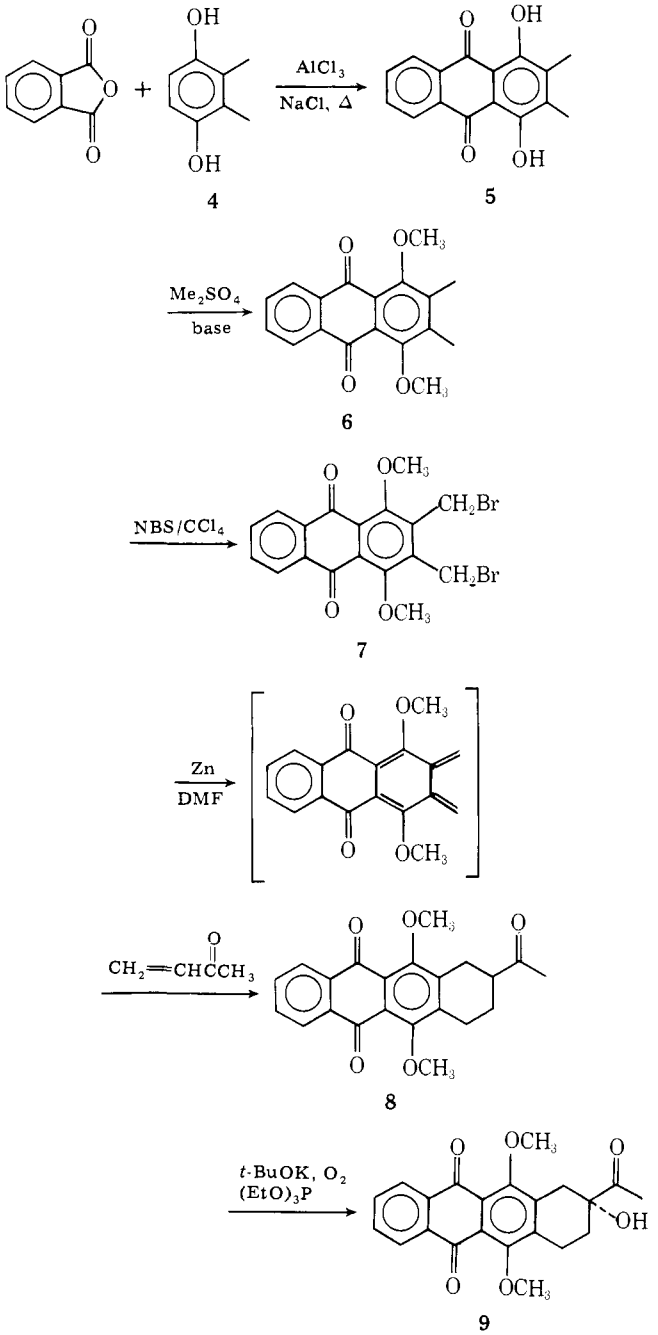
A by the Diels–Alder addition of a reactive *o*-quinodimethane intermediate to the olefinic portion of an $\alpha,\beta$-unsaturated ketone as shown in eq 1.[3] The generation of an *o*-quinodimethane from an *o*-xylene derivative and its trapping by a dienophile has ample precedence in the literature.[4]

Phthalic anhydride was condensed with the readily prepared 2,3-dimethylhydroquinone (**4**)[5] ($AlCl_3$/NaCl, 190 °C, 2 min) to give, after heating with dilute hydrochloric acid, 2,3-dimethyl-1,4-dihydroxyanthraquinone (**5**) (81%, mp 252–253 °C).[6,7] Methylation of **5** ($Me_2SO_4/K_2CO_3$, refluxing 2-butanone, 12 h) afforded the dimethoxy compound **6** (95%, mp 159–160 °C) which was brominated photochemically (NBS/$CCl_4$, reflux, 8 h) to give the key dibromide **7** (95%, mp 171–173 °C). Reaction of dibromide **7** (Zn dust, DMF, 25 °C, 6 h) in the presence of excess methyl vinyl ketone gave, after aqueous workup, the tetracyclic ketone **8** (52%, mp 145–147 °C). Oxidation of ketone **8** (KO-*t*-Bu/$O_2$, DMF, −20 °C, 1 h) followed by reduction ($(EtO)_3P$, DMF, −20 °C, 1 h)[8] gave, after mild acid hydrolysis, the hydroxy ketone **9** (55%, mp 184–186 °C).[9]




4 5 6 7 8 9

Since the conversion of **9** to 4-demethoxydaunomycinone (**3**) has already been described,[2,9,10] our synthesis of **9** also constitutes a new synthesis of **3**.

We are currently studying variations of this *o*-quinodimethane approach, in particular the use of oxy derivatives of methyl vinyl ketone in order to provide a direct route to tetracyclic ketones containing an oxygenated side chain.

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## A General, Selective, and Facile Method for Ketone Synthesis from Acid Chlorides and Organotin Compounds Catalyzed by Palladium

*Sir:*

Transition metal catalyzed coupling reactions of organic halides with Grignard reagents or organolithium compounds generally are not applicable for ketone synthesis via the acid chlorides, since the organometallics react with the product ketone.[1] Alkylrhodium complexes, prepared from a rhodium complex and organolithium or Grignard reagents, however, may be used for alkylation of acid chlorides, giving alkyl ketones.[2,3] Unfortunately, in addition to being a two-stage synthesis, this reaction is stoichiometric with respect to rhodium and will not tolerate a number of other functional groups on the acid chloride.

We have found that organotin compounds readily undergo a palladium catalyzed coupling with acid chlorides, thereby providing a general and simple method for preparation of ketones (eq 1).[4] The reaction is general both with respect to the organotin compound and the acid chloride (Table I).

$$\mathrm{RCOCl} + \mathrm{R'_4Sn} \xrightarrow[\text{HMPA}]{\mathrm{PhCH_2Pd(PPh_3)_2Cl\ (1)}} \mathrm{RCOR'} + \mathrm{R'_3SnCl} \quad (1)$$

The following features make this method synthetically attractive. (1) The yields are high, and in many cases virtually quantitative. (2) The reaction can be carried out in the presence

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**Table I.** Synthesis of Ketones from RCOCl and $R'_4Sn$ According to Eq 1 [a]

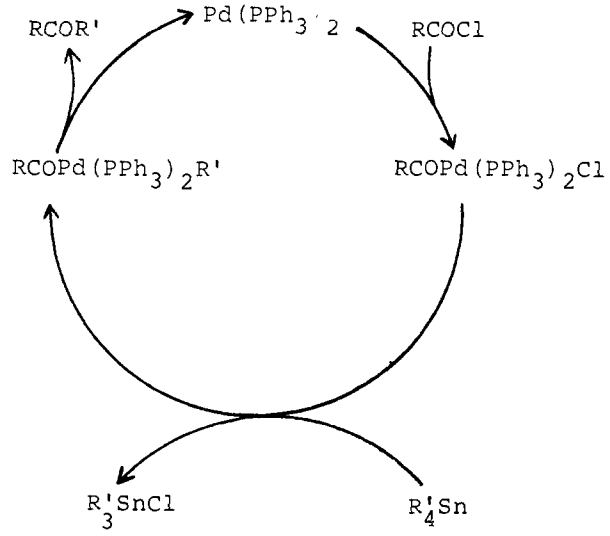
| Entry | R | R′ | Yield[b] of RCOR′, % |
|---|---|---|---|
| 1 | Ph | Me | 97.5 (89)[c] |
| 2 | Ph | Ph | 85.7[c] |
| 3 | Me | Ph | 76.3 |
| 4 | Ph | n-Bu | 91.3 |
| 5 | Ph | $PhCH_2$ | 95.0 |
| 6 | 4-$CH_3OC_6H_4$ | Ph | 84.7 |
| 7 | 4-$CNC_6H_4$ | Me | 99.8 |
| 8 | 4-$ClC_6H_4$ | Me | 97.6 |
| 9 | 4-$BrC_6H_4$ | Me | 67.5[d] |
| 10 | 4-$NO_2C_6H_4$ | Me | 98.7 |
| 11 | 2-$NO_2C_6H_4$ | Me | 73.3 |
| 12 | 4-$CHOC_6H_4$ | Me | 86.0[c,e] |
| 13 | 2-$CH_3COOC_6H_4$ | Me | 95.5 |
| 14 |  | Me | 91.0 |
| 15 | $PhCH_2CH_2$- | Me | 99.5 |
| 16 | $CH_2$=CH- | Me | 93.3 |
| 17 | *trans*-PhCH=CH- | Me | 91.3[c,f] |
| 18 | $(CH_3)_3C$- | Me | 82.2 |

[a] The reactions were carried out using 9.1 mmol of $Me_4Sn$, *n*-$Bu_4Sn$, or $(PhCH_2)_4Sn$, 9 mmol of the acid chloride, and $4.5 \times 10^{-3}$ mmol of **1**, dissolved in 4 mL of HMPA. In reactions with $Ph_4Sn$, a suspension of 3.7 mmol in 15 mL of HMPA was used, together with 3.7 mmol of the acid chloride and 0.04 mmol of **1**. The reaction mixture was heated at 60–65 °C under air atmosphere until blackening occurred. [b] By GLC based on RCOCl. [c] Isolated yield. [d] 25.9% of *p*-methylacetophenone also formed. The reaction mixture did not blacken. [e] To avoid oxidation and Pd metal catalyzed decarbonylation of the aldehyde, the reaction was carried out under argon and stopped after 25 h at 65 °C. [f] Only *trans*-4-phenyl-3-buten-2-one was obtained.

of a wide variety of functional groups; nitro, nitrile, arylhalo, olefin, methoxy, ester, and even aldehyde groups are tolerated. The reaction is applicable for compounds that have a tendency to polymerize (entries 12, 16). *p*-Acetylbenzaldehyde is highly reactive and has a high tendency to undergo self-condensation under conditions which are not strictly neutral.[5,6] Thus, many difficulties are encountered in its preparation by other methods.[6] Sterically hindered acid chlorides (entries 11, 18) react normally; conjugate addition, where possible (entry 17), does not take place. (3) There is no need for an inert atmosphere since both the tin compound and the catalyst are air stable. In fact, the reaction can be carried out in an open vessel provided that the humidity is not high enough to hydrolyze the acid chloride. (4) The reaction is clean. There are virtually no side reactions which complicate isolation and purification. The workup is simple; the solvent and $Me_3SnCl$ are removed by water extraction, and the residue is purified by distillation or crystallization. For reactions producing other triorganotin chlorides that are water insoluble, the chloride is precipitated by addition of an alcoholic solution of KF to the ethereal solution of the product. (5) Reaction times are short; in many cases the reaction is over in 10–15 min. (6) The completion of the reaction is clearly visualized since the catalyst serves as an indicator; as soon as the acid chloride is consumed, Pd metal is precipitated and the clear yellow solution turns black. (7) The reaction is highly catalytic; turnover numbers of 20 000 have been obtained.

This method appears to be among the best methods for ketone synthesis and offers some advantages over the methods presently used. The yields are in most cases higher than those obtained by any other ketone synthesis. There is no further addition to the product ketone, while this is the main side reaction of most organometallic reagents (cadmium, zinc, magnesium). Generally, low temperatures are required to avoid this reaction when organocopper compounds are used.[7] Formation of cadmium enolates and esters is a further disadvantage of these reagents. Lithium derivatives have a very low functional group tolerance and are generally limited to synthesis of unsubstituted ketones. None of these methods tolerate the aldehyde function; the present method is the only one using organometallic reagents for a one-step ketone synthesis from the acid chloride which tolerates this group. In addition, the manipulation and workup seem to be much more convenient (e.g., inert atmosphere is required by all the methods mentioned above). However, the reaction has one limitation. Bromine substituents in a position affected by electron-withdrawing groups (entry 9) compete with the acyl chloride for the tin compounds.

Scheme I




A second organic group attached to tin can also be transferred. Thus, the reaction of $Me_3SnCl$ with benzoyl chloride, catalyzed by **1** yields 90.5% acetophenone. However, this reaction is five times slower than the one using $Me_4Sn$. Unfortunately, $Me_2SnCl_2$ and $MeSnCl_3$ cannot be used owing to their reaction with HMPA. Interestingly, aryltin groups are transferred in preference to alkyltin groups. Thus, reaction of triphenylmethyltin with benzoyl chloride catalyzed by **1** affords 96.8% benzophenone and no acetophenone. This result is consistent with the results of vinylation of platinum complexes by trimethylvinyltin.[8]

The reaction is also catalyzed by $Pd(PPh_3)_4$, but this complex is less effective owing to the triphenylphosphine the complex liberates;[9] triphenylphosphine retards the oxidative addition reaction. In addition, $Pd(PPh_3)_4$ is air sensitive and therefore less convenient to handle.

The following procedure for the preparation of acetophenone is representative. To a solution of 4.8 g (34.5 mmol) of benzoyl chloride in 16 mL of dry HMPA was added 5 mL (36.1 mmol) of $Me_4Sn$ followed by 14 mg ($18 \times 10^{-3}$ mmol) of **1**. The clear yellow solution was heated at 65 °C with stirring and after 10 min an instantaneous color change to black occurred. The solution was cooled to room temperature, and 20 mL of water was added. The organic layer, which settled to the bottom, was separated, and the aqueous solution was extracted by 10 mL of ether. The combined organic solutions were washed with 4 × 20 mL of water and dried over $MgSO_4$, and the solvent was removed by evaporation. The residue was purified by distillation, to afford 3.7 g of acetophenone, bp 90–93 °C (20 mm), corresponding to 89% yield based on benzoyl chloride.

Oxygen has a considerable accelerating effect on the reaction. Thus, the rate at which $Me_4Sn$ reacts with benzoyl chloride under oxygen atmosphere is 12 times faster than the

rate under argon. Also, the rate as function of catalyst concentration passes through a maximum; e.g., the optimal catalyst concentration for the reaction of benzoylchloride with tetramethyltin is $8 \times 10^{-4}$ M, the reaction being slower at both higher and lower concentrations. The active catalyst is probably $Pd(PPh_3)_2$, which is formed by reduction of **1**. Thus, the most plausible mechanism for the reaction is outlined in Scheme I. This oxidative addition-reductive elimination sequence is supported by the observation that the product of oxidative addition of benzoyl chloride to tetrakis (triphenylphosphine)palladium(0) reacts with tetramethyltin to afford acetophenone. The end point of the reaction is realized when bis(triphenylphosphine)palladium(0) undergoes disproportionation in the absence of the acid chloride (eq 2).

$$2Pd(PPh_3)_2 \rightarrow Pd(PPh_3)_4 + Pd \qquad (2)$$

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## A Synthesis of *dl*-Cocaine Using Nitrone Intermediates

*Sir:*

We have already reported[1] an intramolecular nitrone-induced cyclization to afford pseudotropine. Herein we discuss a stereospecific synthesis of *dl*-cocaine (**1**). Previously reported[2-5] syntheses of cocaine encounter stereochemical complication in efforts to introduce the requisite carbomethoxyl group with the necessary axial geometry. Our attack on this problem focuses on the anticipated regiospecific, intramolecular cycloaddition of nitrone **2** to afford cycloadduct **3**. The *E* configuration at the olefinic center in **2** and the concerted nature of the cycloaddition compel the ester function to adopt the exo configuration denoted in **3**. We envisioned little difficulty in converting cycloadduct **3** into *dl*-cocaine by analogy to our earlier pseudotropine synthesis.[1,6]

It has been reported[7] that peracetic acid or hydrogen peroxide can oxidize isoxazolidines with concomitant ring opening to generate nitrones in modest yield. The cases studied suggested that, for those substrates lacking the appropriate symmetry, the more substituted of two possible nitrones would predominate in such oxidative openings.[7] Thus, we were surprised and gratified to find that isoxazolidine **4**, derived from 1-pyrroline 1-oxide (**5**) and styrene, undergoes oxidation with *m*-chloroperbenzoic acid in methylene chloride to give 98% of a light yellow oil, assigned structure **6** (Figure 1) on the basis of its spectral characteristics. The infrared spectrum contains a broad hydroxyl absorption at 2.8-3.2 and bands at 6.3 and

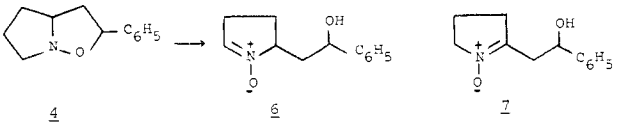
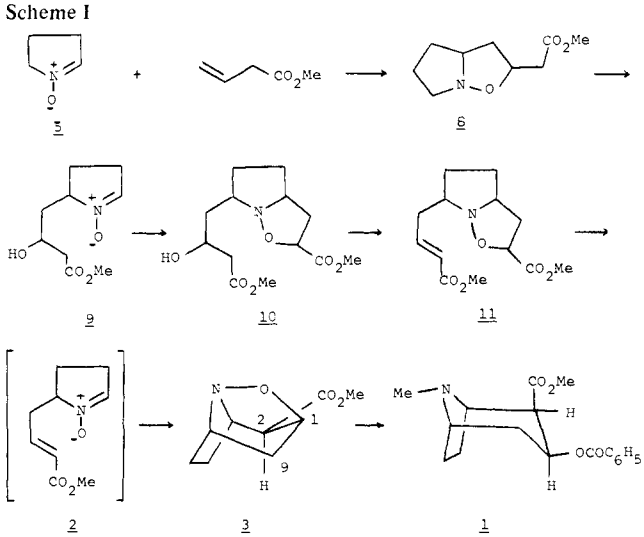


Figure 1.

8.12 $\mu$, which are typical of nitrones. The NMR spectrum has a multiplet at $\delta$ 6.00 (br m) and the nitrone proton (2 position) at 6.70 ppm (m, 1 H). We could uncover no evidence to suggest that any detectable quantity of the more substituted nitrone **7** was formed. This finding suggested to us an efficient synthesis of the desired nitrone (**2**)

The reaction of 1-pyrroline 1-oxide (**5**) with methyl 3-butenoate in refluxing toluene produced ester isoxazolidine **8** (Scheme I) regiospecifically (96%). A quintet at $\delta$ 4.47 ppm (1 H, $J$ = 7 Hz) in the NMR spectrum, assigned to the hydrogen at the 5 position of the isoxazolidine ring, supports the structural assignment. Addition of 1 equiv of *m*-chloroperbenzoic acid to adduct **8** in methylene chloride gave an 89% yield of nitrone **9** as a clear oil. The IR spectrum displays a hydroxyl stretching band at 2.9-3.2 and an intense carbonyl absorption at 5.80 $\mu$. The NMR spectrum exhibits a multiplet at $\delta$ 7.07 (1 H), assigned to the nitrone 2 proton, and a multiplet at 4.32 ppm (2 H). The latter multiplet is comprised of signals from the 5 hydrogen and the alcohol proton (exchangeable, $D_2O$). Successful dehydration of hydroxy nitrone **9** was expected to afford the long sought ester nitrone **2.** The former was remarkably resistant to dehydration, however. Forcing conditions led to resinous material. Clearly, the nitrone function was interfering with the dehydration process. At this point, a nitrone blocking function was deemed desirable. While we were unaware of the use of blocking groups in the synthetic applications of nitrones, several possible approaches suggested themselves. The most direct and precedented of these involves the addition of an appropriate alkene since these cycloadditions are, in principle, capable of reversal.[8,9] Since methyl acrylate is a low boiling, activated olefin, it was chosen as our blocking alkene. Cyclization of nitrone **9** with methyl acrylate in refluxing benzene gave the isoxazolidine ester **11,** as a mixture of stereoisomers, in 77% overall yield from **8.** The IR spectrum of **10,** with bands at 2.89 (hydroxyl) and 5.81 $\mu$ (carbonyl), and the NMR spectrum, indicating the disappearance of the nitrone 2 proton, are supportive of the assigned structure. The methanesulfonate of **10** was prepared (95%) with methanesulfonyl chloride in pyridine. Upon reaction with 1,5-diazabicyclo[4.3.0]non-5-ene in benzene,[10] the methanesulfonate of **10** afforded exclusively the trans olefin **11** in 86% yield. A strong carbonyl band (5.85 $\mu$) is observed in the IR spectrum

Scheme I



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