was recovered (3.6 g, 30.9%).

**Isolation of 2-Pivaloxy-3,5,5-trimethylcyclohex-3-enone (7a).** From the above reaction of 4-bromoisophorone (**1a**) with silver pivalate in pivalic acid one of the recovered products was 2-pivaloxy-3,5,5-trimethylcyclohex-3-enone (**7a**) as shown above. The spectral data for this compound follow: NMR ($CDCl_3$) $\delta$ 5.56 (broad, 2 H, C=CH, HCO), 2.41 (AB pattern, 2 H, $CH_2$), 1.67 (t, $J$ = 1 Hz, 3 H, C=$CCH_3$), 1.23 [s, 9 H, $C(CH_3)_3$], 1.15 (s, 3 H, $CH_3$), 0.99 (s, 3 H, $CH_3$); ir (neat) 1750 (s, ester), 1740 (s, shoulder of 1740, unconjugated ketone); mass spectrum *m/e* (rel intensity) 239 (02), 238 (15), 154 (5.1), 153 (38), 138 (34), 137 (6.5), 136 (30), 125 (8.0), 121 (7.3), 112 (25), 111 (7.6), 109 (15), 98 (14), 91 (5.3), 85 (46), 79 (9.4), 77 (69), 69 (60), 67 (12), 58 (16), 57 (100, base peak), 56 (6.5), 55 (16), 53 (8.7), 43 (13), 42 (6.2), 41 (41).

**Isomerization of 2-Pivaloxy-3,5,5-trimethylcyclohex-3-enone (7a) to 2-Pivaloxyisophorone (2b). Method A.** In a 25-ml flask fitted with a magnetic stirrer, condenser, and drying tube, potassium hydroxide (0.149 g, 2.1 mmol), 0.275 g (1.17 mmol) of **7a**, and 10 ml of 95% ethanol were stirred at room temperature for 50 min. The reaction mixture was then diluted with diethyl ether (100 ml) and the ethereal layer was washed with three 100-ml portions of water. The aqueous layer was back extracted with one 75-ml portion of diethyl ether. The combined ethereal layers were washed with one 50-ml portion of a saturated NaCl solution, dried over $MgSO_4$, and concentrated at room temperature under reduced pressure to yield 0.185 g of a slightly yellow oil which was identical in all respects with **2b**.

**Method B.** Compound **7a** (0.191 g, 0.8 mmol), potassium pivalate (0.157 g, 1.2 mmol), and 2 ml of DMF were placed in a 20-ml flask fitted with a magnetic stirrer. The flask was lightly stoppered and the reaction mixture was stirred for 40.5 hr at ca. 45°. Diethyl ether (15 ml) was added to the reaction mixture and the organic layer was washed with two 25-ml portions of water, one portion (20 ml) of 10% sodium bicarbonate solution, and once (20 ml) with water, dried over $MgSO_4$, and concentrated at room temperature under reduced pressure to give 0.143 g of a slightly yellow oil whose spectral properties matched those of **2b**.

**Method C.** Into a 20-ml flask fitted with a magnetic stirrer, **7a** (0.157 g, 0.65 mmol), potassium pivalate (0.118 g, 0.845 mmol), and 1 g of pivalic acid were added. The reaction mixture was stirred in the corked flask for 40.5 hr at 45 ± 2°. Diethyl ether (20 ml) was added and the ethereal layer was washed with one 20-ml portion of water, two 20-ml portions of 10% sodium bicarbonate, and one 20-ml portion of a saturated sodium chloride solution, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature to yield 0.108 g of a slightly yellow oil whose spectral properties showed it to be **2b**.

**Preparation of 2-Pivaloxyisophorone (2b).** A general method for the esterification of hindered acids was employed.[16] 2-Hydroxyisophorone (**2a**, 1.0 g, 65 mmol) and pivalic acid (0.663 g, 65 mmol) were added to 5 ml of trifluoroacetic anhydride in a 25-ml flask fitted with a magnetic stirrer. The reaction mixture was stirred at room temperature for 3.5 hr. Benzene (20 ml) was added and the benzene solution was washed with three 15-ml portions of 10% sodium hydroxide and once with a 20-ml portion of water, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature. The resulting solution was distilled under reduced pressure to give 0.527 g (34.1%) of a colorless liquid, **2b**: bp 113–115° (2.5 Torr); NMR ($CDCl_3$) $\delta$ 2.33 (s, 2 H, $CH_2$), 2.27 (s, 2 H, $CH_2$), 1.78 (s, 3 H, C=$CCH_3$), 1.30 [s, 9 H, $C(CH_3)_3$], 1.08 (s, 6

H, 2-$CH_3$); ir (neat) 1748 (s, ester), 1685 $cm^{-1}$ (s, conjugated ketone); mass spectrum *m/e* (rel intensity) 239 (1.2), 238 (5.5) 154 (41), 153 (100, base peak), 138 (47), 125 (20), 124 (17), 111 (36), 110 (13), 107 (5.5), 97 (42), 84 (13). 82 (19), 69 (38), 68 (24), 66 (8.8), 58 (8.3); mp of DNP derivative 181–182.5°. Anal. Calcd for $C_{20}H_{26}N_4O_6$: C, 57.40; H, 6.26; N, 13.38. Found: C, 57.68; H, 6.37; N, 13.29.

**Preparation of 4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (1d).** 5,5-Dimethyl-3-phenylcyclohex-2-enone[17] (1.34 g, 6.7 mmol), *N*-bromosuccinimide (1.2 g, 6.7 mmol), a trace of benzoyl peroxide, and 20 ml of carbon tetrachloride were introduced into a 50-ml flask fitted with a magnetic stirrer, condenser, and drying tube. The reaction mixture, irradiated with a long-wavelength uv lamp, was stirred at reflux for a total of 21.75 hr. The reaction flask was cooled in an ice bath and the solid present was suction filtered. The mother liquor was concentrated at room temperature under reduced pressure. The resulting solid was recrystallized from pentane to give 1.04 g (56%) of a white solid: mp 83–85°; NMR ($CDCl_3$) δ 7.50 (m, 5 H, ArH), 6.32 (s, 1 H, C=CH), 4.92 (d, $J$ = 1 Hz, HCBr), 2.50 (AB pattern, 2 H, $CH_2$), 1.33 (s, 3 H, $CH_3$), 1.22 (s, 3 H, $CH_3$); ir (KBr disk) 1655 (s, conjugated ketone). Anal. Calcd for $C_{14}H_{15}BrO$: C, 56.98; H, 5.12; Br, 28.67. Found: C, 56.15; H, 5.22; Br, 28.11.

**Preparation of 5,5-Dimethyl-3-phenyl-2-pivaloxycyclohex-2-enone.** 4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (**1d,** 0.556 g, 2.0 mmol), potassium pivalate (0.364 g, 2.6 mmol), and DMF (5 ml) were added to a 25-ml flask fitted with a magnetic stirrer. The reaction mixture was stirred at 45° for approximately 13 days. The reaction mixture was then dissolved in diethyl ether (20 ml) and washed with two 20-ml portions of water, one 20-ml portion of 10% sodium bicarbonate solution, and one 20-ml portion of water, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature to yield a slightly yellow solid (0.450 g, 75%). This solid was recrystallized four times from petroleum ether (bp 30–60°) to yield a white solid: mp 112–113°; NMR ($CDCl_3$) δ 7.34 (s, 5 H, Ph), 2.69 (s, 2 H, $CH_2$), 2.44 (s, 2 H, $CH_2$), 1.18 (s, 3 H, $CH_3$), 1.13 [s, 9 H, $C(CH_3)_3$], 1.11 (s, 3 H, $CH_3$); ir ($CCl_4$ solution) 1755 (s, ester), 1690 $cm^{-1}$ (s, conjugated ketone); mass spectrum *m/e* (rel intensity) 301 (18), 300 (76), 286 (10), 285 (5), 232 (5.2), 218 (6.1), 217 (49), 216 (100, base peak), 215 (30), 188 (14), 160 (12), 145 (5), 132 (7), 103 (5). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.26; H, 8.33.

**Preparation of Potassium Pivalate.** Pivalic acid (21.0 g, 0.26 mol) was added to 20 ml of water in a 250-ml flask fitted with a magnetic stirrer. The stirred mixture was made basic to a phenolphthalein end point using a 10% KOH solution. After filtration, the solvent was evaporated under reduced pressure (ca. 85°), leaving a white solid which was washed with 200 ml of acetone and 100 ml of diethyl ether, air dried for 4 hr, and then vacuum dried (1 Torr) at room temperature for 18 hr. A white solid (27.4 g, 87.5%) was recovered.

**Preparation of Silver Pivalate.**[18] Pivalic acid (40.8 g, 0.4 mol) and 600 ml of water were placed in a 2-l. flask fitted with a magnetic stirrer. Sodium hydroxide (10%) was added dropwise until the solution was just basic to a phenophthalein indicator (163.8 ml). The reaction flask was covered with aluminum foil and 1 equiv of silver nitrate (68 g, 0.4 mol) in 50 ml of water was added. The resulting precipitate was suction filtered in the dark, washed with 800 ml of water, 463 ml of methanol, and 463 ml of diethyl ether, and dried under high vacuum (1 Torr) for 4 hr to yield 60.2 g (75%) of a slightly gray solid.

**Reactions of 1a with Nucelophiles.** Reactions were generally run in a stoppered flask fitted with a magnetic stirrer at 45 ± 2° for 40.5 hr unless otherwise noted. When silver salts were used, the reaction flask was covered with aluminum foil and the resulting filtered silver bromide was washed with diethyl ether. When the potassium salt was employed, the reaction mixture was diluted directly with diethyl ether. These organic solutions were washed with water, then with 10% sodium bicarbonate if acetic acid or pivalic acid was present; dilute hydrochloric acid if triethylamine was present; or water if water-soluble solvents, such as $Me_2SO$, dioxane, DMF, HMPA, etc., were used. The organic layer was then washed with water, or a sodium chloride solution if the layers did not separate readily, dried over $MgSO_4$, and concentrated. Analysis of the product distribution was usually performed by NMR.

**Registry No.**—**1a,** 16004-91-4; **1b,** 55723-01-8; **1b** DNP, 55723-02-9; **1c,** 14203-59-9; **1d,** 55723-03-0; **2a,** 4883-60-7; **2b,** 55723-04-1; **2b** DNP, 55723-05-2; **2d,** 55723-06-3; **7a,** 55723-07-4; **7c,** 471-01-2; 3-oxido-3,5,5-trimethylcyclohexanone, 41967-76-4; *m*-chloroperbenzoic acid, 937-14-4; pivalic acid, 75-98-9; 5,5-dimethyl-3-phenylcyclohex-2-enone, 36047-17-3; *N*-bromosuccinimide, 128-08-5; potassium pivalate, 19455-23-3; silver pivalate, 7324-58-5.

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