tive alkoxy radicals are mechanistically related, even though different reactive intermediates are involved.

Experimental Section

Ir analyses, neat for liquids and potassium bromide pellets for solids, were done with a Perkin-Elmer 237 B spectrophotometer. NMR analyses were performed with a Perkin-Elmer R-12 spectrometer. A F & M Research Model 720 gas chromatograph with a 6-ft 10% SE 30 on 60–80 diatport S was used for VPC analyses. Melting points were taken with a Melt-temp apparatus and are uncorrected.

A divided electrochemical cell was used and has been previously described.[15] The working and auxiliary electrodes were 5.56 cm^2 platinum sheets. The reference electrode was 0.1 *N* $AgNO_3|Ag$ in acetonitrile which was contained in a separate glass fritted compartment. A platinum disk, 0.0186 cm^2, was used for cyclic studies. A Princeton Applied Research Model 170 electrochemistry unit was used for cyclic voltammetry and controlled potential electrolysis studies. Eastman Kodak acetonitrile was purified by distillation using the method proposed by Mann.[16] Tetra-*n*-butylammonium fluoroborate was prepared by the previously reported synthesis,[17] and Baker anhydrous sodium carbonate was used.

All of the compounds were synthesized by either lithium aluminum hydride reduction of the corresponding ketone, by the corresponding alkyl Grignard and benzaldehyde, or by a phenyl Grignard and the corresponding aliphatic ketone. The compounds were purified by distillation, and Table I lists the pertinent physical constants.

A typical experiment was as follows. The fluoroborate, 8.50 g, was dissolved in 125 ml of acetonitrile and then placed into the cell. The electrodes were put in place and the substrate, 1.0–0.5 g, and anhydrous sodium carbonate, 2.0 g, added. After the electrolysis was completed, the anolyte was placed in a round-bottomed flask and the acetonitrile distilled with the aid of a water pump. The residue was then extracted several times with ether. The ether layer was then dried with magnesium sulfate, filtered, and then concentrated by distillation. The residue was placed in a volumetric flask and analyzed by VPC. Quantitative and qualitative analyses were done with standard solutions of authentic samples. Further spectroscopic analyses were done by collecting the appropriate fraction from the VPC.

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Reactions of Crowded Molecules under High Pressure. Reactions of 2,6-Di-*tert*-butylpyridine with Methyl Iodide and Methyl Fluorosulfonate under High Pressure

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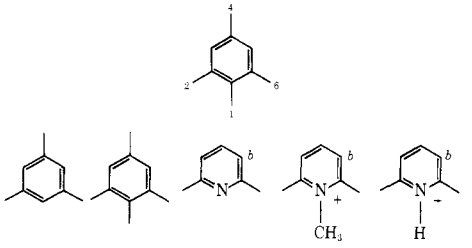
Received November 21, 1974

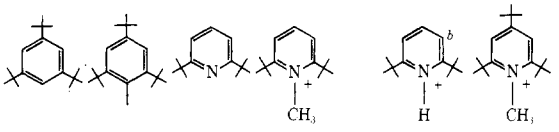
Abstract: 2,6-Di-*tert*-butylpyridine (**1**) was reacted with methyl iodide in dioxane under 5000–6000 atm of pressure at 90° for 10–15 hr. The reaction gave two main products, 2,6-di-*tert*-butyl-*N*-methylpyridinium iodide (**2**) and 2,6-di-*tert*-butylpyridinium hydrogen iodide (**3**). The ratio of these products was about 2 to 8, respectively. Under similar conditions, both **1** and 2,4,6-tri-*tert*-butylpyridine (**4**) were found to react with methyl fluorosulfonate. The solid products from these reactions were also mixtures of the *N*-methyl and protonated compounds. However, the ratio of these products was about 8 to 2, respectively. 4,5-Dimethylacridine was also reacted with methyl fluorosulfonate under high pressure to yield 4,5-dimethyl-*N*-methylacridinium fluorosulfonate. The *N*-methyl compounds of **1** and **4** were thermally very stable and did not decompose at temperatures of up to 300°. The unusual stability of the compounds was accounted for by invoking the steric hindrance of the *tert*-butyl groups. Low-field chemical shifts of methyl and *tert*-butyl protons in the ^1H NMR of **2** and 2,4,6-tri-*tert*-butyl-*N*-methylpyridinium fluorosulfonate (**8**) were discussed and compared with those of their sterical homomorphs in the benzene series.

Menschutkin reactions—typical SN2-type reactions of alkyl halides with amines to form quaternary ammonium salt—have been widely investigated for steric effects.[1] Generally, reaction rates decrease sharply with increased steric hindrance at the reaction site. For example, the reaction rate of pyridine with alkyl iodides decreases sharply as the alkyl iodide is changed through methyl, ethyl, to isopropyl. The activation energy in this case shows a corresponding increase. Introduction of alkyl groups into the 2 and 6 positions of pyridine also results in a decrease in the rate of reaction with alkyl halides which becomes more and more pronounced as the size of the alkyl group increases.

Table I. Effect of Steric Hindrance on the Proton Chemical Shifts, δ Values[a,d]



Methyl proton	2.24	2.22 (2,4,6) 2.06 (1)	2.44	2.84 4.10 (N^+-CH_3)	2.80	



tert-Butyl protons	1.34	1.49 (2,6) 1.33 (4)	1.27	1.66	1.40	1.72 (2,6) 1.42 (4)
Methyl protons		2.51		4.57		4.50
ΔMe[c]	2.51 − 2.06 = 0.45			4.57 − 4.10 = 0.47		
Δ*t*-Bu	1.49 − 1.34 = 0.15			1.66 − 1.40 = 0.26		

[a] All relative to internal tetramethylsilane. [b] Measured in $(CD_3)_2SO$. [c] The difference, in δ value, between the less sterically hindered alkyl substituents and the more hindered substituents. [d] The number in parentheses indicates the positions of substituents.

A highly hindered compound of this series is 2,6-di-*tert*-butylpyridine (**1**) which posesses interesting and unusual properties. The compound was first synthesized by Brown and Kanner.[2,3] They showed that the compound did react with protonic acids but did not react with Lewis acids such as boron trifluoride, or with methyl iodide by conventional procedures, because of steric hindrance between the bulky *tert*-butyl groups and the reactants. A similar sterically hindered base, 4,5-dimethylacridine, prepared by Newman and Powell is another example.[4]

The effect of pressure on Menschutkin reactions has been intensively investigated. The rate of the reaction generally increases with increasing pressure in the system. The increase in rate with pressure was attributed to the decrease of the volume at the transition state.[5] Thus, we have found that **1** reacted with methyl iodide under high pressure (5000–6000 atm).[6] Recently, Le Noble and Ogo, in their systematic study of the effect of pressure on the rates of reaction of 2,6-dialkylpyridines with alkyl iodides,[7] also found that **1** reacted with methyl iodide only at high pressure. However, the reaction product was mainly 2,6-di-*tert*-butylpyridinium hydrogen iodide instead of the *N*-methyl salt.

In this paper, we wish to report further investigations on the reactions of **1** and similar compounds with methyl iodide and methyl fluorosulfonate under high pressure and to discuss the properties of the resulting products.

Results

Reactions of 2,6-Di-*tert*-butylpyridine (1) with Methyl Iodide. Compound **1** was reacted with methyl iodide, either in dioxane solution or with no solvent at all in the following manner. The reactants were placed in a Teflon capsule (volume 4 cm^3), which was subsequently pressurized (5000–6000 atm) and heated (~90°) for 10–15 hr, using the method previously reported.[8] After the solvent was removed under reduced pressure, the solid product was washed with benzene and dried. The ^1H NMR spectrum of the product displays two singlets at δ 1.32 and 1.66 for the *tert*-butyl groups with the low-field signal being much less intense. The signal at δ 1.32 is consistent with the *tert*-butyl groups of 2,6-di-*tert*-butylpyridinium hydrogen iodide (**3**). The expected *N*-methyl peak was not detected. However, after the chloroform solution of the product was treated with aqueous sodium bicarbonate and the solvent distilled off, a solid product was obtained (mp 143–145°). The ^1H NMR spectrum of the compound showed absorption at δ 1.66 for the *tert*-butyl protons and at δ 4.57 for the *N*-methyl protons, the ratio being 6 to 1, respectively. This solid was consistent with di-*tert*-butyl-*N*-methylpyridinium iodide (**2**). Thus the reaction of **1** and methyl iodide under high pressure gave two main products, **2** and 2,6-di-*tert*-butylpyridinium hydrogen iodide (**3**). The ratio of these products was about 2 to 8, respectively, determined by ^1H NMR.

The mass spectrum of **2** showed a parent peak at 206 which corresponds to the 2,6-di-*tert*-butyl-*N*-methylpyridinium moiety.

The N-methylated product **2** was heated to 300° without decomposition, whereas the corresponding 2,6-lutidinium iodide was found to be decomposed at 170°. No change in chemical shifts or splitting patterns of **2** was observed in ^1H NMR spectra as low as −80°.

Reaction of 2,6-Di-*tert*-butylpyridine (1), 2,4,6-Tri-*tert*-butylpyridine (4), and 4,6-Dimethylacridine (5) with Methyl Fluorosulfonate. These bases **1, 4,** and **5** were reacted with methyl fluorosulfonate in methylene chloride under 5500 atm of pressure at 60° for several hours. The solid products were found to be a mixture of *N*-methyl and protonated compounds as in the earlier example. However, in these cases, the N-methylated products were found to predominate over the protonated ones. The ratio of these products was about 8 to 2, respectively. The *N*-methyl products were isolated upon treatment with sodium bicarbonate solution.

2,6-Di-*tert*-butyl-*N*-methylpyridinium fluorosulfonate (**6**), 2,4,6-tri-*tert*-butyl-*N*-methylpyridinium fluorosulfonate (**8**), and 4,5-dimethyl-*N*-methylacridinium fluorosulfonate (**10**) were found to melt without decomposition at 143–145, 149–152, and 165–167°, respectively. Mixtures of **6** or **8** with a large excess of powdered potassium iodide could be heated up to 300° without decomposition. The ^1H NMR spectra of these compounds are shown in Table I.

The mass spectra of compounds **6** and **8** showed peaks at 206 and 262, respectively, corresponding to the 2,6-di-*tert*-butyl-*N*-methyl- and 2,4,6-tri-*tert*-butyl-*N*-methylpyridinium moieties.

Discussion

Recently, the use of high pressure for the study of organic chemistry has been increasing.[9] The pressure dependence of the rate constant of the reaction is:

$$\left(\frac{\partial \ln k}{\partial p}\right)_T = \frac{-\Delta V^{\ddagger}}{RT}$$

where $\Delta V^{\ddagger}$ is the volume of activation. If this value is negative, i.e., the formation of the activated complex from the reactants results in overall contraction, the rate, *k*, will increase with increasing pressure. The effect of pressure on the rate of Menschutkin reactions such as the reaction of substituted pyridines with alkyl iodides has been determined and found to provide large acceleration, the $\Delta V^{\ddagger}$ being between −22 and −35 cm^3/mol.[7]

Highly hindered bases such as 2,4,6-tri-*tert*-butyl-*N*-methyl- (**12**) and 2,6-dimethyl-*N*,*N*-dimethylaniline (**13**) did not react with methyl iodide under ordinary conditions.

We attempted to carry out these reactions by means of high pressure, 5000–5500 atm. The reaction of **12** with methyl iodide gave 2,4-di-*tert*-butyl-*N*,*N*-dimethyl-anilinium iodide (**14**) and isobutylene, instead of the corresponding anilinium salt, 2,4,6-tri-*tert*-butyl-*N*,*N*-dimethylanilinium iodide.[10] The reaction of **13** with methyl iodide gave 2,6-dimethyl-*N*,*N*-dimethylanilinium iodide (**15**) and the α-elimination product from methyl iodide.[11]

As has already been mentioned in the results, the reaction of **1** and methyl iodide under high pressure gave two main products **2** and **3** in which **3** may be produced from the α elimination of methyl iodide. The protonated salt **2** was the predominant reaction product.

Methyl fluorosulfonate is comparable in reactivity to methyl perchlorate and trimethyloxonium salts.[12] However, the reactions of **1** and **4** with methyl fluorosulfonate did not occur at atmospheric pressure. The reaction occurred only under high pressure yielding both the products of SN2 and α-elimination reactions. However, in these cases, the former reaction was favored. The α-elimination reaction of methyl fluorosulfonate with 1,8-bis(dimethylamino)naphthalene has been reported.[13]

The *N*-methyl compounds of **1** and **4** were found to be thermally very stable compared with those of pyridine and 2,6-lutidine. The stabilities of the compounds may be accounted for as follows. Although the basicities of **1** and **4** are lower than that of 2,6-lutidine, methyl iodide and methyl fluorosulfonate were forced to react at the basic nitrogen under high pressure and form the usual coordination bond between nitrogen and carbon, overcoming the steric hindrance of two *tert*-butyl groups. In the product, the two bulky *tert*-butyl moieties surround the methyl group and function like *the chelae of a crab*. Because of the imprisonment of the methyl group by the two bulky substituents, it becomes exceedingly difficult for it to become dissociated, either by nucleophile attack by the anion, or by thermal decomposition. By comparison, the corresponding *N*-methyl compounds of pyridine or 2,6-lutidine do not have that protection. In these cases, the methyl groups are easily dissociated from the nitrogen, or the methyl groups are removed by nucleophilic attack by the anion. Thus the reactions of **1** and **4** with methyl iodide and methyl fluorosulfonate under high pressure are of a class of rare organic reactions in which steric hindrance plays an important role both in the formation of the compounds and in their reverse reactions.

Chemical Shifts. The proton magnetic resonance spectra of the *tert*-butyl and *N*-methyl groups of the compounds investigated and, for comparison purposes, the spectra of 2,6-lutidine, its N-methylated salt and their sterical homomorphs in the benzene series are summarized in Table I. Gibbons and Gil[14] have recently investigated in detail the ^{1}H NMR of monosubstituted trimethyl- and tri-*tert*-butylbenzenes. When a methyl group is substituted between two of the bulky *tert*-butyl groups in 1,3,5-tri-*tert*-butylbenzene, low-field shifts for the protons of both the methyl and *tert*-butyl groups compared with 1,2,3,5-tetramethyl- and 2,4,6-tri-*tert*-butylbenzenes were observed. (Δ = 0.45 and 0.15 ppm, respectively.)

A similar trend was also observed in the spectra of *tert*-butyl substituted *N*-methylpyridinium compounds. The *N*-methyl and *tert*-butyl protons of **2** relative to those of less hindered compounds, 2,6-lutidinium *N*-methyl- and 2,6-di-*tert*-butylpyridinium hydrogen salts, were deshielded by 0.47 and 0.26 ppm, respectively. Also the *N*-methyl and 2,6-di-*tert*-butyl protons of **8** were shifted to a lower field by 0.40 and 0.32 ppm, respectively, while the 4-*tert*-butyl protons were not shifted. These low-field shifts in overcrowded compounds suggest intramolecular van der Waals forces involving the methyl bonded to nitrogen and the ortho *tert*-butyl protons.[14a] Furthermore, examination of the molecular models of compounds **2** and **8** shows that the *tert*-butyl groups approach closer than the van der Waals radii of the hydrogen atom. It is felt that the molecular crowding with van der Waals forces can be possibly relieved by distortion of the angle between the pyridine ring and its substituents.[15] In order to study this possibility, the exact structures of compounds **2** and **8** are being investigated by X-ray measurements.

Experimental Section[16]

All melting points were determined on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 521 spectrophotometer and were calibrated using the 6.23 μ (1603 cm^{-1}) band of polystyrene film. Nuclear magnetic resonance spectra were obtained on a Varian A-60 instrument, using chloroform-*d* as a solvent, unless otherwise specified. Chemical shifts are recorded in δ units from internal tetramethylsilane. A low-temperature NMR spectrum was obtained on a Varian A-60 spectrometer equipped with a variable-temperature probe, using the chemical shifts of methanol to calibrate the temperature. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6 mass spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by Schwartzkopf Laboratories, New York, N.Y.

Materials. 2,6-Di-*tert*-butylpyridine was prepared by the method reported[17] and also obtained from Willow Brook Laboratories, Inc., Waukesha, Wis. The compound was purified by distillation from calcium hydride. 2,4,6-Tri-*tert*-butylpyridine[17] and 4,5-dimethylacridine[4,18] were synthesized by literature preparation methods. In all cases, NMR and VPC were used to ensure a high degree of purity. Methyl fluorosulfonate (Aldrich Chemical Co.) was distilled, and methyl iodide was dried over phosphorus pentoxide and purified by distillation. Methylene chloride was purified by washing with 10% sodium carbonate solution, followed by water, dried over anhydrous calcium chloride, and then distilled. Dioxane of reagent grade was purified by distillation and stored over sodium wire.

Reaction Between 2,6-Di-*tert*-butylpyridine (1) and Methyl Iodide. A solution of 2,6-di-*tert*-butylpyridine (0.573 g, 3 mmol), 0.852 g (6 mmol) of methyl iodide, and 3 ml of dioxane was prepared in a drybox. The solution was placed in a Teflon capsule (1.8 cm i.d., 2 cm long), and the system was pressurized to 5000–6000 atm at 90° for 12 hr.[8] After all excess methyl iodide and dioxane were removed by distillation, a solid was obtained which proved to be a mixture of 2,6-di-*tert*-butyl-*N*-methylpyridinium iodide and 2,6-di-*tert*-butylpyridinium hydrogen iodide by NMR analysis. The solid product was washed with benzene and dissolved in chloroform, treated with saturated aqueous sodium bicarbonate solution and water, and then dried over anhydrous magnesium sulfate. Two hundred milligrams (20% yield) of 2,6-di-*tert*-butyl-*N*-methylpyridinium iodide was obtained after removal of the solvent: mp 143–145°; NMR spectrum ($CDCl_3$) *tert*-butyl protons at δ 1.66 (S, 18 H), *N*-methyl protons at δ 4.57 (S, 3 H), aromatic protons at δ 8.24 (M, 3 H); mass spectrum *m/e* 206 (M^+).

Reactions of 2,6-Di-*tert*-butylpyridine (1), 2,4,6-Tri-*tert*-butylpyridine (4), and 4,5-Dimethylacridine (5) with Methyl Fluorosulfonate. A mixture of 0.573 g (3 mmol) of 2,6-di-*tert*-butylpyridine and 0.376 g (3.3 mmol) of methyl fluorosulfonate in 3 ml of methylene chloride was placed in a Teflon capsule and pressurized at 60° for 15 hr. Evaporation of the methylene chloride afforded a mixture of the 2,6-di-*tert*-butyl-*N*-methylpyridinium salt **6** and 2,6-di-*tert*-butylpyridinium hydrogen fluorosulfonate. The NMR spectrum clearly showed two different proton peaks for *tert*-butyl, δ 1.66 and 1.32 with a ratio of 8 to 2, respectively. Treatment of a chloroform solution of the white crystalline material with aqueous sodium bicarbonate afforded 0.600 g of **6** (mp 143–145°), showing infrared bands (KBr) at 3.19, 3.39, 6.20, 6.32, 6.77, 7.25, 7.78, 8.20, 8.50 9.40, 10.38, 11.62, 12.40, 13.30, 14.00, 14.30, 17.60 μ. The NMR of **6** was essentially identical with that of **2**, not only at room temperature but at −80°. The mass spectrum exhibited a molecular ion peak at *m/e* 206.

Anal. Calcd for $C_{14}H_{24}NO_3SF$: C, 55.07; H, 7.87; N, 4.59. Found: C, 54.81; H, 7.97; N, 4.70.

2,4,6-Tri-*tert*-butyl-*N*-methylpyridinium fluorosulfonate (0.42

g, 60% yield) was obtained from the reaction between 0.50 g (2 mmol) and 0.29 g (2.5 mmol) of methyl fluorosulfonate in 3 ml of methylene chloride under the same condition as the previous reaction: mp 149–152°; NMR ($CDCl_3$) δ 1.73 (s, 18 H), 1.42 (s, 9 H), 4.50 (s, 3 H), and 7.90 (s, 2 H).

The reaction between 0.20 g (1 mol) of 4,5-dimethylacridine and 0.23 g (2 mmol) of methyl fluorosulfonate in 3 ml of methylene chloride yielded 0.19 g (60% yield) of the corresponding *N*-methyl salt after the work-up: mp 165–167°; NMR (Me_2SO-d_6) δ 7.90 (m, 7 H), 2.90 (s, 6 H), and 4.60 (s, 3 H).

Stabilities Studies. A mixture of 0.30 g (1.8 mmol) of potassium iodide and 0.20 g (0.6 mmol) of 2,6-di-*tert*-butyl-*N*-methylpyridinium fluorosulfonate (**6**) or 0.17 g (0.5 mmol) of 2,6-di-*tert*-butyl-*N*-methylpyridinium iodide (**2**) was introduced into a piece of U-shaped tubing 15 cm long and plugged with glass wool at both ends. The glass tubing was heated to 300° in a silicone oil bath under a nitrogen atmosphere. After allowing the mixture to cool to room temperature, it was treated with chloroform. The solid recovered was found to be the original N-methylated salt, by NMR analysis. A mixture of 0.20 g (1 mmol) of *N*-methyl-2,6-lutidinium fluorosulfonate or 0.23 g (1 mmol) of *N*-methyl-2,6-lutidinium iodide and 0.50 g (3 mmol) of potassium iodide was heated under the same conditions described in the cases of **2** or **6**. Decomposition occurred at 170°. Only 2,6-lutidine was recovered; no *N*-methyl peak was observed in the NMR.

Acknowledgment. We thank Mr. H. Shimizu for the preliminary experimental work in this investigation.

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New Synthetic Methods. 1,3-Alkylative Carbonyl Transposition

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Abstract: Reaction of carbonyl compounds with vinyllithium reagents followed by quenching with benzenesulfenyl chloride produces the allylic sulfoxide resulting from [2,3]-sigmatropic rearrangement. Sulfenylation of the corresponding anion results in a net isomerization of the allylic sulfoxide into a γ-hydroxy-α,β-unsaturated thioether. Hydrolysis to the enone or enal accomplishes the equivalent of a directed aldol condensation. Application to carbonyl partners that are easily enolized and that are hindered is illustrated. Addition of organolithium reagents to enones, quenching with benzenesulfenyl chloride, sulfenylation, and hydrolysis effect a 1,3-carbonyl migration and concomitant carbon–carbon bond formation at the former carbonyl carbon. Application of these methods to a model system for fusidic acid and the synthesis of a volatile constituent of Greek tobacco is reported.

The aldol condensation continues to play a fundamental role in carbon–carbon bond forming reactions.[3] Despite its widespread utility, a decided limitation arises when nonidentical carbonyl partners are condensed as a result of the ambiguity in the direction of the cross condensation as well as the self-condensation of the partners. To overcome this restriction, various modifications to the mixed aldol reaction have appeared.

One modification makes use of the regiospecific generation of lithium enolates and/or the addition of magnesium or zinc cations to trap the mixed aldol product as its chelate.[4,5] Chemically differentiating one aldol partner prior to reaction also serves to direct the condensation. Reaction of a silyl enol ether with a carbonyl group[6] or a ketal,[7] or of an enol acetate with a ketal[8] in the presence of titanium tetrachloride results in the desired cross-condensation. Similar results have been noted in the reactions of enol ethers and acetals or aldehydes with boron trifluoride or zinc chloride.[9]

Other methods, which are restricted to the synthesis of aldehydes, also rely on the prior discrimination of the partners. The nucleophilic member of the condensation has been masked as the corresponding dihydro-1,3-oxazine[10] and as the metalated Schiff's base.[11] Improvement in the dehydration portion of these sequences has been found by the use of diethyl 2-(cyclohexylamino)vinylphosphonate which leads directly to the α,β-unsaturated imine.[12,13] The anion of diethyl carboxaldehydomethylphosphonate[14] and the Wittig reagent from β-ketophosphonium salts[15] condense well only with aldehydes.

A quite different approach involves a two-carbon homologation of carbonyl groups which relies upon the initial addition of an allylic Grignard reagent,[16] a vinyl Grignard reagent,[17] or an acetylide anion[18] followed by further modification to the directed aldol product. These procedures especially point out that the aldol condensation can be considered to be an intermolecular 1,3-carbonyl transposition.