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Phase Transfer Catalysis. The Acetoacetic Ester Condensation

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Received November 13, 1973

Great interest has developed in recent years in phase transfer processes, especially liquid–liquid phase transfer.[1,2] The elegant paper of Starks[1] on the usefulness of several liquid–liquid phase transfer catalysts gives several examples of how the process may be used as a routine synthetic tool. We have extended this work to a solid–liquid phase transfer process using the acetoacetic ester condensation as a representative example of this principle.

The catalyst used in this study was a long-chained aliphatic quaternary ammonium salt, "Alaquat 336,"[1,3] which consists of mixed trialkylmethylammonium chlorides (average molecular weight 503[1]). It is insoluble in water and soluble in all common organic solvents. The basic process was to generate a solid reactive anion which is normally insoluble in organic solvents, use the phase transfer catalyst to transport this anion into the organic phase, then allow this anion to react in the organic phase. The reactive anion generated in this study was the methyl acetoacetate anion. Once dissolved by the phase transfer catalyst in the organic solvent, this anion reacted with an alkylating agent to give the traditional acetoacetic ester alkylated product.

There have been numerous studies[4,5] directed at the alkylation pattern of ambident ions in both protic solvents (usually alcohols) and polar aprotic solvents. The major difference in these two systems seems to be that carbon alkylation is favored in protic solvents while O-alkylation is favored in polar aprotic solvents [especially in hexamethylphosphoramide[4a] (HMPA)]. In our study it was found that alkylation of the acetoacetate anion in benzene using benzyl chloride as the alkylation reagent gave predominantly (>99%) carbon alkylation with no detectable oxygen alkylation.[6] Thus, this process offers a reversal of the usually observed results in aprotic solvents in that carbon alkylation is favored, thereby giving an alternative to the usual procedure of using protic solvents to favor carbon alkylation. It also offers the advantage that no solvolysis products arising from alkylating reagent–solvent interactions are possible, thus eliminating a major side product of reactions run in protic solvents. This advantage is especially important when small amounts of valuable alkylating reagents are required, such as geranyl bromide.

The experimental conditions using this solid–liquid phase transfer process are exceedingly simple. The concentration of catalyst has an effect on the rate of reaction.

Table I
Catalyst Concentration Using Benzyl Chloride as the Alkylating Reagent

Ratio[a,b]	Yield,[c,d] %
No catalyst	25
25:1	61
20:1	70
10:1	85

[a] Standard conditions consist of benzene as solvent; 8-hr reflux; sodium methyl acetoacetate/benzyl chloride ratio 2:1; the reaction was protected from moisture during the reaction. [b] Molar ratio of catalyst to alkylating agent. Catalyst av mol wt 503. [c] Isolated yields by distillation. [d] Gc analysis shows only one peak >99% purity by integration.

Table II
Solvent Effects on Alkylation Yields

Solvent[a]	Yield,[b] %
Benzene	85
Toluene	82
Chloroform	56
Carbon tetrachloride	42
Hexane	40

[a] Standard conditions: 8-hr reflux, sodium methyl acetoacetate/benzyl chloride/catalyst ratio 20:10:1. [b] Isolated monoalkylated yields by distillation.

Table III
Alkylation Products

Alkylating agent[a]	Product,[b,c] %
Allyl bromide	85
Benzyl chloride	85
Geranyl bromide	85
Dimethylallyl chloride	37
Allyl chloride	30

[a] Standard conditions: 8-hr reflux, benzene solvent; sodium methyl acetoacetate/alkylating agent/catalyst ratio 20:10:1. [b] Product isolated by distillation. [c] Only monocarbon alkylation observed.

Using benzene as a solvent and 8-hr reflux as a standard condition, we found that a 10:1 alkylating reagent/catalyst molar ratio gave consistently high yields. All reactions with catalyst were accelerated over control experiments without catalyst. These results are tabulated in Table I. We also found that benzene was not the only solvent one could use. In effect, all commonly used solvents ranging from benzene to hexane may be used. These results are tabulated in Table II. One might note that in hexane the monocarbon alkylated product was obtained in 40% yield. The alkylation in hexane, without added catalyst, gave essentially no alkylation product (<5%). The reaction using different alkylating reagents is shown in Table III.

It is interesting to speculate on the anion species in solution. The initial transfer would give a quaternary ammonium methyl acetoacetate species which is soluble in nonpolar solvents because of the large hydrophobic properties and symmetry of the transfer reagent.[7] In our system, we looked for not only oxygen alkylation but dialkylation, both carbon–carbon and carbon–oxygen. Again we found very little, if any, of either product.[4,6] In the studies of alkylation in aprotic solvents two factors seem to control the alkylation pattern, that of the nature of the alkylating reagent and the tightness of the generated ion pair. The latter[4] seems to be most important in the control of these reactions. For example, in solvents like HMPA very loose ion pairs are formed, thus favoring the formation of O-al-

kylated products. This process has been used in several synthetic sequences[8] where O-alkylated material was the desired product. From our work it would seem to us that we are dealing with a very tight ion pair, thus the resulting carbon, instead of oxygen, alkylation. While it is true that activated alkylating agents tend to alkylate on carbon, the shift from polar protic solvents to polar aprotic solvents gives a much higher percentage of oxygen alkylation. Thus, le Noble[4a] reports a 13% yield of O-alkylated product, a 51% yield of C-alkylated product, and a 36% yield of di-C-alkylated product when methyl acetoacetate anion is alkylated with benzyl chloride in HMPA. le Noble[4a] also reports that allyl chloride alkylation of methyl acetoacetate anion gives 17% O-alkylation, 45% C-alkylation, and 38% di-C-alkylation. le Noble[4a] reports that, in a series of activated alkylating reagents (substituted benzyl chlorides), he obtains O-alkylated products ranging from 10 to 40% when HMPA was used as the solvent. These ratios of oxygen *vs.* carbon alkylation are almost never seen when these alkylations are carried out in polar protic solvents.[9]

le Noble, as well as others,[4b,c] also reports high yields of O-alkylated product when ethyl bromide was used as the alkylating agent with HMPA as solvent (*i.e.*, 45% yield). Kurz,[4b,c] *et al.*, observed the same trend with similar nonactivated alkylating reagents. We used *n*-butyl bromide as the alkylation reagent in our system and obtained less than 5% O-alkylated product. This result thus mimicks the alkylation pattern found in polar protic solvents. The reaction, however, had to be run for a longer time period than with our activated alkylating reagents to obtain a reasonable yield. When nonactivated halides are used in the traditional acetoacetic ester condensation (using absolute alcohol as a solvent), very little solvolysis of the alkylating reagent is observed. Thus, our system does not offer any substantial advantage in either yield or product distribution from the traditional procedure when nonactivated halides are used as alkylating reagents. However, when using activated alkylating reagents, an advantage in both alkylation products and suppression of side reactions is achieved by using the solid–liquid phase transfer process. This is especially true when small quantities of radioactive alkylating reagents[10] are used in the synthesis of biogenetic precursor molecules such as geraniol, farnesol, etc.

It is also known that aggregate formation can contribute to the reactivity of an anion[4a,11,12] in solution. We do not know what the aggregate properties of our system are nor how it affects the alkylation distribution. From the alkylating pattern we can only say that our species seems different from most other aprotic ion pairs and that this property may be used synthetically to give carbon alkylation almost exclusively.

Experimental Section

Boiling points and melting points are uncorrected. Nmr spectra were recorded on a Varian A-60 and a Joelco HA-100 nmr spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 457 grating spectrophotometer. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Gas chromatograms were run on a Varian Model 1400 gas chromatograph using a flame ionization detector.

Reaction of Methyl Acetoacetate with Benzyl Chloride. General Procedure. Sodium hydride (5.0 g of a 50% dispersion in mineral oil, 0.104 mol) was added to a 500-ml three-neck flask fitted with a mechanical stirrer (good stirring is essential), reflux condenser, and addition funnel fitted to provide an inert atmosphere. The sodium hydride was washed free of mineral oil with small portions of anhydrous benzene, 200 ml of anhydrous benzene being added as solvent after the mineral oil was removed. With stirring, methyl acetoacetate (11.6 g, 0.100 mol) was added dropwise with the evolution of hydrogen. The solution was stirred until no more evolution of hydrogen was observed. At this point "Alaquat 336" (2.5 g, 0.005 mol, dried by benzene azeotrope and diluted to a 0.001 mol/ml standard solution in benzene) was added and the solution was brought to reflux. At reflux benzyl chloride (6.3 g, 0.050 mol), dissolved in a few milliliters of benzene, was added at a reasonable rate and the solution was refluxed for 8 hr after the addition was completed. The solution was then cooled and acidified with 1 *N* HCl, the organic layers were separated (small amounts of ether may be added to break any emulsion formed at this point), the organic phase was washed with 5% sodium bicarbonate and brine, and the resulting organic phase was dried over magnesium sulfate. The solvent was removed on a rotary evaporator at 16 mm and the resulting oil was distilled to give 8.77 g of 3-carbomethoxy-4-phenylbutanone as a clear oil, bp 98–109° (0.05 mm) (85% yield). The catalyst remained as a dark residue in the distillation flask and was discarded. Gc analysis on a 10 ft 5% FFAP column showed only one peak which was >99% pure by integration. Infrared spectral analysis showed that the 1685- and 1630-cm^{-1} peaks (O-alkylated product) were missing and only those attributed to carbon alkylated acetoacetic esters were present. The nmr showed no absorption at τ 4.8–5.2 (characteristic of vinyl protons). A small portion of the clear oil was hydrolyzed, decarboxylated, and shown to consist of only 4-phenyl-2-butanone.

An alternative procedure for the work-up was to remove the methyl acetoacetate, after removal by solvent, by vacuum evaporation at 0.05 mm pressure and room temperature. The resulting oil was chromatographed, using benzene as solvent, over either alumina or silica gel. This removes the catalyst from the product and the resulting oil was distilled using a Kuhlrohr apparatus after removal of benzene, to give the same product obtained above. This work-up procedure is more convenient when working on a small amount ($\simeq$1–2 g) than the distillation procedure above.

Reaction of Methyl Acetoacetate with Allyl Bromide. The general procedure described above was used. Obtained was a clear oil, 4-carbomethoxy-1-hexen-5-one, bp 38–43° (0.1 mm) (94.7% yield). Ir and nmr analysis showed no peaks characteristic of O-alkylated material.[6] Gc analysis showed only one peak of >99% purity.

Reaction of Methyl Acetoacetate with Allyl Chloride. The general procedure described above was used. Obtained was a clear oil, 4-carbomethoxy-1-hexen-5-one, bp 36–39° (0.05 mm) (30% yield). Ir and nmr analysis showed no peaks characteristic of O-alkylated material.[6] Gc analysis showed only one peak of >99% purity.

Reaction of Dimethylallyl Chloride with Methyl Acetoacetate. Dimethylallyl chloride was synthesized from isoprene according to the procedure of Roux and Kotzanevas.[13] The chloride was kept at −20° until used. The general procedure described above was used for the alkylation. Obtained was a clear oil, 3-carbomethoxy-6-methyl-5-hepten-2-one, bp 55–60° (0.6 mm) (36.8% yield). Ir and nmr analysis showed no peaks characteristic of O-alkylated material. Gc showed one peak of >98% purity with a minor unidentified peak ($\leq$2%).

Reaction of Geranyl Bromide with Methyl Acetoacetate. Geranyl bromide was synthesized according to the procedures of Meyers.[14] The material was used immediately after synthesis. The standard procedure described above was used. Obtained was a slightly yellow oil, 3-carbomethoxy-6,10-dimethyl-5,9-undecadien-2-one, Kuglrohr distillation, bp 120–130° (0.5 mm) (85.1% yield). Ir and nmr analysis showed no absorptions characteristic of O-alkylated material.[6] Gc analysis showed only one peak of >99% purity.

One gram of the above oil was hydrolyzed using KOH in methanol at room temperature for 48 hr. Acidification using glacial acetic acid and removal of solvent gave an oil which was distilled by Kuglrohr distillation at 100° (0.1 mm). The resulting oil was taken up in ether and washed with 5% $NaHCO_3$. The ether was dried ($MgSO_4$) and solvent was removed to yield geranyl acetone which gc analysis showed to be >95% of the trans product. The trans stereochemistry showed that very little isomerization occurred during the reaction.

The 85.1% yield reported above represents our best yield. The synthesis of geranyl bromide gave variable yields depending on how the bromide was generated[14] from the alcohol. Yields of geranyl bromide were estimated to range from 55 to 85%, several synthetic procedures being tried.

Acknowledgment. We would like to thank Mr. J. E. House of General Mills Chemical Co. for his generous gift of "Alaquat 336" for this project and Drs. F. Wudl, C. D. Ritchie, and J. J. Tufariello for helpful discussions on

ion pair alkylations. One of us (L. L.) would like to thank the Undergraduate Research Fund as administered by the State University of New York at Buffalo Student Association for a grant in support of this work. The National Science Foundation provided financial aid in the purchase of the nmr spectrometer used in this research.

Registry No.—Methyl acetoacetate, 105-45-3; benzyl chloride, 100-44-7; 3-carbomethoxy-4-phenylbutanone, 3666-82-8; 4-phenyl-2-butanone, 2550-26-7; allyl bromide, 106-95-6; 4-carbomethoxy-1-hexen-5-one, 3897-04-9; allyl chloride, 107-05-1; dimethylallyl chloride, 503-60-6; 3-carbomethoxy-6-methyl-5-hepten-2-one, 20962-72-5; geranyl bromide, 5389-87-7; 3-carbomethoxy-6,10-dimethyl-5,9-undecadien-2-one, 51933-45-0; geranyl acetone, 3796-70-1.

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(12) Zaugg, *et al.*,[11b] reports using nonpolar solvents, such as benzene, in a malonic ester type alkylation. In this case the solution, although visually homogeneous, was determined to be a colloidal suspension. The molecular weight of these colloidal particles was calculated to be at least 10,000. Thus, the solubility of alkali metal salts in hydrocarbon solvents is relatively low. Although we performed the benzyl chloride alkylations using the phase transfer catalyst in several nonpolar solvents, we only checked the reactivity of the methyl acetoacetate anion without added catalyst in two solvent systems, benzene and hexene. In both cases substantial enhancement of product formation was observed using the phase transfer procedure (25 *vs.* 85% using benzene; <5 *vs.* 40% using hexane as a solvent). We presume that the same trend will be followed with the other solvents.
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Synthetic Reactions by Complex Catalysts. XXXVI. A New Synthesis of Cyclopentanecarboxylates. Cyclization of 1,3-Diiodopropane with α,β-Unsaturated Esters by a Copper–Isonitrile Complex

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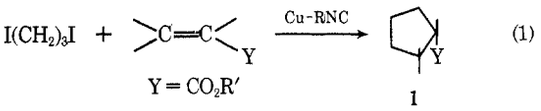
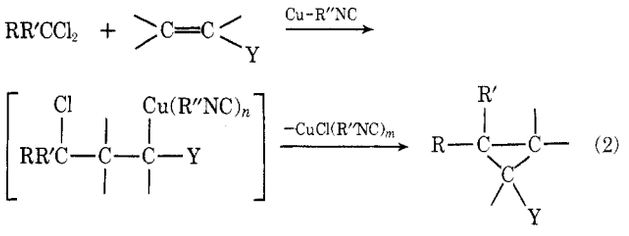
Received March 26, 1974

The present paper describes a new synthetic method for cyclopentanecarboxylates (1) by the reaction of 1,3-diiodopropane with an α,β-unsaturated ester in the presence of copper and isonitrile (RNC) (Table I). This reaction was



(1)

found in the course of exploratory studies on the synthetic reactions caused by Cu–RNC mixture. Previously we have found[1] that an aliphatic halide reacts with metallic copper in the presence of RNC to form the corresponding organocopper–isonitrile complex, which then adds to α,β-unsaturated carbonyl and nitrile compounds in the manner of a conjugate addition. Moreover, an organocopper–isonitrile complex bearing a halogen atom in the same molecule readily undergoes cyclization by the intramolecular elimination of copper halide–isonitrile complex. The following cyclopropane syntheses, for example, have been based upon this interesting reactivity of organocopper–isonitrile complex.



(2)

i, R = Ph, CO_2R''', and CN; R′ = Cl[2]
ii, R = CH_2=CH; R′ = H[3]

The reaction described in the present paper (eq 1) affords a five-membered ring. For this reaction the transient formation of a 3-iodopropylcopper–isonitrile complex may be proposed, which is followed by the subsequent addition to an α,β-unsaturated carbo ester and the final cyclization through the intramolecular elimination of the copper halide–isonitrile complex.

Results and Discussion

On heating a mixture of 1,3-diiodopropane, diethyl fumarate, cyclohexyl isocyanide, and metallic copper in refluxing toluene under nitrogen, *trans*-1,2-dicarbethoxycyclopentane was produced in a high yield and high selectivity. Also the reaction of 1,3-diiodopropane with diethyl maleate by an identical procedure gave the same product. Since it has been found by us that maleate is readily isomerized to fumarate by the Cu–RNC system,[1] and that cyclopropane-, cyclopentane-, and cyclohexane-*cis*-1,2-dicarboxylates are isomerized to the corresponding trans isomers, respectively, under the present reaction conditions, it is conceivable that diethyl maleate is converted to diethyl fumarate prior to the cyclization reaction and/or that *cis*-1,2-dicarbethoxycyclopentane once formed is converted to *trans*-1,2-dicarbethoxycyclopentane.

Similarly, the reaction of 1,3-diiodopropane with methyl acrylate afforded cyclopentanecarboxylic acid methyl ester in 58% yield. Use of electron-deficient olefins other than fumarate, maleate, and acrylate in the present reaction, however, gave rise to decreased yields and selectivities of the corresponding cyclopentane derivatives.

3,3-Bis(iodomethyl)oxetane can be used in place of 1,3-diiodopropane. The product is the corresponding oxaspirane carboxylate (**2**). Cyclization of tetraiodoneopentane with fumarate gave **3** instead of the spirocyclononanetetracarboxylate. Compound **3** is supposed to be produced through intermediate **4**.[4]

Employment of iodides in the present reaction is essen-