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Ruthenium/chloride catalytic system for conjugate addition of terminal alkynes to acrylate esters

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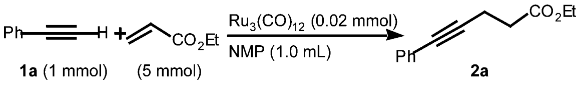
The addition of terminal alkynes to acrylate esters in the presence of a ruthenium catalyst and chloride sources proceeds to give the corresponding γ,δ-alkynyl esters in good yields.

The conjugate addition of carbanions to α,β-unsaturated carbonyl compounds is one of the most attractive methods for constructing a new C–C bond.[1] Among the various kinds of carbon nucleophiles, terminal alkynes are of interest to create internal alkynes having a carbonyl functionality. Usually, the introduction of an alkynyl moiety to organic acceptors by conjugate addition reaction is carried out using the stoichiometric alkynyl species, such as metal-alkynylide.[2] Thus, the direct conjugate addition of terminal alkynes to acceptor alkenes or alkynes would be valuable because of the simple operation and its ability to minimize the metallic wastes.[3] As for the catalytic direct conjugate addition reaction of terminal alkynes to acceptor alkenes, a few examples have been demonstrated by using some rhodium or ruthenium catalysts.[4] For example, Nikishin and Kovalev demonstrated that rhodium catalysed a vinyl ketone–acetylene cross coupling reaction.[4a] Dixneuf and co-workers reported the $[Ru(O_2CH)(CO)_2(PPh_3)]_2$ complex-catalysed Michael reaction of terminal alkyne to butenone.[4b] Recently, Chang and co-workers studied the same reaction using a $[RuCl_2(p\text{-cymene})]_2$/pyrrolidine system.[4c] However, these reactions were limited to reactive vinyl ketones and an example of the reaction of unsaturated esters, especially alkenic esters, is rare.[5] Quite recently, the first Cu-catalysed conjugate addition of terminal alkyne to unsaturated esters derived from Meldrum's acid was reported by Knöpfel and Carreira.[6]

We have recently reported the oxidative alkynylation of alkenes using α,α-dialkylalkynylmethanols as alkynylating reagents in the presence of a palladium catalyst under an atmospheric pressure of oxygen.[7] During the search for the new catalytic system for that reaction, we have now found that $Ru_3(CO)_{12}$ is an effective catalyst for the conjugate addition of phenylacetylene to ethyl acrylate in the presence of a chloride source to give the corresponding γ,δ-alkynyl esters. We report herein the results of the synthesis of γ,δ-alkynyl esters catalysed by ruthenium catalyst under mild conditions.

Treatment of phenylacetylene (**1a**) with ethyl acrylate in the presence of $Ru_3(CO)_{12}$ in *N*-methylpyrrolidinone (NMP) at 100 °C for 3 h gave ethyl 5-phenylpent-4-ynoate (**2a**) in 18% yield irrespective of the complete conversion of **1a** (eqn. (1), Table 1, entry 1). Reactions in the presence of various kinds of additives, such as organic and inorganic bases or alkali metal carbonates and halides, were tested to improve the yield of **2a**. As a result, it was disclosed that the addition of LiCl increased the yield of **2a** and 68% of **2a** was obtained after 21 h at 80 °C (entry 3).[8] Among alkali metal chlorides, lithium chloride was most effective to give **2a** in higher selectivity (entries 3–5). On the other hand, the use of ammonium chloride dramatically decreased the yield (entry 6). A higher concentration of the substrates improved the yield (entry 7). Interestingly, when bis(triphenylphosphine)iminium chloride ([PPN]Cl), a highly dissociated chloride ion, was used, **2a** was obtained in 90% at 80°C and 95% yield at 60 °C (entries 8 and 9).



(1)

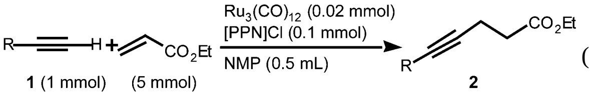
Table 1 Effect of the additives

Entry	Additive/mmol	Temp./°C	Time/h	GLC yield (%)[a]
1	—	100	3	18 (100)
2	LiCl (0.1)	100	3	35 (79)
3	LiCl (0.1)	80	21	68 (100)
4	NaCl (0.1)	80	21	42 (100)
5	KCl (0.1)	80	21	33 (96)
6	NH_4Cl (0.1)	80	21	1 (28)
7[b]	LiCl (0.1)	80	15	79 (100)
8[b]	[PPN]Cl (0.1)	80	12	90 (100)
9[b]	[PPN]Cl (0.1)	60	24	95 (100)
10[b]	—	60	24	11 (66)

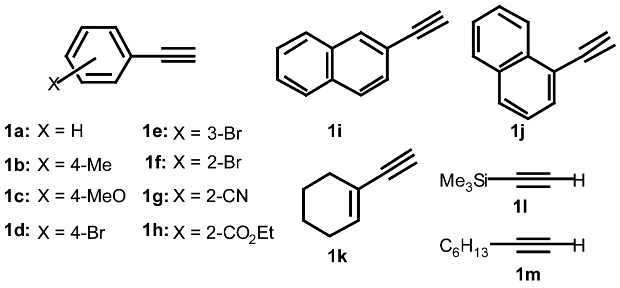
[a] The value in parentheses is the conversion (%) of **1a**. [b] NMP (0.5 mL).

Here again, the reaction in the absence of a chloride source under the same reaction conditions resulted in the formation of **2a** in much lower yield (entry 10). This result clearly shows that the chloride anion accelerates the reaction and increases the selectivity.

The reactions of several terminal alkynes having aromatic or vinylic substituents with ethyl acrylate were next examined in the presence of [PPN]Cl (eqn. 2 and Scheme 1), typical results of which are listed in Table 2.† Aromatic alkynes having an electron-donating substituent on the benzene ring, such as the methyl and methoxy group, gave the corresponding esters in high yields (entries 2 and 3), whereas reactions of aromatic alkynes with an electron-withdrawing group were relatively slow (entries 4–10). Interestingly, bromo-, cyano- and ethoxycarbonyl-substituents were not affected under these reaction conditions to afford the corresponding esters in moderate to good yields (entries 4–10). Naphthylacetylenes **1i** and **1j** also gave **2i** and **2j** in good yields. The reaction of an enyne compound **1k** smoothly proceeded to give **2k** in 69% yield. Next, the reaction of simple alkynes, such as trimethylsilylacetylene and 1-octyne, with ethyl acrylate was carried out under the same reaction conditions. Although the reaction was much slower than that with the aromatic alkynes, the corresponding esters were obtained in 45% and 41% yield, respectively (entries 14–16).



(2)



Scheme 1

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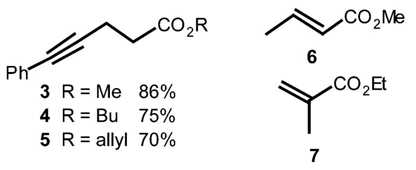
Table 2 Reactions of terminal alkynes with ethyl acrylate

Entry	Alkyne	Temp./°C	Time/h	Product	Isolated yield (%)
1	**1a**	60	24	**2a**	89
2	**1b**	60	24	**2b**	86
3	**1c**	60	24	**2c**	88
4	**1d**	60	42	**2d**	77
5	**1e**	60	48	**2e**	76
6	**1e**	80	15	**2e**	70
7	**1f**	60	48	**2f**	77
8	**1g**	60	60	**2g**	60
9	**1g**	80	24	**2g**	66
10	**1h**	60	24	**2h**	80
11	**1i**	60	24	**2i**	77
12	**1j**	60	24	**2j**	77
13	**1k**	60	24	**2k**	69
14	**1l**	60	24	**2l**	36
15	**1l**	60	60	**2l**	45
16	**1m**	60	48	**2m**	41

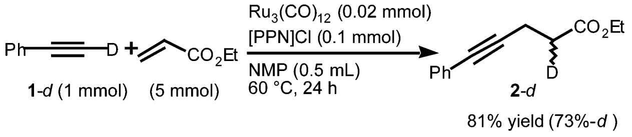
Reactions of **1a** with other unsaturated esters, such as methyl acrylate, butyl acrylate, allyl acrylate, methyl crotonate (**6**) and ethyl methacrylate (**7**) were also examined. The former three acrylate esters afforded the desired products **3**–**5** in good yields, while the reaction of **1a** with **6** and **7** resulted in the formation of a complex mixture of unidentified compounds (Scheme 2).

When the reaction of phenylactylene-*d* with ethyl acrylate was carried out under the standard reaction conditions at 60 °C for 24 h, the α-deuteriated alkynyl ester was obtained in 81% yield with 73% *d*-incorporation (Scheme 3). This result suggests that the reaction may proceed *via* the insertion of ruthenium(0) into an spC–H bond, followed by the insertion of the alkene either into the Ru–H bond[9] or Ru-alkynyl bond to give the product.[10] The reaction of $Ru_3(CO)_{12}$ with [PPN]Cl has been known to give several multinuclear ruthenium complexes, such as $[PPN][Ru_3(\mu\text{-}Cl)(CO)_{10}]$, $[PPN][Ru_3(\mu_3\text{-}Cl)(CO)_9]$, $[PPN][Ru_4(\mu\text{-}Cl)(CO)_{13}]$ and $[PPN]_2[Ru_4(\mu\text{-}Cl)_2(CO)_{11}]$.[11] In our reaction conditions, these species could be generated to induce this conjugate addition reaction, although details are not yet known.[12]

In summary, we found that the effective conjugate addition reaction of terminal alkynes to acrylate esters was catalysed by the commercially available ruthenium catalyst in the presence of a chloride source. This reaction system can be carried out under neutral and mild conditions to give the γ,δ-alkynyl esters in good yields. Studies of the scope and limitations of this catalytic system and a detailed mechanistic investigation are in progress.



Scheme 2



Scheme 3

Notes and references

† *Experimental*: A mixture of $Ru_3(CO)_{12}$ (0.02 mmol), [PPN]Cl (0.1 mmol) and NMP (0.5 mL) in a 10-mL Schlenk tube was stirred at 60 °C under N_2. After 15 min, ethyl acrylate (5.0 mmol) and alkyne (1.0 mmol) were added and the mixture was stirred at 60 °C until the reaction had reached completion by monitoring with TLC analysis. The reaction mixture was cooled to room temperature and then filtered through a pad of Florisil. The filtrate was concentrated under vacuum to give an oil, which was subjected to column chromatography on SiO_2 with EtOAc-hexane (2/98) as eluent.

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