SHORT PAPER

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Hypervalent iodine in synthesis 68: palladium-catalysed double carbonylation of diaryliodonium salts to give α-keto-amides†

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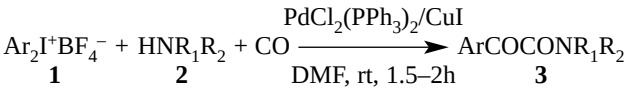
In the presence of a palladium catalyst and the cocatalyst CuI, several diaryliodonium salts have been converted into α-keto amides on treatment with secondary amines and carbon monoxide in good yield and selectivity under mild reaction conditions.

Keywords: hypervalent iodine, palladium catalysis, α-keto-amides

In spite of extensive investigation of the palladium-catalysed carbonylation of diaryliodonium salts for the synthesis of acids,[1] esters[2] and carbonyl compounds,[3] double carbonylation is not known. As a part of our researches on the palladium-catalysed reactions of hypervalent iodonium salts, we found that in the presence of secondary amines the palladium-catalysed double carbonylation of diaryliodonium salts can occur easily to provide a convenient route for the synthesis of α-keto-amides. In fact, simply stirring a mixture of diaryliodonium salt, secondary amine, $PdCl_2(PPh_3)_2$ and CuI in DMF under one atmosphere pressure of carbon monoxide at room temperature gave, after work up and isolation, the α-keto-amide in good yield (Scheme 1). The results are summarised in Table 1. All products gave satisfactory IR or ^1H NMR spectra.



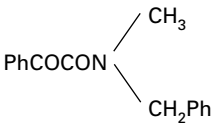
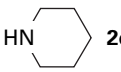
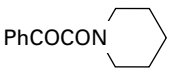
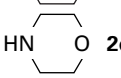
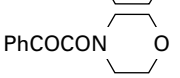
Scheme 1

In the presence of $PdCl_2(PPh_3)_2$ and CuI, the reaction proceeded smoothly and was completed within 1.5–2h in good yield and high selectivity with the formation of α-keto-amide. In the absence of CuI, the yield was lower even with a longer reaction time (entry 2). Hence so the addition of CuI as a cocatalyst is essential. Several diaryliodonium salts with various substituents (such as methyl, chloro and methoxy) and secondary amines were tested. The reaction is general for these substrates. The selectivities for α-keto-amide formation was influenced by reactants. In our test, no trace of amides were found except in entry 4 when N, N-diethyl 4- chloro-benzamide as a by product was formed in 12% yield and in entry 8 entry when 4-benzoyl morpholine was formed in 15% yield.

The proposed mechanism to account for the palladium-catalysed di- and mono-carbonylation of diaryliodonium salts in the presence of secondary amines is illustrated in Scheme 2.

When the arylpalladium intermediate **4** undergoes CO insertion to give the aroylpalladium species **5**, an α-keto amide is formed. On the other hand, coordination of CO to **4** followed by reaction with amine affords the simple amide. Hence the selectivity for α-keto amide formation is predominantly determined by the reactivity of amine to **5**. The faster the rate of the

Table 1 Double carbonylation of diaryliodonium salts to give α-keto amides

Entry	$Ar_2I^+BF_4^-$	HNR_1R_2	Products	Yield/%
1	$Ph_2I^+BF_4^-$ **1a**	$HNEt_2$ **2a**	$PhCOCONEt_2$ **3a**	88
2[a]	**1a**	**2a**	**3a**	33
3	$(Tol)_2I^+BF_4^-$ **1b**	**2a**	$TolCOCONEt_2$ **3b**	82
4	$(p\text{-}ClC_6H_4)_2I^+BF_4^-$ **1c**	**2a**	$p\text{-}ClC_6H_4COCONEt_2$ **3c**	72
5	$(p\text{-}CH_3OC_6H_4)_2I^+BF_4^-$ **1d**	**2a**	$p\text{-}CH_3OC_6H_4COCONEt_2$ **3d**	68
6	**1a**	CH_3NHCH_2Ph **2b**	 **3e**	77
7	**1a**	 **2c**	 **3f**	85
8	**1a**	 **2d**	 **3g**	73
9	**1a**	$HNMe_2$ **2e**	$PhCOCONMe_2$ **3h**	84
10	**1b**	**2e**	$TolCOCONMe_2$ **3i**	74
11	**1d**	**2e**	$p\text{-}CH_3OC_6H_4COCONMe_2$ **3j**	72

[a]CuI is not added, the reaction time is 10h.

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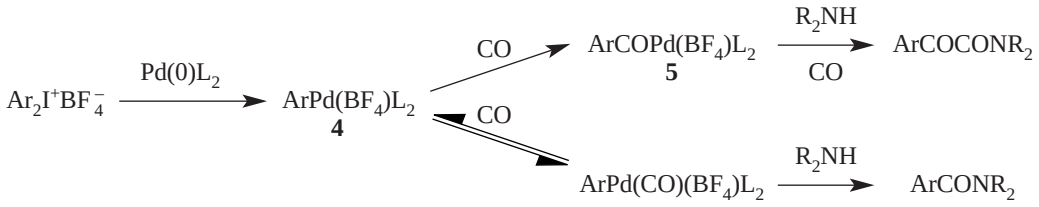
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2

reaction of amine to **5** is, the better the selectivity for α-keto-amide formation is. Possibly because its nucleophilicity is weaker than those of other selected secondary amines because of the strong electronegativity of oxygen, morpholine reacts with **5** with a little more difficulty than the other amines, so more amide is formed. Primary amines are usually not suitable for this reaction. We examined the reaction of diphenyliodonium tetrafluoroborate with benzylamine under one atmosphere of carbon monoxide in the presence of $PdCl_2(PPh_3)_2$ and CuI at room temperature for three hours. Only monocarbonylation product N- benzyl benzamide was obtained in 56% yield (confirmed by m.p., IR and ^{1}H NMR).

The diaryliodonium salt also has an effect on the selectivity for α-keto amide formation. The presence of electron-withdrawing substituent will enhance the eletrophilicity of CO-oordinated arylpalladium species. Therefore the result is a decrease in the selectivity for α-keto formation, such as in entry 4. The result is similar to that of the palladium catalysed double carbonylation of arylhalide.[4]

The α-keto amides have potential applications for the synthesis of a variety of useful products including α-amino acids, α-hydroxy acids, and heterocyclic compounds.[5] Several procedures leading to α-keto amides are available in literature. For example, from ethyl alkylidenecyanoacetate,[6] from the reaction of aryllithium and tetramethyloxamide,[7] and from α-oxo acid chlorides and amines,[8] and from the reaction of dimethyloxanilides and Grignard reagents.[9] These methods have some disadvantages, such as harsh reaction conditions, long procedures and low yields. Although the double carbonylation of aryl halides in the presence of a palladium catalyst[4,10] provides a more convenient synthesis for α-keto amides in contrast to the earlier methods, it requires a high pressure of carbon monoxide and high reaction temperature, otherwise the selectivities for α-keto amides formation are unsatisfactory.

In conclusion, in the presence of $PdCl_2(PPh_3)_2$ and CuI, diaryliodonium salts can react easily with secondary amines under one atmosphere of CO to provide α-keto-amides at room temperature in high yield and good selectivity. The present method is a convenient synthesis for α-keto amides.

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were obtained on PMK-60 Spectrometer using CCl_4 as the solvent with TMS as an internal standard. IR spectra were determined on PE-683 Infrared Spectrometer. MS spectra were recorded on HP5859B Mass Spectrometer. GC purities were determined on Shimada GC-16A.

General procedure for double carbonylation of diaryliodonium salts to give α-keto amides: A mixture of diaryliodonium salt **1** (1mmol), $PdCl_2(PPh_3)_2$ (3mol%), CuI (10mol%), secondary amine **2** (3mmol) and DMF (5ml) was stirred under CO (1atm) at room temperature for 1.5 to 2h. Saturated NH_4Cl aqueous was added to the reaction mixture which was then extracted with ether (3 × 15ml). The combined organic phases were washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by TLC (silica gel) using a mixture of c-hexane/ethyl acetate (4:1) as a developer to give pure α-keto amide.

Physical and spectroscopic data: N, N-diethyl-α-oxo-benzeneacetamide **3a**: oil (lit[10(b)] oil), GC purity 98.86%, δ_H 0.9–1.4 (m, 6H), 2.9–3.6 (m, 4H), 7.2–7.6 (m, 3H), 7.7–8.0 (m, 2H). ν_{max}(cm^{-1}) 1640, 1685. MS *m/z* 205 (M$^+$ 2.24), 105 (88.44), 100 (100).

N, N-diethyl-4-methyl-α-oxo-benzeneacetamide **3b***:* m.p. 46–48°C (lit[11] mp was not reported), GC purity 98.83%, δ_H 0.9–1.5 (m, 6H), 2.3 (s, 3H), 2.9–3.6 (m, 4H), 7.05–7.4 (m, 2H), 7.6–7.9 (m, 2H). ν_{max}(cm^{-1}) 1640, 1680. MS *m/z* 239 (M$^+$, 1.76), 119 (100), 100 (56.53).

N, N-diethyl-4-chloro-α-oxo-benzeneacetamide **3c***:* m.p. 66–67°C (lit[4] m.p. was not reported), GC purity 97.53%, δ_H 0.9–1.4 (m, 6H), 3.15 (q, 2H), 3.45 (q, 2H), 7.3–7.6 (m, 2H), 7.75–8.0 (m, 2H). ν_{max}(cm^{-1}) 1640, 1685. MS *m/z* 239 (M$^+$, 1.06), 139 (24.52), 100 (100).

N, N-diethyl-4-methoxy-α-oxo-benzeneacetamide **3d***:* oil (lit[4]), GC purity 99.21%, δ_H 0.9–1.4 (m, 6H), 2.85–3.6 (m, 4H), 3.73 (s, 3H), 6.7–7.0 (m, 2H), 7.53–7.9 (m, 2H). ν_{max}(cm^{-1}) 1650, 1685. MS *m/z* 235 (M$^+$, 0.54), 135 (100), 100 (12.09).

N-benzyl, N-methyl-α-oxo-benzeneacetamide **3e***:* oil (lit[4]), GC purity 99.52%, δ_H 2.66 (s) and 2.78 (s) (total 3H), 4.2 (s) and 4.53 (s) (total 2H), 7.05–7.53 (m, 8H), 7.7–8.0 (m, 2H). ν_{max}(cm^{-1}) 1650, 1690. MS *m/z* 253 (M$^+$, 1.14), 148 (10.09), 105 (81.77), 91 (100).

1-(α-Oxophenylacetyl)piperidine **3f**: m.p. 105–107°C (lit[12] 107–108°C), δ_H 1.4–1.9 (m, 6H), 3.2 (m, 2H, NCH_2), 3.6 (m, 2H, NCH_2'), 7.25–7.65 (m, 3H), 7.75–8.05 (m, 2H), ν_{max}(cm^{-1}) 1640, 1685.

4-(α-Oxophenylacetyl)morpholine **3g***:* m.p. 69–71°C (lit[10(a)] m.p. was not reported), GC purity 98.55%, δ_H 3.15–3.8 (m, 8H), 7.2–7.6 (m, 3H), 7.75–8.0 (m, 2H), ν_{max}(cm^{-1}) 1645, 1675. MS *m/z* 219 (M$^+$, 1.24), 114 (5.40), 105 (100).

N, N-dimethyl-α-oxo-benzeneacetamide **3h***:* oil (lit[7] oil), GC purity 99.15%, δ_H 2.9 (s, 3H, CH_3), 3.1(s, 3H, CH_3'), 7.2–7.6 (m, 3H), 7.7–8.0 (m, 2H). ν_{max}(cm^{-1}) 1645, 1685.

N,N-dimethyl-4-methyl-α-oxo-benzeneacetamide **3i***:* m.p. 44–46°C (lit[7] mp 45–46°C), δ_H 2.33 (s, 3H), 2.8 (s, 3H, CH_3), 3.0 (s, 3H, CH_3'), 7.0–7.3(m, 2H), 7.55–8.0 (m, 2H). ν_{max}(cm^{-1}) 1645, 1685.

N,N-dimethyl-4-methoxy-α-oxo-benzeneacetamide **3j***:* m.p. 75–77°C (lit[7] m.p. 74–76°C), δ_H 2.8(s, 3H, CH_3), 2.95 (s, 3H, CH_3'), 3.75 (s, 3H), 6.7–7.0 (m, 2H), 7.6–7.9 (m, 2H). ν_{max}(cm^{-1}) 1650, 1685.

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