A solution made from dissolving 0.58 g (0.02 mol) of sodium in 50 ml of anhydrous methanol was added to the hexabromide and the mixture refluxed for 2 h. At the end of the refluxing period, the solution was filtered and solvent removed in vacuo to yield an oil which solidified overnight. The residue was dissolved in 25 ml of dioxane, and 75 ml of water and 5 ml of concentrate hydrogen chloride were added to the stirring solution. The resulting cloudy mixture was stirred at room temperature overnight. After the hydrolysis was complete the aqueous solution was extracted three times with 50-ml portions of ether, dried with anhydrous magnesium sulfate, and evaporated to yield a pale yellow solid. The NMR spectrum of the crude mixture has singlets at δ 4.45 and 3.42, indicating the presence of a $ArCH_2OCH_3$ group. Integration of the mixture indicated that the product was approximately 90% pure trialdehyde. Column chromatography of the mixture gave 0.59 g of material approximately 90% pure, the major contaminant being a methyl ether resulting from incomplete bromination. The following data were determined: IR ($CHCl_3$) 2840 and 2740 (CHO), 1710 (C=O), 1610 and 1510 (Ar), 1140 (C–F), 810 cm^{-1} (para-substituted Ar); NMR δ 7.3 (d, J = 8 Hz), 7.84 (d, J = 8 Hz), 10.04 (s).

Registry No.—**2**, 434-45-7; **3**, 62-53-3; **5**, 61204-04-4; **6**, 23516-79-2; **7**, 61204-05-5; **8**, 61204-06-6; **9**, 61204-07-7; **10**, 61204-08-8; **12**, 394-59-2; **13**, 61204-09-9; **14**, 61204-10-2; **15**, 61204-11-3; 1,1-bis(4-acetamidophenyl)-1-phenyl-2,2,2-trifluoroethane, 61204-12-4; acetic anhydride, 108-24-7; cuprous cyanide, 544-92-3; 1,1,1-tris(4-acetamidophenyl)-2,2,2-trifluorothane, 61204-13-5; toluene, 108-88-3; trifluoromethylsulfonic acid, 1493-13-6.

References and Notes

(1) National Research Council Associate, Ames Research Center, NASA, Moffett Field, Calif. 94035.
(2) D. A. Hey and J. Peters, *J. Chem. Soc.*, 79 (1960).
(3) H. Schell and H. Drim, *Angew. Chem., Int. Ed. Engl.*, **2**, 373 (1963).
(4) B. S. Farah, E. E. Gilbert and J. P. Sibilia, *J. Org. Chem.*, **30**, 998 (1965).
(5) E. E. Gilbert, E. S. Jones, and J. P. Sibilia, *J. Org. Chem.*, **30**, 1001 (1965).
(6) I. L. Knunyants, C. Ching-Yun, N. P. Gambaryan, and E. M. Rokhlin, *Zh. Vses. Khim. O.va*, 114 (1960).
(7) B. S. Farah, E. E. Gilbert, M. Litt, J. A. Otto, and J. P. Sibilia, *J. Org. Chem.*, **30**, 1003 (1965).
(8) D. S. England, French Patent 1 325 204 (1963).
(9) S. Patai and S. Dayagi, *J. Chem. Soc.*, 3058 (1958).
(10) A. Baeyer and V. Villiger, *Ber.* **37**, 2848 (1904).
(11) H. Gilman, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 500.
(12) K. J. Klabunde and D. J. Burton, *J. Org. Chem.*, **35**, 1711 (1970).
(13) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

A Synthetic Route to Highly Substituted Ketones. Acylations of α Anions of Carboxylic Acid Salts with Acid Chlorides[1]

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A versatile synthetic route leading to highly substituted ketones has been developed. Treatment of disubstituted α-lithiated carboxylic acid salts **2** with acyl chlorides leads to the diisopropylammonium salts of the β-keto acids **4**. Thermolysis of these isolated salts produces excellent yields of ketones. In particular, this procedure is useful for the synthesis of symmetrical and unsymmetrical dicycloalkyl ketones. The α anion derived from phenylacetic acid on treatment with acyl chlorides and acidic workup leads directly to ketones in good yield. The α anions derived from acetic acid and propionic acid lead to poor yields of ketones on treatment with acyl chlorides.

Carboxylic acids with aryl or olefinic substituents attached to the α carbon produce "Ivanov" reagents on treatment with Grignard reagents, and many useful synthetic applications of these reagents have been reported.[4] Although α anions derived from salts of aliphatic carboxylic acids have been known for about 40 years,[5] the preparative difficulties have only been recently resolved. These α anions can conveniently be prepared by treatment of alicyclic or aliphatic carboxylic acids with 2 equiv of nonnucleophilic bases such as lithium diisopropylamide (LDA) in solvents like THF.[6] Various researchers have utilized alkali metal radical anions to generate α anions.[7]

The goal of the present research was to explore the reaction of α anions derived from readily available aliphatic and alicyclic carboxylic acid salts with acyl chlorides as a synthetic route to ketones. Two related studies which lead to ketones have been recently described. Treatment of α anions of carboxylate salts with a few esters followed by addition of TMCS leads to β-keto acid trimethylsilyl esters which can be methanolyzed to the β-keto acids and then converted into ketones.[8] Angelo treated α anions (generated from acids with lithium naphthalenide) with esters to produce β-keto acids. The β-keto acids derived from acetic acid could be isolated in good yields, but no β-keto acids could be isolated from mono- or disubstituted carboxylic acids; these acids also led to poor yields of ketones.[7c]

In related studies, α anions derived from esters have been treated with acyl chlorides to yield β-keto esters.[6c,9]

The conversion of carboxylic acid derivatives such as acyl halides to simple and highly substituted ketones using organometallics as alkyl transfer agents[10a-i] and organo derivatives of silicon[11] and boron[12] has been reported. Carboxylate salts have been treated with organometallic reagents to form ketones.[10j,k] Acids have been converted into dihydro-1,3-oxazines[13] and 4,4-dimethyl-2-oxazolines[14,15] and treatment of these heterocycles with 2 equiv of organolithium reagents followed by hydrolysis, or by subsequent addition of an alkyl halide followed by hydrolysis, leads to highly substituted ketones.

Results and Discussion

We wish to report a convenient two-step synthetic procedure in which acid chlorides are treated with carboxylic acids to produce ketones via the following formal transformation:

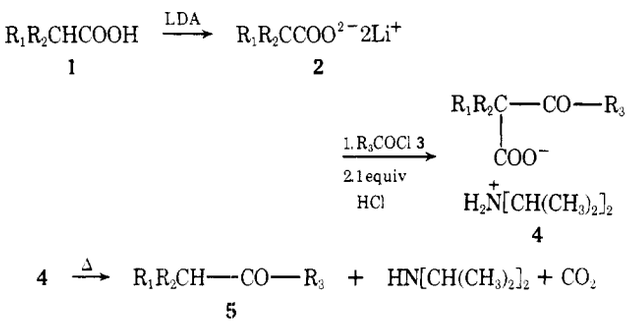
$$R_1R_2CHCOOH + R_3COCl \rightarrow R_1R_2CHCOR_3$$

Table I. Ketones Prepared via Scheme I

Run	Carboxylic acid, 1 R_1	R_2	Registry no.	Acyl chloride, 3, R_3	Registry no.	Ketone, 5[a]
A	$-(CH_2)_5-$		98-89-5	c-C_6H_{11}	2719-27-9	Dicyclohexyl
B	$-(CH_2)_4-$		3400-45-1	c-C_6H_{11}		Cyclohexyl cyclopentyl
C	$-(CH_2)_3-$		3721-95-7	c-C_6H_{11}		Cyclohexyl cyclobutyl
D	$-(CH_2)_5-$			c-C_3H_5	4023-34-1	Cyclohexyl cyclopropyl
E	$-(CH_2)_3-$			c-C_3H_5		Cyclobutyl cyclopropyl[b]
F	CH_3	CH_3	79-31-2	C_6H_5	98-88-4	Isobutyrophenone
G	CH_3	CH_3		c-C_6H_{11}		Cyclohexyl isopropyl
H	CH_3	CH_3		$(CH_3)_3C$	79-30-1	Isopropyl *tert*-butyl
I	CH_3CH_2	CH_3CH_2	88-09-5	$(CH_3)_3C$		2,2-Dimethyl-4-ethyl-3-hexanone[c]
J	CH_3	CH_3		$(CH_3)_3CCH_2$	7065-46-5	Neopentyl isopropyl[d]

[a] The β-keto acid diisopropylammonium salts were isolated and thermolyzed. All ketones were isolated in 50–69% overall yields except where noted. The purity of the ketones was >99% (GLC). [b] Overall yield of 20%. [c] The synthesis of this compound was attempted via the oxazoline route; none of the desired product was formed.[15] [d] Overall yield of 30%.

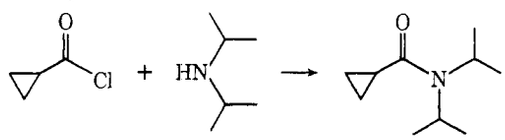
Scheme I



The carboxylic acid functions as a synthon for a carbanion which is formally acylated by the acyl chloride. The steps involved in the synthetic route are outlined in Scheme I. Treatment of disubstituted carboxylic acids 1 (cycloalkane and dialkylated acids were used) with a solution of 2 equiv of lithium diisopropylamide (LDA) in THF leads to the formation of a solution of the α-lithiated carboxylate salt **2**. The acyl chloride **3** was added to this solution of **2** at −70 °C. Since the reaction mixture contains diisopropylamine, the addition of *1* equiv of aqueous HCl leads to the formation of the diisopropylammonium salts of the β-keto acids **4**. These salts **4** can be easily isolated by extractive workup of the aqueous quench with $CHCl_3$ in 60–70% yields and can be readily purified by crystallization without any problems of decomposition. The ketones **5** are formed by thermolysis (150–200 °C) of the salts **4** and can be obtained in excellent yields and high purity without resorting to any further purification.

The ketones **5** prepared by the route depicted in Scheme I are summarized in Table I.

The diisopropylammonium salts **4** which lead to cyclopropyl cyclobutyl ketone and neopentyl isopropyl ketone could only be isolated in 20 and 30% yield, respectively (runs E and J). The low yield in the former case is due to the competitive reaction of diisopropylamine with the cyclopropanecarbonyl chloride to give amide **6** in a 50% yield.

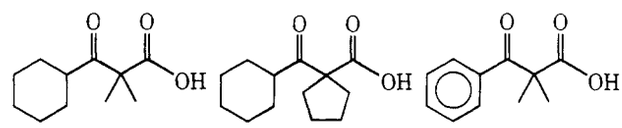


6

In one case a comparison was made between the use of an acyl halide or an ester as the acylating agent. For example, in reaction F (Table I), if methyl benzoate is used instead of benzoyl chloride, the yield of isolated β-keto acid diisopropylammonium salt **4** ($R_1 = R_2 = CH_3$; $R_3 = C_6H_5$) decreases from 60% to 52%.

From the data in Table I it can be seen that this procedure leads to reasonable overall yields of highly substituted ketones. In particular, the dianion **2** derived from 2-ethylbutyric acid reacted with pivaloyl chloride to yield the sterically hindered β-keto acid diisopropylammonium salt **4** (run I, Table I) in a 60% yield. Unsymmetrical and symmetrical dicycloalkyl ketones can be prepared by this procedure. Ketones of this type have not been prepared via the oxazine or oxazoline routes.[13,14]

In several of the reactions described in Table I it was also possible to isolate the β-keto acids by quenching the crude reaction mixture with 3 equiv of HCl followed by extraction with CH_2Cl_2 and concentration. However, it was found that attempts to isolate the pure β-keto acids led to irreproducible and erratic yields.[16] Difficulty was also encountered in crystallization of the β-keto acids because of the solubility of the acid in the ketones partially formed during the isolation attempts. Nevertheless, the β-keto acids **7**, **8**, and **9** were ob-

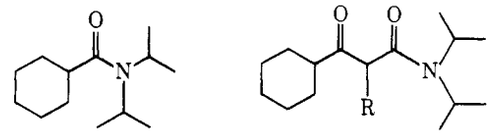


7 **8** **9**

tained in pure form (although in low yields) and once purified were quite stable for long periods in the refrigerator. These compounds, on thermolysis, were readily converted to the corresponding ketones.

It is interesting to note that β-keto acids containing two hydrogens on the carbon between the carbonyl groups were readily isolated from reactions with the dianion of acetic acid and esters which on decarboxylation formed methyl ketones.[7c]

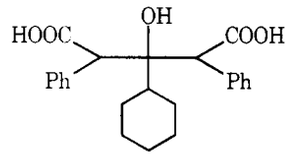
When the insoluble dianion of propionic acid (**2**, $R_1 = H$; $R_2 = CH_3$) was treated with cyclohexanecarbonyl chloride, the β-keto acid diisopropylammonium salt **4** could not be isolated. In this case the crude reaction product was acidified and was thermolyzed until no more CO_2 was evolved. Workup of this mixture led to the isolation of about 20% cyclohexyl ethyl ketone by chromatography. Amide **10** was isolated in a 15%



10 **11**

yield by distillation and keto amide **11** (R = CH_3) in a 14% yield.

When phenylacetic acid dianion **2** ($R_1 = C_6H_5$; $R_2 = H$) was treated with cyclohexanecarbonyl chloride, the β-keto acid diisopropylammonium salt could not be isolated. Workup led to isolated yields of cyclohexyl benzyl ketone (50%), β-keto amide **11** (R = C_6H_5, 11%), the diadduct **12** (9%), cyclohexanecarboxylic acid (21%) from hydrolysis of unreacted acyl chloride, and phenylacetic acid (14%). It might be noted that Ivanov[17] reported that treatment of $C_6H_5CH(MgCl)CO_2Na$ with C_6H_5COCl led to a 75% yield of $C_6H_5COCH_2C_6H_5$ and 16% of the diadduct **13**. The β-keto amide **11** (R = C_6H_5) could



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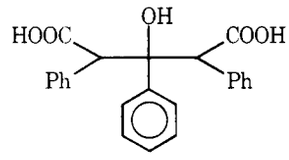


13

be converted into the desired cyclohexyl benzyl ketone by refluxing in concentrated HCl in a 95% yield. Thus the total yield of ketone obtained from this reaction was 60%.

The most discouraging results occurred with the dianion **2** ($R_1 = R_2 = H$) derived from acetic acid. Treatment of this insoluble dianion with cyclohexanecarbonyl chloride led to the isolation of cyclohexyl methyl ketone in a 5% yield. Various modifications of the reaction conditions were tried in attempts to improve the yield. Shorter and longer reaction times, higher (25 °C) and lower (−95 °C) reaction temperatures, addition of 1–3 equiv of hexamethylphosphoric triamide (HMPT) and excess LDA, and reverse addition of the dianion to the acyl chloride did not improve the yield of the desired product. The dianions of acetic and propionic acid form aggregates in THF and are only slightly soluble.[6a,d] Apparently they react slowly with the acyl chloride, permitting the diisopropylamine and any residual LDA in the reaction mixture to effectively compete to form the amide. The dianion of phenylacetic acid is soluble in THF and no formation of amide was observed. Another factor contributing to the low yield may be that the insoluble dianions may react as bases as well as nucleophiles.[6d]

Our work complements that of Angelo[7c] who acylated the dianions of acids with esters. The β-keto acids were isolated and thermolyzed to form ketones. This procedure gives poor yields of ketones with acids more hindered than acetic acid. Our procedure gives good yields of ketones when acids other than acetic and propionic are used.

Conclusions

The procedure we describe is a facile synthesis of symmetrical and unsymmetrical alicyclic, aliphatic, and aromatic ketones. The starting materials (carboxylic acids and carbonyl chlorides) are readily available. The products can be isolated in good yields and in high purity.

Dianions of acids containing two alkyl substituents in the α position react smoothly with acid chlorides to yield stable, readily isolated, β-keto acid, diisopropylammonium salts **4** which are easily purified and converted to highly pure ketones **5**. Dianions containing only one substituent in the α position which are soluble in THF give good yields of ketones. Dianions of acetic and propionic acid (which are only slightly soluble or insoluble in THF) give low yields of ketones when acylated with acid chlorides.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point device and are uncorrected. The NMR spectra were obtained using a JEOL MH-100 or a JEOL C-60HL spectrophotometer with Me_4Si as an internal standard in $CDCl_3$ as solvent, unless otherwise stated. VPC analyses were performed on a Gow-Mac 69-100 chromatograph using a 4 ft × 0.25 in. DC-200 Chromosorb column. All percentage data for VPC analysis are raw data and are uncorrected for variations in detector response. Microanalyses were performed by Robertson Laboratories, Florham Park, N.J., or Baron Consulting Co., Orange, Conn.

General Procedure for the Formation of β-Keto Acid Diisopropylammonium Salts 4. Lithium diisopropylamide was prepared by dissolving 2.02 g (20 mmol) of diisopropylamine in 50 ml of anhydrous THF (freshly distilled from benzophenone sodium ketyl) under N_2 and adding 8 ml (20 mmol) of 2.5 M *n*-butyllithium in hexane at −70 °C. The yellow solution was stirred at −70 °C for 15 min and 10 mmol of the carboxylic acid was added. The mixture was heated to 50 °C for 1 h and then cooled to −70 °C. The acyl chloride (11 mmol) was added rapidly and the reaction mixture stirred at −70 °C for 30 min. The mixture was then poured over 35 g of ice and 5 ml (10 mmol) of 2 M HCl and extracted ten times with 20-ml portions of $CHCl_3$. The combined $CHCl_3$ portions were dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting β-keto acid ammonium salts were recrystallized from CH_2Cl_2/hexane. The physical properties and spectral data of these salts are summarized in Table II.

General Procedure for the Formation of Ketones 5. The β-keto acid diisopropylammonium salt **4** was placed in a glass tube and an aspirator vacuum was applied. The tube was then inserted into a hot block (150–200 °C) until distillation of the ketone ceased. All decarboxylations proceeded in yields of 85–93%. The results of these thermolyses are listed in Table III.

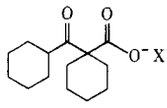
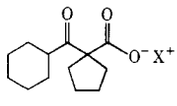
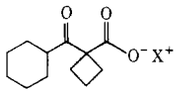
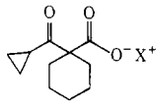
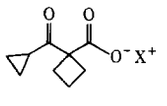
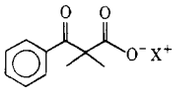
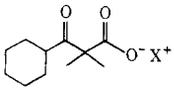
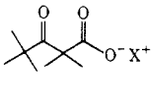
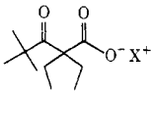
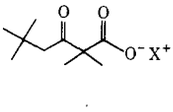
Alternate Procedure for the Formation of Ketones 5. In a flask containing 20 ml of 2 M aqueous HCl was added 4 mmol of β-keto acid ammonium salt **4**. Heat was applied and the ketone **5** was steam distilled from this flask. After 100 ml of water was collected, it was saturated with NaCl and washed with 5 × 10 ml of pentane. The combined pentane fractions were dried ($MgSO_4$) and evaporated under reduced pressure to yield 85–90% colorless **5**.

Formation of 2,2,4-Trimethyl-3-pentanone 5H. When heated under vacuum, **4H** sublimed so readily that decarboxylation could hardly be effected. Under atmospheric pressure, heating **4H** to 200 °C caused some decarboxylation as well as some sublimation. After five such distillation/sublimations (200 °C, 1 atm) pure ketone was isolated (85% yield, >99% purity by VPC, IR showed no absorption >3000 cm^{-1}).

General Procedure for the Isolation of β-Keto Acids. The general procedure for the formation of β-keto acid diisopropylammonium salts was followed up to the part where the reaction mixture was poured on ice. The reaction mixture was instead added to 20 ml (40 mmol) of 2 M HCl and 50 g of ice. The cloudy solution was then washed three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. During this isolation procedure, the temperature of all solutions was kept at 0 °C. The resulting yellow oil, upon treatment with cold pentane, yielded crystalline β-keto acid. The mother liquor could then be distilled to yield ketone. The physical properties of the β-keto acids we isolated are given in Table IV.

Reaction of the Dianion of Phenylacetic Acid with Cyclohexanecarbonyl Chloride. The general procedure was followed up to the point where the reaction mixture was poured on ice. The aqueous portion was washed nine times with $CHCl_3$ and set aside (see below). The combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. From this oil was crystallized ($CHCl_3$/hexane) 1.36 g of keto amide **11** (R = C_6H_5) [mp 135–136 °C; NMR ($CDCl_3$) δ 0.69–2.27 (m, 22 H, $-CH_3$ and $-CH_2-$), 2.3–3.0 (b, 1 H, H α to carbonyl on cyclohexyl ring), 3.2–4.2 (m, 2 H, NCH), 4.93 (s, 1 H, ArCH), 7.47 (s, 5 H, ArH); IR (Nujol mull) 1718, 1622 cm^{-1}]. Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48. Found: C, 76.34; H, 9.53. The mother liquor of these crystals was dissolved in pentane, cooled to −78 °C, and the resulting crystals were filtered at this temperature. The crystals melted below room temperature to form a light yellow oil from which was sublimed (90 °C, 0.03 mm) 0.7305 g of cyclohexyl benzyl ketone. Although it formed a solid on the cold finger, it melted below room temperature. The mother liquor on preparative TLC (SiO_2 eluted with benzene) yielded an additional 0.268 g of ketone (total yield 50%) [NMR ($CDCl_3$) δ 1.0–2.0 (m, 10 H, $-CH_2-$), 2.48 (b, 1 H, COCH), 3.77 (s, 2 H, $COCH_2$), 7.37 (s, 5 H, ArH); IR (neat) 1712 cm^{-1}]. The aqueous layer from the original quench was made strongly acidic (2 M HCl) and washed with ether, dried

Table II

Registry no.	Run	β-Keto acid diisopropylammonium salt 4,[a] X^+ = $H_2N^+[CH(CH_3)_2]_2$	Mp,[b] °C	% yield	NMR, δ ($CDCl_3$)
61259-06-1	A		111–113	62	1.35 (d, J = 6 Hz, 12 H, CH_3) 1.0–2.4 (b, 20 H, $-CH_2-$) 2.4–3.8 (m, 3 H, NCH and H α to carbonyl) 9.3 (bs, 2 H, H_2N)
61259-08-3	B		96–98	65	1.3 (d, J = 6 Hz, 12 H, CH_3) 1.0–2.5 (b, 19 H, $-CH_2-$) 2.85 (bs, 1 H, H α to carbonyl) 3.3 (m, 2 H, NCH) 8.7 (bs, 2 H, H_2N)
61259-10-7	C		108–109	78	1.0–2.1 (b, 12 H, $-CH_2-$ from cyclohexyl and center methylene from cyclobutyl) 1.35 (d, J = 6 Hz, 12 H, CH_3) 2.3–3.0 (m, 5 H, 2 methylene from cyclobutyl and H α to carbonyl) 3.4 (m, 2 H, NCH) 8.7 (bs, 2 H, H_2N)
61259-12-9	D		115–117	62	0.6–1.1 (m, 4 H, $-CH_2-$ from cyclopropyl) 1.1–2.7 (b, 11 H, $-CH_2-$ from cyclohexyl and H α to carbonyl) 1.33 (d, J = 6 Hz, 12 H, CH_3) 3.3 (m, 2 H, NCH) 8.7 (bs, 2 H, H_2N)
61259-14-1	E		102–103	23	0.6–1.1 (m, 4 H, methylene from cyclopropyl) 1.3 (d, J = 6 Hz, 12 H, CH_3) 1.5–3.0 (m, 7 H, $-CH_2-$ from cyclobutyl and H α to carbonyl) 3.32 (m, 2 H, NCH) 8.7 (bs, 2 H, H_2N)
61259-15-2	F		106–108	60	1.23 (d, J = 6 Hz, 12 H, CH_3 from i-Pr) 1.47 [s, 6 H, $(CH_3)_2$] 3.20 (m, 2 H, NCH) 7.3–8.3 (m, 5 H, ArH) 8.4 (bs, 2 H, H_2N)
61259-17-4	G		100–101.5	61	1.09 [s, 6 H, $(CH_3)_2$] 1.09 (d, J = 12 Hz, CH_3 from i-Pr) 0.9–2.1 (bm, 10 H, $-CH_2-$) 2.7 (bs, 1 H, H α to carbonyl) 3.24 (m, 2 H, NCH) 9.0 (bs, 2 H, H_2N)
61259-19-6	H[c]		165–168	61	1.23 (s, t-Bu CH_3) 1.26 (d, J = 6 Hz, i-Pr CH_3) 1.29 [s, $(CH_3)_2$] } 27 H 3.2 (m, J = 6 Hz, 2 H, NCH) 9.0 (bs, 2 H, H_2N)
61259-21-0	I		127–128	60	0.70 (t, J = 8 Hz, 6 H, CH_2CH_3) 1.23 (s, 9 H, t-Bu CH_3) 1.26 (d, J = 6 Hz, 12 H, i-Pr CH_3) 2.87 (q, J = 8 Hz, 4 H, CH_2CH_3) 3.19 (m, J = 6 Hz, 2 H, NCH) 9.6 (bs, 2 H, H_2N)
61259-23-2	J		92–95	34	1.03 (s, 9 H, t-Bu CH_3) 1.28 [s, 6 H, $(CH_3)_2$] 1.38 (d, J = 5.5 Hz, 12 H, i-Pr CH_3) 2.52 (s, 2 H, $-CH_2-$) 3.35 (m, J = 5.5 Hz, 2 H, NCH) 9.3 (bs, 2 H, H_2N)

[a] Satisfactory analytical data were reported for all of these salts. [b] All compounds melted with vigorous evolution of CO_2. [c] Both 60-MHz and 100-MHz spectra appear as follows: δ 1.23 (s) and 1.29 (s) (27 H, all $-CH_3$), 3.2 (m, J = 6 Hz, 2 H, NCH), 9.0 (bs, 2 H, H_2N). When the multiplet at δ 3.2 was irradiated in a double irradiation experiment (100 MHz), the spectra in the upfield region collapsed to three singlets at δ 1.23, 1.26, and 1.29. Hence the doublet of the isopropyl moiety is superimposed on top of two singlets, one resulting from the *tert*-butyl group and one from the geminal methyl groups. Since the singlet at δ 1.23 is larger than the one at δ 1.29, it was judged to represent the *tert*-butyl group.

Table III. Ketones Obtained from the Thermolyses of 4

Registry no.	Run	Ketone 5	NMR, δ ($CDCl_3$)
119-60-8	A	Dicyclohexyl[a]	1.0–2.0 (m, 20 H, $-CH_2-$) 2.2–2.6 (bs, 2 H, H α to carbonyl)
17773-63-6	B	Cyclohexyl cyclopentyl[a]	1.0–2.0 (m, 18 H, $-CH_2-$) 2.1–2.6 (bs, 1 H, H α to carbonyl) 2.6–3.3 (bs, 1 H, H α to carbonyl)
32446-20-1	C	Cyclohexyl cyclobutyl[b]	1.1–2.9 (m, 17 H, all cyclohexyl protons and $-CH_2-$ from cyclobutyl ring) 3.2–3.6 (m, 1 H, H α to carbonyl from cyclobutyl ring)
58688-35-0	D	Cyclohexyl cyclopropyl[c]	0.5–1.0 (m, 4 H, $-CH_2-$ from cyclopropyl ring) 1.0–2.8 (m, 12 H, cyclohexyl and H α to carbonyl)
14114-01-3	E	Cyclobutyl cyclopropyl[d]	0.6–1.05 (m, 4 H, $-CH_2-$ from cyclopropyl) 1.6–2.4 (m, 6 H, $-CH_2-$ from cyclobutyl) 3.1–3.8 (m, 2 H, H α to carbonyl)
611-70-1	F	Isobutyrophenone[e]	1.22 (d, J = 8 Hz, 6 H, $-CH_3$) 3.6 (m, J = 8 Hz, 1 H, COCH) 7.2–8.4 (m, 5 H, ArH)
1125-17-9	G	Cyclohexyl isopropyl[b]	1.0–2.2 (m, 10 H, $-CH_2-$) 1.08 (d, J = 6 Hz, 6 H, $-CH_3$) 2.5 (bs, 1 H, H α to carbonyl on cyclohexyl ring) 2.9 (m, 1 H, H α to carbonyl on isopropyl moiety)
5857-36-3	H	Isopropyl *tert*-butyl[f]	1.08 (d, J = 6 Hz, 6 H, $-CH_3$) 1.16 (s, 9 H, *tert*-butyl) 3.0 (m, J = 6 Hz, H α to carbonyl)
40239-63-2	I	2,2-Dimethyl-4-ethyl-3-hexanone[g]	0.94 (t, J = 7 Hz, 6 H, $-CH_3$) 1.15 (s, 9 H, *tert*-butyl) 1.14 (m, 4 H, $-CH_2-$) 2.8 (m, 1 H, H α to carbonyl)
40239-50-1	J	Neopentyl isopropyl[f,h]	1.02 (s, 9 H, *tert*-butyl) 1.06 (d, J = 7 Hz, 6 H, CH_3) 2.36 (s, 2 H, $-CH_2-$) 2.9 (m, J = 7 Hz, H α to carbonyl)

[a] H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 4528 (1967). [b] S. A. Monti and C. K. Ward, *Tetrahedron Lett.*, 697 (1971). [c] Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.54; H, 10.92. [d] M. Hanack and H. M. Ensslin, *Justus Liebigs Ann. Chem.*, **697**, 100 (1966). [e] See ref 9b. [f] F. C. Whitmore and F. S. Forster, *J. Am. Chem. Soc.*, **64**, 2966 (1942). [g] Haller and E. Bauer, *C. R. Acad. Sci.*, **150**, 582 (1910). [h] See ref 10f.

Table IV

Registry no.	β-Keto acid[b]	Mp,[a] °C	NMR, δ ($CDCl_3$)
61259-16-3	**7**	75–77	1.0–2.0 (b, 10 H, $-CH_2-$) 1.43 (s, 6 H, CH_3) 10.8 (bs, 1 H, COOH)
61259-07-2	**8**	59–61.5	1–2.4 (m, 18 H, $-CH_2-$) 2.5–2.9 (b, 1 H, H α to carbonyl) 9.9–10.3 (b, 1 H, COOH)
38744-73-9	**9**	97–98	1.58 (s, 6 H, CH_3) 7.3–8.1 (m, 5 H, aromatic H's) 10.7 (bs, 1 H, COOH)

[a] All β-keto acids melted with vigorous evolution of CO_2. [b] Satisfactory elemental analyses were reported for these compounds.

($MgSO_4$), and evaporated under reduced pressure to yield an oil which on crystallization ($CHCl_3$/pentane) gave 0.332 g of **12** [mp 179–180 °C dec; NMR ($CDCl_3$–Me_2SO-d_6) δ 0.5–2.2 (m, 11 H, $-CH_2-$), 4.43 (s, 2 H, ArCH), 5.97 (bs, 1 H, OH), 7.16–8.0 (m, 5 H, ArH), 10–12 (b, 1 H, COOH); IR (Nujol mull) 1700 (b), 2400–3150 cm^{-1}]. Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 71.84; H, 6.97. The mother liquor from **12** was evaporated to an oil (0.4809 g) and was shown by NMR analysis to contain a 3:2 ratio of cyclohexanecarboxylic acid and phenylacetic acid.

Hydrolysis of Keto Amide 11 (R = C_6H_5). To a flask charged with 60 mg of **11** (R = C_6H_5) was added 15 ml of concentrated HCl. The resulting suspension was refluxed with stirring for 48 h. During this period the precipitate vanished. The resulting solution was washed five times with 5-ml portions of pentane. The pentane was dried ($MgSO_4$) and concentrated to yield colorless cyclohexyl benzyl ketone (35 mg, 95% yield).

Reaction of the Dianion of Propionic Acid with Cyclohexanecarbonyl Chloride. The general procedure was followed until the reaction mixture was placed on ice. The aqueous solution was made weakly acidic with 2 M HCl (pH 6) and extracted with ether, and the ether was dried ($MgSO_4$) and evaporated to yield an oil. This oil was heated to 130 °C in a flask equipped with a reflux condenser until gas evolution ceased. Pentane (30 ml) was added and the solution was washed with 10 ml of 5% aqueous KOH. The KOH extract was then backwashed with 2 × 10 ml of pentane. The combined organic layers were dried ($MgSO_4$) and evaporated to a dark oil (1.758 g, mixture A). Amide **10** could be isolated from mixture A in 15% yield by distilling (80 °C, aspirator pressure) a yellow oil which, upon dissolution in pentane and cooling (−78 °C), produces 0.300 g of white crystals [mp 74–75 °C; NMR ($CDCl_3$) δ 1.0–2.0 (m, 22 H, $-CH_2-$ and CH_3), 2.0–2.5 (b, 1 H, CHCO), 3.4–4.2 (m, 2 H, NCH); IR (Nujol mull) 1642 cm^{-1}]. Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92. Found: C, 73.95; H, 11.91. If mixture A is instead distilled at 100 °C (0.1 mm) followed by treatment with hot hexane, a 14% yield of keto amide **11** (R = CH_3) is isolated [mp 80–82 °C; NMR ($CDCl_3$) δ 1.0–2.0 (m, 25 H, $-CH_2-$ and CH_3), 1.55 (bs, 1 H, H α to carbonyl on cyclohexyl ring), 3.2–4 (m, 2 H, CONCH), 3.66 (q, 1 H, H α to both carbonyls); IR (Nujol mull) 1712, 1624 cm^{-1}; mass spectrum m/e 267, 224, 156, 128, 111, 100, 83]. Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.87; H, 10.93. Found: C, 71.89; H, 11.00. If mixture A is instead chromatographed (SiO_2, 50:1 pentane–ether), cyclohexyl ethyl ketone is obtained in 16% yield (0.2207 g) [NMR ($CDCl_3$) δ 0.92 (t, 3 H, CH_3), 1.0–2.0 (m, 10 H, $-CH_2-$), 2.34 (q, 2 H, $COCH_2$), 2.6 (bs, 1 H, CHCO); IR (neat) 1714 cm^{-1}].

Reaction of the Dianion of Acetic Acid with Cyclohexanecarbonyl Chloride. LDA was generated as described in the general procedure. To this, at −78 °C was added 0.600 g (10 mmol) of acetic acid [distilled from $B(OAc)_3$] and 5.3 ml (30 mmol) of hexamethylphosphoric triamide (HMPT). The resulting white suspension was heated to 50 °C for 1 h, then cooled to −65 °C. A solution of 1.6 ml (11

mmol) of cyclohexanecarbonyl chloride in 3 ml of THF was then added quickly. The temperature of the reaction mixture rose 15 °C and the still turbid mixture was stirred for 20 min at −65 °C. It was then allowed to warm to −10 °C and the cloudy solution was added to 35 g of ice and shaken for 10 min (to destroy any unreacted carbonyl chloride) and then acidified with 20 ml of 2 M HCl and extracted with ether, which was dried ($MgSO_4$) and evaporated under reduced pressure to an orange oil. This was heated (130 °C) in a flask equipped with a reflux condenser until evolution of gas ceased. This oil (containing much HMPA) was then steam distilled to yield 0.732 g of yellow oil. Column chromatography (SiO_2, 1:50 ether–pentane) yielded 60 mg (5% yield) of cyclohexyl methyl ketone [NMR ($CDCl_3$) δ 1.1–2.0 (m, 10 H, $-CH_2-$), 1.1–1.6 (b, 1 H, CHCO), 1.18 (s, 3 H, $COCH_3$); IR (neat) 1715 cm^{-1}].

Reaction of the Dianion of Cyclobutanecarboxylic Acid with Cyclopropanecarbonyl Chloride. When the general procedure is followed, a 23% yield of the keto acid ammonium salt is obtained. When the procedure was modified so that when the reaction mixture was poured on ice, the aqueous portion was washed five times with pentane, which was then dried ($MgSO_4$), concentrated, cooled (−78 °C), and filtered (−78 °C), a 51% yield (0.855 g) of *N,N*-diisopropylcyclopropanecarboxamide was isolated [mp 20–22 °C; NMR ($CDCl_3$) δ 0.6–0.8 (m, 4 H), 1.28 (d, J = 6 Hz, 12 H), 1.56 (b, 1 H), 3.25–4.20 (m, 2 H); IR (neat) 1630 cm^{-1} (b)]. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 70.98; H, 11.20.

Registry No.—**2** (R_2 = C_6H_{11}), 61288-77-5; **2** (R_2 = C_5H_9), 61288-76-4; **2** (R_2 = C_4H_7), 61288-75-3; **2** (R_1 = Me; R_2 = Me), 57344-34-0; **2** (R_1 = R_2 = Et), 61259-24-3; **2** (R_1 = H; R_2 = Ph), 56842-55-8; **2** (R_1 = H; R_2 = Me), 60334-04-5; **2** (R_1 = R_2 = H), 60419-47-8; **10**, 61259-25-4; **11** (R = C_6H_5), 61259-26-5; **11** (R = CH_3), 61259-27-6; **12**, 61259-28-7; cyclohexyl benzyl ketone, 61259-29-8; cyclohexyl ethyl ketone, 1123-86-0; cyclohexyl methyl ketone, 823-76-7; *N,N*-diisopropylcyclopropanecarboxamide, 61259-30-1; lithium diisopropylamide, 4111-54-0.

References and Notes

(1) Presented in part at the First Chemical Congress of the North American Continent, Mexico City, Mexico, Nov 30–Dec 5, 1975, Abstracts, No. ORGA-021.
(2) Research Fellow of the Humphrey Chemical Co., North Haven, Conn.
(3) National Defense Education Act Fellow, 1972–1974.
(4) (a) B. Blagoev and D. Ivanov, *Synthesis*, 615 (1970); (b) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, Englewood Cliffs, N.J., 1954, p 948 ff.
(5) A. A. Morton, F. Fallwell, Jr., and L. Palmer, *J. Am. Chem. Soc.*, **60**, 1426 (1938).
(6) (a) P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967). (b) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972); Creger presents an excellent review of the literature regarding the formation of α anions using organometallics and alkali amides and discusses some of the problems encountered in previous research in this area. (c) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 582 (1973). (d) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., *J. Org. Chem.*, **37**, 451 (1972). (e) D. Ivanov, G. Vassilev, and I. Panayotov, *Synthesis*, **83** (1975).
(7) (a) N. L. Holy, *Chem. Rev.*, **74**, 243 (1974), and references cited therein; (b) H. Normant and B. Angelo, *Bull. Soc. Chim. Fr.*, 810 (1962), for studies using sodium naphthalenide; (c) B. Angelo, *C. R. Acad. Sci., Ser. C*, **276**, 293 (1973), and reference cited therein; (d) T. Fujita, S. Watanabe, and K. Suga, *Aust. J. Chem.*, **27**, 2205 (1974), and references cited therein; (e) B. Angelo, *C. R. Acad. Sci., Ser. C*, **278**, 383 (1974).
(8) (a) Y. N. Kuo, J. A. Yahner, and C. Ainsworth, *J. Am. Chem. Soc.*, **93**, 6321 (1971); (b) C. Ainsworth and Y. N. Kuo, *J. Organomet. Chem.*, **46**, 73 (1972).
(9) (a) M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971); (b) M. W. Logue, *J. Org. Chem.*, **39**, 3455 (1974).
(10) (a) G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973), and references cited therein. Many references are listed to classical organometallic reagents and newer approaches using organo derivatives of iron, rhodium, boron, silicon, and copper. (b) G. H. Posner, C. E. Whitten, and P. E. McFarland, *ibid.*, **94**, 5106 (1972). (c) L. S. Hegedus, P. M. Kendall, S. M. Lo, and J. R. Sheats, *ibid.*, **97**, 5448 (1975). (d) J. Schwartz and J. B. Cannon, *ibid.*, **96**, 4721 (1974). (e) J. E. Dubois, M. Boussu, and C. Lion, *Tetrahedron Lett.*, 829 (1971). (f) J. A. MacPhee and J. E. Dubois, *ibid.*, 467 (1972). (g) J. E. Dubois, F. Hennequin, and M. Boussu, *Bull. Soc. Chim. Fr.*, 3615 (1969). (h) J. E. Dubois and M. Boussu, *Tetrahedron*, **29**, 3943 (1973). (i) S. Patai, "The Chemistry of the Carbonyl Group", Interscience, New York, N.Y., 1966, Chapter 6. (j) D. A. Shirley, *Org. React.*, **8**, 28 (1954). (k) M. J. Jorgenson, *ibid.*, **18**, 1 (1970).
(11) S. P. Dent, C. Eaborn, and A. Pidcock, *Chem. Commun.*, 1703 (1970).
(12) A. Pelter, M. G. Hutchings, and K. Smith, *Chem. Commun.*, 1529 (1970).
(13) A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, **38**, 2129 (1973), and references cited therein.
(14) A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, **15**, 270 (1976).
(15) C. Lion and J. E. Dubois, *Tetrahedron*, **29**, 3417 (1973).
(16) (a) M. W. Logue, R. M. Pollack, and V. P. Vitullo, *J. Am. Chem. Soc.*, **97**, 6868 (1975), and references cited therein. (b) Logue in ref 9b prepares several β-phenyl β-keto esters from the condensation of *tert*-butyl α-lithioisobutyrate and acid chlorides. These keto esters were converted to the β-keto acids (TFA, 15 min, 25 °C) or directly to the ketones (TFA, 1 h, reflux). (c) E. J. Corey and R. H. K. Chen, *J. Org. Chem.*, **38**, 4086 (1973). (d) K. Taguchi and F. H. Westheimer, *J. Am. Chem. Soc.*, **95**, 7413 (1973), and references cited therein.
(17) D. Ivanoff and N. I. Nicoloff, *Bull. Soc. Chim. Fr.*, **51**, 1331 (1932).

Rhodium-Mediated Alkylation of Acid Chlorides. A Facile Solid State Ketone Synthesis Using a Recyclable Polymer-Bound Rhodium Complex

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Polymer-bound bis(triphenylphosphine)chlorocarbonylrhodium(I) was found to be a regeneratable reagent for the synthesis of ketones from acid chlorides and organolithium reagents. $RhCl(CO)(PPh_3)_2$ was anchored to diphenylphosphinated styrene–divinylbenzene resins by ligand exchange. Treatment of these resins with organolithium, in THF, at −78 °C, gave $(Ⓟ\text{-}PPh_2)_2RhR(CO)$. The resin was then treated with an acid chloride which oxidatively added giving the anchored rhodium(III) complex, $(Ⓟ\text{-}PPh_2)_2Rh^{III}Cl(R'CO)(R)(CO)$. Upon warming, reductive elimination gave ketone, R'COR, and $(Ⓟ\text{-}PPh_2)_2RhCl(CO)$ was regenerated. Using this method, alkyl or aryl organolithium reagents could be selectively added to the acid chloride function in the presence of cyano, aldehyde, or ester functions. The polymer-bound reagent, $(Ⓟ\text{-}PPh_2)_2RhCl(CO)$, is much easier to handle, separate from reaction mixtures, and recycle than is $(RhCl(CO)(PPh_3)_2$.

The reaction of an acid chloride with either an organolithium reagent or a Grignard reagent is complicated by the fact that the ketone, resulting from the initial reaction, can further react to produce tertiary alcohols. Thus, poor ketone yields are usually achieved using this route (eq 1).

$$R'COCl + RM \rightarrow R'COR \rightarrow R'C(OH)R_2 \qquad (1)$$

The classic reaction of acid chlorides with dialkylcadmium reagents provides an alternative, but little used, path which is limited by the cadmium reagent. The reaction of both organolithium and Grignard reagents with rhodium(I) halides is well established.[1-3] Similarly, the oxidative addition of acid chlorides to rhodium(I) complexes to give acyl rhodium(III) complexes is well known.[4-6] Therefore, it seemed likely to us