1), 77028-23-0; **15** (isomer 2), 77028-24-1; *dl*-**16**, 77028-25-2; *l*-**16**·(+)-DHAA, 77096-10-7; *dl*-**16** acid chloride, 77028-26-3; *l*-**16**, 77059-44-0; **17**, 77028-27-4; **18**, 77028-28-5; **19**, 77028-29-6; **20**, 77028-30-9; **21**, 77028-31-0; *dl*-**23**, 77028-32-1; *l*-**23**, 77059-45-1; *dl*-**24**, 77028-33-2; *l*-**24**, 77059-46-2; *dl*-**25**, 77028-34-3; *d*-**25**, 77059-47-3; *d*-**26**, 3886-69-9; **27** (isomer 1), 77028-35-4; **27** (isomer 2), 77028-36-5; *d*-**28**, 22038-87-5; **29** (isomer 1), 77028-37-6; **29** (isomer 2), 77028-38-7; *l*-menthoxyacetic acid chloride, 15356-62-4; *d*-camphor-10-sulfonic acid chloride, 21286-54-4; *d*-3-bromo-π-camphorsulfonic acid chloride, 72002-59-6; diethyl oxalate, 95-92-1; methyl iodide, 74-88-4.

A Procedure for Diethoxymethylation of Ketones[1]

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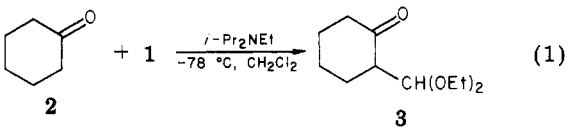
Reaction of a number of ketones with diethoxycarbenium fluoroborate in the presence of *N,N*-diisopropylethylamine at low temperature in methylene chloride results in a preparatively useful conversion to α-(diethoxymethyl) ketones. The method is compatible with arene, alkene, nitrile, chloride, and ester functional groups. With unsymmetrically substituted ketones, it is regioselective for the less substituted α-position. In favorable cases α,α'-dialkylation occurs. Conjugated ketones react normally at the saturated position adjacent to the carbonyl group. The mechanism of the reaction is considered.

Oxonium ions have unrealized potential as synthetic reagents. We describe an application of diethoxycarbenium fluoroborate (**1**) for the conversion of aliphatic

$$\underset{\mathbf{1}}{\mathrm{EtO{-}CH^{+}{-}OEt}} \leftrightarrow \mathrm{EtO^{+}{=}CHOEt}$$

and aromatic ketones to protected derivatives of the formyl ketone type. Our finding is that a variety of acyclic and cyclic ketones (e.g., **2**) are transformed into β-keto acetals by **1** in methylene chloride at −78 °C in the presence of *N,N*-diisopropylethylamine (eq 1). The reactant **1** is, of



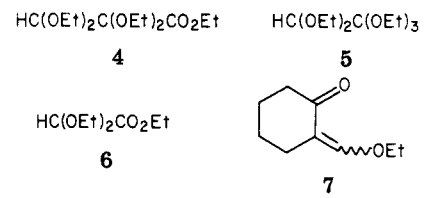
2 **3** (1)

course, an analogue of the Vilsmeir reagent, a well-known formylating species,[2] and the transformation shown also has some resemblance to the Mannich reaction, with regard to functionalization of an unactivated ketone.

The characteristics of the new reaction are the subject of this investigation, which was undertaken because the product (**3**) appeared promising synthetically and because the procedure is simpler, milder, and more direct than other acid-induced formylation techniques.[2,3] We report here the results of a modest examination of the scope and mechanism of this reaction.

Results

Description of Technique. The optimum method for carrying out the reaction of eq 1 was determined by systematic variation of experimental parameters. The preferred conditions in the case of cyclohexanone require the addition of 1 equiv of ketone to 2 equiv of in situ generated diethoxycarbenium fluoroborate (from triethyl orthoformate), slurried in methylene chloride at −78 °C with efficient stirring, followed by dropwise addition of 3 equiv of *N,N*-diisopropylethylamine over the course of approximately 0.5 h. The product is subsequently obtained by an aqueous sodium bicarbonate quench followed by phase separation, acid washing, and simple distillation. Yields are generally acceptable (Table I), although the procedure was optimized only for cyclohexanone. Minor byproducts which have been identified are **4**–**7**. The first three are



4 **5** **6** **7**

thought to arise from reactions involving diethoxycarbene, which previous work has suggested may be generated under the reaction conditions.[4] (They are also produced when no ketone is present in the reaction mixture.) Formation of **7** (an elimination product of **3**) may be avoided by exercising care in the acid extraction during workup of the reaction mixture. Under the procedure described, none of these substances amounts to more than a few percent of the distilled product. The hindered, nonnucleophilic base *N,N*-diisopropylethylamine, a fairly expensive but indispensable reagent for this transformation,[5] is routinely recovered from the aqueous extracts of the reaction mixture.

Scope. The method has been applied to an illustrative selection of ketones. The results are summarized in Table I. Comments on the individual examples follow. **(1) Cyclohexanone.** The minor product results from further alkylation. A 2.5-fold increase in the amount of diethoxycarbenium salt and amine diminishes the yield of the major product to 73%, while giving only 9% of dialkylation. **(2) Cyclopentanone.** Additional condensations are suggested by color development in the reaction mixture. **(3) Acetone.** Clean dialkylation occurs under the con-

(1) (a) Taken from the Ph.D. Thesis of H.-R. Tsou, University of Illinois at Chicago Circle, 1978; *Diss. Abstr. B*, *39*, 242 (1978). (b) Reported in preliminary form: W. L. Mock and H.-R. Tsou, Abstracts of the 175th National Meeting of the American Chemical Society, Anaheim, CA, Mar 1978, No. ORGN-78.

(2) G. A. Olah and S. J. Kuhn, "Friedel–Crafts and Related Reactions", Vol. 3, Wiley, New York, 1964, Part 2, Chapter 38, p 1211; F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **19**, 151 (1980).

(3) (a) T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974); (b) E. C. Taylor and J. L. LaMattina, *Tetrahedron Lett.*, 2077 (1977); (c) R. R. Sauers and P. A. Odorisio, *J. Org. Chem.*, **44**, 2980 (1979).

(4) R. A. Olofson, S. W. Walinsky, J. P. Marino, and J. L. Jernow, *J. Am. Chem. Soc.*, **90**, 6554 (1968).

(5) Other successful uses of this proton scavenger with oxonium salts have been recorded: (a) ref 4; (b) D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971); (c) M. J. Diem, D. H. Burow, and J. L. Fry, *J. Org. Chem.*, **42**, 1801 (1977).

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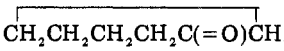
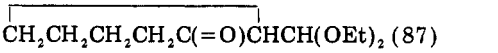
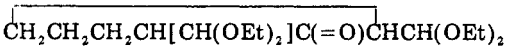
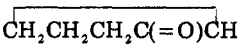
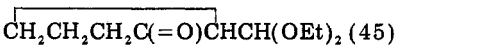
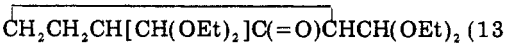
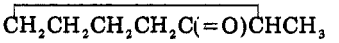
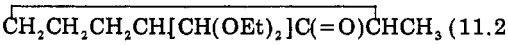
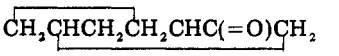
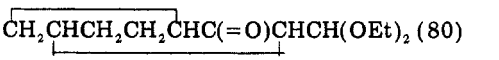
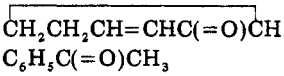
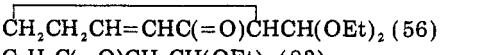
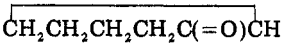
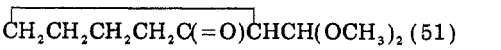
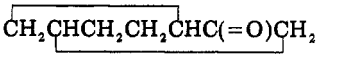
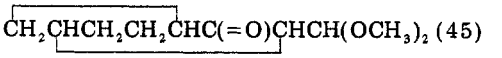
Table I. Illustrative Examples of Diethoxymethylation Reaction

no.	ketone (1.0 equiv)	equiv of $(EtO)_2CH^+$	equiv of *i*-Pr_2NEt	products (% yield)[a]
1		2.0	3.0	 (87)  (1.4)
2		2.0	3.0	 (45)  (13)
3	$CH_3C(=O)CH_3$	5.2	6.0	$(EtO)_2CHCH_2C(=O)CH_2CH(OEt)_2$ (76) $CH_3C(=)CH_2CH(OEt)_2$ (1)
4	$CH_3CH_2C(=O)CH_3$	0.2	0.3	$CH_3CH_2C(=O)CH_2CH(OEt)_2$ (7.6) $CH_3CH[CH(OEt)_2]C(=O)CH_3$ (1.7)
5		2.0	3.0	 (11.2) $CH_2CH_2CH_2CH_2C(=O)C(CH_3)CH(OEt)_2$ (3.8)
6		2.0	3.0	 (80)
7	$(CH_3)_2C=CHC(=O)CH_3$	2.0	3.0	$(CH_3)_2C=CHC(=O)CH_2CH(OEt)_2$ (58)
8		2.5	3.8	 (56)
9	$C_6H_5C(=O)CH_3$	2.5	3.75	$C_6H_5C(=O)CH_2CH(OEt)_2$ (83)
10	p-$N{\equiv}CC_6H_4C(=O)CH_3$	2.0	3.0	p-$N{\equiv}CC_6H_4C(=O)CH_2CH(OEt)_2$ (68)
11	$CH_2=CHCH_2CH_2C(=O)CH_3$	2.0	3.0	$CH_2=CHCH_2CH_2C(=O)CH_2CH(OEt)_2$ (66) $CH_2=CHCH_2CH[CH(OEt)_2]C(=O)CH_2CH(OEt)_2$ (15)
12	$CH_3C(=O)CH_2Cl$	2.0	3.0	$CH_3C(=O)CHClCH(OEt)_2$ (44)
13	$EtO_2CCH_2CH_2C(=O)CH_3$	2.0	3.0	$EtO_2CCH_2CH_2C(=O)CH_2CH(OEt)_2$ (59) $EtO_2CCH_2CH[CH(OEt)_2]C(=O)CH_3$ (8)
14	$CH_3C(=O)CH_2CH_2C(=O)CH_3$	2.0	3.0	$CH_3C(=O)CH_2CH_2C(=O)CH_2CH(OEt)_2$ (31) $CH_3C(=O)CH_2CH[CH(OEt)_2]C(=O)CH_3$ (12) $(EtO)_2CHCH_2C(=O)CH_2CH_2C(=O)CH_2CH(OEt)_2$ (12) $CH_3C(=O)CH[CH(OEt)_2]CH_2C(=O)CH_2CH(OEt)_2$ (9)
15		2.5[b]	3.0	 (51)
16		2.0[b]	3.0	 (45)

[a] Satisfactory analytical data (±0.4% for C, H) were obtained for all new compounds listed in the table, except as noted in the Experimental Section. [b] Amount of $(CH_3O)_2CH^+$.

ditions specified, yielding a potentially useful masked tricarbonyl compound. Decreasing the amounts of carbenium salt and amine by half yields approximately 40% each of mono- and dialkylation products. **(4) 2-Butanone.** The reaction was deliberately carried to low conversion in order to reveal the intrinsic regioselectivity for an unsymmetrically substituted ketone. The product ratio, 4.5:1 in favor of attack upon the less substituted position, is mechanistically significant. Repetition with a greater proportion of carbenium salt and amine (10-fold increase) gave 54% of the major monoalkylation product and 24% of dialkylation. **(5) 2-Methylcyclohexanone.** A similar product ratio (3:1) was obtained in this case. No dialkylation was detected. The low conversion (50% recovery of methylcyclohexanone) was only marginally improved by extending the reaction time fourfold. **(6) Norcamphor.** The strained bicyclic system was alkylated normally. **(7) 4-Methyl-3-penten-2-one.** The influence of conjugation is demonstrated in this and the following example. According to spectral evidence, alkylation occurs exclusively at the saturated position adjacent to the ketone. **(8) 2-Cyclohexenone.** Again attack is directed away from the unsaturation. The structure proof in this and the preceding case required hydrogenation in conjunction with NMR and IR examination. We note that an alternative procedure exists for achieving formylation of the 4-position of cyclohexenone.[6] **(9) Acetophenone.** Aromatic ketones appear to be unexceptional. **(10) 4-Cyanoacetophenone.** This and subsequent examples demonstrate the compatibility of the alkylation procedure with various additional (remote) functionalities. **(11) 5-Hexen-2-one.** There is no cyclization product as might have been anticipated from a cationic process. **(12) Chloroacetone.** Attack appears to be directed toward the halogenated position predominantly. Less volatile distillation fractions contain an approximately 3% yield of dialkylation product. It should be noted, however, that no product could be isolated in attempted alkylation of phenacyl chloride or 2-chlorocyclohexanone. **(13) Ethyl 4-Oxopentanoate.** The presence of an ester functionality is tolerated. Also formed in approximately 4% yield is a dialkylation product. **(14) 2,5-Hexanedione.** Not unexpectedly, the product mixture in this case is complex but is quite understandable in light of selectivities previously noted. Also produced were some diketo triacetals (<2%). As anticipated, polyalkylation was suppressed when reduced amounts of reagents were employed, at the expense of overall conversion. It is

(6) E. Wenkert and T. E. Goodwin, *Synth. Commun.*, 7, 409 (1977).

noteworthy that no cyclization reactions accompanied this alkylation, as would certainly be expected with a base-induced formylation procedure. **(15) Use of Dimethoxycarbenium Fluoroborate (from Trimethyl Orthoformate).** This reagent appears to be inferior to its ethyl homologue (compare with 1 and 6 in Table I). It is thought that this species methylates the *N,N*-diisopropylethylamine coreagent.[5c]

In an attempt to extend the scope of the reaction, we incorporated methyldiethoxycarbenium fluoroborate (8) into the reaction mixture as the alkylating reagent. None of the expected product was obtained. Oligomerization products of the carbenium salt were recovered, whether or not a ketone (cyclohexanone) was present (eq 2). The

$$\underset{8}{CH_3C^+(OEt)_2\ BF_4^-} \xrightarrow[-78\ °C\ (C_6H_{10}C=O)]{i\text{-}Pr_2EtN,\ CH_2Cl_2} \underset{9}{CH_3C(OEt)_2CH_2C(OEt)=CHCO_2Et} + \ldots \quad (2)$$

ester **9** was a significant product, isolable by distillation. It is presumed to arise by way of repeated cationic addition of 8 to 1,1-diethoxyethylene (which would form by deprotonation of 8). This substance appeared to be accompanied by many related species, which will not be described.[1a]

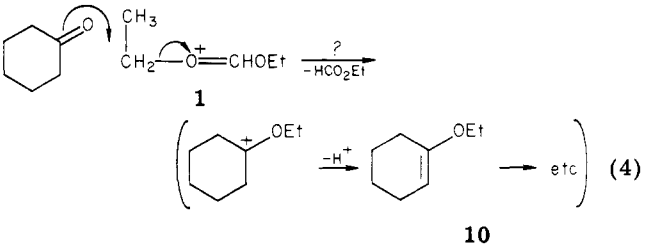
Mechanism. Several possible reaction paths have to be considered. Since Olofson has demonstrated the generation of a dialkoxycarbene from dimethoxycarbenium fluoroborate and *N,N*-diisopropylethylamine under similar conditions,[4] and since byproducts involving diethoxycarbene appear to be formed in our reaction mixture (4–6), a direct carbene insertion (or abstraction–recombination) mechanism has to be entertained.[3c] This possibility was excluded by deuterium labeling (eq 3). With either deu-

$$RC(=O)CD_3 \begin{cases} \not\rightarrow\ RC(=O)CD_2CD(OEt)_2 \\ \rightarrow\ RC(=O)CD_2CH(OEt)_2 \end{cases} \quad (3)$$

terioacetone or deuterioacetophenone as the ketone reactant, the isolated product contained no deuterium in the newly introduced formyl carbon. Taking into account all conceivable exchange processes, we conclude that the intermediacy of diethoxycarbene may be ruled out.

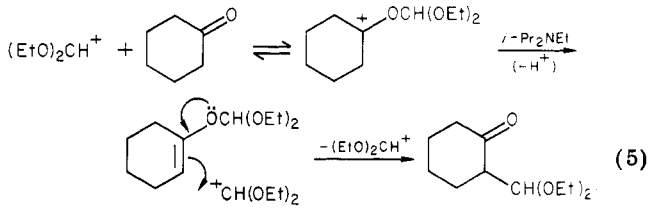
Some form of an enolization mechanism must therefore occur. (Enolate formation by *N,N*-diisopropylethylamine can probably be excluded at −78 °C.) The regioselectivity exhibited for unsymmetrically substituted ketones provides a clue. Except for chloroacetone, alkylation consistently occurs preferentially at the less substituted α-carbon (Table I). This behavior parallels that of the acid-catalyzed bromination of ketals in carbon tetrachloride solution, which must proceed through the intermediacy of an *enol ether*.[7] In contrast, acid-catalyzed bromination of ketones (proceeding through the *enol*) commonly exhibits the opposite regioselectivity. This has been interpreted in terms of a unique *steric requirement* in formation of the enol ether. Therefore, a reasonable mechanistic proposal for the diethoxymethylation reaction is that the ketone is activated by some form of O-alkylation, and is then deprotonated to an enol ether, which subsequently yields the observed reaction product by electrophilic addition of diethoxycarbenium ion to the double bond.

It remains to decide the nature of the O-alkylating moiety, which serves to activate the ketone in such a mechanism. An attractive possibility is that given in eq 4, since a previous study has shown that triethyloxonium



(4)

fluoroborate, a much weaker alkylating reagent than **1**, is capable of transient O-ethylation of ketones in a catalytic step of the ethyl diazoacetate homologation of ketones[8] (albeit at a somewhat higher temperature). This hypothesis was submitted to experimental verification. An authentic sample of the putative intermediate, ethyl cyclohexenyl ether (**10**), was prepared and incorporated into the reaction mixture in place of cyclohexanone, in order to see whether it would be kinetically competent. The results were negative. A substantial portion (27%) of **10** was recovered unchanged, and no diethoxymethylation product was formed. We therefore believe that some other enolic species must intervene. Since the diethoxycarbenium ion itself ought to be a potent Lewis acid, we suggest the mechanism of eq 5, which seems consistent with all



(5)

available evidence for the reaction. It should be noted that traces of boron trifluoride etherate or other acidic contaminants may also catalyze the reaction in some cases. However, the reaction still occurs when precautions are taken for their removal by purification of the carbenium salt. A kinetic test of the proposed mechanism is not feasible because of heterogeneity of the reaction mixture.

Discussion

Since our investigation of this reaction was prompted by a perceived synthetic utility, we shall conclude with a summary of what to us seem to be its notable preparative features. (1) Yields are acceptably high for a variety of ketones. (2) Reactions are carried out in a single reaction vessel and involve no isolation and purification of the intermediate reagents. (3) Preparation of crude diethoxymethylated ketones can be routinely accomplished within 2 h. (4) The yields of side products are typically less than 7%, and removal of byproducts can usually be accomplished by distillation. (5) Reactions take place in reasonably high yields for ketones having other potentially interfering functional groups, such as Cl, CN, CO_2R, C=C, or additional C=O groups. Alkenyl ketones react cleanly at an unconjugated position. (6) A steric requirement is prominent. In unsymmetrically substituted ketones, the less substituted α-carbon usually shows preference for alkylation. For geometrically crowded ketones, yields drop sharply, implying potential steric selectivity. (7) α,α′-

(7) M. Bettahar and M. Charpentier, *Chem. Commun.*, 629 (1970); M. Gaudry and A. Marquet, *Tetrahedron*, **26**, 5611 (1970); Y. Jasor, M. Gaudry, A. Marquet, and M. Bettahar, *Bull. Soc. Chim. Fr.*, 2732 (1973); Y. Jasor, M. Gaudry, and A. Marquet, *ibid.*, 2735 (1973); *Tetrahedron Lett.*, 53 (1976).

(8) W. L. Mock and M. E. Hartman, *J. Org. Chem.*, **42**, 459, 466 (1977).

Bis(diethoxymethyl) ketones can be obtained in sterically uncrowded cases (in particular, acetone). (8) The reaction products suffer ready conversion to β-keto aldehydes (by hydrolysis) or ethoxymethylidene ketones (by elimination). These are intermediates of proven utility. Other practical sequences (e.g., reduction–elimination) can be envisioned.

Experimental Section

2-(Diethoxymethyl)cyclohexanone (3). To 16.5 mL (0.1 mol) of triethyl orthoformate at −30 °C under a nitrogen atmosphere was added dropwise, with magnetic stirring over a period of 20 min, a solution of 15.0 mL (0.12 mol) of freshly distilled boron trifluoride etherate in 50 mL of methylene chloride. The mixture was then allowed to warm to 0 °C, and stirring was continued for 15 min. The resulting slurry of **diethoxycarbenium fluoroborate (1)** may be purified by filtration;[9] however, it is expedient to use the slurry, as obtained, immediately for subsequent reactions. The mixture was cooled to −78 °C while a nitrogen atmosphere was maintained, and 5.0 g (0.05 mol) of cyclohexanone (2) was added, followed by dropwise addition of 19.4 g (0.15 mol) of *N,N*-diisopropylethylamine over a period of 30 min, while efficient stirring was continued. After an additional 1 h (−78 °C, stirring, nitrogen atmosphere), the cold reaction mixture was poured rapidly into 500 mL of saturated aqueous sodium bicarbonate solution at 25 °C. More methylene chloride (200 mL) was added. After the mixture had been stirred vigorously for 10 min at room temperature, the organic phase was separated and washed with cold (0–5 °C), dilute sulfuric acid, followed by extraction with cold water. The methylene chloride solution was dried over anhydrous magnesium sulfate, the solvent was removed by rotary evaporation, and the residue was distilled at reduced pressure to give 8.8 g (87%) of **2-(diethoxymethyl)cyclohexanone (3)**: bp 55–57 °C (0.1 mm); NMR (CCl_4) δ 1.15 (t, 6 H, J = 7 Hz), 1.4–2.8 (m, 9 H), 3.28–3.85 (m, 4 H), 4.7 (d, 1 H, J = 5 Hz); IR (neat) 1715 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.15; H, 9.94. From a higher boiling distillation fraction was obtained 0.2 g (1.4%) of **2,6-bis(diethoxymethyl)cyclohexanone** of uncertain purity (no elemental analysis): bp 80–83.5 °C (0.025 mm); NMR (CCl_4) δ 1.07 (t, 6 H, J = 7 Hz), 1.1 (t, 6 H, J = 7 Hz), 1.4–2.9 (m, 8 H), 3.2–3.8 (m, 8 H), 4.76 (d, 2 H, J = 6.5 Hz); IR (neat) 1715 cm^{-1}. The *N,N*-diisopropylethylamine reagent was recovered by addition of sodium hydroxide pellets to the aqueous phase of the quenched reaction mixture.

Byproducts from the foregoing procedure will be briefly described so that they may be recognized if encountered. Should the acid wash during workup be conducted at a temperature much above 0 °C, some **2-(ethoxymethylidene)cyclohexanone (7)** may form, as evidenced by an NMR singlet at δ 7.14 in the distilled product. Other potential contaminants, which must originate from triethyl orthoformate are **pentaethoxyethane** [5: bp 40–40.5 °C (0.1 mm); NMR (CCl_4) δ 1.1 (t, 6 H, J = 7 Hz), 1.17 (t, 9 H, J = 7 Hz), 3.6 (q, 10 H, J = 7 Hz), 4.1 (s, 1 H)] which codistills with and may be converted (H_2O, glyme, H_2SO_4) into **ethyl diethoxyacetate**[4] [6: bp 42–42.5 °C (0.1 mm); NMR (CCl_4) δ 1.2 (t, 6 H, J = 7 Hz), 1.32 (t, 3 H, J = 7 Hz), 3.62 (m, 4 H), 4.17 (q, 2 H, J = 7 Hz), 4.73 (s, 1 H); IR (CCl_4) 1760 cm^{-1}] and **ethyl 2,2,3,3-tetraethoxypropionate**[4] [4: bp 56–58 °C (0.02 mm); NMR (CCl_4) δ 1.16 (t, 12 H, J = 7 Hz), 1.3 (t, 3 H, J = 7 Hz), 3.7 (m, 8 H), 4.15 (q, 2 H, J = 7 Hz), 4.53 (s, 1 H); IR (CCl_4) 1760 cm^{-1}; mass spectrum, m/e 278 (M^+). Anal. Calcd for $C_{13}H_{26}O_6$: C, 56.10; H, 9.42. Found: C, 55.71; H, 9.32]. The preceding three substances were preparatively obtained from a control reaction in the absence of cyclohexanone at −10 °C (yields: 4, 35%; 5, 11%; 6, 2%). They are formed in only trace amounts at −78 °C but might be identifiable spectroscopically in the products of some alkylation reactions. For many synthetic applications they should be innocuous.

Additional Examples. Essentially the same procedure was applied to the other ketones in Table I. In each case the products were fully characterized spectroscopically and gave carbon and hydrogen analyses[10] within 0.4% of the theoretical values, except as noted below. Only structurally pertinent properties of the products will be recorded (NMR spectra in CCl_4; IR spectra, neat). From cyclopentanone were obtained **2-(diethoxymethyl)cyclopentanone** [bp 73–73.5 °C (1.4 mm); IR 1740 cm^{-1}] and **2,5-bis(diethoxymethyl)cyclopentanone** [bp 87–90 °C (0.055 mm)] contaminated with 4 (resulting in low carbon analysis). From acetone were obtained **1,1,5,5-tetraethoxy-3-pentanone** [bp 71–71.5 °C (0.025 mm)] and **4,4-diethoxy-2-butanone**[11] [bp 70–71 °C (8 mm)]. From 2-butanone were obtained **1,1-diethoxy-3-pentanone** [bp 76–77 °C (8 mm); NMR δ 2.4 (q, 2 H, CH_3CH_2CO), 2.6 (d, 2 H, $COCH_2CH$), 4.8 (d, 1 H, CH_2CHO_2)], **4,4-diethoxy-3-methyl-2-butanone** (spectral identification only in mixture from low conversion), and **2-methyl-1,1,5,5-tetraethoxy-3-pentanone** [bp 130–130.5 °C (10 mm); NMR δ 4.4 (d, 1 H), 4.8 (t, 1 H)]. From 2-methylcyclohexanone were obtained **6-(diethoxymethyl)-2-methylcyclohexanone** and **2-(diethoxymethyl)-2-methylcyclohexanone**, codistilling at 42–42.5 °C (0.025 mm). The product ratio was estimated by NMR integration, and an elemental analysis was obtained on mixture. From norcamphor was obtained **3-(diethoxymethyl)norcamphor**: bp 48.5–49.5 °C (0.05 mm); NMR δ 4.47 (d, 1 H, J = 4.5 Hz); IR 1750 cm^{-1}; carbon analysis was high. From 4-methyl-3-penten-2-one was obtained **1,1-diethoxy-5-methyl-4-hexen-3-one**: bp 76–76.5 °C (0.25 mm); NMR δ 1.9 (s, 3 H), 2.12 (s, 3 H), 2.57 (d, 2 H, J = 5.5 Hz, $CHCH_2C{=}O$), 4.79 (t, 1 H, J = 5.5 Hz, CH_2CHO_2), 5.97 (m, 1 H); IR 1690, 1625 cm^{-1}. This material was hydrogenated (Pd/C, EtOH): NMR δ 0.94 (d, 6 H, Me_2CH), 2.03 (m, 1 H, Me_2CH), 2.27 (d, 2 H, J = 1.5 Hz, Me_2CHCH_2), 2.6 (d, 2 H, J = 5.5 Hz), 4.83 (t, 1 H, J = 5.5 Hz). From 2-cyclohexenone was obtained **6-(diethoxymethyl)-2-cyclohexenone**: bp 80–80.5 °C (0.8 mm); NMR δ 1.2 (t, 3 H), 1.9–2.7 (m, 5 H), 4.87 (d, 1 H), 5.83 (dd, 1 H), 6.6–7 (m, 1 H); IR 1680 cm^{-1}. This material upon hydrogenation gave an NMR spectrum identical with that of **3**. From acetophenone was obtained **3,3-diethoxypropiophenone**, bp 77–77.5 °C (0.025 mm). From *p*-cyanoacetophenone was obtained **3,3-diethoxy-*p*-cyanopropiophenone**: bp 121–121.5 °C (0.025 mm); NMR δ 3.33 (d, 2 H), 5.07 (t, 1 H); carbon analysis was high. From 5-hexen-2-one were obtained **1,1-diethoxy-6-hepten-3-one** [bp 73–73.5 °C (0.37 mm); NMR δ 2.57 (d, 2 H, J = 6 Hz), 4.75 (t, 1 H, J = 6 Hz); IR 1720, 1647 cm^{-1}] and **1,1-diethoxy-4-(diethoxymethyl)-6-hepten-3-one** [bp 80–80.5 °C (0.025 mm); IR 1720, 1647 cm^{-1}]. From chloroacetone was obtained **3-chloro-4,4-diethoxy-2-butanone**: bp 86–86.5 °C (10 mm); NMR δ 2.23 (s, 3 H, $CH_3C{=}O$), 4.05 (d, 1 H, CHClCH), 4.65 (d, 1 H, $CHCHO_2$). From ethyl 4-oxopentanoate were obtained **ethyl 6,6-diethoxy-4-oxohexanoate** [bp 75–75.5 °C (0.025 mm)] and **ethyl 3-(diethoxymethyl)-4-oxopentanoate** [bp ~74 °C (0.025 mm)] (ratio estimated by NMR integration). A pure analytical sample of the first isomer (only) was obtained by fractional distillation (major product, less volatile): NMR δ 4.77 (t, 1 H); isomers separable by silica TLC (PhH–EtOAc, 4:1). From 2,5-hexanedione were obtained mixed isomers, partially resolvable by fractional distillation [bp 69–72 °C (0.015 mm)]: **7,7-diethoxy-2,5-heptanedione** [NMR δ 4.74 (t, 1 H)] and **3-(diethoxymethyl)-2,5-hexanedione** [NMR δ 4.3 (d, 1 H)]. The ratio was estimated by NMR integration, and an elemental analysis was obtained on mixture. Bisalkylation products (mixed isomers) were also obtained which were also partially resolvable by fractional distillation [bp 117–121 °C (0.01 mm)]: **7,7-diethoxy-3-(diethoxymethyl)-2,5-heptanedione** [NMR δ 4.78 (d, 1 H), 4.32 (d, 1 H)] and **1,1,8,8-tetraethoxy-3,6-octanedione** [NMR δ 4.75 (t, 2 H)]. The ratio was estimated by NMR integration, and an elemental analysis was again obtained on the mixture. With dimethoxycarbenium fluoroborate[9] were obtained **2-(dimethoxymethyl)cyclohexanone** [bp 50–51 °C (0.025 mm)] and **3-(dimethoxymethyl)norcamphor** [bp 73–75.5 °C (0.44 mm)]; their spectra were similar to those of their ethyl homologues.

Reaction of Methyldiethoxycarbenium Fluoroborate.[9] Under the standard reaction conditions, in the presence or in the absence of cyclohexanone, the salt 8 gave multiple products, including a yield of ca. 14% of a substance, purified by distillation [bp 87–88 °C (0.025 mm)] and preparative silica TLC (PhH–

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EtOAc, 20:1), to which is assigned the structure **ethyl 3,5,5-triethoxy-2-hexenoate (9)**: NMR (CCl_4) δ 1.1 (t, 6 H, J = 7 Hz), 1.24 (s, 3 H), 1.35 (t, 6 H, J = 7 Hz), 3.12 (s, 2 H), 3.43 (q, 4 H, J = 7 Hz), 3.9 (q, 2 H, J = 7 Hz), 4.04 (q, 2 H, J = 7 Hz), 4.9 (s, 1 H); IR (neat) 1715, 1625 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 63.83; H, 9.79. Because of the poor elemental analysis, the product was hydrolyzed (H_2SO_4, H_2O, glyme, 30 min, 25 °C) to give **ethyl 3-ethoxy-5-oxo-2-hexenoate**: bp 71-72 °C (0.005 mm); NMR (CCl_4) δ 1.2 (t, 3 H), 1.33 (t, 3 H), 2.1 (s, 3 H), 3.7 (s, 2 H), 3.5-4 (m, 4 H), 5.0 (s, 1 H); IR (neat) 1730, 1710, 1630 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.79; H, 8.12.

Registry No. 1, 1478-41-7; 2, 108-94-1; 3, 77070-73-6; 4, 77070-74-7; 5, 58995-69-0; 6, 6065-82-3; 7, 15839-65-3; 8, 21872-75-3; 9, 77070-75-8; 2,6-bis(diethoxymethyl)cyclohexanone, 77070-76-9; 2-(diethoxymethyl)cyclopentanone, 77070-77-0; 2,5-bis(diethoxymethyl)cyclopentanone, 77070-78-1; 1,1,5,5-tetraethoxy-3-pentanone, 77070-79-2; 4,4-diethoxy-2-butanone, 20082-91-1; 1,1-diethoxy-3-pentanone, 31086-94-9; 4,4-diethoxy-3-methyl-2-butanone, 64943-25-5; 2-methyl-1,1,5,5-tetraethoxy-3-pentanone, 77070-80-5; 6-(diethoxymethyl)-2-methylcyclohexanone, 15839-41-5; 2-(diethoxymethyl)-2-methylcyclohexanone, 77070-81-6; 3-(diethoxymethyl)-norcamphor, 77070-82-7; 1,1-diethoxy-5-methyl-4-hexen-3-one, 77070-83-8; 6-(diethoxymethyl)-2-cyclohexenone, 77070-84-9; 3,3-diethoxypropiophenone, 36234-10-3; 3,3-diethoxy-p-cyanopropiophenone, 77070-85-0; 1,1-diethoxy-6-hepten-3-one, 77070-86-1; 1,1-diethoxy-4-(diethoxymethyl)-6-hepten-3-one, 77070-87-2; 3-chloro-4,4-diethoxy-2-butanone, 77070-88-3; ethyl 6,6-diethoxy-4-oxohexanoate, 77070-89-4; ethyl 3-(diethoxymethyl)-4-oxopentanoate, 77070-90-7; 7,7-diethoxy-2,5-heptanedione, 66622-96-6; 3-(diethoxymethyl)-2,5-hexanedione, 77070-91-8; 7,7-diethoxy-3-(diethoxymethyl)-2,5-heptanedione, 77070-92-9; 1,1,8,8-tetraethoxy-3,6-octanedione, 77070-93-0; 2-(dimethoxymethyl)cyclohexanone, 15839-38-0; 3-(dimethoxymethyl)norcamphor, 77070-94-1; cyclopentanone, 120-92-3; acetone, 67-64-1; 2-butanone, 78-93-3; 2-methylcyclohexanone, 583-60-8; norcamphor, 497-38-1; 4-methyl-3-penten-2-one, 141-79-7; 2-cyclohexenone, 930-68-7; acetophenone, 98-86-2; p-cyanoacetophenone, 1443-80-7; 5-hexen-2-one, 109-49-9; chloroacetone, 78-95-5; ethyl 4-oxopentanoate, 539-88-8; 2,5-hexanedione, 110-13-4; dimethoxycarbenium fluoroborate, 18346-68-4; ethyl 3-ethoxy-5-oxo-2-hexenoate, 33663-70-6; triethyl orthoformate, 122-51-0.

Palladium-Assisted Functionalization of Olefins: A New Amination of Electron-Deficient Olefins

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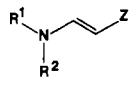
Palladium chloride catalyzed the reaction of substituted anilines with methyl vinyl ketone, methyl acrylate, and acrylonitrile to produce vinylogous arylamino ketones, esters, and nitriles. *N*-Methylaniline gave the highest yields. Aniline and benzylamine failed to react in the desired fashion. The reaction was restricted to enones lacking α and β substitution.

Introduction

Vinylogous arylamino ketones, esters, and nitriles (**1a-c**)



1a R^1 or R^2 = Ar; Z = COR_3
1b R^1 or R^2 = Ar; Z = $COOR_3$
1c R^1 or R^2 = Ar; Z = CN

are useful synthetic intermediates, particularly in the construction of heterocyclic compounds. Vinylogous arylamino ketones (**1a**) have been prepared by the reaction of substituted anilines with β-chloro-[1] and β-(acetylmethyl)acrylate.[2] The addition of aniline to acetylacetone gives a derivative of **1a** substituted in the 4-position.[3] Synthesis of vinylogous arylamino esters (**1b**) has been accomplished by the reaction of aniline with methyl propiolate and other conjugated alkynes.[4] Vinylogous arylamino nitriles (**1c**, R = Ph, R = H) are available from the reaction of $NaNH_2$ with 1-phenylimidazole in xylene at reflux.[5] Heating 1-phenyl-4-cyanotriazole at 80 °C in 1% Et_3N/C_6H_6 also gives the same product.[6] Vinylogous arylamino nitriles substituted with a methyl group in the 3-position have been prepared by the reaction of aniline and 3-methyl-3-aminoacrylonitrile in H_2O[7] and by the action of aniline on 3-cyanoallene.[8]

In connection with efforts toward the total synthesis of ergot alkaloids by means of our previously developed indole synthesis,[9] the reaction shown in eq 1 was investigated. Compound **2** had been shown to undergo palladium-catalyzed closure to 4-bromoindole, presumably via the σ-alkylpalladium intermediate **3**.[10] Since the methodology necessary to trap σ-alkylpalladium intermediates by insertion processes was well established,[11] it was anticipated that subjection of compound **2** to catalytic indole-formation conditions in the presence of methyl acrylate would yield the insertion product **4**. However, none of compound

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