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Acryloyl Chloride: An Excellent Substrate for Cross-Metathesis. A One-Pot Sequence for the Synthesis of Substituted α,β-Unsaturated Carbonyl Derivatives

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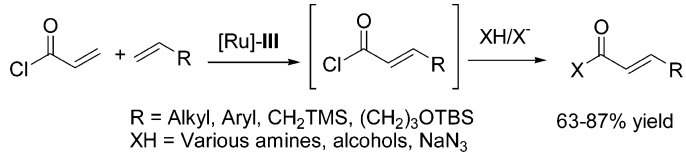
ABSTRACT



A diverse set of functionalized α,β-unsaturated carbonyl compounds were synthesized in good yield by utilizing a very simple one-pot process involving a cross-metathesis between acryloyl chloride and a terminal olefin followed by the addition of a nucleophile.

One of the challenges in synthetic chemistry is the development of reactions and strategies that allow a facile conversion of simple and inexpensive compounds into complex molecules, while keeping in mind the principle of atom economy. One of these reactions is olefin metathesis, which has emerged as a powerful synthetic tool due to the development of active, selective, and stable catalysts. The most common catalysts used are [Ru]-**I**,[1] [Ru]-**II**,[2] [Ru]-**III**[3] and, to a lesser extent, [Ru]-**IV**[4] (Figure 1).

Cross-metathesis (CM) is commonly used to form C═C bonds under mild conditions, and by using this reaction, even trisubstituted and functionalized olefins can be synthesized. However, cross-metathesis has some limitations as, for example, the efficiency of the CM between α,β-unsaturated amides and terminal olefins depends on the nitrogen substituents of the amide group. It is worth noting that the presence of electron-donating substituents on the nitrogen of α,β-unsaturated amides, such as alkyl groups, results in low yields in CM products.[5]

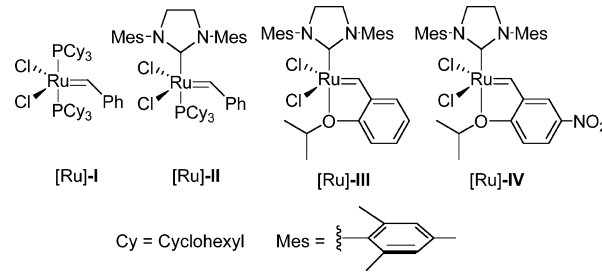


Figure 1. Ruthenium catalysts.

Here, we report a two-step one-pot process that allows the synthesis of α,β-unsaturated amides in good to excellent yields by realizing a cross-metathesis between acryloyl

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(1) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039. (b) Schwab, P.; Grubbs, R. R.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

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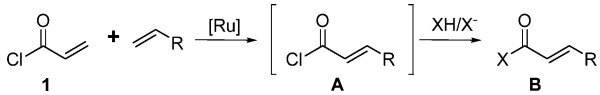
chloride **1** and terminal olefins followed by the addition of various amines on the formed intermediate **A** (Scheme 1).

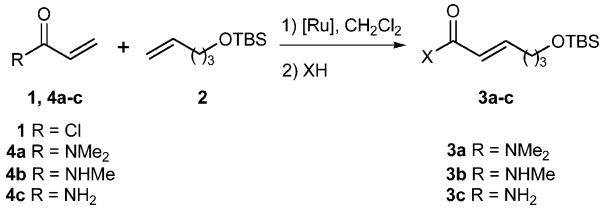
Scheme 1. One-Pot Sequence CM/Nucleophile Addition



Furthermore, addition of various nucleophiles, such as alcohols or sodium azide, on the very reactive CM intermediate **A** provides α,β-unsaturated esters and α,β-unsaturated azides respectively (products **B**) (Scheme 1).

In order to synthesize *N,N*-dialkyl α,β-unsaturated amides, preliminary CM studies were achieved with freshly distilled acryloyl chloride **1** (1.5 equiv) and olefin **2** (1 equiv) in the presence of a ruthenium catalyst (5 mol %) in CH_2Cl_2, at a concentration of 0.2 M, at rt. After 16 h, *N,N*-dimethylamine (33% in ethanol) was added to the reaction media and the mixture was purified by flash chromatography on silica gel chromatography to afford **3a**. Four different catalysts were screened in order to obtain the best yields in olefin **3a**. The results are summarized in Table 1.

Table 1. Screening of Ruthenium Catalysts[a]



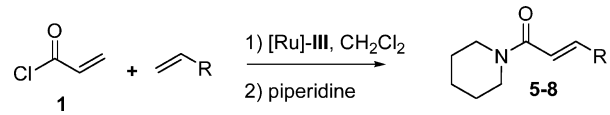
entry	[Ru]	temp (°C)	R	HX	product	yield[b] (%)
1	[Ru]-**I**	rt	Cl	$HNMe_2$[c]	**3a**	traces
2	[Ru]-**II**	rt	Cl	$HNMe_2$[c]	**3a**	19
3	[Ru]-**II**	40 °C	Cl	$HNMe_2$[c]	**3a**	74
4	[Ru]-**III**	rt	Cl	$HNMe_2$[c]	**3a**	**73**
5	[Ru]-**IV**	rt	Cl	$HNMe_2$[c]	**3a**	54
6	[Ru]-**III**	rt	Cl	H_2NMe[c]	**3b**	80
7	[Ru]-**III**	rt	Cl	H_3N[d]	**3c**	81
8	[Ru]-**III**	rt	NH_2	none	**3c**	71
9	[Ru]-**III**	rt	NHMe	none	**3b**	11
10	[Ru]-**III**	rt	NMe_2	none	**3a**	traces

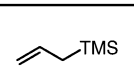
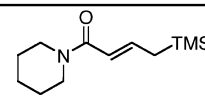
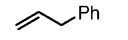
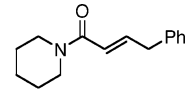
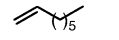
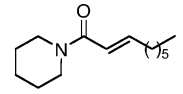
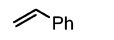
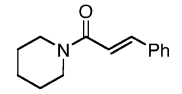
[a] Conditions: [Ru] catalyst (5 mol %), terminal olefin (1 equiv), **1** or **4a**−**c** (1.5 equiv), CH_2Cl_2 0.2 M, 16 h then amine (6 equiv), 1 h. [b] Yields of isolated products. [c] Amine solution, 33% in EtOH. [d] NH_3 28% in H_2O. TBS = *tert*-butyldimethylsilyl.

At first, the one-pot sequence was performed, at rt, with [Ru]-**I** and [Ru]-**II** (Table 1, entries 1 and 2). By using [Ru]-**I**, only traces of **3a** were observed (Table 1, entry 1) and by using with [Ru]-**II**, a low yield in **3a** was obtained (19%) (Table 1, entry 2). On the contrary, when the reaction was performed in refluxing CH_2Cl_2 in the presence of [Ru]-**II**, **3a** was produced in good yield (74%) (Table 1, entry 3). It was also noticed that [Ru]-**III** was more efficient than [Ru]-**II** as **3a** was isolated with a similar yield when the reaction was performed at rt (73% yield versus 74% yield) (Table, entries 3 and 4). It is worth noting that by using [Ru]-**IV** at rt, **3a** was obtained in only 54% (Table 1, entry 5). Because of these results, all the reactions were performed with [Ru]-**III** at rt. This one-pot sequence CM/addition of amines is general. When a secondary amine (*N*-methylamine) and ammonia were added after completion of the CM between acryloyl chloride **1** and olefin **2**, the corresponding amides **3b**,**c** (Table 1, entries 6 and 7) were isolated in good yields (80−81%). This process is more efficient than the CM between primary, secondary, or tertiary acrylamides and olefin **2**, as yields of **3** depend on the substituents on the nitrogen atom of acrylamides (Table 1, entries 8−10). For comparison with our one-pot sequence, the CM between acrylamide **4c** and **2** gave good yield in **3c**, whereas the yield in the CM product using *N*-methylacrylamide **4b** and **2** dropped dramatically and the CM was inefficient with *N,N*-dimethylacrylamide **4a**. These results are in agreement with the results already reported in the literature.[5]

Different olefin partners were examined, and the results are reported in Table 2.

Table 2. Terminal Olefin Partners[a]



entry	terminal olefin	product		yield %[b]
1			**5**	87
2			**6**	86
3			**7**	86
4			**8**	54

[a] Conditions: [Ru]-**III** catalyst (5 mol %), terminal olefin (1 equiv), **1** (1.5 equiv), CH_2Cl_2 0.2 M, 16 h then piperidine (6 equiv), 1 h. [b] Yields of isolated products.

This one-pot CM/nucleophile addition sequence using acryloyl chloride **1** and various electron-rich terminal olefin partners followed by the addition of piperidine were screened. Good to excellent yields in CM products **5**−**8** were obtained (Table 2).

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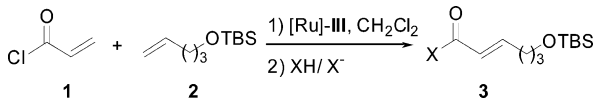
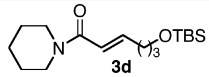
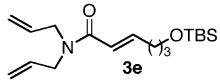
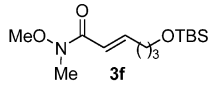
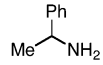
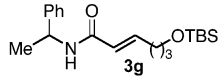
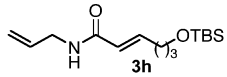
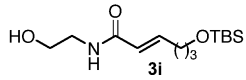
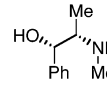
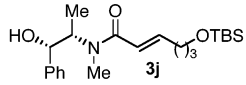
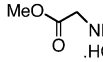
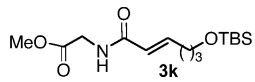
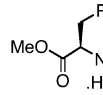
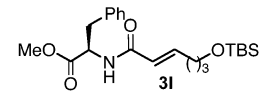
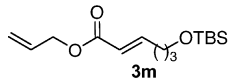
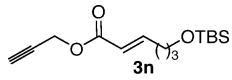
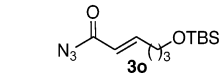
We have to point out that this reaction seems to be limited to the utilization of Type I olefins (in the Grubbs olefin classification)[6] as allyl acetate and methyl-2-pentene do not produce the corresponding CM product. The addition of various amines to intermediate **A** was realized, and excellent yields in the corresponding substituted acrylamides were obtained (65−81%) (Table 3). It is worth noting that when cheap amines were utilized, a large excess of the amine was introduced in the reaction mixture (Table 3, entries 4−5).

Table 3. Addition of Various Nucleophiles[a]



entry	HX/X⁻	product	additive	yield %[b]
1[c]		 **3d**	K_3PO_4 3.8 equiv	75
2[c]		 **3e**	K_3PO_4 3.8 equiv	65
3[c]	HNMe(OMe) .HCl	 **3f**	NMM 6 equiv	69
4[d]		 **3g**	none	73
5[d]		 **3h**	none	76
6[c]		 **3i**	K_3PO_4 3.8 equiv	68
7[c]		 **3j**	K_3PO_4 3.8 equiv	70
8[c]		 **3k**	NMM 6 equiv	74
9[c]		 **3l**	NMM 6 equiv	78
10[e]		 **3m**	Pyridine 3 equiv 0°C	63
11[e]		 **3n**	Pyridine 3 equiv 0°C	65
12[f]	NaN_3	 **3o**	MeCN (0.2 M)	63

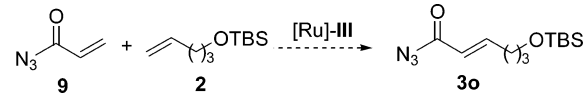
[a] Conditions: [Ru]-**III** catalyst (5 mol %), **2** (1 equiv), **1** (1.5 equiv), CH_2Cl_2 0.2 M, 16 h then nucleophile, quench additive 1 h. [b] Yields of isolated products. [c] 1.6 equiv of amine. [d] 6 equiv of amine. [e] 3 equiv of alcohol 0 °C. [f] Reaction performed in toluene followed by addition of dry MeCN (0.2 M), 3 equiv of NaN_3 (3 equiv), 2 h stirring. NMM = *N*-methylmorpholine. TBS = *tert*-butyldimethylsilyl.

In the case of more valuable amines, 1.6 equiv of amine was added to the reaction media as well as an additive, K_3PO_4 (3.8 equiv)[7] (Table 3, entries 1, 2, 6, and 7[8]). When amine hydrochlorides were used, including Weinreb amine hydrochloride,[9] the best results in substituted acrylamides were obtained when *N*-methylmorpholine was introduced in the reaction media (Table 3, entries 3, 8, and 9).

The CM products resulting from acryloyl chloride **1** and olefin **2** can also be trapped with nucleophiles other than amines such as allylic and propargylic alcohols. The corresponding esters **3m** and **3n** were formed in good yields (63−65%) at 0 °C in the presence of pyridine (Table 3, entries 10 and 11).

Sodium azide is also able to react with intermediate **A** as the azido derivative **3o** was formed in 63% yield (Table 3, entry 12). It is worth noting that **9** is unstable and cannot be used to prepare **3o** (Scheme 2);[10] the latter can be a useful intermediate for the preparation of vinyl isocyanates.[11]

Scheme 2



In conclusion, a very simple one-pot process involving a CM between acryloyl chloride and terminal olefins followed by the addition of nucleophiles leads to a diversity of functionalized α,β-unsaturated carbonyl compounds in good yields. Extension to other nucleophiles and the use of this one-pot sequence to synthesize a library of biologically active compounds is underway in our laboratory and will be reported in due course.

Supporting Information Available: General procedure for the cross-metathesis reactions and ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(10) **12** must be kept in solution; see: Wieber, J. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649.

(11) (a) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735. (b) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413. (c) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443. (d) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185.