

Palladium-catalyzed acyldemetalation and carbonylation reactions of organomercurials for the synthesis of unsymmetrical ketones

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Abstract

The palladium-catalyzed acyldemetalation reactions of organomercurials (R_2Hg or $AlkHgI$) provide a mild, selective, and general method for the synthesis of unsymmetrical heterocyclic ketones. High yields of ketones ($RCOR'$) were obtained along with small amounts of homocoupling products (R_2). The reaction is accelerated by a nucleophilic catalyst with both organic groups of R_2Hg taking part in the reaction. The selectivity of the reaction towards the ketone can be increased by carrying out the reaction with a suitable combination of reactants under vacuum.

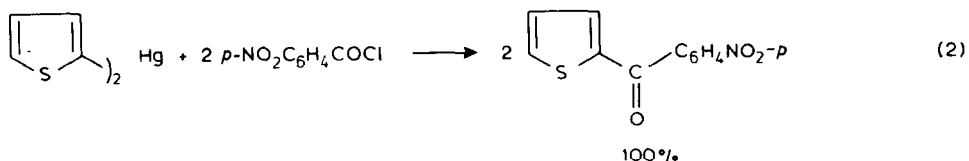
The palladium-catalyzed carbonylation of organomercurials in the presence of ArI is another route to unsymmetrical ketones. The $AlkHgI-ArI$ system undergoes carbonylation in the presence of palladium complex and excess of iodide ion under mild conditions to give high yields of unsymmetrical ketones. The selectivity and rate of the reaction depend upon the nature of the catalyst, solvent, and the concentration of iodide ion.

Acyldemetalation

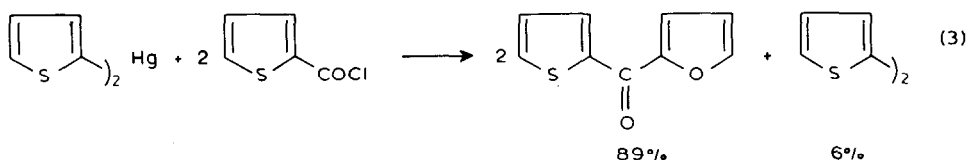
We recently described [1] the reaction of organomercurials (R_2Hg or $RHgX$) with $R'COCl$ in the presence of palladium complex and iodide ion, giving high yields of unsymmetrical ketones $RCOR'$ ($R = Alk, Ar, PhC\equiv C$; $R' = Alk, (E)-PhCH=CH, Ar$). Here we report on the synthesis of unsymmetrical heterocyclic ketones ($RCOR'$) by palladium-catalyzed acyldemetalation of organomercurials (R_2Hg or $RHgX$) with acyl chlorides ($R'COCl$).

The reaction of R_2Hg or $RHgX$ and $R'COCl$ proceeds in acetone in the presence of palladium catalyst (1 mol-%) and iodide ion (sodium iodide) at 20°C in 5–30

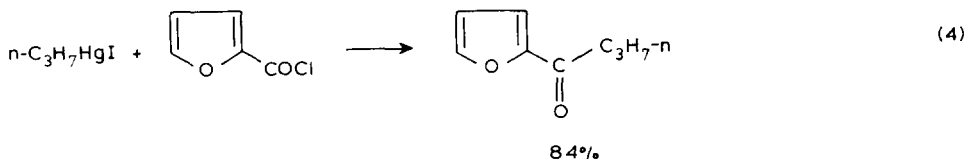
Acyl chloride ($R'COCl$) reacts with NaI to give $R'COI$ (reaction 1), which in turn participates in the acyldemetalation. The selectivity of the reaction towards $RCOR'$ and R_2 depends on the nature of R and R' and the type of catalyst. These conclusions are based on the following reactions. The reaction of bis-thienyl mercury and $p\text{-NO}_2\text{C}_6\text{H}_4\text{COCl}$ (reaction 2) proceeds in the presence of "ligandless" palladium catalyst, $PdCl_2(MeCN)_2$, and NaI to give a quantitative yield of the ketone (Table 1, entry 1), in contrast to the reaction of 2-furoyl chloride under the



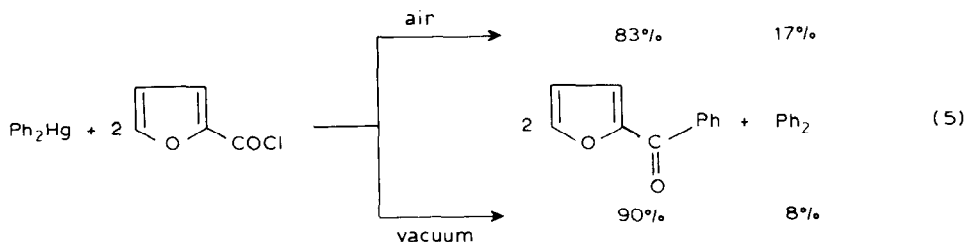
same conditions which gives 2-(2-furoyl)thiophene in 70% yield and bis-thienyl in 20% yield. But the same reaction carried out in the presence of phosphine palladium complex, $p\text{-NO}_2\text{C}_6\text{H}_4\text{PdI}(PPh_3)_2$ and under vacuum gives the product in 89% yield (Table 1, entry 3, reaction 3).



2-Furoyl chloride reacts rapidly with $n\text{-PrHgI}$ (containing β -hydrogen atom) in the presence of $PhPdI(PPh_3)_2$ to give the product in 84% yield (Table 1, entry 4, reaction 4).



The effect of an oxygen atmosphere on the selectivity of the reaction is an interesting aspect, and to investigate this we chose the reaction of Ph_2Hg with 2-furoyl chloride in the presence of $PhPdI(PPh_3)_2$. We found that the selectivity towards ketone is increased when the reaction is performed under vacuum (Table 1, entries 5 & 6, reaction 5).



Similar results were obtained in the reaction of Ph_2Hg and nicotinyl chloride. The yield of ketone increased from 78% (under an atmosphere of air) to 87% (under

the selectivity of this complex during the oxidative addition (insertion step). Such a picture was also observed in the reaction of R_2Hg with ArI in the presence of palladium complex and iodide ion [7], in which increased activity of the catalyst led to the formation of more by-product. During aryl- and acyldemetallation, organotins do not react as rapidly with Pd^0 complex as do ArI or $R'COX$. In the presence of phosphine palladium complex and under an air atmosphere acceleration of cross-coupling reaction took place [8–10]. This may be due to an increase in the catalytic activity of such complexes.

Iodide ion performs several functions in the reaction: (1) Transformation of acyl chloride into acyl iodide, which is more reactive in the oxidative addition step. (2) Iodide ion coordinates to Hg atom [11] and thus polarizing the bond so enabling its heterolytic fission during the transmetallation step. (3) Iodide ion may form an anionic complex with Pd^0 (analogous to that of Rh^I complex [12]); which may facilitate the oxidative addition of the acyl halides to Pd^0 complex. (4) The coordination of iodide ion to Hg atom (in R_2Hg) and to Pd atom in the Pd^0 complex thus forming the anionic complexes, $(R_2HgI)^-$ and $(Pd^0I)^-$, may lead to slowing of the oxidative demercuration.

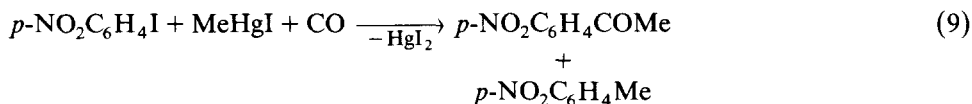
Carbonylation

We have previously reported that the $RX-R'SnMe_3$ system undergoes palladium-catalyzed carbonylation under mild conditions (1 atm CO, 20 °C) to give the unsymmetrical ketones, $RCOR'$, in high yields [13]. We have also reported the synthesis of symmetrical ketones R_2CO by the palladium-catalyzed carbonylation of $R_2Hg-ArI$ system in the presence of iodide ion under mild conditions (1 atm CO, 20 °C) [14]. It was found that in the $R_2Hg-ArI$ system only R_2Hg undergoes carbonylation to give R_2CO . The cross-coupling reactions of organomercurials with aryl and acyl halides in the presence of transition metal complexes and nucleophilic catalyst have also been studied [1,7].

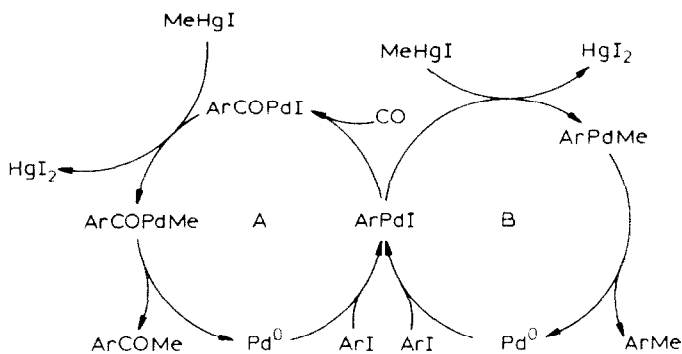
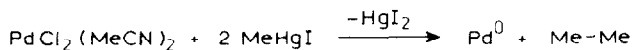
Here we describe the synthesis of unsymmetrical ketones by the palladium-catalyzed carbonylation of the $AlkHgI-ArI$ system in the presence of iodide ion (reaction 8).



Experiments on the palladium-catalyzed carbonylation of $p\text{-NO}_2\text{C}_6\text{H}_4\text{I}-\text{CH}_3\text{HgI}$ system (reaction 9) were performed by varying the palladium complex, solvent and concentration of iodide ion to study the influence that all these factors have on the selectivity and the rate of the reaction. We found that the highest yield of unsymmetrical ketone, the best selectivity and the highest reaction rate were obtained in HMPA in the presence of “ligandless” palladium catalyst [5] (1 mol %), with an excess of iodide ion (Bu_4NI , 4 equiv.), at 1 atm CO, at room temperature. The results are summarized in Table 2.



The catalytic cycle (ligands are omitted) of the reaction is depicted in Scheme 2.



Scheme 2.

The concentration of iodide ion plays an important role in the reaction. Reaction 9, when performed in the presence of $\text{PdCl}_2(\text{MeCN})_2$ (1 mol %), NaI (1 equiv.) and 1 atm CO in DMF (70–80 °C) or in HMPA (20 °C), showed low reaction rates and poor selectivity (Table 2, entries 1 & 2). In the presence of 2 equiv. of NaI or Bu_4NI the reaction in HMPA gives the relevant ketones in 63 and 74% yield (Table 2, entries 3 & 4). A maximum yield of the ketone (92%), practically without by-product, was obtained in HMPA under optimal conditions, namely $\text{PdCl}_2(\text{MeCN})_2$ (1 mol %), Bu_4NI (4 equiv.), 1 atm CO, 20 °C (Table 2, entry 5).

The catalytic cycle of the reaction (Scheme 2) consists of a carbonylation process (cycle A) and a cross-coupling process (cycle B). We found that a large excess of iodide ion enhances the carbonylation process.

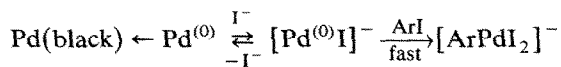
The reaction in the presence of a large excess of iodide ion proceeds without precipitation of palladium black and may be due to the formation of an anionic complex with Pd^0 , which reacts quickly with ArI in the oxidative addition step (Scheme 3).

Table 2

Carbonylation reactions of $p\text{-NO}_2\text{C}_6\text{H}_4\text{I}$ with MeHgI (Pd^{II} complex (1 mol-%), NaI or Bu_4NI , 1 atm CO, $c_0 = 0.25 \text{ M}$)

Entry No.	Solvent	Catalyst ^a	Reaction temperature (°C)	Reaction time (h)	Yield (%) ^b	
					$p\text{-NO}_2\text{C}_6\text{H}_4\text{COMe}$	$p\text{-NO}_2\text{C}_6\text{H}_4\text{Me}$
1	DMF	A + 1 eq. NaI	70–80	8	30	30
2	HMPA	A + 1 eq. NaI	20	15	37	29
3	HMPA	A + 2 eq. NaI	20	18	63	33
4	HMPA	A + 2 eq. Bu_4NI	20	13.5	74	16
5	HMPA	A + 4 eq. Bu_4NI	20	1.5	92	—
6	HMPA	B + 2 eq. NaI	20	17	42	37
7	HMPA	A + 2 eq. Bu_4NBr	20	15	57	21

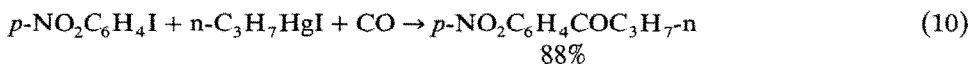
^a A = $\text{PdCl}_2(\text{MeCN})_2$; B = $p\text{-NO}_2\text{C}_6\text{H}_4\text{PdI}(\text{PPh}_3)_2$. ^b Determined by TLC and UV spectroscopy.



Scheme 3

In the presence of phosphine palladium complex ($p\text{-NO}_2\text{C}_6\text{H}_4\text{PdI}(\text{PPh}_3)_2$, 1 mol-%) and NaI (2 equiv.) the reaction proceeds slowly and less selectivity (Table 2, entry 6). Unsatisfactory results were obtained when Bu_4NBr was used in the reaction (Table 2, entry 7).

Under optimal conditions $n\text{-C}_3\text{H}_7\text{HgI}$ (containing β -hydrogen atom) reacts readily to give the ketone in high yield, but the time required for completion of the reaction is increased two-fold compared with the reaction of CH_3HgI (Table 3, entry 3, reaction 10).



The rate of the carbonylation also depends on the nature of the substituent in the aromatic ring of ArI. We found that when a strong electron-withdrawing group is introduced into the aromatic ring, the carbonylation proceeds readily. For example, the reaction of $p\text{-NO}_2\text{C}_6\text{H}_4\text{I}$ took place in 1.5 h, whereas the reactions of $p\text{-CNC}_6\text{H}_4\text{I}$ and $p\text{-OHCC}_6\text{H}_4\text{I}$ required 9 to 10 h to go to completion. Thus, the palladium-catalyzed carbonylation of ArI (containing strong electron-withdrawing group)–AlkHgI system proceeds smoothly under mild conditions to give the unsymmetrical ketone in high yield.

Since organomercurials of all types are readily available by a number of synthetic routes, these reactions (acyldemetallation and carbonylation) are mild, selective, and efficient methods for the synthesis of unsymmetrical ketones.

Experimental

The palladium complexes, organomercurials (R_2Hg , AlkHgI), acyl chlorides and aryl iodides were prepared by standard procedures, sodium iodide was dried under vacuum (0.01 mm Hg) for 2 h before use. Analytical grade Bu_4NI was used. Acetone, benzene, DMF and HMPA were purified by standard methods and distilled before use. The yields of the products were determined by TLC on Silufol-254 and UV-spectroscopy (Hitachi-124 spectrophotometer). The products

Table 3

Carbonylation reactions of $p\text{-YC}_6\text{H}_4\text{I}$ with AlkHgI , (HMPA, $\text{PdCl}_2(\text{MeCN})_2$ (1 mol-%), Bu_4NI (4 equiv.), 1 atm CO, 20 °C, $c_0 = 0.25 \text{ M}$)

Entry No.	Y	Alk	Time (h)	Yield (%) ^a of $p\text{-YC}_6\text{H}_4\text{COAlk}$
1	NO_2	Me	1.5	92 (85)
2	CN	Me	9	80 (73)
3	NO_2	$n\text{-C}_3\text{H}_7$	3	88 (81)
4	CN	$n\text{-C}_3\text{H}_7$	10	72 (60)
5	CHO	$n\text{-C}_3\text{H}_7$	8	75 (63)

^a Determined by TLC and UV-spectroscopy. Isolated yield is given in brackets.

were isolated by TLC on silica gel and identified from their IR, NMR and mass spectra.

Acylde metallation

Synthesis of 2-(p-nitrobenzoyl)thiophene. The reaction was carried out in a 5-ml round bottom flask. 4 ml of acetone, 0.3 g (2 mmol) of NaI, 0.1864 g (1 mmol) of $p\text{-NO}_2\text{C}_6\text{H}_4\text{COCl}$, 0.1835 g (0.5 mmol) of bis(2-thienyl)mercury and 0.0026 g (0.01 mmol) of $\text{PdCl}_2(\text{MeCN})_2$ were placed in the flask and the slurry was stirred vigorously at room temperature. After 10 min it was found that the mixture contained quantitative amount of the ketone (by TLC and UV spectroscopy). The mixture was then diluted with 10 ml of water and extracted with 3×5 ml of ether. The ether solutions were combined and washed with 2×5 ml of an aqueous solution of NaI to remove any traces of the mercury salt from the organic layer. The ether layer was then dried over MgSO_4 and evaporated to give 0.187 g (80% yield) of 2-(*p*-nitrobenzoyl)thiophene, m.p. 172–173 °C [15].

The properties of the ketones (RCOR') (Table 1) are consistent with published data 2-butyrylfuran [16], 2-benzoylfuran [17], 2-benzoyl-5-methylfuran [18], 2-(2-furyl)thiophene [19] and 3-benzoylpyridine [20].

Carbonylation

Synthesis of p-NO₂C₆H₄COCH₃. 2.5 ml of HMPA, 0.125 g (0.5 mmol) of $p\text{-NO}_2\text{C}_6\text{H}_4\text{I}$, 0.738 g (2 mmol) of Bu_4NI and 0.188 g (0.55 mmol) of CH_3HgI were placed in a 5-ml round bottom flask and the slurry was stirred under 1 atm of CO till it became saturated with CO. 0.0013 g (0.005 mmol) of $\text{PdCl}_2(\text{MeCN})_2$ was then added with stirring under CO. After 1.5 h the mixture contained $p\text{-NO}_2\text{C}_6\text{H}_4\text{COCH}_3$ in 92% yield (by TLC and UV spectroscopy). The mixture was diluted with 10 ml of water and extracted with 3×5 ml of ether. The ether solutions were combined and washed with 2×5 ml of aqueous solution of NaI to remove any traces of the Hg salt from the organic layer. The ether layer was dried over MgSO_4 and then evaporated to give $p\text{-NO}_2\text{C}_6\text{H}_4\text{COCH}_3$ (85% yield), m.p. 80 °C [21].

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