followed by elution with 2% LiCl/20% MeOH/78% H_2O. Under these conditions, **1** is retained on the column. Products (contaminated with LiCl) were isolated by evaporation of the column eluent to dryness. An NMR spectrum of these products was essentially identical with a spectrum of an equimolar mixture of sodium phenolsulfonate (**6**) and sodium methallylsulfonate (**5**) (δ 2.33, 4.07, 5.47, and 5.53 for **5**). An aqueous solution of the products showed the ultraviolet shift expected for **6** when the solution pH was raised (λ_{max} 231 nm at pH 6, 254 nm at pH 10).

Analysis of Reaction Products by High-Pressure Liquid Chromatography (HPLC). A Waters Associates ALC 202 liquid chromatograph equipped with a Model U6K injector and a Bondapak AX anion exchange column was used. With 0.05 M $NaClO_4$ in 90% H_2O/10% MeOH as the mobile phase components were eluted in the order **6**, **1**, **3**, and were detected using a Perkin-Elmer Model LC-55 variable wavelength detector set at 231 nm.

Acknowledgments. The author is grateful to E. W. Wilburn, W. W. Lanier, and H. A. Taylor for product separations and analyses using liquid chromatography, and to Claudette Deatherage for NMR analyses.

Registry No.—**1**, 1208-67-9; **3**, 59219-47-5; **5**, 1561-92-8; **6**, 825-90-1; sodium bisulfite, 7631-90-5.

References and Notes

(1) M. S. Kharasch, E. M. May, and F. R. Mayo, *J. Org. Chem.*, **3**, 175 (1938).
(2) F. R. Mayo and C. Walling, *Chem. Rev.*, **27**, 351 (1940).
(3) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2d ed, Wiley, New York, N.Y., 1961, p. 172.
(4) Under these conditions little or no sodium methallylsulfonate (**5**) is detected, presumably because of its reaction with excess bisulfite.
(5) L. H. Peebles, Jr., *J. Appl. Polym. Sci.*, **17** 113 (1973).
(6) J. C. Masson (to Monsanto Co), U.S. Patent 3 426 104 (Feb 4, 1969).

A Simple Synthesis of 2-Alkylcyclohexenones[1]

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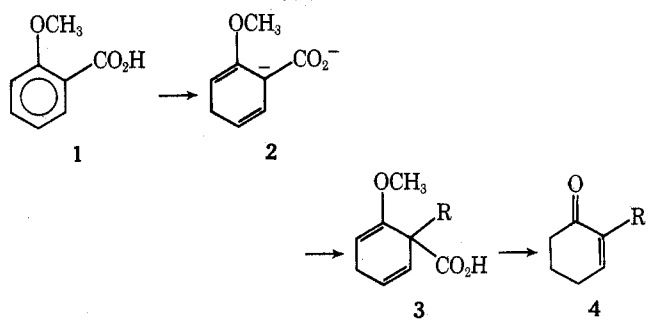
Cyclohexenones are versatile intermediates in organic synthesis. Among other applications, they are useful precursors to substituted cyclohexanones by conjugate addition,[2] enolate trapping,[3] and Diels–Alder addition,[4] as well as to alkynyl aldehydes.[5] While several procedures[6] have been employed for the preparation of 2-alkylcyclohexenones, by and large these procedures are lengthy or lead to isomeric mixtures of products.

The report[7] of the reductive alkylation of an *o*-methoxy substituted benzoic acid derivative led us to investigate this approach as a possible simple approach to 2-alkylcyclohexenones. Thus, addition of alkali metal to a suspension of the ammonium salt of **1** in liquid ammonia should give the dianion **2**, which could be alkylated. Evaporation of the ammonia followed by the hydrolysis of **3** with aqueous acid should then give the cyclohexenone **4**.

Scheme I



1 **2** **3** **4**

In fact, this one-pot procedure (see Experimental Section) works well, and is amenable to large-scale application. Thus, the enones listed (Table I) were prepared pure in gram quantity from the inexpensive acid **1**. Even given the modest yields achieved, this is currently the method of choice for preparing most 2-alkylcyclohexenones.

Experimental Section

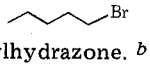
General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalysis was performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. All chemicals were used as received, except for allyl chloride, which was distilled immediately prior to use. Tetrahydrofuran was stored over Linde 4A molecular sieve after opening. NMR spectra were recorded on a JEOLCO MH-100 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer.

The general procedure for reductive alkylation followed by hydrolysis is illustrated by the synthesis of 2-allylcyclohexenone.

2-Allylcyclohexenone. A 1-l. three-neck round-bottom flask was charged with 15.2 g (100 mmol) of *o*-methoxybenzoic acid and 100 ml of THF. The solution was stirred magnetically, and ammonia (400 ml) was distilled in to give a thick white suspension. The reaction mixture was then maintained at reflux under a nitrogen atmosphere. Lithium wire (washed sequentially with hexane, methanol and hexane) was added in 7-cm pieces until a blue solution was maintained.[9] The reaction vessel was cooled in a dry ice–acetone bath and 1,2-dibromoethane (2 ml) was added, followed by allyl chloride (12.0 ml, 120 mmol).

The reaction mixture was allowed to warm to room temperature under a stream of nitrogen. The resultant brown slurry was diluted with 100 ml of ethylene chloride, then acidified with 100 ml of concentrated aqueous HCl (*foams!*). Water (100 ml) and hydroquinone (200 mg) were added, and the two-phase mixture was refluxed for 30 min. The mixture was diluted with water (300 ml), the organic phase was separated, and the aqueous phase was extracted with one 50-ml portion of ethylene chloride. The combined organic phase was washed with 100 ml of aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was distilled through a 10-cm Vigreux column to yield 3.65 g (27%) of colorless oil: bp 67–68 °C (3.2 mm); NMR ($CDCl_3$) δ 1.98, m, 2 H; 2.36, m, 4 H; 2.88, bd, J = 6 Hz, 2 H; 4.92, bd, J = 12 Hz, 2 H; 5.5–6.0,

Table I. Preparation of 2-Substituted Cyclohexenones

Registry no.	Alkylating agent	Bp, °C (mm)	Yield, %	Lit. bp, °C (mm)	Mp of derivative, °C	Lit. mp, °C	Ref.
107-05-1		67–68 (3.2)	27	98–103 (15)	174[a]	171[a]	6a
107-08-4		65–66 (2.4)	30	95 (14)	172[a,b]	163–164[a]	8
75-30-9		56–58 (2.3)	26	150	168[c]	163–164[c]	6g
110-53-2		74 (0.5)	27	72–78 (0.5)	113[a]	112[a]	6b

[a] 2,4-Dinitrophenylhydrazone. [b] Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.58; H, 5.70; N, 17.61. Found: C, 56.88; H, 5.78; N, 17.53. [c] Semicarbazone.

m, 1 H; 6.61, t, J = 4 Hz, 1 H. Ir (CCl_4) 3070, 2920, 1670, 1630, 910 cm^{-1}.

Registry No.—I, 579-75-9; II (R = $CH_2CH{=}CH_2$, 38019-50-0; II (R = Pr), 59034-18-3; II (R = Pr) 2,4-DNPH, 59034-20-7; II (R = Pr-*i*), 59034-19-4; II (R = $(CH_2)_4CH_3$), 25435-63-6.

References and Notes

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(3) E. S. Binkley and C. H. Heathcock, *J. Org. Chem.*, **40**, 2156 (1975), and references cited therein.
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(5) E. J. Corey and H. S. Sachdev, *J. Org. Chem.*, **40**, 579 (1975).
(6) (a) Alkylation of cyclohexenone: J.-M. Conia and A. Le Craz, *Bull. Soc. Chim. Fr.*, 1934 (1960). (b) Alkylation of cyclohexane-1,3-dione, followed by enol ether formation, reduction, and hydrolysis: M. F. Angell and T. M. Kafka, *Tetrahedron*, **25**, 6025 (1969). (c) Bromination–dehydrobromination of a 2-alkylcyclohexanone: E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Synth.*, **37**, 8 (1957). (d) Sulfenylation of a 2-alkylcyclohexanone, followed by oxidation and elimination: B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973). (e) Selenation of a 2-alkylcycloxanone, followed by oxidation and elimination: H. J. Reich, J. M. Renga, and I. L. Reich, *Ibid.*, **97**, 5434 (1975). (f) Reduction of a 2-alkylpyridine, followed by hydrolysis and aldol condensation: S. Danishefsky and P. Cain, *J. Org. Chem.*, **40**, 3607 (1975). (g) Oxidation of a 1-alkylcyclohexene: V. F. Belyaev, *Chem. Abstr.*, **58**, 4435d (1963).
(7) M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, **34**, 126 (1969).
(8) H. Christol, M. Mousseron and F. Plenat, *Bull. Soc. Chim. Fr.*, 543 (1959).
(9) The thick white suspension is the ammonium salt of the *o*-methoxybenzoic acid. As lithium metal is added this suspension dissolves to give a pale yellow solution. As more lithium is added this color deepens to a dark orange, which deepens further to a brown before going to the blue color typical of the presence of excess lithium. On addition of 1,2-dibromethane to consume the lithium the blue color is discharged, leaving a reddish-orange solution which fades to a yellow-white suspension almost immediately on the addition of the alkylating agent.

N,N,N′,N′-Tetramethylmethanediamine. A Simple, Effective Mannich Reagent

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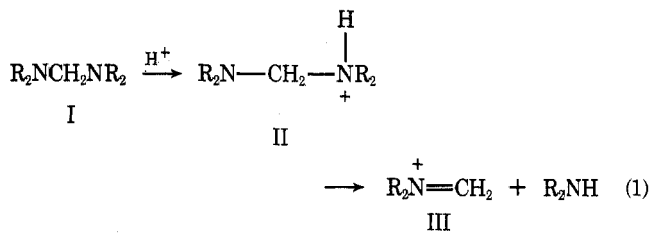
The Mannich reaction followed by β-elimination has long been used to convert a ketone into an α,β-unsaturated analogue. Under the usual reaction conditions, a methylenebisamine (I) is formed which, under acid conditions, forms the resonance-stabilized aminocarbonium ion (III) (eq 1).[1]

Ahond et al.[2,3] found that a similarly reactive intermediate formed by the treatment of trimethylamine oxide with a methylene chloride solution of trifluoroacetic anhydride proved to be an excellent Mannich reagent. Using this principle, Taylor[4] used *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride to generate an α,β-unsaturated ketone without utilizing the Mannich base.



In the preparation of the recently discovered uricosuric saluretics, (1-oxo-2,2-disubstituted-5-indanyloxy)acetic acids,[5] it was desired to introduce a methylene group under Mannich conditions α to an alkyl aryl ketone. Treatment of $ArC(=O)CH_2$-aryl with paraformaldehyde, dimethylamine hydrochloride, and acetic acid[6] did not afford high yields of α,β-unsaturated ketone in our hands.[7]

The desired transformation was successfully carried out by using *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride constituting an extension of the reaction described by Taylor. We found that the mild conditions employed allowed for the isolation of the α,β-unsaturated ketones in excellent yields with no by-products. For reaction to take place at <40°C, enhanced activation of the adjacent methylene by both the ketone and aryl moieties, $ArC(=O)CH_2$-aryl, was necessary since ketones of the type $ArC(=O)CH_2$-alkyl did not react under similar conditions. However, treatment of $ArC(=O)CH_2$-alkyl compounds with *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride at higher temperatures (90°C) did give the desired α,β-unsaturated ketones in good yields.

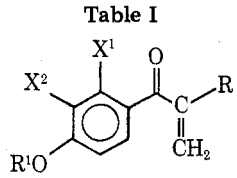
Experimental Section

General Procedure. Acetic anhydride (50 ml) was added dropwise to a suspension of the alkyl aryl ketone (0.1 mol) in *N,N,N′,N′*-tetramethylmethanediamine (50 ml). The reaction temperature was maintained at <40°C by ice-bath cooling. After 1 h of stirring at 25 °C, the solution was added slowly to crushed ice–water (1 l.) with stirring to precipitate analytically pure product in 80–100% yield (Table I).

Acknowledgments. The author wishes to thank Dr. E. J. Cragoe, Jr., and Mr. O. W. Woltersdorf, Jr., for their guidance and assistance throughout this work.

Registry No.—2,3-Dichloro-4-phenylacetylanisole, 59043-83-3; 2-chloro-3-methyl-4-phenylacetylanisole, 59043-84-4; 2,3-dichloro-4-phenylacetyl-α-carboxyanisole ethyl ester, 59043-85-5; 2,3-dichloro-4-[(*p*-bromophenyl)acetyl]anisole, 59043-86-6; 2,3-dichloro-

Table I



Registry no.	R	R^1	X^1	X^2	Mp, °C	% yield	Empirical[a] formula
57296-59-0	C_6H_5	CH_3	Cl	Cl	87–89	98	$C_{16}H_{12}Cl_2O_2$
59043-79-7	C_6H_5	CH_3	Cl	CH_3	81–85	85	$C_{17}H_{15}ClO_2$
59043-80-0	C_6H_5	$CH_2CO_2C_2H_5$	Cl	Cl	60–64	78	$C_{19}H_{16}Cl_2O_4$
57296-97-6	4-BrC_6H_4	CH_3	Cl	Cl	110–116	97	$C_{16}H_{11}BrCl_2O_2$
59043-81-1	4-FC_6H_4	CH_3	Cl	Cl	102–104	80	$C_{16}H_{11}Cl_2FO_2$
59043-82-2	C_2H_5	CH_3	Cl	Cl	46–48	86[b]	$C_{12}H_{12}Cl_2O_2$

[a] Satisfactory analytical data (±0.4% for C and H) for all compounds were submitted for review. [b] At <40 °C, no reaction; at 90 °C, 86% yield.