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134. Shigehiko Sugasawa and Hisayuki Matsuo : Synthesis of α,β-Unsaturated Esters by Application of Wittig Reaction.

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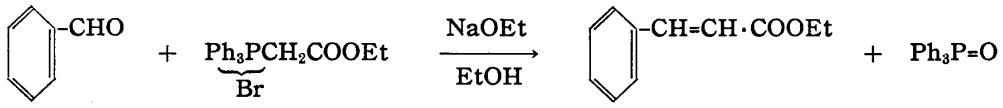
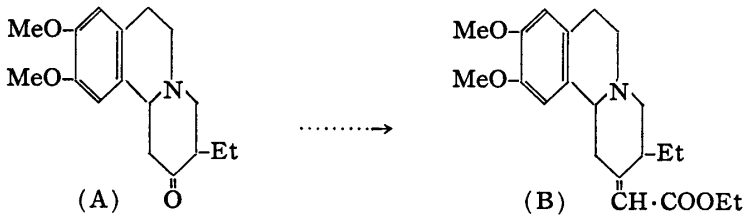
In 1954, Wittig and his co-worker[1] reported a novel synthetic method for olefins, the so-called Wittig reaction. The unique feature of this method is its use of alkylidene-triphenylphosphorane as olefin-formation agent, which reacts with carbonyl group to afford ethylenic linkage without any isomerisation. The specificity of this reaction was concisely described by Wittig[1] himself as follows : "Der mit dieser neuen Methode sich abzeichnende präparative Fortschritt liegt darin, dass die C=C-Bindung ohne Verschiebung am Ort der ursprünglichen C=O-Bindung ausgebildet wird." The remarkable feature mentioned above has been well displayed in the field of polyene synthesis and others.[2]

In connection with the extension of this method, Wittig and Haag[3] accomplished the synthesis of ethyl cinnamate from benzaldehyde, as illustrated below :



This fact suggests that Wittig's method would be generally applicable to the preparation of α,β-unsaturated esters.

One of the present authors (S. Sugasawa) who has been studying the total synthesis of a natural alkaloid, emetine, for years intended to convert the ketone (A) to (B) by applying this reaction, both of which were considered as important intermediates to emetine.



Since, however, little information is available in the literature about this type of Wittig reaction,[4] it was decided as a preliminary, to take up the reaction of ethoxycarbonylmethylene-triphenylphosphorane upon various carbonyl compounds, some of which are closely related to (A) in structure. As model compounds, to which this type of Wittig reaction has not yet been applied, 13 kinds of aldehyde and ketone were chosen, which was classified structurally into three groups as follows : i) Aromatic carbonyl compounds with basic nitrogen, i.e., 2- (I-α), 3- (I-β),[*2] and 4-formylpyridine (I-γ), and

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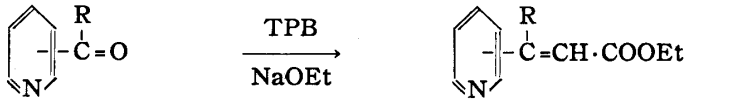
1) G. Wittig, U. Schöllkopf : Ber., **87**, 1318(1954).
2) G. Wittig : Experientia, **12**, 41(1956); U. Schöllkopf : Angew. Chem., **71**, 260(1959); J. Levisalles: Bull. soc. chim. France, **1958**, 1021; H. H. Inhoffen, *et al.* : Angew. Chem., **67**, 276(1957); Ann., **603**, 25(1957).
3) G. Wittig, W. Haag : Ber., 88, 1654(1955).
4) O. Isler, *et al.* : Helv. Chim. Acta, **40**, 1242(1957); F. Bohlmann : Ber., **90**. 1519(1957). Also refer to J. Levisalles (*loc. cit.*) and Footnote (3).

2-(II-α), 3-(II-β), and 4-acetylpyridine (II-γ).*2 ii) Alicyclic ketones, i.e., cyclohexanone (III), and 2-methyl- (IV) and 2-ethyl-cyclohexanone (V).[5] iii) Cyclic ketones with basic nitrogen, i.e., N-benzyl-4-piperidone (VI),[6] and its 3-methyl derivative (VII), N-phenethyl-3-methyl- (VIII),[7] and -3-ethyl-4-piperidone (IX).[7] So far as the present experiments as described in this paper are concerned, the expected unsaturated esters were produced and some findings were thereby also obtained.

I. Wittig Reaction of Formylpyridines and Acetylpyridines



(I)-series, R=H (α, β, γ) (I')-series, R=H (α, β, γ)
(II)-series, R=Me (α, β, γ) (II')-series, R=Me (α, β, γ)

Table I.

Starting Material	Product (Yield)	
2-Formylpyridine (I-α)	Ethyl 3-(2-pyridyl)acrylate (I'-α)	(97.5%)
3-Formylpyridine (I-β)	Ethyl 3-(3-pyridyl)acrylate (I'-β)	(91.0%)
4-Formylpyridine (I-γ)	Ethyl 3-(4-pyridyl)acrylate (I'-γ)	(89.3%)
2-Acetylpyridine (II-α)	Ethyl 3-(2-pyridyl)crotonate (II'-α)	(71.0%)
3-Acetylpyridine (II-β)	Ethyl 3-(3-pyridyl)crotonate (II'-β)	(88.6%)
4-Acetylpyridine (II-γ)	Ethyl 3-(4-pyridyl)crotonate (II'-γ)	(90.0%)

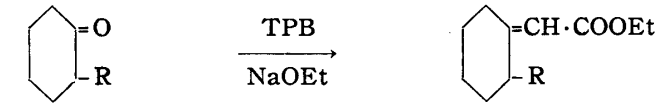
In order to examine the effect of basic nitrogen on the Wittig reaction, formyl- ((I)-series) and acetyl-pyridines ((II)-series) were treated with ethoxycarbonylmethylene-triphenylphosphorane after the manner described by Wittig, *et al.*[3] As was expected the corresponding unsaturated esters (I' and II') were obtained in fair yields. Thus, to an ethanolic solution of sodium ethoxide an ethanolic solution of ethoxycarbonylmethyl-triphenylphosphonium bromide (TPB)[3] was added in one portion. After several minutes, the solution of (I) or (II) in ethanol was added to the faint yellow solution obtained as above and the mixture was kept standing at room temperature. All procedures were carried out in nitrogen atmosphere. After three days, the solvent was evaporated to afford a slightly brown oil, containing crystals of triphenylphosphine oxide. The oily substance thus obtained was taken up in benzene, extracted with 5% hydrochloric acid, and the extract was worked up as usual to afford the expected ester (I' or II'). After examinations of various working conditions, the best yield was obtained under conditions described in experimental part. The results obtained here are summarized in Table I.

The expected structure (I') for the product obtained from (I) was supported by elemental analytical data and infrared absorptions, which were in good accordance with Katritzky's descriptions[9] of (I'). Moreover, each sample of (I')-series was identified by mixed fusion test and infrared spectral comparison with authentic specimens synthesized by the known methods.[10~12] The analytical values and infrared spectral data of (II') also gave reliable evidences to support the structure of ethyl pyridylcrotonates, which were not yet known in the past. The structure of (II') was also evidenced by the fact that (II')

5) F.K. Signaigo, P.L. Cramer : J. Am. Chem. Soc., **55**, 3329(1933).
6) F.E. King, *et al.* : J. Chem. Soc., **1945**, 279.
7) C. Grob, P. Breneisen : Helv. Chim. Acta, **41**, 1184(1958).
8) A.H. Beckett, A.F. Casy, G. Kirk : J. Med. Pharm. Chem., **1**, 37(1959).
9) A.R. Katritzky, *et al.* : J. Chem. Soc., **1958**, 2182, 2198, 2202,
10) A. Einhorn : Ann., **265**, 221(1891).
11) L. Panizzon : Helv. Chim. Acta, **24**, 24E(1941).
12) A.A. Alberts, G.B. Bachmann : J. Am. Chem. Soc., **57**, 1285(1935).

furnished the starting ketones (II) by oxidation with potassium permanganate and were identified with authentic samples. Consequently, it was proved that the basicity of (I) and (II) did not show any hindrance on Wittig reaction to give the corresponding unsaturated esters in a fair yield.

II. Wittig Reaction of Cyclohexanones



(III) R=H
(IV) R=Me
(V) R=Et

(III′) R=H
(IV′) R=Me
(V′) R=Et

Table II.

Starting Material	Product (Yield)	
Cyclohexanone (III)	Ethyl cyclohexylideneacetate (III′)	(44.5%)
2-Methylcyclohexanone (IV)	Ethyl 2-methylcyclohexylideneacetate (IV′)	(7.3%)
2-Ethylcyclohexanone (V)	Ethyl 2-ethylcyclohexylideneacetate (V′)	(6.0%)

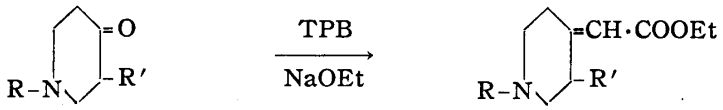
There are not a few records on the Wittig reaction introducing alkenyl group into cyclic ketones but the preparation of cyclohexylideneacetate by this method has not yet been investigated. Consequently, the Wittig reaction of cyclohexanones was carried out with the expectation of obtaining ethyl cyclohexylideneacetates. First, cyclohexanone (III) was treated with TPB in the presence of sodium ethoxide under the same condition as in the case of pyridine derivative but the yield of the expected ester (III′) was not more than 20%. By prolongation of the reaction time to seven days, the yield of (III′), colorless oil of $b.p_{25}$ 98~102°, was raised to 44.5%, accompanied with 22% recovery of the starting ketone (III), which was separated from the former by fractional distillation. The ester thus obtained showed reasonable absorption bands for ethyl cyclohexylideneacetate (III′) in its infrared spectrum, i.e., the bands at 1715(C=O), 1640(C=C), and 1169 cm^{-1} due to α,β-unsaturated ester. This structure (III′) was also proved by elemental analytical values and ultraviolet spectral data, having λ_{max}^{EtOH} 219 mμ(ε 13,500), which tallies well with Dauben's description.[13] The more accurate characterization was given by the fact that (III′) afforded cyclohexylideneacetic acid, m.p. 90~91°, in 97% yield by hydrolysis, which was identified by mixed fusion with an authentic sample prepared by the method of Kon and Linstead.[14] Thus, the structure and uniformity of the product was ascertained.

To examine the effect of α-alkyl substituent on this reaction, 2-methyl- (IV) and 2-ethyl-cyclohexanones (V) were treated under the same conditions as in the case of (III) and resulted in formation of the expected esters, (IV′) and (V′), respectively, but in poorer yields, which remained still as low as 6~7% notwithstanding prolongation of the reaction time. Elemental analytical values and infrared spectra of the products were reasonable for those of ethyl 2-alkylcyclohexylideneacetates, (IV′) and (V′). Ultraviolet absorptions, λ_{max}^{EtOH} 220 mμ(ε 13,200) and λ_{max}^{EtOH} 220 mμ (ε 12,900), also supported their structures. In conformity with their structure, (IV′) and (V′) were readily oxidized with potassium permanganate to afford starting ketones (IV) and (V) in a fair yield, which were identified as their oximes or 2,4-dinitrophenylhydrazones. These facts revealed that cyclohexanones also produced the expected α,β-unsaturated esters having

13) W. G. Dauben, P. D. Hance : J. Am. Chem. Soc., **75**, 3353(1953).
14) G. A. R. Kon, R. P. Linstead : J. Chem. Soc., **1927**, 1269.

exocyclic double bond, though in poor yield, especially in the case of (IV) and (V), perhaps due to 2-alkyl substituent.

III. Wittig Reaction of 4-Piperidones



(VI) R=$PhCH_2$-, R′=H (VI′)
(VII) R=$PhCH_2$-, R′=Me (VII′)
(VIII) R=$PhCH_2CH_2$-, R′=Me (VIII′)
(IX) R=$PhCH_2CH_2$-, R′=Et (IX′)

Table III.

Starting Material (4-Piperidones)	Product (Yield) (Ethyl 4-piperidylideneacetate)	
1-Benzyl- (VI)	1-Benzyl- (VI′)	(80.0%)
1-Benzyl-3-methyl- (VII)	1-Benzyl-3-methyl- (VII′)	(21.0%)
1-Phenethyl-3-methyl- (VIII)	1-Phenethyl-3-methyl- (VIII′)	(19.2%)
1-Phenethyl-3-ethyl- (IX)	1-Phenethyl-3-ethyl- (IX′)	(20.4%)

For the purpose of examining the behavior of 4-piperidones, 1-benzyl-4-piperidone (VI),[7] chosen as one of the model compounds, was subjected to the Wittig reaction as described above. Standing the reaction mixture for eight days at room temperature was required to furnish ethyl 1-benzyl-4-piperidylideneacetate (VI′) as colorless oil of $b.p_3$ 160~163° in 80% yield, with simultaneous recovery of the starting (VI) in 7% yield. Its ultraviolet and infrared spectral data agreed well with the structure of (VI′). The ester obtained above was submitted to paper chromatography by ascending method, using BuOH–AcOH–H_2O (3:5:1) as the solvent system and exhibited a single spot positive to the Dragendorff reagent at Rf 0.82, which differed from that of (VI), Rf 0.67. The methiodide of (VI′) was recrystallized from ethanol to give colorless microneedles of m.p. 191~193° (decomp.), whose analytical values agreed well with $C_{16}H_{21}O_2N \cdot CH_3I$. For characterisation another synthesis was attempted as follows: Ethyl 1-benzyl-4-hydroxy-4-piperidylacetate prepared by the method of Grob, *et al.*[7] was dehydrated with acetic anhydride in pyridine to afford oily substance of $b.p_3$ 160~167°, which was converted to its methiodide.

Recrystallization of the methiodide was repeated from ethanol to give colorless microneedles of m.p. 191~192° (decomp.), along with a small amount of another crop of m.p. 208~210° (decomp.). The former was proved to be identical with (VI′)-methiodide of the above base, while the latter did not agree with the former in infrared spectrum and m.p., except in elemental analytical values. Even though not investigated further, this is probably $\Delta^{3,4}$-piperidyl derivative. The ester (VI′) giving a single spot of Rf 0.82 was oxidized with permanganate-acetone solution in the cold and the starting piperidone (VI) was recovered in a fair yield (79%). This fact justified the structure of (VI′).

In order to examine the effect of 1- and 3-substituent on this reaction, 1-benzyl-3-methyl-(VII), 1-phenethyl-3-methyl- (VIII),[7] and N-phenethyl-3-ethyl-4-piperidone (IX)[7] were submitted to the Wittig reaction under the same condition as above and the corresponding esters, (VII′), (VIII′), and (IX′), were respectively obtained. This result is shown in Table III.

The piperidone (VII) was synthesized, as in the case of (VIII) and (IX), by the Michael condensation of ethyl 3-benzylamino-2-methylpropionate (X) and ethyl acrylate, followed by the Dieckmann ring-closure of the diester (XI) thus obtained, and subsequent decarboxylation by heating with 20% hydrochloric acid. Wittig reaction of these piperidones

was carried out in a similar manner as before, except that reaction time was prolonged to 15 days. As can be seen from Table III, the yields of (VII′), (VIII′), and (IX′) were much worse than that of (VI′). This fact suggested that α-alkyl substituent adjacent to carbonyl exerts unfavorable influence on this reaction as in the cyclohexanone series.

Infrared spectra of unsaturated ester thus obtained exhibited the characteristic absorption bands of α,β-unsaturated ester in the range of 1725～1720, 1645～1650, and 1170～1150 cm^{-1}. They also gave correct analyses.

Both (VIII′) and (IX′) were obtained in crystalline form, melting at 101～103° and 111～112°, respectively, while the effort to crystallize (VII′) was fruitless. Paper chromatography of (VII′), (VIII′), and (IX′) as before exhibited a single spot each positive to the Dragendorff reagent at Rf 0.81, 0.78, and 0.72, respectively, indicating uniformity of each sample.

Further, all esters were oxidized at room temperature with potassium permanganate in acetone to yield the corresponding starting piperidones in a fair yield and were identified by parer chromatography and mixed fusion with authentic piperidones or their picrates.

Experimental

Wittig Reaction of Formylpyridines and Acetylpyridines

Ethyl 3-(2-Pyridyl)acrylate (I′-α)—To EtOH solution of NaOEt prepared from metallic Na (260 mg.; 1.2 atom equiv.) and anhyd. EtOH (20 cc.), a solution of ethoxycarbonylmethyl-triphenylphosphonium bromide (TPB) (6.05 g.; 1.5 mol. equiv.) in anhyd. EtOH (30 cc.) was added in one portion. After several minutes, a solution of 2-formylpyridine (I-α) (1.0 g.; 1.0 mole equiv.) in anhyd. EtOH (20 cc.) was added to the faint yellow solution thus obtained and the mixture was kept standing at room temperature. All treatments were carried out in N_2 atmosphere to exclude the air rigorously. After 3 days, the solvent was evaporated to leave a faint brown oil, containing white crystals. To the residue thus obtained a small portion of H_2O was added and an oily substance which separated out, was taken up in benzene. The benzene layer was extracted with 5% HCl and aqueous layer was basified with anhyd. K_2CO_3 under ice-cooling to obtain an oil, which was extracted with benzene. The benzene extract was dried over anhyd. K_2CO_3 and evaporoted *in vacuo* to afford faint brown oil (1.67 g.). Vacuum distillation gave colorless oil of b.p_5 128～129°. Yield; 1.62 g. or 97.5%. UV: λ_{max}^{EtOH} 252 mμ (log ε 4.15). IR $\nu_{max}^{Capil.}$ cm^{-1} : 1712 (C=O), 1648 (C=C), 1161 (COO). These spectral data were in good accordance with Katritzsky's description of (I′-α) and those of an authentic sample.
Picrate : Yellow needles of m.p. 164～165° (from EtOH). No m.p. depression was observed on admixture with an authentic specimen of (I′-α)-picrate. *Anal.* Calcd. for $C_{10}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 47.29; H, 3.47; N, 13.79. Found : C, 47.06; H, 3.41; N, 13.68.

After extraction of (I′-α) with 5% HCl, the benzene layer was washed with 10% Na_2CO_3 and water, dried, and evaporated *in vacuo*. Recrystallisation of the residual white crystalline mass from benzene-hexane gave 2.5 g. of colorless prisms, m.p. 151～152. This substance was identified as triphenylphosphine oxide by the mixed fusion test with an authentic sample.

Ethyl 3-(3-Pyridyl)acrylate (I′-β)—Synthesized from 3-formylpyridine by a method similar to above, in a yield of 91%. Colorless oil of b.p_2 102～103°. UV λ_{max}^{EtOH} 259 mμ (log ε 4.09). IR $\nu_{max}^{Capil.}$ cm^{-1}: 1715 (C=O), 1646 (C=C), 1175 (COO).
Picrate : Yellow scales of m.p. 154～155° (from EtOH). No m.p. depression was observed on admixture with an authentic specimen of (I′-β) picrate. *Anal.* Calcd. for $C_{10}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 47.29; H, 3.47; N, 13.79. Found : C, 47.07; H, 3.69; N, 13.85.

Ethyl 3-(4-Pyridyl)acrylate (I′-γ)—Synthesized from 4-formylpyridine as above in a yield of 89.3%. Colorless scales of m.p. 63～64° (from hexane), which was identified with an authentic specimen by mixed fusion test. *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91. Found : C, 67.65; H, 6.31; N, 7.69. UV λ_{max}^{EtOH} 258 mμ (log ε 4.13). IR : ν_{max}^{Nujol} cm^{-1} : 1715 (C=O), 1645 (C=C), 1178 (COO).
Picrate : Yellow needles of m.p. 162～163° (from EtOH). *Anal.* Calcd. for $C_{10}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 47.29; H, 3.47; N, 13.79. Found : C, 47.54; H, 3.50; N, 14.13.

Ethyl 3-(2-Pyridyl)crotonate (II′-α)—TPB (5.30 g.; 1.5 mol. equiv.) in anhyd. EtOH (30 cc.) was added in one portion to an ethanolic solution of NaOEt prepared from metallic Na (230 mg.; 1.2 atom equiv.) and anhyd. EtOH (20 cc.). To the resulting solution was added a solution of 2-acetylpyridine (II-α) (1.0 g.; 1.0 mol. equiv.) in anhyd. EtOH (20 cc.) and allowed to stand at room temperature for 3 days. All treatments were carried out in N_2 atmosphere. Worked up as in the case of (I′), colorless oil (II′-α) of b.p_5 121～123 was obtained in a yield of 1.11 g. or 71%. UV λ_{max}^{EtOH} 249 mμ (log ε 4.11). IR $\nu_{max}^{Capil.}$ cm^{-1} : 1720 (C=O), 1640 (C=C), 1175 (COO).

Picrate : Yellow prisms of m.p. 145~146°(decomp.) (from EtOH). *Anal.* Calcd. for $C_{11}H_{13}O_2N \cdot C_6H_3O_7N_3$: C, 48.57; H, 3.84; N, 13.33. Found : C, 48.21; H, 3.63; N, 13.71.

For the characterisation of (II'-α), 1.0 g. of above-obtained sample was oxidized with $KMnO_4$-acetone at room temperature to give 0.51 g. of 2-acetylpyridine, which was identified as its oxime of colorless needles, m.p. 118~120°; yield, 77.7%. Any m.p. depression was not observed on admixture with an authentic specimen.

Ethyl 3-(3-Pyridyl)crotonate (II'-β)—Synthesized from 3-acetylpyridine (II-β) in a similar manner as above. Colorless oil of $b.p_2$ 110~111°. Yield, 88.6%. UV : λ_{max}^{EtOH} 255 mμ (log ε 4.16). IR $\nu_{max}^{Capil.}$ cm^{-1}: 1718 (C=O), 1638 (C=C), 1175 (COO).

Picrate : Yellow needles of m.p. 135.5~136.5 (from EtOH). *Anal.* Calcd. for $C_{11}H_{13}O_2N \cdot C_6H_3O_7N_3$: C, 48.57; H, 3.84; N, 13.33. Found : C, 48.29; H, 3.93; N, 13.41.

For the characterisation, 0.6 g. of (II'-β) was oxidized under the same condition as in above cases to yield 0.31 g. of 3-acetylpyridine, which was identified as its picrate, yellow prisms of m.p. 130~131° (from EtOH), in a yield of 0.89 g. (82%).

Ethyl 3-(4-Pyridyl)crotonate (II'-γ)—Synthesized from 4-acetylpyridine (II-γ) under the same condition as in above cases in a yield of 90%. Colorless oil of $b.p_2$ 126°. UV : λ_{max}^{EtOH} 252 mμ (log ε 4.13). IR $\nu_{max}^{Capil.}$ cm^{-1} : 1720 (C=O). 1634 (C=C), 1178 (COO). *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found : C, 69.03; H, 6.63; N, 7.41.

Picrate : Yellow needles of m.p. 125~126° (from EtOH). *Anal.* Calcd. for $C_{11}H_{13}O_2N \cdot C_6H_3O_7N_3$: C, 48.57; H, 3.84; N, 13.33. Found : C, 48.32; H, 3.87; N, 13.42.

0.72 g. of (II'-γ) was oxidized in the same manner as in above cases to yield 4-acetylpyridine (77.2%), which was characterised as its oxime, colorless prisms of m.p. 155~157°, by the mixed m.p. test with an authentic sample.

Wittig Reaction of Cyclohexanones

Ethyl Cyclohexylideneacetate (III')—TPB (10.5 g.; 1.5 mol. equiv.) in anhyd. EtOH (50 cc.) was added in one portion to an ethanolic solution of NaOEt prepared from metallic Na (0.5 g.; 1.2 atom equiv.) and anhyd. EtOH. To the resulting solution was added cyclohexanone (2.0 g.; 1.0 mol. equiv.) in anhyd. EtOH (10 cc.) and kept standing at room temperature. All procedures were carried out in N_2 atmosphere to exclude the air rigorously. After 7 days, the solvent was evaporated to dryness. To the residue was added 20 cc. of dehyd. ether to precipitate out white crystalline mass, which was filtered and washed with ether. The ethereal layer was evaporated to leave oily substance, which was submitted to fractional distillation to give two fractions; (i) $b.p_{50}$ 72~78°; colorless oil (0.44 g.) and (ii) $b.p_{25}$ 98~102°; colorless oil (1.61 g.). Fraction (i) was the recovery of the starting ketone, which was derived to its 2,4-dinitrophenylhydrazone, m.p. 160°, and identified by the mixed fusion test with an authentic speciman.

Fraction (ii) was redistilled to give colorless oil (III') of $b.p_{30}$ 109~112° in a yield of 1.52 g. or 44.5%. *Anal.* Calcd. for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52. Found : C, 71.03; H, 9.08. UV : λ_{max}^{EtOH} 219 mμ (ε 13,500). IR $\nu_{max}^{Capil.}$ cm^{-1} : 1715 (C=O), 1640 (C=C), 1160 (COO). These spectral data were in complete agreement with those of an authentic specimen prepared according to the method of Kon and Linstead.[14]

The ether-insoluble crystalline mass stated above was dissolved in benzene, washed with water, dried, and evaporated to afford 3.5 g. of oil, which soon solidified. Recrystallization from benzene-hexane gave colorless prisms of m.p. 151~152°, which did not show any m.p. depression on admixture with an authentic triphenylphosphine oxide.

Cyclohexylideneacetic Acid—1.0 g. of above-obtained ester (III') was treated with KOH (335 mg.) in anhyd. MeOH (10 cc.) and kept standing at room temperature over night. To the resulting solution was added 20 cc. of water and, after extraction with ether, aqueous layer was acidified with conc. HCl under cooling to form white crystals, which were collected on a filter and washed with cold water. Recrystallization from hydr. EtOH gave colorless prisms of m.p. 90~91° in a yield of 0.18 g. or 97%. Any m.p. depression did not occur on admixture with an authentic sample prepared according to the method of Kon and Linstead.[14]

Ethyl 2-Methylcyclohexylideneacetate (IV')—2-Methylcyclohexanone (2.0 g.; 1.0 mol. equiv.) was treated with NaOEt (prepared from metallic Na (445 mg.; 1.2 atom equiv.)) and TPB (9.9 g.; 1.5 mol. equiv.) in the same manner as in the case of (III'). The resulting mixture was kept standing for 12 days at room temperature in N_2 atmosphere and worked up as in above cases. The expected ester (IV') was obtained as colorless oil of $b.p_{12}$ 81~82°, in a yield of 237 mg. or 7.3% with 61% recovery of starting ketone (1.22 g.). UV : λ_{max}^{EtOH} 220 mμ (ε 13,200). IR $\nu_{max}^{Capil.}$ cm^{-1} : 1720 (C=O), 1638 (C=C), 1165 (COO). *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 72.52; H, 9.64. Found : C, 72.54; H 9.38.

For the characterisation, 200 mg. of above-obtained ester was oxidized with $KMnO_4$ (350 mg.) in acetone at room temperature to afford 2-methylcyclohexanone, which was derived to its semicarbazone. Recrystallisation from EtOH gave colorless prisms of m.p. 190~192° in a yield of 145 mg. or 78%, which was identified with an authentic specimen by the mixed fusion.

Ethyl 2-Ethylcyclohexylideneacetate (V′)—Synthesized from 2.0 g. of 2-ethylcyclohexanone in the same manner as above, in a yield of 187 mg. or 6.0% with simultaneous recovery of starting 2-ethylcyclohexanone in a yield of 1.32 g. or 66%. Colorless oil of b.p_{35} 112~115°. UV : λ_{max}^{EtOH} 220 mμ (ε 12,900). IR $\nu_{max}^{capil.}$ cm^{-1} : 1720 (C=O), 1640 (C=C), 1165 (COO). *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found : C, 73.01; H, 9.92.

For characterisation, 150 mg. of above-obtained sample was oxidized with $KMnO_4$-Me_2CO to form 2-ethylcyclohexanone, which was induced to its 2,4-dinitrophenylhydrazone. Recrystallized from EtOH to form orange needles of m.p. 161~162° in a yield of 190 mg. or 81%. Identified with an authentic specimen by mixed m.p. test.

Wittig Reaction of 4-Piperidones

Ethyl 1-Benzyl-4-piperidylideneacetate (VI′)—To an ethanolic solution of EtONa prepared from metallic Na (240 mg.; 1.2 atom equiv.) and anhyd. EtOH (20 cc.) was added TPB (5.0 g.; 1.5 mol. equiv.) in anhyd. EtOH (30 cc.). To the resulting solution 2.0 g. of 1-benzyl-4-piperidone (b.p_2 123~124°) in anhyd. EtOH (10 cc.) was added and kept standing for 8 days at room temperature. All treatments were carried out in N_2 atmosphere to exclude the air rigorously. The resulting mixture was worked up as in the case of (I′) to obtain 2.62 g. of basic oily substance. The oil thus obtained was submitted to fractional distillation. The expected ester was afforded as colorless oil of b.p_3 160~163° in a yield of 2.2 g. or 80%, with recovery of starting material of b.p_3 120~123°(yield; 0.14 g. or 7%), which was identified as its picrate of m.p. 170~180° by mixed fusion. IR $\nu_{max}^{Capil.}$ cm^{-1} : 2805 (>N-), 1725 (C=O), 1650 (C=C), 1153 (COO). UV λ_{max}^{EtOH} mμ (log ε) : 217(4.21), 260(2.18).

Methiodide : Colorless microneedles of m.p. 191~193°(decomp.) (from EtOH). *Anal.* Calcd. for $C_{16}H_{21}O_2N \cdot CH_3I$: C, 50.89; H, 5.97; N, 3.50. Found : C, 50.40; H, 5.97; N, 3.37.

For the purpose of characterisation, another synthesis of (VI′) was executed through the following route. Ethyl 1-benzyl-4-hydroxy-4-piperidylacetate (2.0 g.), prepared from 1-benzyl-4-piperidone according to the method of Grob, *et al.*,[7] was subjected to dehydration reaction by refluxing with 5.0 g. of Ac_2O and 0.5 g. of pyridine in an oil bath for 5 hr. The resulting solution was evaporated *in vacuo* and poured into cooled 10% HCl. The aqueous layer was basified with anhyd. K_2CO_3 under cooling and the oil that separated out was extracted with benzene. The organic layer was dried over anhyd. K_2CO_3 and evaporated *in vacuo* to leave oily residue, which distilled at 160~167°/3 mm. Hg to form 1.42 g. of colorless oil. This oil was treated with excess of CH_3I to afford amorphous methiodide. Repeated recrystallisations from EtOH gave colorless microneedles of m.p. 191~192°(decomp.), which did not show any depression on admixtue with the sample above-obtained by Wittig reaction. Yield, 1.48 g. *Anal.* Calcd. for $C_{16}H_{21}O_2N \cdot CH_3I$: C, 50.89; H, 5.97; N, 3.50. Found : C, 50.62; H, 5.71; N, 3.60.

From the mother liquor of recrystallisation, another crop of m.p. 208~210°(decomp.) was obtained in colorless needles, not identical with (VI′)-methiodide. Yield, 110 mg. *Anal.* Calcd. for $C_{16}H_{21}O_2N \cdot CH_3I$: C, 50.89; H, 5.97; N, 3.50. Found : C, 50.90; H, 6.23; N, 3.33.

Even though this was not further investigated, it seemed presumably to be 1-benzyl-$\Delta^{3,4}$-piperidylacetate methiodide.

Preparation of 1-Benzyl-3-methyl-4-piperidone (VII)

Ethyl 2-Methyl-3-benzylaminopropionate (X)—A solution of ethyl methacrylate (12.5 g.) in anhyd. EtOH (5 cc.) was added to a solution of benzylamine (10.0 g.) in anhyd. EtOH (5 cc.) and the mixture left standing for 30 days at room temperature. The product was fractionally distilled under reduced pressure to give (X) as a colorless oil of b.p_2 121~122°, in a yield of 14.2 g. or 68%. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: C, 70.50; H, 8.65; N, 6.33. Found : C, 70.82; H, 8.23; N, 6.51.

Picrolonate : Faint yellow prisms of m.p. 128°(from EtOH). *Anal.* Calcd. for $C_{13}H_{19}O_2N \cdot C_{10}H_8O_5N_4$: C, 56.89; H, 5.56; N, 14.40. Found : C, 56.75; H, 5.37; N, 14.52.

N-(2-Ethoxycarbonylpropyl)-N-(ethoxycabonylethyl)-benzylamine (XI)—A mixture of the amino-ester above-obtained (X) (10.0 g.) and ethyl acrylate (8.0 g.) was heated on a boiling water bath for 3 days. The product was fractionally distilled under reduced pressure to afford (XI) as a colorless oil of b.$p_{0.2}$ 161~163° in a yield of 6.8 g. or 47%. *Anal.* Calcd. for $C_{18}H_{27}O_4N$: C, 67.27; H, 8.47; N, 4.36. Found : C, 66.98; H, 8.42; N, 4.28.

1-Benzyl-3-methyl-4-piperidone (VII)—To a solution of the diester obtained as above (XI) (6.0 g.) in dehyd. xylene (50 cc.) was added NaH (0.5 g.) and the mixture, protected from moisture, warmed at 60° to start the reaction. Then the mixture was refluxed in an oil bath for about 3 hr. until the evolution of H_2 ceased. After cool, the product was poured into water (50 cc.). The aqueous phase separated was washed with ether and acidified with conc. HCl to 20% final concentration. The acidic solution thus obtained was refluxed for 2 hr. until the evolution of CO_2 was not observed. The resulting solution was basified with anhyd. K_2CO_3 under effective cooling to liberate the free base, which was extracted with benzene. After drying over anhyd. K_2CO_3, the solvent was evaporated and the residual oil was distilled under reduced pressure to give 1-benzyl-3-methyl-4-piperidone of b.$p_{0.3}$ 131~134°, in a yield of 3.1 g. or 87%. *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99;

N, 7.40. Found : C, 75.91; H, 8.02; N, 7.13.

Picrate : Yellow prisms of m.p. 190~191° (from EtOH). *Anal.* Calcd. for $C_{12}H_{15}ON \cdot C_6H_3O_7N_3$: C, 51.67; H, 4.34; N, 13.19. Found : C, 51.55; H, 4.25; N, 13.16.

Ethyl 1-Benzyl-3-methyl-4-piperidylideneacetate (VII′)—1-Benzyl-3-methyl-4-piperidone (VII) (2.5 g.) obtained as above was subjected to the Wittig reaction, treated with NaOEt and TPB in anhyd. EtOH in the same method as in the case of (VI′), except the prolongation of the reaction time to 15 days. The crude basic oil obtained after usual working up was fractionally distilled to give the expected ester (VII′) as a colorless oil of $b.p_{0.2}$ 157~160° in a yield of 0.72 g. or 21%, with simultaneous recovery of the starting piperidone (VII) in a yield of 1.8 g. or 72%. IR $\nu_{max}^{Capil.}$ cm^{-1} : 2850 (>N-), 1723 (C=C), 1648 (C=C), 1157 (COO). Rf 0.81 (single spot positive to Dragendorff reagent) (Toyo Roshi No. 50, ascending method using BuOH-AcOH-H_2O (3:5:1)). *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H 8.48; N, 5.12. Found : C, 74.32; H, 8.51; N, 5.06.

For the characterisation, the sample obtained as above (0.5 g.) was oxidized with $KMnO_4$-Me_2CO at room temperature to form the starting piperidone (VII) in a yield of 0.28 g. or 76%, which was identified as its picrate of m.p. 190~191° by the mixed fusion with an authentic specimen.

Ethyl 1-Phenethyl-3-methyl-4-piperidylideneacetate (VIII′)—Synthesized from 1-phenethyl-3-methyl-4-piperidone (VIII) (3.0 g.), prepared according to the method of Beckett, *et al.*,[8] by the same method as described for the above case (VII′) as a colorless oil of $b.p_{0.2}$ 164~166°, which solidified soon. Recrystallisation from EtOH gave colorless needles of m.p. 101~103°. Yield, 0.77 g. or 19.2%. IR $\nu_{max}^{Capil.}$ cm^{-1} : 2805 (>N-), 1725 (C=O), 1650 (C=C), 1155 (COO). *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found : C, 74.82; H, 8.15; N, 4.98.

The sample thus obtained gave a single spot positive to Dragendorff reagent on paper chromatogram as in the above cases. Rf 0.78.

For the purpose of characterisation, the aboves ample (0.35 g.) was oxidized as in the case of (VII′) to give 0.14 g. of (VIII), which was identified as its picrate of m.p. 169~170°[8] and paper chromatographically with an authentic piperidone (VIII).

Ethyl 1-Phenethyl-3-ethyl-4-piperidylideneacetate (IX′)—Synthesized from 1-phenethyl-3-ethyl-4-piperidone[9] (IX) by the same manner as above (VIII′). Colorless oil of $b.p_{0.15}$ 162~165° solidified soon which was recrystallised from EtOH in colorless needles of m.p. 111~112°. Yield, 20.4%. IR ν_{max}^{Nujol} cm^{-1}: 2804 (>N-), 1722 (C=O), 1650 (C=C), 1153 (COO). *Anal.* Calcd. for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. Found : C, 75.33; H, 8.64; N, 4.63. Rf 0.72.

The sample thus obtained afforded the starting material (IX) on oxidation with $KMnO_4$-Me_2CO in fair yield, which was identified as its picrate of m.p. 176~178° (decomp.) and paper chromatographically with an authentic specimen (IX).

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Summary

Thirteen kinds of aldehyde and ketone, including some basic and/or alicyclic carbonyl compounds, were subjected to Wittig reaction, using ethoxycarbonylmethyl-triphenylphosphonium bromide and sodium ethoxide in dehyd. ethanol at room temperature in nitrogen atmosphere, and corresponding α,β-unsaturated ethyl esters were formed as expected.

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