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COMMUNICATION

Ruthenium-catalyzed synthesis of vinylamides at low acetylene pressure

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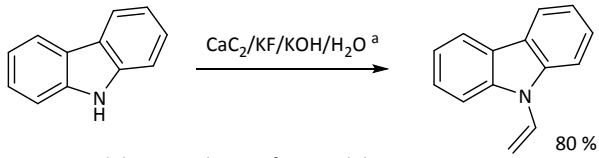
The reaction of cyclic amides with acetylene under low pressure, using ruthenium-phosphine catalysts, afforded a broad variety of *N*-vinylated amides including (azabicyclic) lactams, oxazolidinones, benzoisoxazolones, isoindolinones, quinoxalinones, oxazinanones, cyclic urea derivatives (imidazolidinones), nucleobases (thymine), amino acid anhydrides and thiazolidinone.

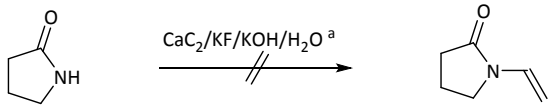
Vinylamides are widely used as monomers in polymerization processes[1], for example *N*-vinylpyrrolidone (NVP) for the synthesis of the water-soluble copolymers.[2-3] The copolymers obtained by polymerizing *N*-vinyl lactams are used as solubilizers of poorly water soluble bioactive substances for cosmetic or pharmaceutical industry.[3] They are also compatible with biological systems, nontoxic, stable within a wide pH range, and soluble in hydrophilic as well as lipophilic systems.[4] *N*-Vinyl-5-methyloxazolidinone (VMOX) is of particular interest to the printing industry due to its copolymerization with acrylates and excellent adhesion on all common substrates.[5-7]
Already in 1939, Reppe *et al.* showed that the reaction of amides with acetylene under pressure and in the presence of strong bases gives variety of *N*-vinyl compounds. Despite the well-developed Reppe approach for the vinylation of a wide range of substrates, there are some limitations due to the sensitivity of the starting materials or products towards harsh conditions, such as high temperature, pressure and/or basic environment. For example, the synthesis of vinyl oxazolidinone suffers from the basic conditions due to the instability of the starting material 2-oxazolidinone and, therefore, requires an alternative synthesis which includes several synthetic steps.[8-11] Hence, developing a new approach towards direct *N*-vinylation of amides is still an alluring and challenging task.
Today, only three processes remain for the commercial production of acetylene: the calcium carbide route, in which the carbide is produced electrically, the arc process, and the partial oxidation of natural gas.[12-13] The acetylene production method depends on availability and cost of the raw material in each particular region. Calcium carbide can act as a solid acetylene source and there are several reports where it was applied in the vinylation process of *N*- and *O*-nucleophiles (Scheme 1, A).[14-17] Nevertheless, the aforementioned system is hardly applicable on the industrial scale due to necessity for a stoichiometric amount of potassium fluoride as an additive. Moreover, the process requires potassium hydroxide which would cause the same incompatibility towards sensitive substrates. A preliminary testing of the vinylation reaction of 2-pyrrolidinone by means of the CaC_2 method gave a complex mixture without formation of the desired product (Scheme 1, B)

Scheme 1. Use of CaC_2 for direct vinylation

A: Direct vinylation of cyclic amines (Ananikov *et al*., *Molecules*, **2018**)



B: Attempted direct vinylation of 2-pyrrolidinone



Not formed

[a] CaC_2 (2.0 equiv), KF (1.0 equiv), KOH (1.1 equiv), H_2O (4.0 equiv), DMSO, 130˚C, 4 h (*Ref. 16*)

The vinylation process with gaseous acetylene under high pressure has its drawbacks, such as the need for sophisticated and costly highly pressure tolerance equipment which should be designed for the pressure of approx. 12 times the working pressure of acetylene.[18] Acetylene is also prone to dissociate or decompose into its elements spontaneously whenever its pressure reaches 2 bar at elevated temperature, in addition to forming explosive mixtures with air and other gases, hence, the strict safety requirements must be satisfied.[19] Therefore, the operation of vinylation reactions under low pressure of acetylene will facilitate the utilization of less costly equipment as well as simplifying the process.
A metal-catalyzed nucleophilic addition across an alkyne bond is a synthetically important reaction offering an atom-economic route to a diverse range of compounds.[1] Previously, Gooßen *et al.* reported a Ru-based homogeneous catalytic system for the addition of terminal alkynes to nitrogen containing nucleophiles such as secondary amides and imides leading to the formation of anti-Markovnikov products.[20-27] To the best of our knowledge, the aforementioned catalytic system has not been

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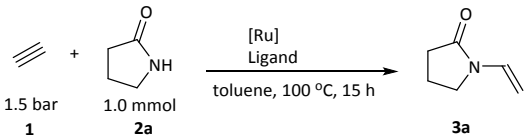
applied for the addition of *N*-nucleophiles to acetylene. Often the well-developed reactions for substituted alkynes are not applicable to ethyne due to its facile di-/tri-/polymerisation in the presence of transition metal catalysts.[28-31] However, we were pleased to find that the aforementioned Ru-based system is catalyzing the addition of lactams and other *N*-nucleophiles under low acetylene pressure of 1.5 bar. The absence of a strong base as required for typical Reppe synthesis makes this system applicable for broad range of *N*-nucleophiles.

The previously reported catalyst system formed in situ from 1,5-cyclooctadienebis(2-methallyl)ruthenium [Ru(COD)(met)$_2$] (COD = 1,5-cyclooctadiene, met = methallyl), P(*n*Bu)$_3$ (tributylphosphine) and DMAP (*N*,*N*-Dimethylpyridin-4-amine) for the vinylation of 2-pyrrolidinone **2a** in toluene at 100 °C and at 1.5 bar acetylene pressure led to the full conversion of the starting material and high isolated yield of the desired product **3a** (Table 1, entry 1).[23] Further optimization of reaction condition revealed that the addition of DMAP has not a crucial impact on the reaction outcome (Table 1, entry 2). The analysis of the crude reaction mixtures by ICP MS from both aforementioned experiments showed that about 100% of the used Ruthenium remains in the filtered crude reaction solution. This indicates that the catalyst is not precipitating as ruthenium-black during the reaction (see ESI, S2). Additionally, the utilization of ruthenium on charcoal (Ru/C), a typical heterogeneous catalyst, did not provide the desired vinylated substrate. (Table 1, entry 3).[32] Next, we investigated the ligand scope including mono-, bi- and tridentate phosphines as well as NHC ligands using a ChemSpeed Screening Robot (see ESI, S3). Among all the investigated ligands, P(*n*Bu)$_3$, P(*n*Oct)$_3$ and PCy$_3$ gave the best conversion within the parallel run. These selected ligands then were tested in independent autoclave runs and the obtained results were in agreement with the results of the initial screening (see ESI, S3). Moreover, the use of PPh$_3$ as a ligand gave full conversion of starting **2a** (Table 1, entry 4), however, when it was applied to 5-methyloxazolidinone **2b**, the conversion dropped to 20 % (see ESI, S3). Furthermore, several different Ru sources including ruthenium(III) chloride hydrate (RuCl$_3$·3H$_2$O), ruthenium(III) acetylacetonate (Ru(acac)$_3$), triruthenium dodecacarbonyl (Ru$_3$(CO)$_{12}$) as well as [Ru(COD)(met)$_2$] were tested in the absence of phosphine ligand, resulting in zero or poor reactivity towards the desired **3a** (Table 1, entries 5-8). Also, adding solely tributylphosphine does not lead to product formation (Table 1, entry 9). Lowering the amount of [Ru(COD)(met)$_2$] to 1 mol % and P(*n*Bu)$_3$ to 5 mol% still gave a high conversion of 95%, but further decrease of the catalyst loading causes a drop in conversion (Table 1, entries 10 and 11, respectively). Interestingly, the reaction of 2-pyrrolidinone **2a** with acetylene in the presence of 2 mol% [Ru(COD)(met)$_2$] and 10 mol% P(*n*Bu)$_3$ without solvent afforded a very good conversion of 95% to product **3a** what makes a room for the vinylation of the liquid cyclic amides in the solvent-free manner (Table 1, entry 12).

The direct vinylation of 5-methyloxazolidinone **2b** and caprolactam **2c** using the best optimized conditions successfully afforded VMOX **3b** and *N*-vinylcaprolactam (NVC) **3c** in a good isolated yield of 84% and 80%, respectively. Together with NVP **2a**, VMOX **2b** and NVC **2c** are of particular interest for our current research due to their various industrial applications (*vide supra*).

Table 1: Optimization of the reaction conditions [a]



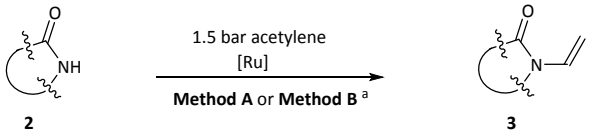
Entry	[Ru] (mol%)	Ligand (mol%)	Conversion of **2** [b] (isolated yield, %)
1	[Ru(COD)(met)$_2$] (2)	P(*n*Bu$_3$) (10)	100 (89)
2 [c]	[Ru(COD)(met)$_2$] (2)	P(*n*Bu$_3$) (10)	100
3	Ru/C (2)	-	< 1
4	[Ru(COD)(met)$_2$] (2)	PPh$_3$ (10)	100
5	RuCl$_3$·3H$_2$O (2)	-	5
6	Ru(acac)$_3$ (2)	-	0
7	Ru$_3$(CO)$_{12}$ (2)	-	8
8	[Ru(COD)(met)$_2$] (2)	-	< 1
9	-	P(*n*Bu$_3$) (10)	0
10	[Ru(COD)(met)$_2$] (1)	P(*n*Bu$_3$) (5)	95 (78)
11	[Ru(COD)(met)$_2$] (0.1)	P(*n*Bu$_3$) (0.5)	30 (26)
12 [d]	[Ru(COD)(met)$_2$] (2)	P(*n*Bu$_3$) (10)	95

[a] Reactions were set up in the glove box under argon atmosphere. [b] Determined by GC area. [c] 4 mol% DMAP was used as an additive. [d] 5.88 mmol **2a**, without solvent.

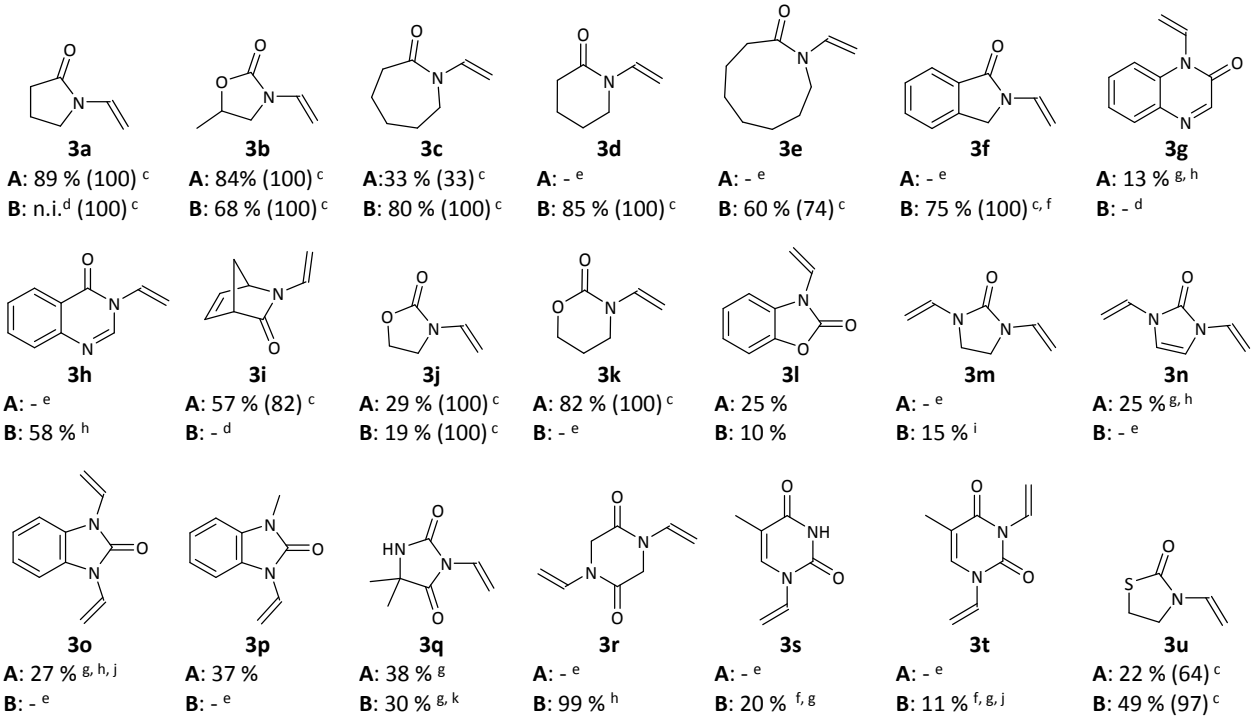
Further, we investigated the reaction scope of the optimized protocol by applying it to the vinylation of various other *N*-nucleophiles (see Table 2 and ESI, S3). DMF was used as a solvent for some substrate to increase solubility. In order to get a full conversion of less reactive nucleophiles, such as **2g**, **2n**, **2o**, **2q**, **2s**, **2t**, the catalyst load together with the reaction temperature were varied giving no significant improvements. Only starting materials together with unidentified side products were observed in the crude reaction mixtures. In some cases, the low yield despite a full conversion could be explained by instability of vinylated substrates which are prone to polymerization (Table 2, **3j** and **3u**). The role of DMAP addition could be traced in a few cases. For example, when the vinylation of oxazolidinone **3j** was performed in absence of DMAP, the isolated yield was 10% higher compared to the reaction with DMAP (Table 2, **3j**). In case of caprolactam **2c** and thiazolan-2-one **2u** the addition of DMAP doubled the conversion and the overall yield of the desired products **3** (Table 2, **3c** and **3u**). Vinylation of imidazolidinones gives divinylated products in moderate yields (Table 2, **3m**, **3n**, **3o**). When hydantoins were treated with acetylene only monovinylated products were observed, presumably having the structure as reported in the table 2 (for 5,5-dimethylhydantoin **2q**: see Table 2, **3q**; for hydantoin **2v**: see ESI, S4, S8, S9, **3v**). Vinylation of glycine anhydride provided the divinylated piperazinedione **3r** in a high yield of 99%. *N*-Vinylpyrimidinones are valuable building blocks for the synthesis of oligonucleotides and polymeric analogues of nucleic acid and nucleosides.[33] The synthesis of such

pyrimidinones includes a multistep procedure with a low overall yield.[34-35] Here we report a direct vinylation of thymine **2s** under the described conditions. Due to low solubility of the substrate in toluene, the reaction was performed in DMF at 150 °C. A monovinylated product **3s** was obtained as the major substrate in 20% yield with a traces of the divinylated **3t** also detected (Table 2).[36] When the catalyst loading was increased, the divinylated thymine **3t** was isolated as a major product, although in low yield of 11% (Table 2). In addition, the direct vinylation of bicyclic γ-lactam 2-azabicyclo(2.2.1)-hept-5-en-3-one **2i** afforded the vinylated product **3i** in a good yield of 57 %. It is worth noting, that the aforementioned γ-lactam, also known as Vince lactam, act as a key intermediate for the synthesis of nucleosides with medicinal applications.[37]. To the best of our knowledge, the only one synthetic route to bicyclic lactam **3i** available in the literature employs a large excess of vinyl acetate, is.[38] To summarize, the reported catalytic system works efficiently for small ring size lactams, including substrates with fused aromatic rings and bicyclic γ-lactams, as well as for oxazolidinones and oxazinanones. The optimized conditions for the desired targets **3a-c** provide a lower activity for the vinylation of substrates bearing cyclic imide and imidazolidon functionality. Nevertheless, the reaction conditions could be further optimized for particular substrates of potential interest. Additionally, the catalytic system has limitations towards the vinylation of several different substrate types (See ESI, S5). For example, acyclic amides including formamide, *N*-methylformamide, *N*-methylacetamide and *N*-methylbenzamide, lactams with a larger ring size (C_{12}), cyclic and acyclic amines, imidazole, as well as *O*-nucleophiles were not giving the vinylated products (See ESI, S5). Previously, mechanistic investigations on the Ru-catalyzed hydroamidation of terminal alkynes were performed by Niedner-Schatteburg´s and Gooßen´s research groups.[39] The path, consisting of an oxidative addition of the amide, followed by insertion of an alkyne into a ruthenium-hydride bond, rearrangement to a vinylidene species, nucleophilic attack of the amide, and elimination to the product, was proposed. Our preliminary tests support the path above, however, further evaluation of the mechanism of this ruthenium-catalyzed vinylation and the influence of nucleophile structures are in progress and would be beyond the scope of this communication.

Table 2: Scope of the vinylation reaction [a, b]



2 3



3a	3b	3c	3d	3e	3f	3g
A: 89 % (100) [c]	**A**: 84% (100) [c]	**A**:33 % (33) [c]	**A**: - [e]	**A**: - [e]	**A**: - [e]	**A**: 13 % [g, h]
B: n.i.[d] (100) [c]	**B**: 68 % (100) [c]	**B**: 80 % (100) [c]	**B**: 85 % (100) [c]	**B**: 60 % (74) [c]	**B**: 75 % (100) [c, f]	**B**: - [d]

3h	3i	3j	3k	3l	3m	3n
A: - [e]	**A**: 57 % (82) [c]	**A**: 29 % (100) [c]	**A**: 82 % (100) [c]	**A**: 25 %	**A**: - [e]	**A**: 25 % [g, h]
B: 58 % [h]	**B**: - [d]	**B**: 19 % (100) [c]	**B**: - [e]	**B**: 10 %	**B**: 15 % [i]	**B**: - [e]

3o	3p	3q	3r	3s	3t	3u
A: 27 % [g, h, j]	**A**: 37 %	**A**: 38 % [g]	**A**: - [e]	**A**: - [e]	**A**: - [e]	**A**: 22 % (64) [c]
B: - [e]	**B**: - [e]	**B**: 30 % [g, k]	**B**: 99 % [h]	**B**: 20 % [f, g]	**B**: 11 % [f, g, j]	**B**: 49 % (97) [c]

[a] **Method A**: 1.0 mmol **2**, 2 mol% $[Ru(COD)(met)_2]$, 10 mol% P(*n*Bu)$_3$, 5 mL toluene, 100 °C, 15 h. **Method B**: 1 mmol **2**, 2 mol% $[Ru(COD)(met)_2]$, 6 mol% P(*n*Bu)$_3$, 4 mol% DMAP, 5 mL toluene, 100 °C, 15 h. [b] Purification by column chromatography, isolated yield %. [c] Conversion of starting material to product determined by GC analysis of the crude reaction mixture. [d] Not isolated. [e] The method was not applied for this substrate. [f] Reaction was performed at 150 °C. [g] Reaction was performed in DMF. [h] Reaction was performed at 140 °C. [i] Reaction was performed at 120 °C. [j] 6 mol% $[Ru(COD)(met)_2]$, 18 mol% P(*n*Bu)$_3$. [k] Reaction was performed at 130 °C.

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Additionally, simple $RuCl_3$ could be used as the metal source for the direct vinylation of 5-methyloxazolidinone **2b** affording full conversion to the product **3b** (see ESI, S6). After a brief optimization of the reaction conditions it was found that the best result is achieved by using 6 mol% of $RuCl_3$ hydrate and 12% of P(*n*Bu)$_3$ in toluene at 100 °C. Notably, the addition of DMAP led to a decrease of the conversion of product **3b** while the use of PPh_3 afforded zero product formation (see ESI, S6). $RuCl_3$ would give an economical advantage due to the inexpensiveness of the ruthenium source.

Conclusion

In conclusion, here we reported for the first time the use of acetylene under low pressure for one step vinylation of different cyclic *N*-nucleophiles, affording a broad scope of *N*-vinyl amides of high industrial interest. Additionally, the reported catalytic system has a great advantage for preparative application due to its suitability for an expanded range of *N*-nucleophiles, which are often not compatible with the harsh reaction conditions of standard Reppe chemistry. Among the synthesis of the commercially important *N*-vinylated compounds (**3a**, **3b**, **3c**), a number of new substrates with potential application as a versatile synthetic building blocks were prepared (**3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3l**, **3m**, **3n**, **3o**, **3p**, **3r**, **3u**).

Conflicts of interest

A patent application from the same authors on this topic was also filed (EP 19218545.2)

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