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Palladium-catalyzed coupling of alkynes with chloroformates to form alkynecarboxylic acid esters

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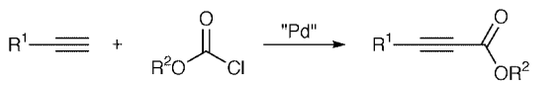
Received (in Cambridge, UK) 25th October 1999, Accepted 5th November 1999

The preparation of alkynecarboxylic acid esters, which are versatile building blocks for the synthesis of heterocyclic compounds, is described by means of the palladium-catalyzed coupling of alkynes with chloroformates for the first time.

Alkynecarboxylic acid esters can be employed as building blocks for diverse purposes, *e.g.* for the synthesis of heterocyclic compounds.[1] The methods used most frequently for the preparation of alkynecarboxylic acid esters proceed *via* the deprotonation of terminal alkynes using a Grignard reagent or organolithium compounds. The lithium acetylides are scavenged by chloroformates to form the desired alkynecarboxylic acid esters.[2] Another possibility for their preparation is the Pd-catalyzed alkoxycarbonylation of alkynes with carbon monoxide in alcohols.[3,4]

The coupling of alkynes with chloroformates catalyzed by a transition metal has so far not been described although the field of catalyzed alkyne coupling reactions has undergone enormous growth.[5–8] For example suitable methods have been developed for the preparation of many alkynyl-substituted aromatics which would not have been possible without metal catalysis. The reaction of alkynes with acid chlorides and carbamoyl chlorides for the preparation of alkynyl ketones using transition metal catalysis has also been described.[9–11]

A transition-metal catalyzed variant for the coupling of alkynes with chloroformates (Scheme 1) could on the one hand



Scheme 1

yield significant cost advantages in industrial use and on the other hand allow the reaction of labile molecules which in the presence of a Grignard reagent or organolithium compounds undergo different secondary reactions. In initial trials the conditions used for the coupling of acid chlorides with alkynes[10] were chosen. These did not result in product formation. Problems arose in particular from the sensitivity of the chloroformates which readily decompose at elevated temperatures. Chloroformates also impose limits on the choice of solvent. In solvents such as DMF or DMSO they are not stable and they react rapidly by decarboxylation to form alkyl chlorides. Suitable solvents, however, include dichloromethane or acetonitrile for example. A third limitation is in the choice of base. In the presence of nucleophilic bases, such as triethylamine for example, chloroformates were likewise found to decompose rapidly.

As a first step, therefore, it was important to find a sterically hindered base in the presence of which chloroformates do not decompose.

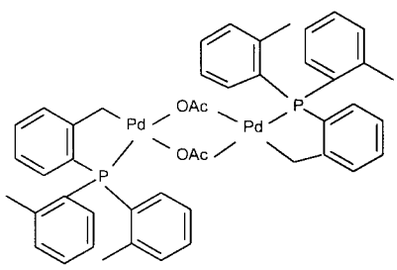


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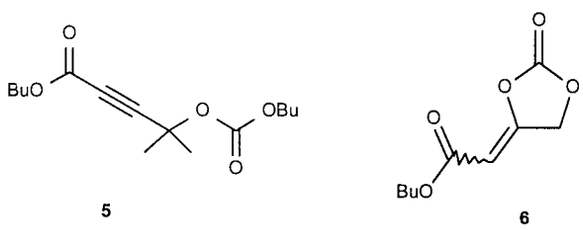
Fig. 1



5 **6**

Fig. 2

The first successful results were obtained by using $[PdCl_2(PPh_3)_2]$–PPh_3 and a stoichiometric quantity of the sterically hindered base 1,2,2,6,6-pentamethylpiperidine. The coupling of phenylacetylene with *n*-butyl chloroformate to form butyl phenylpropiolate succeeded with a 14% yield using this system. In combination with catalytic quantities of dimethylaminopyridine it was possible to raise this yield to 28%. On the other hand with the Pd(II) complex $[Pd(Ph_2P(CH_2)_2PPh_2)Cl_2]$ no reaction to form the desired alkynecarboxylic acid ester was observed. With palladium(II) acetate–triphenylphosphine a conversion level as high as 79% with good selectivity was found. It was possible to achieve a marked improvement by the direct use of Pd(0) complexes. Particularly good yields were obtained with tetrakis(triphenylphosphine)palladium, the combination $Pd_2(dba)_3$–tri-*o*-tolylphosphine and the cyclometallized complex **4** (Fig. 1; see Table 1).[12]

With the chelate Pd(0) complex $[Pd(Ph_2P(CH_2)_2PPh_2)_2]$ incomplete reaction was found although selectivity was good.

It was also possible to couple ethyl chloroformate with phenylacetylene in good yield. However, the reaction is restricted so far to alkyl chloroformates, there being no reaction with aryl chloroformates. Phenylacetylene, hexyne, propyne and 2-methylbut-3-yn-2-ol have been successfully used as alkynes. In the case of the methylbutynol the reaction proceeded with better yields in acetonitrile. Byproducts are the carbonates **5** and **6**.

The mechanism of the reaction is not yet known. Presum-

Table 1 Reaction of alkynes with chloroformates to form alkynecarboxylic acid esters[a]

No.	R^1	R^2	Catalyst	Conversion (%)	Selectivity (%)
1	Ph	Bu	$Pd(OAc)_2$–PPh_3 (1:4)	79	89
2	Ph	Bu	$Pd_2(dba)_3$–P(*o*-tolyl)$_3$ (1:4)	100	98
3	Ph	Bu	$Pd(PPh_3)_4$	100	94
4	Ph	Bu	Binucleate Pd cycle[b] (**4**)	93	97
5	Ph	Bu	$[Pd(Ph_2P(CH_2)_2PPh_2)_2]$	62	100
6	Ph	Bu	$[Pd(Ph_2P(CH_2)_2PPh_2)Cl_2]$	0	0
7	Ph	Et	$Pd_2(dba)_3$–P(*o*-tolyl)$_3$ (1:4)	100	97
8	Bu	Bu	$Pd_2(dba)_3$–P(*o*-tolyl)$_3$ (1:4)	79	100
9	Me	Bu	$Pd(PPh_3)_4$	92	77
10[c]	$C(CH_3)_2OH$	Bu	$Pd_2(dba)_3$–P(*o*-tolyl)$_3$	93	79

[a] Conditions: catalyst concentration 2.2 mol%; $T = 40$ °C; solvent: dichloromethane; 1,2,2,6,6-pentamethylpiperidine–4-dimethylaminopyridine as base. [b] Palladium complex as described by Herrmann and Beller.[12] [c] Solvent: acetonitrile, 70 °C, 2.3 mol% catalyst.

ably the chloroformate first of all adds by oxidation to the palladium(0) (corresponding (alkoxycarbonyl)chlorobis(phosphine)palladium(II) complexes have been described).[13,14] The alkynecarboxylic acid ester would have to be eliminated by reduction from an alkynyl complex formed subsequently. In those cases in which the reaction proceeded only moderately or not at all when Pd(II) complexes were used it is probable that insufficient amounts of palladium(0) were formed.

To summarize, alkyl chloroformates can be coupled to alkynes in very good yields in the presence of stoichiometric quantities of the sterically hindered base 1,2,2,6,6-pentamethylpiperidine and small amounts of dimethylaminopyridine. In this way a new and efficient route to the valuable class of compounds represented by the alkynecarboxylic acid esters has been found.

Experimental

Representative preparation of butyl phenylpropiolate

0.64 g (0.55 mmol) of tetrakis(triphenylphosphine)palladium in 50 ml of dichloromethane were stirred under an atmosphere of argon for 1 h. 0.03 g (0.25 mmol) of dimethylaminopyridine, 4.3 g (27.5 mmol) of 1,2,2,6,6-pentamethylpiperidine and 2.6 g (25 mmol) of phenylacetylene were then added and heated under slow reflux. Over a period of 25 minutes 7.5 g (55 mmol) of butyl chloroformate were then added dropwise. The reaction was monitored by GC. After 26 h 100% of the phenylacetylene had reacted. The yield of butyl phenylpropiolate was 98%.

Representative preparation of butyl 3-hydroxy-3-methylpent-2-ynoate

0.255 g (0.28 mmol) of tris(dibenzylidene acetone)dipalladium(0) and 0.644 g (2.12 mmol) of tri-*o*-tolylphosphine were dissolved in 25 ml of acetonitrile and stirred for 1 h at room temperature. 2.13 g (13.7 mmol) of 1,2,2,6,6-pentamethylpiperidine, 0.015 g (0.12 mmol) of dimethylaminopyridine and 1.04 g (12.4 mmol) of methylbutynol were then added and the mixture heated to 70 °C. 1.73 g (12.7 mmol) of butyl chloroformate were metered in slowly over 90 minutes. The reaction was monitored by GC. After 16.5 h 93% of the phenylacetylene had reacted. The yield of butyl 3-hydroxy-3-methylpent-2-ynoate was 79%.

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Communication 9/08458D