is disturbing. Hydrogen bonding of the terminal oxygen with the distal imidazole in HbO_2 might afford some lowering of $\nu(O_2)$, but surely not by 280 cm^{-1}. In view of this large difference and the low resolution indicated in Caughey's published spectra,[11] we intend to reinvestigate the ir spectra of $Hb^{16}O_2$ and $Hb^{18}O_2$ at low temperatures.

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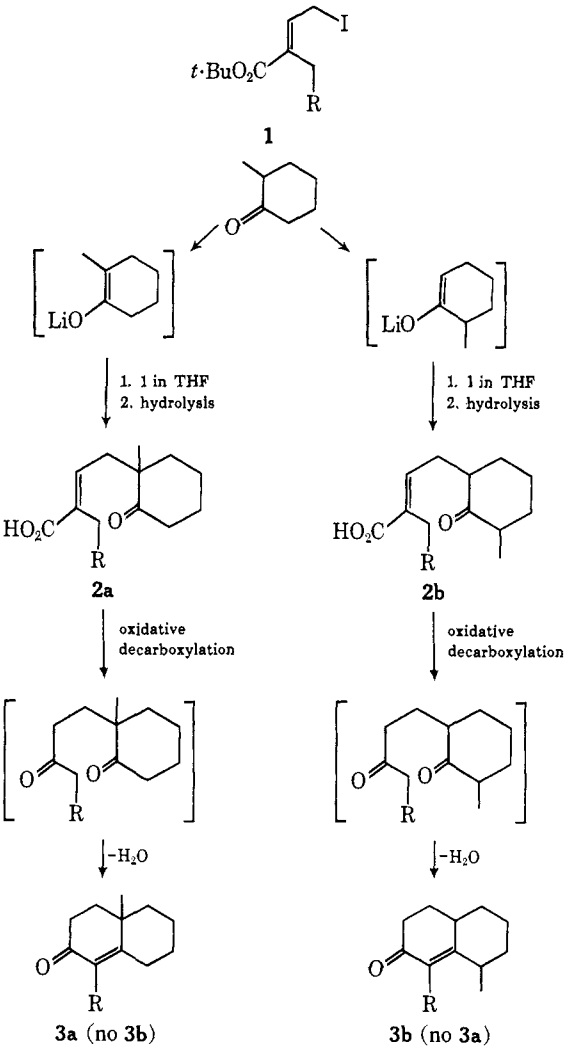
γ-Halotiglates. I. A Simple, Efficient Position-Specific Annelation of Unsymmetrically Substituted Cyclohexanones

Sir:

For some time,[1] we have been seeking a superior method of introducing a 3′-ketoalkyl substituent specifically at either the α or α′ position of an unsymmetrically substituted ketone. The desired product, a structurally specific δ-diketone is the requisite intermediate for a *position-specific* "Robinson annelation"[2] of the starting ketone. We now wish to report a new and viable solution to the problem of position-specific annelation. We have found that γ-iodotiglate esters, **1**,[1b] function well as "masked ketoalkyl" alkylating agents for lithium enolates (specifically generated[3,4] under aprotic conditions) and for enamines;[2b] the alkylated products are easily isolated as carboxylic acids (*e.g.*, **2** in Scheme I) in good to excellent yields. Oxidative decarboxylation readily degrades the side-chain α,β-unsaturated acid to the requisite 3′-ketoalkyl functionality, which can directly cyclize under basic catalysis to a single structural isomer of the desired annelated product (*e.g.*, enone **3**). To illustrate the overall procedure, as outlined in Scheme I, we have position-specifically annelated 2-methylcyclohexanone producing either **3a** or **3b** in greater than 70% overall yield, uncontaminated by the alternative structural isomer.

Scheme I



We chose to investigate γ-halotiglates, **1**, as alkylating agents in this scheme for the following reasons. (a) As allylic halides, they offered the promise of *high reactivity* in the alkylation of structurally specific enolates and enamines (thus reducing the probability

(1) (a) Preliminary reports of our continuing work with γ-halotiglates were made in the following oral communications: 159th National Meeting of the American Chemical Society, Houston, Texas (Feb 1970), Abstract ORGN 117; 161st National Meeting of the American Chemical Society, Los Angeles, Calif. (March 1971), Abstract ORGN 030, ORGN 138; Second International Symposium on Synthesis in Organic Chemistry, Cambridge, England (July 1971). (b) γ-Iodotiglates, **1**, were prepared from chloroacetaldehyde and α-carbalkoxyalkylidenetriphenylphosphoranes, followed by iodide exchange (in acetone); details will be described in P. L. Stotter and K. A. Hill, "γ-Halotiglates. II. A High Yield Stereoselective Preparation," manuscript submitted for publication.

(2) Annelations proceeding *via* introduction of a 3′-ketoalkyl substituent α to an existing ketone and subsequent cyclodehydration of the resulting δ-diketone intermediate may be classed in two categories depending on the method of introducing the 3′-ketoalkyl substituent. For examples of introduction of 3′-ketoalkyl substituents by Michael or Michael-type addition to electrophilic olefins see (a) E. C. DuFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); (b) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); (c) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964), and references cited therein. (d) S. Danishefsky and R. Cavanaugh, *J. Amer. Chem. Soc.*, **90**, 520 (1968), and references cited therein. (e) S. Danishefsky and B. H. Migdalof, *ibid.*, **91**, 2806 (1969). (f) C. H. Heathcock, J. E. Ellis, J. E. McMurry, and A. Coppolino, *Tetrahedron Lett.*, 4995 (1971). (g) G. Stork and B. Ganem, *J. Amer. Chem. Soc.*, **95**, 6152 (1973). For examples of introduction of 3′-ketoalkyl substituents by alkylations using "masked ketoalkyl" alkylating agents see (h) O. Wichterle, J. Prochazka, and J. Hoffmann, *Collect. Czech. Chem. Commun.*, **13**, 300 (1948); (i) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967); G. Stork and J. E. McMurry, *ibid.*, **89**, 5461, 5463, 5464 (1967); (j) D. Caine and F. N. Tuller, *J. Org. Chem.*, **34**, 222 (1969). For general review articles, see (k) J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 99 (1953); E. D. Bergmann, D. Ginsberg, and R. Pappo, *ibid.*, **10**, 179 (1959); I. V. Torgov, *Pure Appl. Chem.*, **6**, 525 (1963); G. Stork, *ibid.*, **9**, 131 (1964); L. Velluz, J. Valls, and G. Nominé, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965); G. Stork, *Horm. Steroids, Proc. Int. Congr. 3rd*, 101 (1970) (*Excerpta Med. Found. Int. Congr. Ser.*, **No. 219**).

(3) (a) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); (b) H. O. House and B. M. Trost, *ibid.*, **30**, 2502 (1965), and references cited therein.

(4) (a) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968); (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971).

Table I. Representative Procedures and Yields for the Preparation of Acids, 2, from 2-Methylcyclohexanone and Cyclohexanone

Enamines or enolate precursors (reference to preparation)	Alkylating agent[a]	Alkylation procedures[b]	Isolated acid 2[a] (after hydrolysis)
	From 2-Methylcyclohexanone		
1-Acetoxy-2-methylcyclohexene (3a)	1 (R = H)	Q	2a (R = H) 90%
	1 (R = CH_3)	Q	2a (R = CH_3) 93%
1-Trimethylsiloxy-6-methylcyclohexene (4b)	1 (R = H)	R	2b (R = H) 90%
2-Methylcyclohexanone	1 (R = H)	S	2b (R = H) 85%
1-(*N*-Pyrolidino)-6-methylcyclohexene (2b)	1 (R = H)	T	2b (R = H) 52%
	From Cyclohexanone		
1-Acetoxycyclohexene (*c*)	1 (R = H)	Q	2c (R = H) 92%
	1 (R = CH_3)	Q	2c (R = CH_3) 91%
Cyclohexanone	1 (R = H)	S	2c (R = H) 87%
1-(*N*-Pyrolidino)cyclohexene (2b)	1 (R = H)	T	2c (R = H) 90%

[a] Methyl esters or *tert*-butyl esters of 1 could be used interchangeably in the alkylation procedure, without substantially affecting isolated yields of 2; however, we have found the *tert*-butyl esters more *convenient* for high-yield preparation of 1 and isolation of 2. [b] Alkylation procedures: Q, CH_3Li (2 equiv) in THF, addition of 1 equiv of enol acetate at room temperature, addition of 0.95 equiv of 1 at 0°, bicarbonate work-up (see ref 3); R, CH_3Li in THF, addition of 1 equiv of enol silyl ether at 50°, addition of 0.95 equiv of 1 at 0°, bicarbonate work-up (see ref 4); S, lithium diisopropylamide in THF, addition of 1 equiv of ketone at room temperature, addition of 0.95 equiv of 1 at 0°, bicarbonate then dilute acid work-up (see ref 4b); T, enamine and 1 in methanol at reflux 12–20 hr, dilute acid work-up (see ref 2b). [c] H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

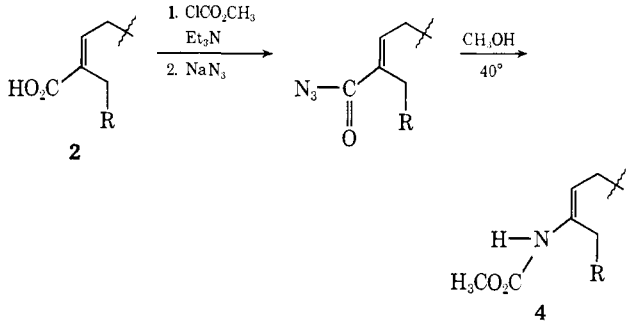
of competitive positional equilibration of enolates before alkylation is complete and, consequently, inhibiting the formation of mixtures of polyalkylated and/or structurally isomeric products). (b) Despite this expected reactivity of 1 toward nucleophilic displacement, we anticipated that the inductive effect of a carboxyate substituent on the double bond would *suppress* E-1 1,4-*elimination* of hydrogen halide from 1 (thus further reducing the possibility of enolate positional equilibration). (c) We hoped that this same carboxyl group would serve to *simplify isolation* and *purification* of the alkylated ketones, prior to "unmasking" the 3′-ketoalkyl substituent. (d) The α,β-unsaturated carboxylic acid moiety can be "unmasked" to the desired ketone under *mild, nonacidic* conditions; these conditions are compatible with acid-labile functionality elsewhere in the molecule and are incompatible with acid-catalyzed cyclodehydration *side reactions* (potential sources[5] of bridged bicyclic enone contaminants in any acid-catalyzed liberation of δ-dione precursors to annelated products 3). Our experimental observations now corroborate each of these hypotheses.

Since conversion of intermediate acids, 2, to annelated products, 3, proved to be as efficient a procedure as we had anticipated (see below), our primary synthetic problem lay in defining the scope and limitations of alkylations using γ-halotiglates. In this regard, γ-chloro analogs of 1[1b,6] were effective alkylating agents for enamines but not for lithium enolates;[7] in contrast, we have found that γ-iodo esters, 1,[6] gave monoalkylation products, usually in excellent yield (no polyalkylation by glc), either with enamines or with lithium enolates derived from cyclohexanone and 2-methylcyclohexanone. It is generally convenient to convert the alkylation products directly to easily isolable and usually crystalline unsaturated acids 2 (*tert*-butyl esters were cleaved by reflux in anhydrous benzene containing catalytic toluenesulfonic acid; the corresponding methyl esters could be saponified in comparable good yield). Table I records representative alkylation procedures and yields of carboxylic acids, 2, derived from 2-methylcyclohexanone and cyclohexanone.

Although enolate solutions prepared from enol acetates (method Q[3]) contain 1 equiv of lithium *tert*-butoxide, no products derived by base-catalyzed 1,4-elimination of HI from 1 were observed. Similarly, alkylations of kinetically generated enolates (method S, lithium diisopropylamide as base[4b]) could be carried out readily in the presence of diisopropylamine with no deleterious effect and without the necessity of adding excess 1. In fact, the presence of this amine may facilitate alkylation.[8]

Carboxylic acids 2 were degraded and cyclized to enones, 3, using the Weinstock-modified[9] Curtius degradation. The high-yield procedure can be effected under mildly basic to neutral reaction conditions, *via* the mixed anhydride, acyl azide, and *N*-vinyl methyl carbamate, 4, as indicated in Scheme II. The conversion

Scheme II



(5) J. A. Marshall and D. J. Shaeffer, *J. Org. Chem.*, 30, 3642 (1965), and references cited therein.

(6) The γ-halotiglates used in these alkylations are a mixture of trans–cis isomers, the latter present in less than 8%. Use of this mixture is satisfactory since the "unmasking" sequence converts both double bond isomers to the same final product. Since (after recrystallization) analytically pure acids, 2, were primarily trans-isomer (by nmr), slightly higher yields of annelated products, 3, were obtained when the degradation scheme was directly applied to amorphous acids 2, without extensive recrystallization.

(7) Attempts to alkylate the lithium enolate of cyclohexanone using γ-chlorotiglates (under conditions described for alkylations using γ-iodotiglates) led to complex mixtures of products containing less than 20% of the desired alkylation product (by glc).

(8) Alkylation of the lithium enolate derived from 1-acetoxy-6-methylcyclohexene with 1 (using method Q) produced the desired alkylation product (the ester corresponding to 2b) in only moderate yield (>60%). However, addition of 1 equiv of diisopropylamine to the enolate solution *prior* to addition of 1 significantly raised the yield of this alkylation product (>90% yield).

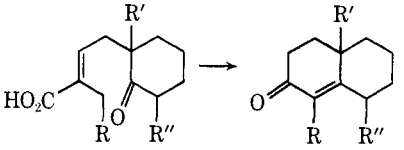
(9) J. Weinstock, *J. Org. Chem.*, 26, 3511 (1961).

requires no protection of the existing ketone and is compatible with acid-sensitive functionality. Typically, yields for the conversion of unsaturated acids **2** to *N*-vinyl carbamates, **4**, were greater than 90% overall; spectral properties of the oily intermediates were consistent, in each case, with the structures anticipated.

Final "unmasking" of the newly introduced 3′-ketoalkyl substituent was effected *via* 2% KOH in 4:1 methanol–water for 1 hr at 25° then 2 hr at 70°, thus allowing for direct cyclization of the intermediate δ-diketones to annelated products **3** in high yield (usually about 90%). These conditions, which are essential for cyclodehydration in any "Robinson annelation," are the most drastic in this "unmasking" sequence.

Table II describes yields of distilled enones **3** derived from keto-unsaturated acids **2**. All annelation products

Table II. Representative Examples and Yields for the Conversion of Acids, **2**, to Annelated Products, **3**



	Mp, °C	% of **3** distilled yield (based on **2**)	Reference to comparison data for **3** and derivatives
2a, R′ = CH_3; R = R″ = H	98–100	80	2a
2a, R = R′ = CH_3; R″ = H	103–104	85	*a*
2b, R = R′ = H; R″ = CH_3	106–108	83	2a, 2b
2c, R = R′ = R″ = H	85.5–86.5	82	2b
2c, R = CH_3; R′ = R″ = H	63–68	81	*b*

[a] F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952); F. J. McQuillin, *ibid.*, 528 (1955). [b] Y. Kawase, *Bull. Chem. Soc. Jap.*, **31**, 336 (1958).

3 were identified by comparison of their physical and spectral properties as well as those of their solid 2,4-dinitrophenyl hydrazones with data previously reported. In each case, the annelations were position-specific and no structural isomers were observed.

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Carbonyl n → π* Solvent Blue Shift. Excited State Solvation *vs.* Ground State Solvation

Sir:

The well-known blue shift of the n → π* transition of carbonyl compounds on going to more polar solvents can be attributed to superior solvation of the polar ground state by the polar solvent[1] or to inferior solvation of the excited state by the polar solvent.[2] The following evidence shows that, in the case of acetone, solvation of the ground state accounts for only about a half of the above phenomenon, the other half being caused by desolvation of the excited state[3] in the polar solvent. Figure 1 illustrates this fact for the n → π* transition of acetone in CCl_4 and H_2O solvents, using λ_{max} values for the acetone n → π* transition in these two solvents of 280.1[4] and 264.9 nm,[5] respectively, and heats of solution of acetone in the two solvents of 0.79[6] and −2.37 kcal/mol,[7] respectively. As can be seen, the CCl_4–H_2O solvent shift of 15.2 nm or 5.86 kcal/mol is caused by a 3.16 kcal/mol exothermic enthalpy of transfer of the acetone ground state ($\delta\Delta H_s$) and a 2.70 kcal/mol *endothermic* enthalpy of transfer of the excited state ($\delta\Delta H^*$) into the more polar solvent.[8]

To see whether this conclusion holds generally we can next examine the behavior of benzophenone in a more extensive series of solvents. The necessary heats of solution were measured and are shown in Table I. From these, and the data of Ito,[4] *et al.*, the enthalpies of solvent transfer of the excited states were calculated and are tabulated in Table II and shown graphically in Figure 2.

The most general conclusion that can be drawn is that changes in solvation of the excited state of benzophenone contribute significantly to the magnitude of the solvent blue shift. Thus, the large blue shift on going from hexane to ethanol or acetonitrile is clearly due to the same kind of cooperative effect which causes the acetone blue shift on going from CCl_4 to H_2O solvent (*cf.* Figures 1 and 2), *i.e.*, increased ground state solvation accompanied by diminished excited state solvation on going to the more polar solvent. On the other hand the other four solvents examined (methyl acetate, carbon

(1) *E.g.*, G. J. Brealey and M. Kasha, *J. Amer. Chem. Soc.*, 77, 4462 (1955); M. Pestemer and D. Brück in "Methoden der Organischen Chemie (Houben-Weyl)," Vol. III, part II, E. Müller, Ed., G. Thieme Verlag, Stuttgart, 1955, p 738; G. C. Pimentel, *J. Amer. Chem. Soc.*, **79**, 3323 (1957); S. F. Mason, *Quart. Rev., Chem. Soc.*, **15**, 287 (1961); S. K. Freeman, "Interpretive Spectroscopy," Reinhold, New York, N. Y., 1965, p 31; H. Suzuki, "Electronic Absorption Spectra and Geometry of Organic Molecules," Academic Press, New York, N. Y., 1967, p 99; E. F. H. Brittain, W. O. George, and C. H. J. Wells, "Introduction to Molecular Spectroscopy," Academic Press, New York, N. Y., 1970, p 46.

(2) *E.g.*, R. S. Becker, "Theory and Interpretation of Fluorescence and Phosphorescence," Wiley, New York, N. Y., 1969, p 37; N. Mataga and T. Kubota, "Molecular Interactions and Electronic Spectra," Marcel Dekker, 1970, p 399.

(3) The excited state referred to here is, of course, not the "equilibrium" excited state after vibrational and solvent relaxation. The Franck–Condon principle requires that the observed electronic transition be to an excited state having a geometry and solvent shell geometry identical with that of the ground state. It is to this Franck–Condon excited state that our discussion pertains.

(4) M. Ito, K. Inuzuki, and S. Imanishi, *J. Amer. Chem. Soc.*, **82**, 1317 (1960).

(5) P. Maroni, *Ann. Chim. (Paris)*, **13**, 757 (1957); J. E. Dubois, E. Goetz, and A. Bienvenue, *Spectrochim. Acta*, **20**, 1815 (1964).

(6) J. W. Larsen, *J. Amer. Chem. Soc.*, **92**, 5136 (1970).

(7) E. M. Arnett, *J. Amer. Chem. Soc.*, **88**, 2598 (1966).

(8) $\delta\Delta H^* = \delta\Delta H_s + \delta\Delta E^{n\rightarrow\pi^*}$ where $\delta\Delta E^{n\rightarrow\pi^*}$ is the solvent blue shift in kcal/mol.