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REGIOSELECTIVE SYNTHESIS OF ISOPROPENYL ESTERS BY RUTHENIUM CATALYSED ADDITION OF N-PROTECTED AMINO-ACIDS TO PROPYNE

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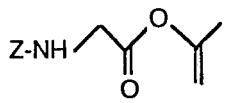
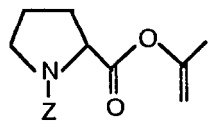
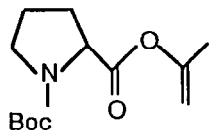
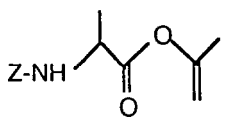
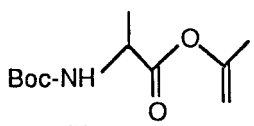
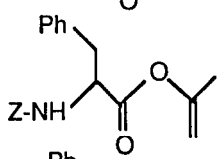
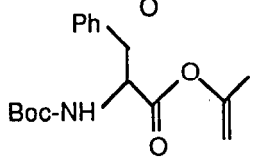
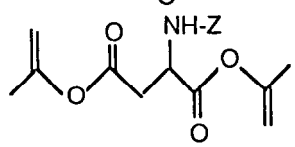
Summary : A general route to isopropenyl esters of N-protected amino-acids is reported, by direct addition of Z-N or Boc-N amino-acids to propyne catalysed by ruthenium(II) complexes; it takes place without racemization. The isopropenyl esters are activated towards amines to afford at 20°C the amide derivatives.

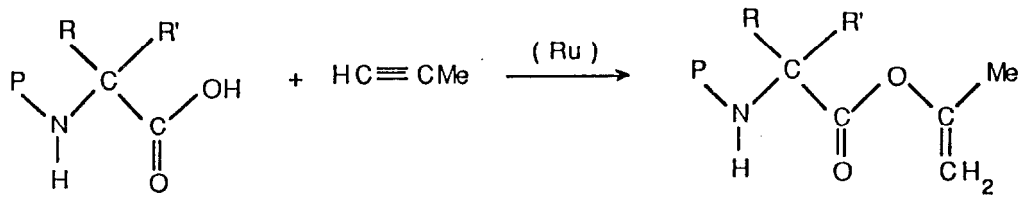
Isopropenyl esters have been used as mild acylating reagents for the selective access to α-pyrones with malonates[1] the protection of amides or imines with acid catalysts[2] and the formation of stearoylbenzene or β-diketones[2]. They also are convenient precursors for carbon-carbon bond formation by coupling with ketones[3] or the introduction of a 2-oxoalkyl group[4]. Isopropenyl esters were previously made either by acid catalysed transesterification of isopropenyl acetate[5] or by addition of carboxylic acids to propyne in the presence of mercury salts[6] or zinc oxide[7] catalysts. The limitations of these syntheses are the parallel formation of anhydride for the first method and, for the second, the moderate yields and toxicity with mercury salts and the drastic conditions (160-180°C, 25-30 bar) required with ZnO. These inconveniences strongly restrict the scope of the use of isopropenyl esters in organic synthesis, especially of the derivatives of optically active carboxylic acids or amino-acids.

In this communication we report a convenient, general synthesis of a variety of isopropenyl esters by regioselective direct addition of N-protected amino-acids to propyne, catalysed by arene-ruthenium-phosphine complexes under mild conditions (100°C, 2-3 bar, 4h). This method arises from our initial study giving evidence for the activation by ruthenium of phenyl and diphenyl acetylene towards carboxylic acids[8].

Table 1 : Synthesis of isopropenyl aminoesters catalysed by $RuCl_2(PPh_3)$(p-cymene) [a]

N-protected α-(L)-aminoacid 1	ester 2	yield % [b]	m.p °C	$[\alpha]_D^{20}$ c=1, EtOH
Z-Gly-OH **a**		76	oil	- -
Z-Pro-OH **b**		84	oil	-58°
Boc-Pro-OH **c**		10	oil	-56°
Z-Ala-OH **d**		63	oil	-34°
Boc-Ala-OH **e**		66	oil	-38°
Z-Phe-OH **f**		68	74-76	-22°
Boc-Phe-OH **g**		64	55-57	-16°
Z-Asp-OH **h**		56	46-48	-22°

a) General conditions: 100°C , 4h
b) Isolated pure product. All compounds have been fully characterized spectrally (IR, NMR) and by high resolution mass spectroscopy.



1 a-h **2 a-h**

P: protecting group Z or Boc; Z : Ph-CH_2-O-C(=O)- Boc : $(H_3C)_3$ C-O-C(=O)-

In a typical experiment, $RuCl_2(PPh_3)(\eta^6$-p-cymene) catalyst (113.6 mg, 0.2 mmol), Z-phenylalanine **1f** (5.98 g, 20 mmol) and dry toluene (20 mL) were successively placed in a 100 mL autoclave. The autoclave was then purged under vacuum, and after cooling (-30°C), propyne gas (30 mmol, 735 mL) was dissolved. The reaction mixture was then stirred at 100°C for 4h. The residual amino-acid **1f** was extracted using $NaHCO_3$ saturated aqueous solution. The solid material which precipitated on evaporation of solvent was recrystallized from a diethyl ether/hexane mixture (1/3) to give ester **2f** as white crystals in 68% yield.

Other isopropenyl esters were obtained in a similar way from N-protected amino-acids **1a-h** (Table I). They were isolated and purified by crystallization (**2f-h**) or by silica-gel chromatography with ether as eluent (**2a-e**).

Under similar conditions the esters of various saturated and unsaturated carboxylic acids such as crotonic, benzoic and aromatic acids were prepared. However, unprotected amino-acids do not add to propyne. The ester formation is restricted to N-protected amino-acids but occurs without deprotection of the amino group and with retention of the optical activity. The hydrolysis of **2b** gives back **1b** with the same optical rotation ($[\alpha]_D$ = -53°) as the starting Z-Proline **1b**. This observation is consistent with the retention of configuration during the transformation 1-2.

The yields and the regioselectivity of the transformation do not depend on the nature of the protecting group (Z or Boc) of the amino-acids (**2d-g**) except in the case of the proline derivatives (**2b, 2c**). Other $RuCl_2(PR_3)$(p-cymene) complexes were used to optimize the reaction, especially in the case of Boc-Pro (**1c**) and show that the catalyst efficiency strongly depends on the nature of the phosphorus ligand: the yields in **2c** (100°C, 10 h), respectively 8% (PPh_3), 26% ($P(OMe)_3$), 30% (PMe_2Ph) and 68% (PMe_3), increase with basic phosphines with a small cone angle.

The activity of isopropenyl esters **2** as mild acylating reagents is shown by their reaction with amine at room temperature, leading to the corresponding optically active amides **3** in good yields (Table II). This reaction shows the potential of isopropenyl esters in peptide synthesis and for the access to amides with pharmacological activity.

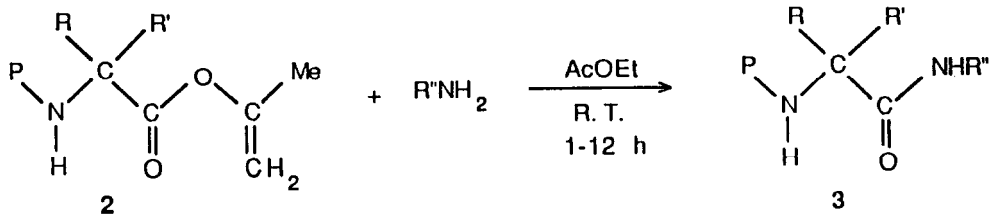
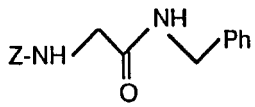
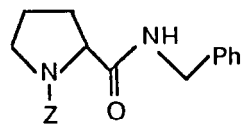
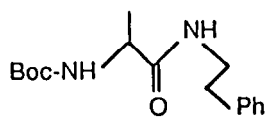


Table II : Preparation of amides [a)]

ester 2	amine	product 3	yield %	m.p. °C	$[\alpha]_D^{20}$
2a	H_2NCH_2Ph		91	113-114	--
2b	H_2NCH_2Ph		77	95-97	-35°
2e	$H_2NCH_2CH_2Ph$		83	77-79	-32°

a) General conditions : isopropenyl ester (10 mmol), amine (12 mmol), AcOEt (10mL), at room temperature.

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