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Microwave assisted hydroaminomethylation of alkenes

Elena Petricci,[a] André Mann,[b] Jessica Salvadori[a] and Maurizio Taddei[a,*]

[a]*Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via A. Moro 2, 53100 Siena, Italy*
[b]*CNRS, Laboratoire de Pharmacochimie de la Communication Cellulaire UMR 7175/LC174, route du Rhin, BP 60024, F-67401 Illkirch Cedex, France*

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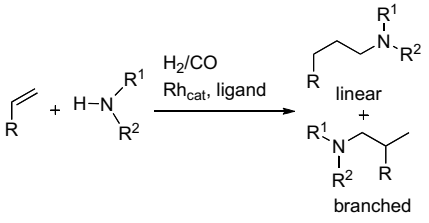
Abstract—Hydroaminomethylation of terminal alkenes can be regioselectively carried out in less than 30 min with secondary amines in EtOH under MW irradiation using $(PPh_3)_3RhCO(H)$ and Xantphos or Biphephos as ligands. When primary amines were employed, the corresponding enamines were obtained in good yields. Tris-benzyl allylglycine was transformed into different (basic) benzylated α-amino acids. Moreover, the benzyl protection was removed in few minutes under MW irradiation with $Pd(OH)_2$ under H_2 atmosphere.

The presence of an amino group in chemical structures is often decisive for biological activity. Indeed many natural compounds or drugs reveal their bioactivity via a basic or a cationic amino function. Therefore several amination reactions have been developed over the years to realize the C–N bond: from the classical N-alkylations to the recent palladium-catalyzed aminations. Amongst the available chemical tactics, the reductive amination is probably the most useful method for the production of a C–N bond.[1] This reaction needs an amine, a hydride and acidic condition for performing the reaction. But if sensitive functional groups are present in the substrate, the acidic conditions may be detrimental. Certainly for practical, economic and environmental considerations new amination protocols are highly desirable especially when the starting materials are easily available.[2] Direct hydroaminomethylation of terminal alkenes may represent an atom-economic approach towards the introduction of the amino group. This cascade reaction (hydroformylation and reductive amination) has the advantage of using a gaseous mixture (CO/H_2) in presence of an amine: the olefin is converted to an aldehyde that subsequently become an enamine (or imine) ready for in situ hydrogenation. The process is orchestrated by Rh(I) as catalyst.[3] Probably the practicality of this reaction, originally discovered by Reppe and Kindler,[4] is underestimated by the organic chemists. Indeed a body of few synthetic applications have been reported by the groups of Eilbracht,[5] Beller[6] and Breit.[7] Standard hydroaminomethylation is carried out always in the presence of a rhodium catalyst and under a pressure of H_2/CO higher than 400 psi for more than 12 h. The regioselectivity of the reaction towards the linear or the branched isomer (ratio l/br) is set in the hydroformylation step.

The choice of the ligand and, in some cases, of the substrates are decisive for directing the l/br ratio (Scheme 1). Recently, hydroformylation has considerably extended its potential by the assistance of microwaves. We reported that hydroformylation of 1-octene to the corresponding nonanal can be carried out in 4 min at 110 °C and under 40 psi of syngas (H_2/CO 1/1) using a commercially available microwave synthetizer.[8] As a consequence, the time required for this chemical transformation is considerably shortened. New possibilities



Scheme 1. General scheme for hydroaminomethylation of terminal alkenes.

Keywords: Microwaves; Hydroformylation; Amine; Amino acids; Deprotection.
* Corresponding author. Tel.: +39 0577 234280; fax: +39 0577 234275; e-mail: taddei.m@unisi.it

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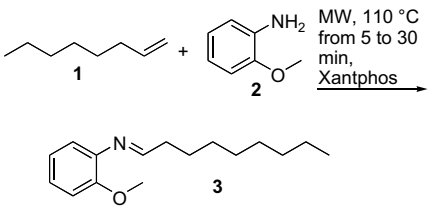
Table 1. Exploration of reaction conditions

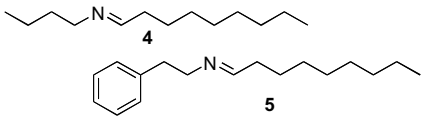


Cat.	Solvent	CO/H_2(psi)	Yield (%)
$(PPh_3)_3RhCO(H)$	Toluene (0.04 M sol. of [bmim][BF_4])	1: 1 (100)	90
$(PPh_3)_3RhCO(H)$	THF (0.04 M sol. of [bmim][BF_4])	1: 1 (100)	85
$(PPh_3)_3RhCO(H)$	EtOH	1: 1 (100)	95
$(PPh_3)_3RhCO(H)$	Toluene (0.04 M sol. of [bmim][BF_4])	2: 1 (100)	90
$(PPh_3)_3RhCO(H)$	[bmim][BF_4]	1: 1 (100)	0
$Rh(acac)(CO)_2$	Toluene (0.04 M sol. of [bmim][BF_4])	1: 1 (100)	85

are thus available for rapid screenings of novel conditions. Therefore we decided to investigate the possibility of carrying out hydroaminomethylation under microwave irradiation.

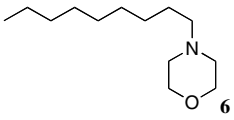
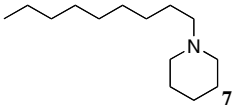
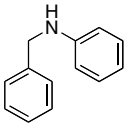
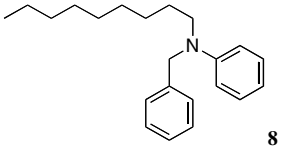
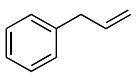
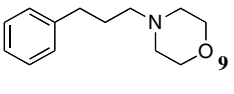
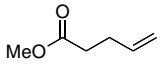
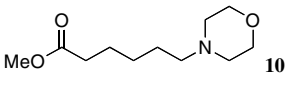
Based on our previous experience with hydroformylation, the reaction of 1-octene (**1**) with *o*-anisidine (**2**) was choosen as a model system to investigate various experimental conditions (Table 1). Our previous conditions ($Rh(PPh_3)_3HCO$, Xantphos[9a] as ligand, toluene containing small amounts of [bmim][BF_4],[9b] 110 °C, 40 psi of syngas for periods ranging from 4 to 25 min) gave exclusively imine **3** as the main product.

Changes in the nature of the solvent, catalyst or increase in the pressure of H_2 had no effect on the nature of the reaction product, as imine **3** was always formed in very good yields. Remarkably, in no case we observe the formation of the branched isomer (NMR, 200 MHz). The change in the nature of the ligands (Biphephos instead of Xantphos) produced a more complex mixture where compound **3** was present together with starting material. Analogously, other primary amines such a butylamine or phenethylamine gave, respectively, the corresponding imines **4** and **5** as products under these reaction conditions (Scheme 2).[10]



Scheme 2. Products of the reaction of 1-octene with primary amines.

Table 2. Hydroaminomethylation of terminal alkenes with secondary amines

Entry	Alkene	Amine	Product	Temperature, time, syngas pressure	Yield[a] (%)
1	1-Octene		 **6**	110 °C, 10 min, 90 psi	90
2	1-Octene		 **7**	110 °C, 10 min, 90 psi	89
3	1-Octene		 **8**	110 °C, 40 min, 90 psi	55
4			 **9**	110 °C, 20 min, 90 psi	90
5			 **10**	110 °C, 20 min, 90 psi	60

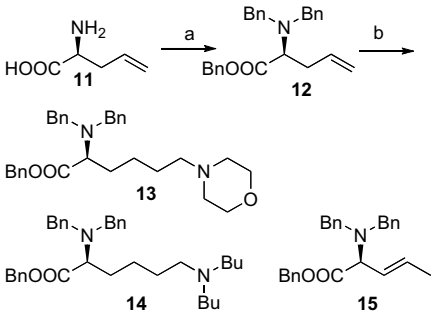
[a] Isolated yields.

Then a mixture of 1-octene and morpholine was submitted to hydrofomylation. After 10 min of irradiation at 110 °C (H_2/CO 100 psi) in toluene (0.04 M solution of [bmim][BF_4]) with (PPh_3)$_3$RhCO(H)/Xantphos as catalyst, the corresponding enamine was obtained (90% yield). Using EtOH as the solvent, a mixture of the enamine and the amine was obtained after 5 min at 110 °C. Increasing the MW irradiation time to 10 min amine **6** was exclusively formed in 89% yield (Table 2, entry 1).[1] Other secondary amines were submitted to the same procedure and the corresponding tertiary amines were obtained in very good yields without the formation of the branched isomers.[11]

In order to obtain useful building blocks for the preparation of biologically active molecules, we decided to investigate the hydroaminomethylation of allylglycine (**11**). This compound, commercially available in enatiomerically pure form, has been used as the starting material for the synthesis of natural and non-natural amino acids.[12] Suitably protected allylglycine has been transformed via metathesis into unsaturated amino acids[13] employed for natural product synthesis.

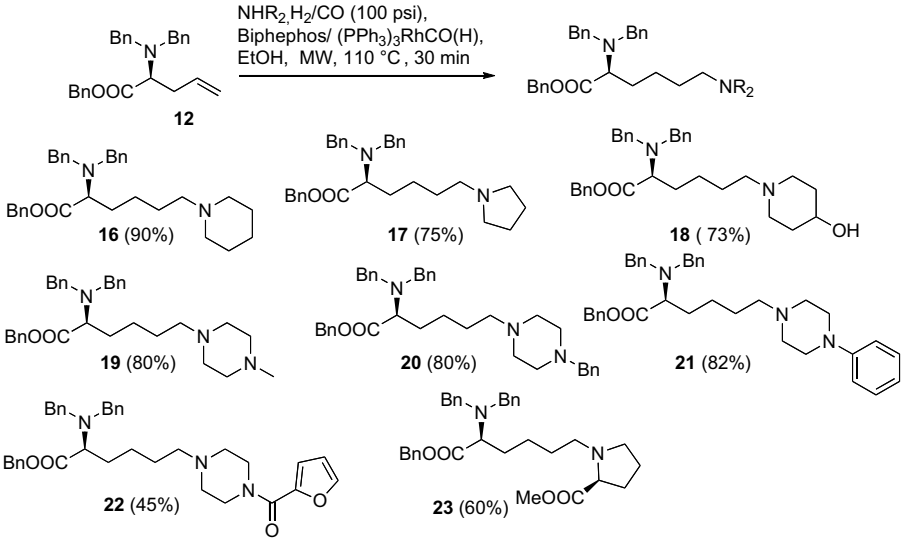
To avoid intramolecular reaction between the amino residue and the transient aldehyde produced during the hydrofomylation, we decided to protect allylglycine as the tris-benzyl derivative **12** by direct benzylation of allylglycine with benzyl bromide NaOH/Na_2CO_3.[14] This compound was submitted to MW assisted reaction with H_2/CO and morpholine in EtOH in the presence of (PPh_3)$_3$RhCO(H)/Xantphos as the catalyst and product **13** was obtained after 10 min of irradiation at 110 °C in 94% yield (Scheme 3).

However, when the same procedure was applied to **12** using *N*,*N*-dibutylamine, a very low yield of the expected aminomethylated product **14** was obtained. The major compound was **15** produced by isomerization of the double bond during the reaction (Scheme 3). In the search of more effective reaction conditions, we experimented Biphephos[15] as the ligand and found that reaction with *N*,*N*-dibutylamine gave **14** in 45%. Consequently, tris-benzylated allylglycine **12** was reacted with a large variety of secondary amines in EtOH. Using (PPh_3)$_3$RhCO(H)/Biphephos as the catalyst system, after MW irradiation for 20–30 min at 110 °C, the corresponding benzylated α-amino acids **16**–**23** (Scheme 4) were obtained in good yields.[16] The reaction was compatible with different functional groups allowing the introduction of diverse basic moieties in the side chain of the amino acid scaffold.

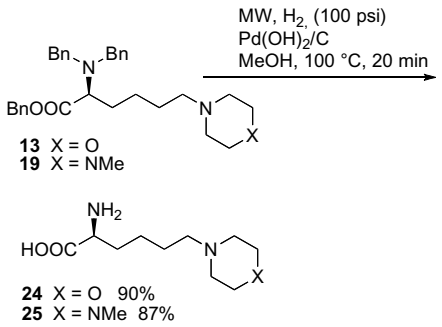


Scheme 3. Reagents and conditions: (a) BnBr, NaOH, Na_2CO_3, H_2O, reflux 1 h, 85%; (b) H_2/CO 1/1, 100 psi, morpholine, (PPh_3)$_3$-RhCO(H)/Xantphos, EtOH, MW, 110 °C, 10 min, 94%.

Deprotection of these benzylated α-amino acids could be carried out under microwave irradiation. When compounds **13** and **19** in methanolic solution were submitted to 100 psi of H_2 in the presence of $Pd(OH)_2$/C as the catalyst, to MW irradiation for 20 min at 80 °C, the free amino acids **24** and **25** (Scheme 5) were isolated in very good yields.[17] These compounds can be manipulated in order to obtain the amino acid in a suitable form for peptide synthesis.



Scheme 4. Preparation of an array of functionalized benzylated α-amino acids.



Scheme 5. MW assisted hydrogenolysis.

In conclusion, we have demonstrated that hydroaminomethylation of alkenes can be carried out in short time with a commercially available MW apparatus and that hydrogenolysis of benzylamines and benzyl esters can be accelerated under MW irradiation. Several new substituted α-amino acids were obtained from allylglycine using this approach.

Acknowledgements

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16. In a typical experiment, a secondary amine (1 mmol) and allylglycine **12** (1 mmol) were dissolved in dry EtOH (2 mL). $(PPh_3)_3Rh(CO)H$ (18 mg, 0.02 mmol) and Biphephos (63 mg, 0.08 mmol) were added. The yellow solution obtained was submitted to pressurized syngas at 90 psi (6 atm) and heated for 30 min at 110 °C by microwave irradiation at 150 W (value previously settled on the microwave oven). The flask was cooled and the internal gas released. The reaction mixture was evaporated in vacuo and the yellow oil obtained was purified by flash chromatography.
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