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How to Control the Chemoselectivity of the Catalytic Formation of Chiral γ-Lactams or 2,3-Disubstituted Pyrroles by the Choice of Solvent

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Summary. The reaction of the unsaturated imine methyl(3-phenylallylidene)amine with ethylene and carbon monoxide in the presence of catalytical amounts of $Ru_3(CO)_{12}$ leads to the formation of two heterocyclic products. One of the products is a chiral γ-lactam, the other one a 2,3-disubstituted pyrrole derivative, in which only the carbon atom from carbon monoxide is incorporated. The selectivity in the formation of the products may be controlled by the choice of solvent. In general, in nonpolar solvents the formation of the lactam is preferred whereas the use of more polar solvents enhances the yield of the pyrrole. For most of the solvents used there is a linear dependence of the product ratio on the relative permittivity of the corresponding solvent. Typically, polar aprotic solvents do not follow this rule.

Keywords. C–H Activation; Ruthenium; Lactams; Pyrroles; Solvent effects.

Introduction

Catalytic transformations proceeding *via* the activation of C–H bonds have been intensively studied during the last years due to their inherent atom economy as well as due to the possibility to omit several synthetic steps, i.e. the synthesis of intermediates like halogenated compounds [1–4]. Following the pioneering work of *Murai et al.* started with their report on the alkylation of aromatic ketones with olefins in the presence of ruthenium catalysts [5], a number of reports have been published in which substrates with an additional coordinating site like keto or imine functions or heteroatoms are catalytically treated with alkenes, alkynes, carbon monoxide, isocyanides, and other suitable substrates [1–4].

Recently, we reported the synthesis of chiral γ-lactams in a catalytic three-component reaction from α,β-unsaturated imines, alkenes, and carbon monoxide (Fig. 1) [6–12]. The formation of the lactams obviously proceeds *via* the activation of the C–H bond in β-position with respect to the imine double bond. A cyclisation reaction then produces the lactam ring, which is further modified by another insertion reaction of the alkene into the C–H bond at C-3 of the lactam. Several ideas proposing a mechanism of the lactam formation following this reaction sequence have been proposed [6, 10, 13]. Nevertheless, the reaction mechanism still is not confirmed in detail by experimental means or by high level theoretical calculations although it has been concluded from deuteration experiments that the C–H activation step is not the rate determining elementary step of the reaction sequence [13]. It is therefore reasonable that the rate determining step is either related to the formation of the new carbon carbon bond between the β-carbon of the imine and one of the carbon monoxide ligands or to the formation of the five-membered ring system.

The reaction produces a new stereogenic center at C-3 and is therefore a potentially useful method of synthesising chiral non-natural amino acid derivatives. We have already shown that the reaction can be optimised to be completely diastereoselective

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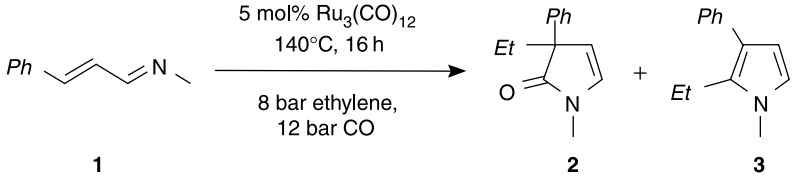

Fig. 1. Synthesis of **2** and **3**

using chiral amines as the substrates [9]. If no alkene is present in the reaction mixture the 1,3-dihydropyrrolone is only supposed to be an intermediate in the reaction pathway since it readily tautomerises to give the more stable 1,5-dihydro-pyrrolone [14].

Results and Discussion

We also recognised that 2,3-disubstituted pyrrole derivatives are formed as by-products in minor amounts [10]. From experiments with ^{13}CO we were able to show that during the formation of the pyrrole the substrate carbon monoxide is split so that only the carbon atom is incorporated into the heterocyclic compound (C-2). The oxygen atom is transferred to another molecule of carbon monoxide leading to the observation of carbon dioxide in an amount being equimolar to the amount of pyrrole formed [10].

The only substrate leading to an increased yield (20%) of the pyrrole derivative was the reaction of methyl(3-phenylallylidene)amine (**1**), which is derived from cinnamaldehyde and methylamine [10]. The formation, purification, and spectroscopic properties of the corresponding lactam **2** and the pyrrole derivative **3** have already been described by some of us [10]. In this report we will focus on the solvent dependency of this catalytic reaction allowing to switch between a reaction being perfectly selective in terms of the formation of the lactam **2** to reactions in which the yield of **3** is increased to 64% just by the choice of the appropriate solvent.

The lactam/pyrrole ratio is easily obtained by ^1H NMR spectroscopy of the crude reaction mixture. The two protons at C-4 and C-5 of the lactam or the pyrrole each give rise to a dublett in the NMR spectrum. The two dubletts arising from **2** are observed at 5.64 and 6.48 ppm ($^3J_{HH} = 5$ Hz) whereas the pyrrole **3** shows the corresponding resonances at 6.23 and 6.57 ppm ($^3J_{HH} = 2.8$ Hz) [10]. Table 1 shows the product ratio of the catalyzed reaction

Table 1. Solvent dependence of the lactam/pyrrole ratio

Solvent	Yield of **2**/%	Yield of **3**/%	ε_R [15]
acetone	58.1	41.9	20.56
acetonitrile	89.3	10.7	35.94
diethylether	86.6	13.4	4.20
THF	88.5	11.5	7.58
DMSO	58.4	41.6	46.45
DMF	83.6	16.4	36.71
methanol	35.9	64.1	32.66
ethanol	84.2	15.8	24.55
2-propanol	63.2	36.8	19.92
n-pentane	100	0	1.84
n-hexane	100	0	1.88
cyclohexane	89.2	10.8	2.02
pyridine	76.7	23.3	12.91
benzene	91.0	9.0	2.27
toluene	90.9	9.1	2.38

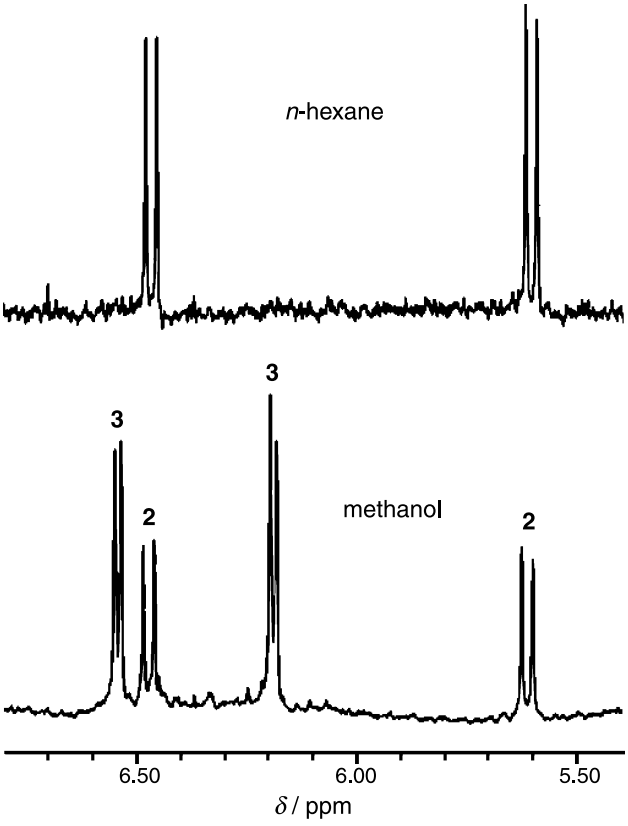

Fig. 2. ^1H NMR signals corresponding to the protons at C-4 and C-5 of **2** and **3** produced in different solvents

performed in different solvents. In each case the completeness of the reaction was shown by the fact that the typical resonances of the imine proton of **1** were missing in the spectrum. In addition, in no case hydrolysis of the imine resulting in the formation of cinnamaldehyde was observed. Figure 2 shows the relevant sections of the ^{1}H NMR spectra of the crude reaction mixtures if either *n*-hexane or methanol were used as the solvents. The former reaction leads to the exclusive formation of **2**, whereas the use of methanol produces a mixture of **2** and **3** in an approximate 1:2 ratio.

The results of fifteen different solvents are summarized in Table 1. It is obvious that the ratio of products formed in the catalytic reactions highly depends on the solvent used. Very unpolar solvents as hydrocarbons produce **2** in high yields or even quantitatively. More polar solvents lead to the formation of higher amounts of **3** with the yield of **3** being the highest if the reaction is carried out in methanol. The use of deoxygenated water as the solvent does not lead to the formation of either **2** or **3** although no cinnamaldehyde is produced also. If dichloromethane is used as the solvent again neither **2** nor **3** are detectable in the ^{1}H NMR spectrum, but from MS measurements it becomes evident that carbon monoxide or ethylene are inserted more than once, most probably also at C-1 and C-2 of the imine chain. Unfortunately, we were not able to isolate this product up to now since in addition polyethylene and ethylene oligomers are formed from which it is very difficult to separate.

In Fig. 3 the yields of **3** *vs.* the relative permittivities (dielectric constants) of the corresponding solvents [15] are depicted. From this figure it can be concluded that there is a linear dependency of the product ratio from ε_R if nonpolar and polar protic solvents are taken into account (with the exception of ethanol) whereas the use of polar aprotic solvents leads to a different behaviour. Some of us have already demonstrated that C-2 of the pyrrole **3** originates from carbon monoxide and that in the catalytic reaction the same stoichiometric amounts of carbon dioxide and **3** are produced. From the results presented in this work we therefore assume that the transfer of oxygen from one carbon monoxide to another may be favoured by a more polar environment.

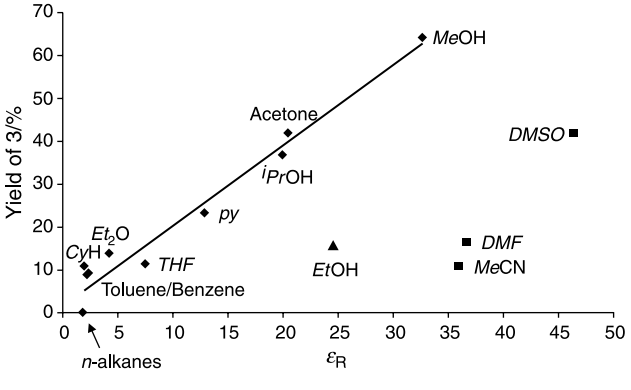

Fig. 3. Solvent dependence of the catalytic reaction

In conclusion, the observed solvent dependency of the catalytic reaction of imines with carbon monoxide and ethylene should therefore lead to the possibility of selectively switching between the two reaction channels producing different types of heterocyclic compounds. We will therefore focus our attention on the use of ionic liquids as solvents of this catalytic reactions, which should give access to aprotic solvents with higher relative permittivities than methanol.

Experimental

Infrared spectra were recorded on a Perkin Elmer FT-IR System 2000 using 0.2 mm KBr cuvettes. Mass spectra were recorded on a Finnigan MAT SSQ 710 instrument. NMR spectra were recorded on a Bruker AC 200 spectrometer (^{1}H: 200 MHz, ^{13}C: 50.32 MHz, $CDCl_3$ as internal standard).

Experimental Procedures

In a typical reaction a 50 cm^3 autoclave charged with 145 mg (1 mmol) methyl(3-phenylallylidene)amine, 19 mg (0.03 mmol) $Ru_3(CO)_{12}$ and 5 cm^3 of the corresponding solvent was pressurized with carbon monoxide (12 bar) and ethene (8 bar) and heated at 145°C overnight. After the reaction mixture was cooled to room temperature it was transferred to a *Schlenk* tube and all volatile material was removed under reduced pressure. The remaining oily residue was used to determine the yields of the products **2** and **3** by NMR spectroscopy.

Acknowledgements

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