

PALLADIUM CATALYSED SYNTHESIS OF N AND S HETEROCYCLIC ESTERS

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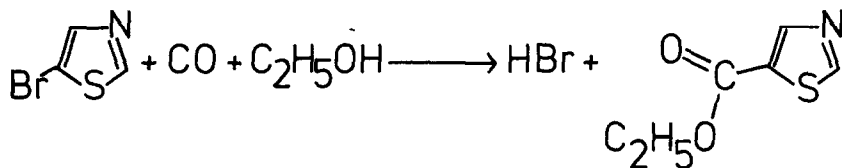
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ABSTRACT

Palladium catalysed alkoxy carbonylation of heterocyclic halides affords a simple and versatile synthesis of both N and S heterocyclic esters where a range of catalysts have been studied and a method to employ inexpensive inorganic bases has been found.

Although the alkoxy carbonylation of aryl halides mediated by homogeneous palladium catalysts is well documented¹, there have been no similar reports using heterocyclic halides. Where² heterocyclic halides have been used in carbonylation reactions, for example amide³ and aldehyde⁴ syntheses, high CO pressures and long reaction times have generally been required.

We now report that the alkoxy carbonylation of N and S heterocyclic halides can be achieved at high rates under mild conditions using a range of palladium catalysts. Essentially quantitative yields of esters are obtained by this highly versatile route using a simple isolation procedure during which a catalyst precursor can be recovered and reused.



In a typical experiment, a mixture of heterocyclic halide (4 to 19g), ethanol (40ml), triethylamine (8ml), PdCl₂(PPh₃)₂ (0.2-0.3g) and a magnetic stirrer bar was charged into the glass liner of a 100ml autoclave. No precautions were taken to exclude air. After sealing, the autoclave was pressurised to 100 psig (6.8 atm)

with CO and heated to 100°C for the required period of time. During reaction, the magnetic stirrer was rotated by means of an air driven magnet located directly below the autoclave. Upon cooling and venting of excess CO, the contents of the autoclave were removed and volatiles evaporated using a rotary evaporator. The crude product was dissolved in CHCl_3 (50ml), washed with water (3x50ml) and, after drying over anhydrous Na_2SO_4 , the CHCl_3 was removed to give the corresponding ethylester in near quantitative yield.

This synthetic approach has been used to prepare a variety of heterocyclic esters, Table 1, not readily accessible using conventional organic methods. The purity and nature of the products have been confirmed by a combination of i.r. and $^1\text{Hnmr}$ spectroscopy and HPLC techniques. Reactions are found to be faster with bromides than chlorides and only with 2-chloropyrimidine has there been no evidence of reaction. The CO pressure of 100psig used in most experiments was the lowest reliably obtained on the equipment but lower pressures can be used with varied success. For instance, at 1atm and 90°C about 20% reaction occurred in 6h while at 120°C no product was observed at all, examples 8 and 9 respectively. The lack of reactivity at low pressure is attributed to the very low solubility of CO under such conditions.

The results in Table 2 show both the importance of the palladium species and nature of the base. Both with $\text{PdCl}_2(\text{PPh}_3)_2$ and the zerovalent $\text{Pd}(\text{PPh}_3)_4$, reactions are rapid and conversions nearly quantitative in contrast to the bisdiphenylphosphinoethane complex, $\text{PdCl}_2(\text{dppe})$, which is inactive under similar conditions. We find that during the product isolation, the water wash causes precipitation of a yellow crystalline palladium compound which can be isolated and re-used without loss of activity.

The palladium catalyst need not be homogeneous and a grey heterogeneous catalyst prepared by refluxing $\text{PdCl}_2(\text{PhCN})_2$ with phosphonated styrene-divinylbenzene copolymer exhibits good activity under rather more severe reaction conditions. The somewhat lower activity of the heterogeneous catalyst is best explained as a mass transfer effect and even at the higher temperatures at which it has been examined, we have seen no evidence of palladium leaching into solution.

Our studies into the reaction mechanism confirm that the initial step is formation of a zerovalent complex, such as $\text{Pd}(\text{CO})_2(\text{PPh}_3)_2$, to which the heterocyclic halide oxidatively adds giving the corresponding aryl complex. Insertion of CO into the Pd-C bond followed by attack of alcohol upon the resulting aryl complex, affords free heterocyclic ester and $\text{PdHBr}(\text{PPh}_3)_2$, which is reduced to the active Pd(0) species. The rate of this final step is dictated by the nature of the base, since it is essentially a dehydrobromination reaction. From the results shown in Table 2 it is seen that triethylamine is particularly efficient in contrast to Na_2CO_3 . However, we now find that a combination of Na_2CO_3 with a catalytic amount of triethylamine combines high activity with the consumption of an inexpensive base. This interesting effect is due to the triethylamine assisted reduction of $\text{PdHBr}(\text{PPh}_3)_2$ with formation of Et_3NBr which subsequently reacts with Na_2CO_3 to regenerate free amine.

TABLE 1. Alkoxy carbonylation of various heterocyclic halides^a

No.	Heterocyclic halide(gm)	Reaction Time(hr)	Product (w/w%)
1	3,5-dibromopyridine (4)	3	diethyldinicotinate (100)
2	3,5-dichloropyridine (3)	8	5-chloroethylnicotinate (35)
3	5-bromonicotinonitrile (6)	8	5-cyanoethylnicotinate (100)
4	5-bromopyrimidine (5)	3	5-ethoxycarbonylpyrimidine (100)
5	5-bromothiazole (19)	8	5-ethoxycarbonylthiazole (>95)
6	4-bromoisoquinoline (4.5)	6	4-ethoxycarbonylisoquinoline (100)
7	2-chloropyrimidine (10)	15	No reaction
8	3,5-dibromopyridine (5)	6 ^b	5-bromoethylnicotinate (40)
9	3,5-dibromopyridine (5)	6 ^c	No reaction

a Reactions were carried out using PdCl₂(PPh₃)₂ (0.2-0.3gm) as catalyst at 100°C, 100psig CO pressure in ethanol (~40ml) and triethylamine (8ml)

b 90°C, 1 atm CO, n-decanol (40ml) and tri-n-propylamine (8ml)

c 120°C, 1 atm CO, 1-propanol (40ml) and tri-n-propylamine (8ml)

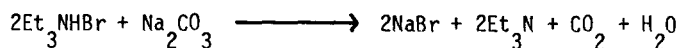
TABLE 2 Effect of palladium compound and base upon alkoxy carbonylation of 3,5-dibromopyridine^a

No.	Catalyst (gm)	Reaction time (hr)	Base	Product Composition (w/w %)
1	Pd(PPh ₃) ₄ (0.3)	3	Et ₃ N (7.5ml)	diethyldinicotinate (100)
2	Pd/Polymer (1.2) ^b	10 ^c	Et ₃ N (7.5ml)	diethyldinicotinate (21) 5-bromoethylnicotinate (39)
3	PdCl ₂ (dppe) (0.3)	3	Et ₃ N (7.5ml)	No reaction
4	PdCl ₂ (PPh ₃) ₂ (0.3)	3	Na ₂ CO ₃ (2.5gm)	5-bromoethylnicotinate (30)
5	PdCl ₂ (PPh ₃) ₂ (0.3)	3	Na ₂ CO ₃ (2.5gm) + NEt ₃ (0.3ml)	diethyldinicotinate (100)

a Reactions were performed using 3,5-dibromopyridine (4gm), ethanol (50ml) and 100 psig CO pressure at 100°C

b 4% Pd

c 120°C



The high versatility under mild conditions combined with the use of an inexpensive base makes the alkoxy carbonylation reaction attractive for synthesis on a commercial scale.

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REFERENCES

- 1) 'Organic synthesis with palladium compounds', J. Tsuji, Springer-Verlag, 1980.
A. Schoenberg, I. Bartoletti and R.F. Heck, J. Org. Chem., 1974, 39(23), 3318.
- 2) A. Schoenberg and R.F. Heck, J. Org. Chem. 1974, 39(23), 3327.
- 3) F. Ozawa, H. Soyama, T. Yamamoto and A. Yamamoto, Tet. Letts. 1982, 23(33), 3383.
- 4) A. Schoenberg and R.F. Heck, J. Amer. Chem. Soc., 1974, 96, 7761.
- 5) R.A. Head and D.T. Williams, to be published.

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