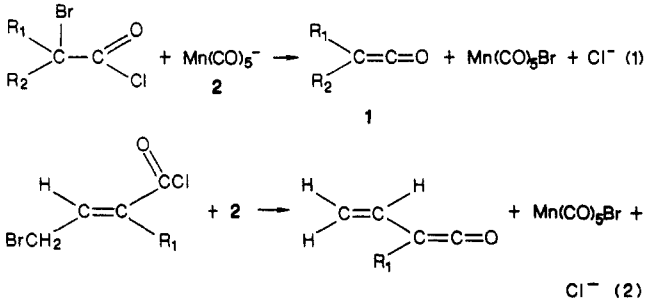
A New Synthesis of Reactive Ketenes (Solutions)

Summary: Distilled solutions of reactive ketenes are conveniently prepared by the reaction of α-bromoacyl chlorides and pentacarbonylmanganese anion.

Sir: Ketenes **1** can be synthesized by a variety of methods.[1] However, yields are often mediocre, the solutions sometimes contaminated with other products, or the reactions not suitable for small-scale preparations (ketene itself). We have found that the reaction of pentacarbonylmanganate anion (**2**) with α-bromoacyl chlorides (or bromides) unexpectedly leads in good yield to ketenes or with vinylogous γ-bromo compounds to vinyl ketenes.



R_1 and R_2 = H or alkyl

The reactions shown in eq 1 and 2 are extremely rapid at or well below room temperature and this feature is what makes this synthetic method particularly adaptable for the preparation of distilled solutions of the less stable ketenes.[2]

For the millimolar-scale preparative procedures for which this method is ideally suited, the reagent PPN^+-$Mn(CO)_5^-$ (**2a**)[3,4] is preferred since this yellow salt can be weighed in air and is soluble in many organic solvents.

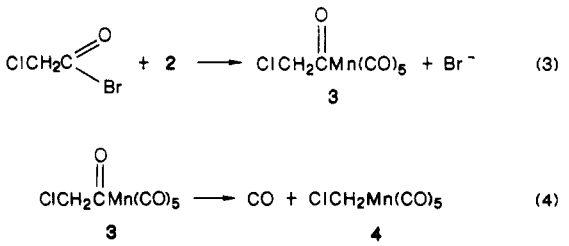
Procedure A. To prepare a ca. 0.5 M ketene solution (0.5-mmol scale), one sequentially adds α-bromoacetyl chloride in 0.5 mL of $CHCl_3$ and then **2a**, also in 0.5 mL $CHCl_3$, to a liquid N_2 cooled trap containing a magnetic stirring bar. This trap is connected to a second liquid N_2 cooled receiver and the system evacuated to ca. 0.1 mmHg and closed. The reactant trap is allowed to rapidly warm up in air (to ca. 0 °C) with stirring beginning as soon as the $CHCl_3$ solution melts. Distillation of the $CHCl_3$–ketene solution is controlled by the depth of cooling of the receiver and is completed in ca. 3–5 min. (or less than 0.5 h total time for all operations starting from stable reagents). For exploratory purposes, the ketene concentrations ($CDCl_3$) were determined by low temperature (−40 to −50 °C) ^1H NMR spectroscopy.[5] In the case of ketene, the distilled yields are in the 95% range. Although this procedure is not suitable if large amounts of ketene are needed, it is convenient, reliable, and quick for the preparation of millimolar quantities and we believe this to be the method of choice in such situations.[6] Furthermore, the yields are sufficiently quantitative that a standardization of the solution may not always be needed. Dimethyl ketene can also be prepared by this procedure (95% yield, high purity). Ketene and dialkyl ketenes are amongst the more stable members of this group, and a more stringent test is provided by methyl or ethyl ketene.[7] In this case, the procedure had to be modified.

Procedure B. The α-bromoacyl chloride (or bromide) in $CHCl_3$ is rapidly added in several increments via a stoppered long syringe needle to just above a concentrated $CHCl_3$ solution of the $Mn(CO)_5^-$ salt (initial frozen vacuum of ca. 0.1 mmHg, operating vacuum under $CHCl_3$ distillation is ca. 20 mm) with stirring at ca. 0 °C (the constant $CHCl_3$ distillation keeps the solution cold even though no external cooling is provided at this point). On a ca. 0.5-mmol scale, the total addition time is 2–3 min, and both methyl and ethyl ketene are collected as ca. 0.5 M solutions in about 90% yield.

Methyl vinyl ketene can be prepared from γ-bromotigloyl chloride in >80% yield by using either procedure but vinyl ketene itself has proven even more difficult to prepare than methyl or ethyl ketene. Procedure B has been used under exacting conditions to provide ca. 35% yield on a 0.1-mmol scale of this very reactive species.[8] It is imperative in this case to keep the PPN^+ salt nearly dry during the $CHCl_3$ solution addition, i.e., distill off the $CHCl_3$ very rapidly after it contacts the salt.[9] A description of this synthesis is provided as supplementary material, including a detailed description of the apparatus used in all experiments.

Since both PPN^+Cl^- and $Mn(CO)_5Br$ are relatively inert compounds, we have shown that some in situ ketene preparations are also possible, using temperatures of about −40 °C in the generation.

The present ketene synthesis has some similarity to the Staudinger method;[1] however, the present reaction is much faster and may well involve a distinct reaction mechanism. In our case, interchanging the halogens in a α-bromoacyl chloride virtually completely changes the course of the reaction to give mainly the (α-chloroacyl)manganese compound **3**[10] (eq 3). On heating to 80 °C in $CDCl_3$ in a sealed tube, the major reaction is a decarbonylation to give **4**,[11] a normal type of acylmanganese reactivity (eq 4).



(1) *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; Parts 1 and 2

(2) Many diarylketenes have been isolated in good yield by using existing methods, and there is no need to use the present method in such cases.

(3) (a) Duffy, D. N.; Nicholson, B. K. *J. Organomet. Chem.* **1979**, *164*, 227. (b) Gladysz, J. A.; Williams, G. M.; Tam, W.; Johnson, D. L.; Parker, D. W.; Selover, J. C. *Inorg. Chem.* **1979**, *18*, 553.

(4) The reagent is reported to be unchanged after 1 year when stored in a freezer under nitrogen.[3a]

(5) In the case of the ketene analysis only, the distillate was collected in an NMR tube, which was subsequently sealed as a precaution against any ketene loss during the analysis. Infrared spectra and ^1H NMR analysis of dimerization products were also carried out in some cases. All ^1H NMR data is provided as supplementary material.

(6) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 528. Here the pyrolysis of diketene is recommeded as the method of choice for making ketene.

(7) McCarney, C. C.; Ward, R. S. *J. Chem. Soc., Perkin Trans.* **1975**, 1600.

(8) Trahanovsky, W. S.; Surber, B. W.; Wilkes, M. C.; Preckel, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6779 and references therein.

(9) A glass wool plug is added to the transfer line to trap small amounts of the PPN^+ salt which tend to spray out of the mixing flask. A twofold excess of the PPN^+ salt was also used in this preparation, and the total reaction time was only 45 s.

(10) (a) Dilgassa, M.; Curtis, M. D. *J. Organomet. Chem.* **1979** *172*, 177. (b) Calderazzo, F.; Noack, K.; Schaerer, U. *J. Organomet. Chem.* **1966**, *6*, 265.

(11) Botha, C.; Moss, J. R.; Pelling, S. *J. Organomet. Chem.* **1981**, *220*, C21–C24. When we heat **3**, compound **4** is the major product, but there are other high-field ^1H peaks present as well. There is *no* sign of diketene in this solution.

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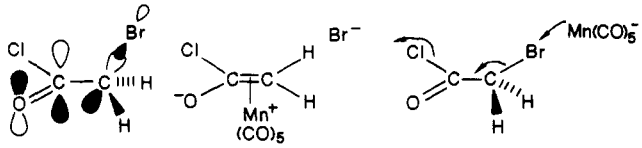
From these results, one can probably exclude, for the mechanism of the ketene forming reaction, the transient formation of a (α-bromoacyl)manganese (like **3**) followed by elimination of $Mn(CO)_5Br$. Additionally, in eq 2, such an intermediate would leave the bromine and manganese on opposite sides of a double bond and spatially distant, an unlikely scenario for rapid vinyl ketene formation.

The normal reactivity of **2** and an acyl halide is the very rapid formation of the acyl manganese compound. The complete circumvention of this "normal" reaction by the ketene forming mechanism implies that the latter reaction rate would have to be very rapid indeed, *exactly as one finds*.

In treating the eq 1 or 2 reactions in terms of a HOMO–LUMO interaction, the C–Br bond has been oriented perpendicular to the carbonyl group plane in the computed [12] LUMO of the α-bromoacyl chloride **5**. This LUMO has π-character, and a direct attack from underneath could lead smoothly with Br^- loss to the π-complex ion pair **6**, which might then collapse to $Mn(CO)_5Br$, Cl^- and ketene. Complex **6** has close analogies in cyclopentadienyliron dicarbonyl complexes.[13] However, a direct attack on **5** via the α-bromine looks like an even more straightforward mechanism (electron transfer?), i.e. structure **7**.



5 **6** **7**

In summary, we believe that this new synthetic procedure offers a convenient small-scale preparation of ketene and monoalkyl ketenes and a synthesis of vinyl ketenes free of pyrolysis coproducts.

We are extending this investigation to the generation of other reactive ketenes, as well as investigating the utility of other metal-centered nucleophiles in carrying out these reactions.

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Registry No. 1 ($R_1 = R_2 = H$), 463-51-4; 1 ($R_1 = CH_3$, $R_2 = H$), 6004-44-0; 1 ($R_1 = CH_3CH_2$, $R_2 = H$), 20334-52-5; 1 ($R_1 = R_2 = CH_3$), 598-26-5; 1 (R_1 = vinyl, $R_2 = H$), 50888-73-8; 1 (R_1 = vinyl, R_2 = methyl), 83897-55-6; **2a**, 52542-59-3; $BrCH_2COCl$, 22118-09-8; $BrCH(CH_3)COCl$, 7148-74-5; $BrCH(CH_2CH_3)COBr$, 26074-52-2; $BrC(CH_3)_2COCl$, 20469-89-0; $BrC(CH_3)_2COBr$, 20769-85-1; $BrCH_2CH{=}CHCOCl$, 51544-74-2; $BrCH_2CH{=}C(CH_3)COCl$, 103500-00-1.

Supplementary Material Available: Experimental procedure, apparatus, and NMR specta of the ketenes (3 pages). For ordering information see any current masthead page.

(12) All calculations were based on the HFS-LCAO method of Baerends: Baerends, E. J.; Ellis, D. E.; Raos, P. *Chem. Phys.* **1973**, *2*, 41.

(13) (a) Ariyaratne, J. K. P.; Green, M. H. L. *J. Chem. Soc.* **1964**, 1. (b) Giering, W. P.; Rosenblum, M.; Tancrede, J. *J. Am. Chem. Soc.* **1972**, *94*, 7170.

Andrew P. Masters, Ted S. Sorensen,* Tom Ziegler

The Department of Chemistry
The University of Calgary
Calgary, Alberta, T2N 1N4, Canada

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Modification of Guanine Bases: Reaction of N^2-Acylated Guanine Nucleosides with Dichloro-(*N*,*N*-diisopropylamino)phosphine

Summary: N^2-acylated guanine nucleosides (acyl = benzoyl, isobutyryl, acetyl) reacted rapidly with dichloro-(*N*,*N*-diisopropylamino)phosphine in the presence of diisopropylethylamine to give novel phosphitylated tricyclic guanine nucleoside derivatives in 60–96% yield.

Sir: We wish to describe the synthesis and structure determination of novel phosphitylated tricyclic guanine nucleoside derivatives. These derivatives are readily formed by the reaction of N^2-acylated guanine nucleosides (widely used in nucleotide synthesis) with dichloro-(*N*,*N*-diisopropylamino)phosphine (**1**) in the presence of diisopropylethylamine (**2**). These novel derivatives were unexpectedly detected during a ^{31}P NMR study of the reaction of N^2-acylated guanine nucleosides with chloro-(*N*,*N*-diisopropylamino)methoxyphosphine (**3**), a reagent commonly used for the preparation of nucleoside-3′-*O*-[1,2] and 5′-*O*-(*N*,*N*-diisopropylamino)phosphoramidites,[3] key intermediates in the chemical synthesis of DNA and RNA molecules. Dichloro-(*N*,*N*-diisopropylamino)phosphine (**1**) was obtained as an impurity during the preparation of reagent **3**.

Compound **1** was prepared by the reaction of phosphorous trichloride (1 equiv) and diisopropylamine (2 equiv) in ether (0 °C) in 67% isolated yield.[4] This material showed spectroscopic properties (^{31}P NMR, $\delta_{CDCl_3} = 169.8$ ppm) identical with those of the impurity in our original phosphite reagent **3** (^{31}P NMR, $\delta_{CDCl_3} = 184.2$ ppm). When nucleoside **4a** (1.0 mmol), the dichloroaminophosphine reagent **1** (1.1 mmol), and diisopropylethylamine (7.8 mmol) were combined (3 mL of $CHCl_3$, 20 °C, 20 min), **5a** was isolated as a yellow solid, mp 93–97 °C, $C_{41}H_{71}N_6O_6PSi_3$,[5] in 96% yield after silica gel chromatography (dichloromethane as eluant; R_f 0.64, 1:6 chloroform–ether).

The structure of **5a** was established by spectroscopic means. The ^{31}P NMR spectrum showed two resonance signals at 93.7 and 93.5 ppm. The UV spectrum (EtOH) was indicative of the extended ring system: λ_{max} (ϵ) 377 sh (8700), 356 (14 100), 344 (14 500), 262 (19 500). The ^1H NMR and the coupled INEPT ^{15}N NMR showed no indication of the two NH signals present in guanosine **4a**.[6] Further evidence for the structure of this product was provided by the ^{13}C and ^{15}N NMR and IR spectra. The ^{13}C NMR resonance of the carbonyl group of the benzoyl moiety of **4a** appears as a singlet at 167.14 ppm, while in the tricyclic derivative **5a**, this carbon signal is coupled to phosphorus and appears as a doublet centered at 160.58 (isomer 1) and 160.53 ppm (isomer 2) with $^2J_{^{13}C-^{31}P} = 6.0$ and 6.9 Hz, respectively. The upfield shift experienced by this carbon strongly suggests that the amido carbonyl

(1) McBride, L. J.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *24*, 245–248.

(2) Adams, S. P.; Kavka, K. S.; Wykes, E. J.; Holder, S. B.; Galluppi G. R. *J. Am. Chem. Soc.* **1983**, *105*, 661–662.

(3) Damha, M. J.; Pon, R. T.; Ogilvie, K. K. *Tetrahedron Lett.* **1985**, *26*, 4839–4842.

(4) During the preparation of this manuscript Tanaka et al. reported the synthesis of this reagent: Tanaka, T.; Tamatsukuri, S.; Ikehara, M. *Tetrahedron Lett.* **1986**, *27*, 199–202.

(5) Satisfactory microanalyses, UV, FAB mass spectra, and ^1H, ^{13}C, and ^{31}P NMR data were obtained for each compound here reported.

(6) ^1H NMR ($CDCl_3$) in ppm from Me_4Si. **4a**: 12.12 (NH), 8.62 (NH, D_2O exchangeable). INEPT ^{15}N NMR ($CDCl_3$) in ppm from $^{15}NH_4NO_3$: [0.3 M **4a**] 224.8 (N7, $J_{N7-H8} = 11.6$ Hz), 149.7 (N9, $J_{N9-H8} = 8.3$ Hz), 129.0 (*N1*, $J_{N1-H1} = 91.6$ Hz), 106.7 (N2, $J_{N2-H2} = 94.8$ Hz). 0.6 M **5a**: 225.1, 224.1 (N7, isomers 1, 2, $J_{N7-H8} = 11.6$, 11.6 Hz, respectively), 149.9, 149.8 (N9, isomers 1, 2, $J_{N9-H8} = 6.6$, 8.3 Hz, respectively).

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