Alkoxycarbonylation of 3,3,3-Trifluoropropyne: an Intriguing Reaction to Prepare Trifluoromethyl-Substituted Unsaturated Acid Derivatives

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Received: February 6, 2002; Accepted: March 24, 2002

Abstract: The addition of CO and methanol to 3,3,3-trifluoropropyne is catalysed by $Pd(OAc)_2$ in the presence of (6-methylpyrid-2-yl)diphenylphosphine and CH_3SO_3H. The main products of the reaction are the methyl esters of 2-(trifluoromethyl)propenoic acid **1** and of 3-(trifluoromethyl)propenoic acid **2** (4,4,4-trifluorobut-2-enoic acid). The regioselectivity of the reaction can be controlled to a great extent by a suitable choice of the composition of the catalytic system and the reaction conditions. Thus, **1** can be obtained in 93% yield by using $P(CO) = 20$ atm and high ligand/Pd and acid/Pd ratios. On the other hand, selectivity up to 85% in **2** can be achieved using $P(CO) = 80$ atm and a low ligand/Pd ratio together with a high acid/Pd ratio. The reaction mechanism is also discussed.

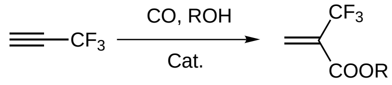
Keywords: alkyne; carbonylation; fluorine; homogeneous catalysis; palladium

Introduction

Homo- or copolymers of fluorinated acrylates are materials of remarkable interest for the coating industry.[1] As a matter of fact, the presence of the fluorine atoms grants to these materials outstanding resistance to weathering and UV rays.[1] Accordingly, these polymers should display – along with the well-known good mechanical, optical and thermal properties of the acrylic materials – an exceptional resistance to ageing agents. In particular, this latter characteristic makes them especially well suited to be used in the field of the cultural heritage conservation.[2–4]

However, a wide employment of fluorinated coatings is hampered by the lack of simple and economically sustainable processes for the synthesis of the starting monomers such as the esters of 2-trifluoromethylacrylic acid. In our opinion, the most elegant and effective approach to the synthesis of fluorinated acrylates is the alkoxycarbonylation of 3,3,3-trifluoropropyne, as shown in Scheme 1.

In a recent study,[5] we have shown that, when the carbonylation of 3,3,3-trifluoropropyne is carried out using as catalyst $Pd(OAc)_2$ in combination with 2-pyridyldiphenylphosphine and methanesulfonic acid (Drent's catalytic system[6,7]), it is possible to adjust the reaction conditions in order to enhance either the activity of the catalyst or the regioselectivity of the reaction. These intriguing preliminary results, and our interest in the development of a practical synthesis of new coatings for cultural heritage, prompted us to investigate the possibility of further improve the efficiency of our synthetic approach by using more active and selective ligands such as (6-methylpyrid-2-yl)diphenylphosphine.[6] Indeed, according to Drent, the methyl substituent on the pyridyl moiety of this ligand would force the regioselectivity of the carbonylation reaction towards the formation of the sought branched methyl 2-trifluoromethylacrylate.[6]



Scheme 1.

Results and Discussion

The catalytic efficiency of 2-(6-Me)$PyPh_2P$ as ligand in the alkoxycarbonylation of 3,3,3-trifluoropropyne was preliminarily evaluated by some experiments carried out in methanol. The relevant data and reaction conditions are reported in Table 1.

From these data it appears that the presence of the trifluoromethyl group depresses the reactivity of the alkyne. In fact, the carbonylation rate is much lower than that usually achieved with other unfluorinated alkynes.[6,7] Also the chemoselectivity of the reaction is lower than usual, and four different products are formed

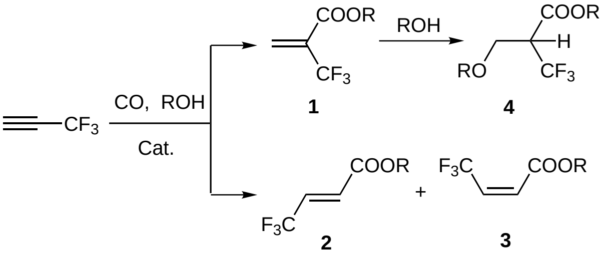
Table 1. Carbonylation of 3,3,3-trifluoropropyne in methanol.

Run [a]	T [°C]	t [h]	Conv. [%]	Product yield [%] [b]			
				1	**2**	**3**	**4**
1	50	48	58	28	19	7	1
2	80	48	65	31	17	6	6
3	110	72	87	–	–	–	16
4[c]	80	48	97	39	22	1	10

[a] Substrate/Pd: 320; Pd(OAc)$_2$: 0.025 mmol; 2-(6-Me)PyPh$_2$P/Pd: 10; CH_3SO_3H/Pd: 20; P(CO): 20 atm; CH_3OH: 20 mL.

[b] Variable amounts of polymeric materials are also formed.

[c] 2-(6-Me)PyPh$_2$P/Pd: 40; CH_3SO_3H/Pd: 40.



Scheme 2.

during the reaction (Scheme 2). In fact, GC-MS analysis indicates that alongside with the two expected esters **1** and **2**, small amounts of **3** and **4** are also produced.[8]

The formation of the saturated ester **4** is due to the addition of methanol to the double bond of **1**, a process which frequently accompanies the palladium-catalysed alkoxycarbonylation of unsaturated substrates,[9,10] and does not deserve particular comments. On the contrary, the formation of the *cis*-unsaturated ester **3** is rather remarkable since it arises from a formal *trans*-addition of the H and COOR moieties to the triple bond. This finding contrasts with our previous observation that, in the presence of Drent's catalytic system, the addition of the H and COOR moieties to the C-C triple bond of 2-butyne occurs in a stereospecific *cis*-fashion.[11] Although some peculiar features of Pd-hydride chemistry can rationalise this finding (see below), it further highlights the outstanding influence exerted by the trifluoromethyl moiety on the reaction.

Comparing the data in Table 1 with those obtained using 2-pyridyldiphenylphosphine under analogous conditions[5] it appears that, while the new ligand affords lower reaction rates, it allows one to obtain higher regioselectivities towards **1**.

On increasing the reaction temperature, no significant improvement in the catalyst efficiency can be attained: only a modest gain in reaction rate is observed at 80 °C, and even if at 110 °C the substrate conversion is much higher, the only product detected by GLC and GC-MS is **4** (Table 1, Run 3). This finding can be rationalised by assuming that the unsaturated reaction products polymerise. The polymerisation is probably induced by the pyridyl group of the ligand itself, since a carbonylation experiment (not reported in the Table) carried out in the presence of hydroquinone ruled out a radical mechanism, and it is known that the polymerisation of trifluoromethyl substituted acrylates is initiated by pyridine.[12] The involvement of the ligand in the formation of the polymeric species is also suggested by the data of Run 4. By increasing the ligand to palladium ratio up to 40/1 and the ligand to acid ratio to 1, the substrate conversion is almost complete but the yield in esters **1** – **4** is only 72% owing to polymer formation.

Much more promising results were obtained using dichloromethane as solvent; in this case some methanol was added as carbonylation co-reagent (Table 2).

As a matter of fact, in this solvent the chemoselectivity is high: alongside with the unsaturated esters only very small amounts of **4** are formed (Table 2, Run 1). Although at 50 °C the catalytic activity is lower than in methanol, the reaction rate can be strongly improved by increasing the temperature to 80 °C. This large enhancement of catalytic activity is accompanied by only a modest decrease of the regio- and chemoselectivity. A further increase of temperature to 100 °C does not cause sensible variations in the product composition.

A strong influence on the regioselectivity is exerted by the CO pressure (Table 2, compare Runs 2 and 4). As a matter of fact, on increasing the P(CO) from 20 to 50 atm the branched/linear esters ratio is halved.

Although unusual, this result can be explained by invoking an "hydride-based" reaction mechanism (Scheme 3) in which the formation of the vinyl intermediates **A** and **B** is reversible, in agreement with the results of our previous studies.[11]

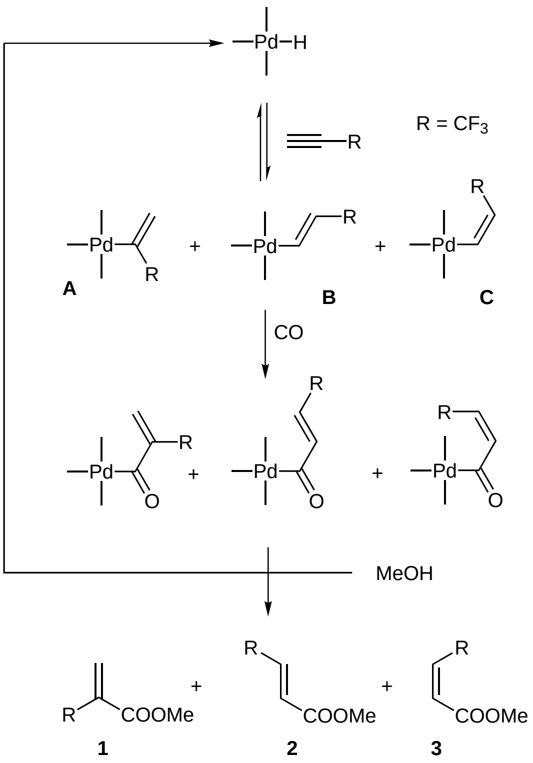
In fact, an increase of the P(CO) should mainly enhance the rate of the CO insertion which leads to the formation of the acyl intermediates. This would result in an enhanced formation of the kinetically controlled regioisomer. According to this hypothesis, the vinyl intermediate **B** appears to be the one formed under

Table 2. Carbonylation of 3,3,3-trifluoropropyne in dichloromethane: influence of temperature and P(CO).

Run[a]	T [°C]	P(CO) [atm]	Conv. [%]	Product yield [%]			
				1	**2**	**3**	**4**
1	50	20	31	19	10	1	1
2	80	20	100	53	43	1	3
3	100	20	99[b]	47	40	2	7
4	80	50	100	37	55	6	2

[a] Substrate/Pd: 320; CH_3OH: 25 mmol; Pd(OAc)$_2$: 0.025 mmol; t: 48 h; 2-(6-Me)PyPh$_2$P/Pd: 20; CH_3SO_3H/Pd: 20; CH_2Cl_2: 20 mL.

[b] Polymeric materials are also formed.



Scheme 3.

kinetic control, while **A** is the thermodynamically more stable species.

A hydride-based mechanism may also explain the formation of **3**. As a matter of fact, even if usually the insertion of alkynes into a Pd-H bond occurs in a *cis*-fashion,[13] it is known that in some cases this process proceeds with *trans*-stereochemistry.[14] In our case, such stereochemistry would result in the formation of the vinyl intermediate **C** in Scheme 3 which finally leads to ester **3**. According to our hypothesis that the hydropalladation is reversible and that **A** is the thermodynamically more stable vinyl intermediate, the formation of **3** decreases when low *P*(CO) is used (Table 2, Run 2).

Even if the above rationalisation suitably accounts for many features of the catalysis, it is to be pointed out that it needs to be confirmed by mechanistic investigations.

Table 3. Carbonylation of 3,3,3-trifluoropropyne in dichloromethane: influence of the ligand/Pd and acid/Pd ratios.

Run[a]	Ligand/ Pd[b]	Acid/Pd[b]	Conv. [%]	Product yield [%]			
				1	**2**	**3**	**4**
1	10	20	100	22	78	–	–
2	20	20	100	53	43	1	3
3	40	40	100	82	11	2	5

[a] Substrate/Pd: 320; CH_3OH: 25 mmol; $Pd(OAc)_2$: 0.025 mmol; t: 48 h; *T*: 80 °C; *P*(CO): 20 atm; 2-(6-Me)-$PyPh_2P$/Pd: 20; CH_3SO_3H/Pd: 20; CH_2Cl_2: 20 mL.
[b] mol/mol.

Indeed, the carbonylation rate of 3,3,3-trifluoropropyne is ca. 1000 times slower that the one of butyne or phenylacetylene, the substrates we used in our previous mechanistic studies.[11] Even if the much lower reaction rate can be ascribed to an intrinsic low reactivity of the fluorinated substrate, a different explanation such as the involvement of a completely different reaction mechanism (an alkoxycarbonyl-based one, for example) could be invoked.[15]

In order to increase the catalyst efficiency and the yield in the unsaturated ester **1**, the influence of the most important reaction parameters was investigated (Tables 3 and 4). In fact, owing to the ternary composition of Drent's catalytic system, the optimisation of the process requires the investigation of the effects brought about by both the ligand to metal and the acid to metal ratios (Table 3).

In particular, it appears that the formation of the branched ester **1** is favoured by increasing the ligand to palladium ratio to levels of *ca.* 40/1 (Table 3, Run 3). Correspondingly, acid/phosphine ratios close to 1 give the best results. In the presence of an excess of ligand the chemoselectivity decreases owing to the formation of the saturated side product **4** and to polymerisation of **1**, while when an excess of acid is present, there is a loss in regioselectivity in **1** (Table 3, Run 1).

To further enhance the regioselectivity towards **1**, we have tested the effect of the addition of some 1-methyl-2-pyrrolidynone (NMP) to dichloromethane (Table 4); in fact, it is known that the use of this highly polar aprotic

Table 4. Carbonylation of 3,3,3-trifluoropropyne in dichloromethane/1-methyl-2-pyrrolidynone.

Run[a]	Solvent	Ligand/Pd[b]	Acid/Pd[b]	Conv. [%]	Product yield [%]			
					1	**2**	**3**	**4**
1	CH_2Cl_2/NMP (1/9)[c]	20	20	90	47	39	2	2
2	CH_2Cl_2/NMP (1/9)[c]	40	40	100	89	8	–	3
3	CH_2Cl_2/NMP (1/9)[c]	40	80	100	50	42	2	6
4	CH_2Cl_2/NMP (1/1)[c]	40	40	100	55	5	–	40

[a] Substrate/Pd: 320; CH_3OH: 25 mmol; $Pd(OAc)_2$: 0.025 mmol; t: 48 h; *T*: 80 °C; *P*(CO): 20 atm; solvent: 20 mL.
[b] mol/mol.
[c] vol/vol.

solvent allows one to obtain very high selectivities towards methacrylates in propyne carbonylation.[6] Accordingly, using a mixture NMP/CH_2Cl_2 (18 mL/2 mL) as solvent, it is possible to obtain regioselectivities in **1** close to 90%; also in this solvent mixture, the best ligand/Pd and ligand/acid ratios are 40/1 and 1/1, respectively.

A further increase in the relative amount of NMP (Run 4) does not provide substantial benefits. In fact, even if the regioselectivity in the branched ester further increases (up to 95% taking into account that **4** is formed at the expense of **1**), the yield in **1** is drastically lowered owing to an enhanced formation of the saturated product **4**. This result can be explained by the "basic" properties of NMP[16] which favour the palladium-catalysed addition of methanol to the double bond of **1**.

The experiments reported in Tables 2–4 were carried out with a fixed duration of 48 hours and, in most cases, at that time the substrate conversion turned out to be complete. Therefore, some experiments were carried out to monitor the progress of the reaction over time using the conditions adopted in Run 2 of Table 4. These experiments (Table 5) revealed that the substrate conversion is very high (60%) after only 6 h and is complete after 16 h: the methyl ester of 2-(trifluoromethyl)propenoic acid **1** is obtained in *ca.* 93% yield (the regioselectivity reaches 94%, Table 5, Run 2). Higher temperatures do not allow any improvement; on the contrary, a decrease in regioselectivity and in chemoselectivity is observed.

Table 5. Carbonylation of 3,3,3-trifluoropropyne: influence of reaction time and temperature.

Run[a]	T [°C]	t [h]	Conv. [%]	Product yield [%]			
				1	**2**	**3**	**4**
1	80	6	60	53	5	–	2
2	80	16	98	91	6	–	1
3	100	6	66	53	11	–	2
4	120	3	44	26	11	–	7

[a] Substrate/Pd: 320; CH_3OH: 25 mmol; $Pd(OAc)_2$: 0.025 mmol; P(CO): 20 atm; 2-(6-Me)$PyPh_2P$/Pd: 40; CH_3SO_3H/Pd: 40; CH_2Cl_2/NMP: 18 mL/2 mL.

The data reported in Tables 1–4 demonstrate that by choosing appropriate reaction conditions it would be possible to tune the catalytic activity towards the synthesis of the linear regioisomer **2**. With this aim, we have carried out some experiments in CH_2Cl_2 at 80 °C varying P(CO), ligand/Pd and acid/Pd ratios and reaction times (Table 6) beginning from the conditions we have found as worst for the regioselectivity in the branched isomer. Accordingly, it was possible to maximise the regioselectivity in the linear unsaturated ester **2** which in Run 4 of Table 6 reaches 85%.

Conclusion

The data reported herein demonstrate the practical applicability of carbonylation reactions for the synthesis of fluorinated methacrylates and crotonates, important monomers for special coatings industry, which otherwise require laborious multi-step synthetic processes.

A key feature of the process is the possibility to control the regiochemistry of the reaction by an adequate tuning of the catalyst composition and the reaction conditions. Although this behaviour is quite unusual, it can be rationalised by a "Pd-H based mechanism" in which the formation of the σ-vinyl-palladium intermediates is reversible.

Experimental Section

General Remarks

All the operations were carried out under argon in Schlenk-type glassware. Commercial solvents (J. T. Baker) were purified following methods described in the literature.[17] 3,3,3-Trifluoropropyne (Fluorochem) and $Pd(OAc)_2$ (Engelhard Industries) were used as received. High purity CO was obtained from SIAD.

The ^1H and ^{31}P NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200.213 and 81.015 MHz, respectively. GC-MS analyses were carried out on an HP 5830 II series gas chromatograph interfaced to a Hewlett-Packard 5971 mass detector.

Table 6. Carbonylation of 3,3,3-trifluoropropyne in dichloromethane: influence of different parameters.

Run[a]	Ligand/Pd[b]	Acid/Pd[b]	t [h]	P(CO) [atm]	Conv. [%]	Product yield [%]			
						1	**2**	**3**	**4**
1	20	20	48	20	100	53	43	1	3
2	10	20	48	20	100	22	78	–	–
3	10	40	16	20	62	13	49	–	–
4	10	20	16	80	74	11	63	–	–
5	10	80	16	80	81	14	67	–	–

[a] Substrate/Pd: 320; CH_3OH: 25 mmol; $Pd(OAc)_2$: 0.025 mmol; T: 80 °C; CH_2Cl_2: 20 mL.
[b] mol/mol.

(6-Methylpyrid-2-yl)diphenylphosphine was synthesised by a modification of the literature method:[17] Na (2.0 g, 86 mmol) was added to a solution of $ClPPh_2$ (9.6 g, 43 mmol) in dioxane (70 mL). The mixture was heated at reflux for 4 h to give a yellow suspension of $NaPPh_2$. After cooling at room temperature, a solution of 2-chloro-6-methylpyridine (5.8 g, 46 mmol) dissolved in dioxane (10 mL) was added dropwise. The resulting mixture was left under stirring overnight, then the solvent was removed in vacuum. The remaining solid was extracted (3 × 100 mL) with a mixture of *n*-hexane/diethyl ether (80/20). The organic phase was taken to dryness and the remaining solid recrystallised from methanol to give white crystals; yield: 7.8 g (65%). ^1H NMR ($CDCl_3$): $\delta = 2.58$ (s, 3H, CH_3), 6.83 (d, 1H, 5-py), 7.06 (d, 1H, 4-py), 7.26 – 7.41 (m, 10H, arom), 7.46 (m, 1H, 3-py); ^{31}P NMR ($CDCl_3$): $\delta = -4.54$ (s).

Carbonylation Experiments

The carbonylation experiments were carried out in a magnetically stirred stainless steel autoclave (total volume *ca.* 150 mL). To illustrate the carbonylation procedure, the experimental details for Run 2 of Table 4 are reported. Under an inert atmosphere, a Schlenk flask containing a small magnetic bar was charged with 18 mL of CH_2Cl_2, 2 mL of NMP, 800 mg (25 mmol) of methanol, 5.9 mg (0.025 mmol) of $Pd(OAc)_2$, 277 mg (1 mmol) of (6-methylpyrid-2-yl)diphenylphosphine, 65 µL, (96 mg, 1 mmol) of CH_3SO_3H, and 83 mg (0.7 mmol) of mesitylene (as GC internal standard) in that order. The resulting solution was transferred *via* a cannula into the autoclave. Then the latter was cooled in liquid nitrogen and connected to a 3,3,3-trifluoropropyne reservoir. After charging the desired amount (800 mg, 8.5 mmol) of substrate, the reactor was pressurised with 20 atm of CO and heated at 80 ± 1 °C by circulating a thermostatic fluid. At the end of the reaction the autoclave was cooled to –78 °C and the residual gas carefully vented off.

Analytical and spectroscopic data for **1**, **2** and **4** have been reported elsewhere,[5] we report here the mass spectrum of **3**: MS: $m/e = 135\ [M-F]^+$, $123\ [M-OCH_3]^+$, $95\ [M-COOCH_3]^+$, $85\ [M-CF_3]^+$, $69\ [CF_3]^+$, $59\ [COOCH_3]^+$.

Acknowledgements

This work was supported by the Italian CNR – Progetto Finalizzato "Beni Culturali".

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