A Convenient and Efficient Unsymmetrical Ketone Synthesis from Acid Chlorides and Alkyl
Iodides Catalyzed by Palladium
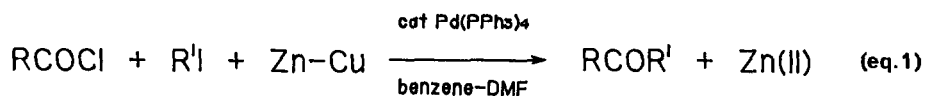
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Summary: Unsymmetrical ketones are prepared in good or excellent yields by a palladium
catalyzed coupling reaction of acid chlorides and alkyl iodides mediated by Zn-Cu couple.

One of the most pronounced characteristics of organozincs is the reaction with acid
chloride to provide ketone.    However, despite its apparent convenience, this method has not
been appreciated so much owing to its low structural flexibility and modest or low yield
formation of ketone.[1] Negishi[2] reported that palladium(0) nicely catalyzes the coupling reaction
of acid chloride and organozinc to provide ketone in excellent yield.    The organozincs used
are prepared by the transmetallation of organolithiums with $ZnCl_2$.    Fujisawa[3] succeeded in
the similar coupling reaction with organozincs prepared directly from zinc metal and benzyl
bromides.    This reaction, however, seems to be restricted to benzylic substrate.[4]
    In this communication we describe that alkylzinc iodides with a wide structural variety can
be prepared in good yields by the direct reaction with alkyl iodides[5] and Zn-Cu couple[6] in
benzene containing a small amount of N,N-dimethylformamide (DMF, 1.1 equiv to Zn metal) and
their use for the high yield synthesis of multifunctionalized unsymmetrical ketones by the
palladium catalyzed coupling reaction with acid chlorides (equation 1).    Interestingly, the
organozinc iodides prepared in benzene-DMF were unreactive toward acid chlorides at room
temp.    n-Propyl phenyl ketone was obtained in less than 20% yield by heating the mixture of
n-propylzinc iodide and benzoyl chloride at 70°C for 1 - 4 hours.       However, in the
presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) the reaction
proceeded spontaneously and attained the completion within 30 min at room temperature.
Reaction was performed as follows: The heterogeneous mixture of Zn-Cu couple (150 mg, 2.3
mmol) and alkyl iodide (1.5 mmol) in 3 mL of dry benzene and 0.2 mL of dry DMF was stirred
vigorously at room temp. for 1 hour and then at 60 °C for 3 - 4 hours under nitrogen.
Then a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and acid chloride (1.0 mmol) in 2 mL of dry
benzene was added at room temperature.    The mixture was stirred until the exothermic
reaction subsided (20 - 30 min.).    After usual extractive workup, the reaction mixture was
subjected to column chromatography on silica gel (n-hexane - ethyl acetate gradient) to
provide the expected ketones.    The ketones were properly characterized by comparison of the
spectral data (^{1}H, ^{13}C NMR, IR) with those of authentic samples and partly by means of high

$$\text{RCOCl} + \text{R'I} + \text{Zn–Cu} \xrightarrow[\text{benzene–DMF}]{\text{cat Pd(PPh}_3\text{)}_4} \text{RCOR'} + \text{Zn(II)} \quad \text{(eq.1)}$$

Table I. Ketone Synthesis from Acid Chlorides and Alkyl Iodides[a]

| entry | R of acyl chlorides | R' of iodides | % yields[b] of ketones |
|-------|---------------------|---------------|------------------------|
| 1 | Ph | Methyl | 94 |
| 2 | Ph | n-Propyl | 85 |
| 3 | Ph | n-Dodecyl | 98 |
| 4 | Ph | iso-Propyl | 98 |
| 5 | Ph | cyclo-Hexyl | 100 |
| 6 | Ph | $Cl(CH_2)_4$ | 100 |
| 7 | Ph | $EtC \equiv C(CH_2)_2$ | 100 |
| 8 | Ph | $CH_2 = CHCH_2CHMe$ | 78 |
| 9 | $2\text{-MeC}_6H_4$ | n-Propyl | 94 |
| 10 | $4\text{-MeOC}_6H_4$ | n-Propyl | 90 |
| 11 | $4\text{-ClC}_6H_4$ | n-Propyl | 89 |
| 12 | $4\text{-NO}_2C_6H_4$ | n-Propyl | 66 |
| 13 | CHMe(Cl) | n-Octyl | 82 |
| 14 | Ethyl | n-Octyl | 86 |
| 15 | n-Heptyl | n-Propyl | 93 |
| 16 | $PhCH_2$ | n-Propyl | 97 |
| 17 | Vinyl | n-Octyl | 100 |
| 18 | 1-Propenyl | n-Octyl | 100 |
| 19 | 1-Methylvinyl | n-Octyl | 95 |
| 20 | $\beta$-Styryl | n-Propyl | 88 |

a) For the reaction conditions and the structures of acid chlorides and iodides, see text and eq 1, respectively.
b) Yields refer to the isolated ones based on acid chlorides and are not optimized.

resolution mass spectra or elemental analysis.  The results obtained under the above conditions are summarized in Table I.   Although not examined in every case, the amount of the catalyst (usually 4 mol%) may be reduced to 0.5 mol%.   Even with this amount almost the same results were obtained (n-PrCOPh  96% yield; iso-PrCOPh 95% yield, cf. entries 2 and 4).

With respect to organozincs, both primary ($C_1 \sim C_{12}$) and secondary ones were prepared quantitatively and reacted with acid chlorides to offer the expected ketones in equally high yields.   Especially rewarding here is the satisfactory results obtained in the reactions with secondary organozincs (entries 4, 5 and 8).   The secondary organozincs are usually prepared in ca. 60% yield according to the Blaise's modification.[7]   Organozincs functionalized with double bonds or triple bonds also reacted with acid chlorides to give ketones in good to excellent yields (entries 7 and 8).   The high yield formation of phenyl 4-chlorobutyl ketone further demonstrates the utility of the present direct method over transmetallation method (entry 6).   With respect to acid chloride most of the acid chlorides examined (saturated, unsaturated and aromatic) gave satisfactory results.   In addition to these characteristics, the following outstanding points should be emphasized, which make the present reaction synthetic-ally viable.   First, no condensations or other side reactions take place for ketones possessing highly enolizable protons (e.g., entry 16).   Second, $\alpha,\beta$-unsaturated ketones which are generally prone to undergo Michael additions or polymerizations, are obtained in high yields (entries 17 - 20).   Third, it is difficult to prepare the ketones with electron withdrawing substituents at the $\alpha$-position by the reaction of $\alpha$-substituted acid chlorides with organozincs, because the ketones are prone to react further with organozincs.[8]

**Scheme I**



1  a: $R^1 = R^2 = H$
   b: $R^1 = H$, $R^2 = Me$
   c: $R^1 = Me$, $R^2 = H$

2

3  a: 95%
   b: 100%
   c: 89%

4
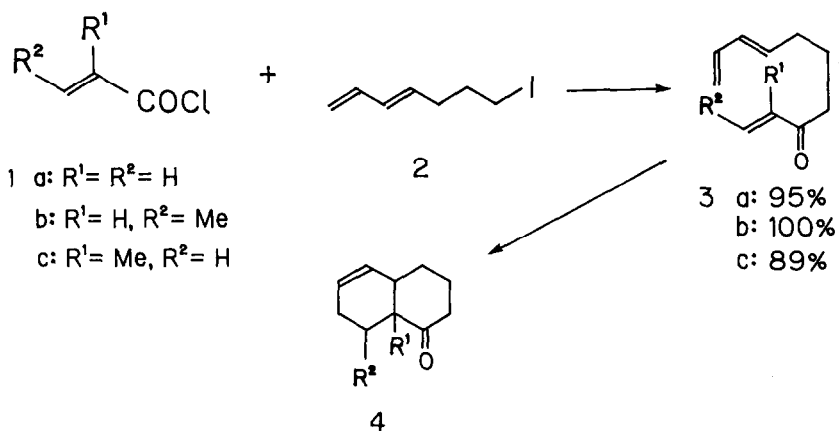
Under our conditions, such a ketone could be obtained in good yield (entry 13).   All these features may be ascribed to (1) the good yield formation of organozincs in benzene-DMF,[9] (2) low reactivity of the thus formed organozincs probably owing to coordination to DMF, and (3) selective activation of acid chloride with Pd(0) by forming acylpalladium species.
Finally, the present reaction can be performed in mmol scales with high reproducibility and may have some advantages over the organotin method, recently developed by Stille.[10]   The organotin method is successfully applied to unsaturated ketone synthesis, however, for the

saturated ketone synthesis this method seems to be uneconomical because only a part (one or two) of the alkyl groups of tetraalkyltins is utilized for the reaction.

In scheme I is shown one of the useful applications of our method. The intramolecular Diels-Alder substrates 3 could be synthesized in one pot as a mixture with Diels-Alder products[11] uniformly in high yields irrespective of the substitution pattern of acryloyl chloride 1. Usually, the 1,7,9-decatrien-3-one system 3 has been constructed by a two step synthesis in moderate overall yields (50 - 60%): the coupling of dienyl aldehydes and vinyllithium or magnesium reagents, followed by the oxidation of the thus obtained allylic alcohols.[12]

### REFERENCES AND NOTES

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(4) For a Fe(III) catalyzed coupling reaction of acid chlorides and Grignard reagents, see Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. Tetrahedron Lett. 1984, 25, 4805.

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(7) Ref. 1b, pp. 637-638.     (8) Ref. 1b, pp. 790-791.

(9) DMF is essential for generation of alkylzincs. For example, in the presence of DMF, smooth disappearace of n-dedecyl iodide and concomitant appearance of n-dodecane was observed by VPC analyses of aliquots of the reaction after hydrolyses (n-decane as an internal standard). In the absence of DMF, no n-dodecane was discernible.

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(11) The yields listed in Scheme I refer to the isolated yield of mixture of 3 and 4 (3a:4a = 0:100; 3b:4b = 80:20; 3c:4c = 50:50).

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