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Zirconium-catalysed *N*-acylation of lactams using unactivated carboxylic acids

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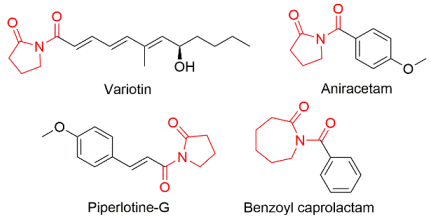
ABSTRACT

A large number of chemicals including surfactants, nootropic drugs and pesticides contain an *N*-acylated lactam moiety in their molecular structure. In this work, the direct, catalytic *N*-acylation of a number of lactams with various unactivated carboxylic acids is reported. Several Lewis acid catalysts were evaluated for their activity in the *N*-acylation of pyroglutamic acid methyl ester with palmitic acid; the highest activities were observed for zirconium-based catalysts. Yields of up to 97% were obtained utilising 10 mol% $Zr(propoxide)_4$ in mesitylene at reflux temperature, but $ZrOCl_2.8H_2O$ was determined as the most stable catalyst. The substrate scope was investigated and a number of lactam-carboxylic acid combinations were successfully converted into the desired products in 57-97% yield. This method provides an alternative synthetic pathway towards the drug aniracetam, which can be produced in 84% yield. A plausible catalytic mechanism is presented based on kinetic experiments.

1. Introduction

N-Acylated lactam derivatives have important applications as active ingredients in antifungal agents (e.g. variotin),[1] nootropic drugs (e.g. aniracetam),[2] anticoagulants (e.g. piperlotine-G),[3] permeation enhancers and surfactants (e.g. benzoyl caprolactam),[4] and bleach activators (e.g. *N*-(4-nitrobenzoyl)caprolactam) (Scheme 1).[5] These examples illustrate that amide bond formation is a key reaction for the pharmaceutical industry.[6] Similar to primary amines, the *N*-acylation of lactams proceeds easily with activated acylating agents like acyl chlorides in the presence of excess bases such as pyridine or triethylamine.[7] However, these procedures are associated with high waste. The atom economy can be significantly improved by using unactivated carboxylic acids as alternative acylating agents in the absence of base, which generates only water as a co-product. This approach is more challenging because both lactams and carboxylic acids lack the inherent reactivity towards condensation, and hence a catalyst is required to obtain the corresponding amides in satisfactory yields. In contrast to the *N*-acylation of primary amines,[8] the catalytic *N*-acylation of lactams has been scarcely reported to date. Examples are limited to the dehydrogenative reaction of lactams and aldehydes in the presence of Shvo's catalyst,[9] and amidine-based catalysts which have been applied in combination with acid anhydrides as acylating agents.[10]

In this study, we report the transition metal-catalysed direct *N*-acylation of lactams with unactivated carboxylic acids. Potential catalysts were selected based on their activity in the related acylation of primary amines or alcohols. For the best performing zirconium catalyst, the substrate scope was investigated and a kinetic study was performed for the synthesis of selected bio-active compounds.



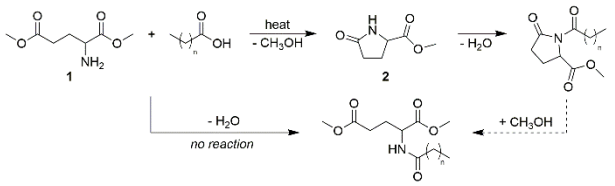
Scheme 1. Selected examples of active ingredients of agrochemicals, detergents and drugs containing an *N*-acylated lactam moiety.

2. Results and Discussion

2.1. Catalyst screening and optimization

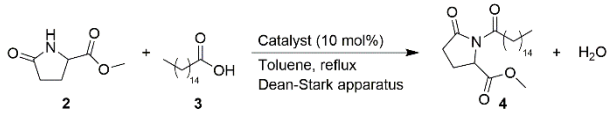
Initially, the direct *N*-acylation of glutamic acid dimethyl ester (**1**) with long-chain fatty acids was examined. These bifunctional building blocks can be used in the synthesis of bio-based alkyd resins, which have potential applications in the production of inks, paints, varnishes and coatings. The *N*-acylation of amines typically proceeds at higher temperature, but upon thermal treatment > 110 °C, **1** was completely converted into pyroglutamic acid methyl ester (**2**) by intramolecular cyclization (Scheme 2).[11] Nevertheless, the formation of *N*-acylated pyroglutamic acid methyl ester was also observed under these conditions and the latter can be converted back into *N*-acylated glutamic acid dimethyl ester by acid-catalyzed methanolysis.[12] Therefore the *N*-acylation of **2** with palmitic acid (**3**) was selected as a model reaction. Several Lewis acid catalysts were evaluated

for their activity at 10 mol% loading in toluene at reflux (Table 1).



Scheme 2. Lactamization of glutamic acid dimethyl ester (**1**) into pyroglutamic acid methyl ester (**2**), followed by *N*-acylation with a carboxylic acid. The *N*-acylated lactam can be converted back into the desired *N*-acylglutamic acid dimethyl ester by acid-catalysed methanolysis.

Table 1. Catalyst screening for the *N*-acylation of pyroglutamic acid methyl ester (**2**) with palmitic acid (**3**)[a]



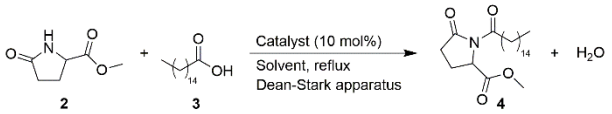
Entry	Catalyst + additive	X (%)[b]	S (%)[b]
1	-	< 1	-
2	Ti(isopropoxide)$_4$	16	77
3[c]	Ti(isopropoxide)$_4$	6	6
4	Sn(2-ethylhexanoate)$_2$	< 1	-
5	La(OTf)$_3$	< 1	-
6	H_3BO_3	10	88
7	Zr(OAc)$_4$	5	> 99
8	Zr(propoxide)$_4$	78	94[d]
9	Zr(propoxide)$_4$ + $NaOCH_3$	73	79[d]
10	Zr(acac)$_4$	71	98
11	Zr(acac)$_4$ + $NaOCH_3$	27	> 99
12	$ZrOCl_2$•$8H_2O$	63	> 99
13	$Zr(SO_4)_2$•$4H_2O$	18	2
14	$ZrO(NO_3)_2$	37	92
15	ZrO_2 (< 5 µm)	< 1	-

[a]Reagents and conditions: **2** (5.8 mmol), **3** (5.8 mmol), catalyst (0.58 mmol), additive (5.8 mmol), toluene (20 mL), reflux (110 °C), 18 h, water removal using a Dean-Stark apparatus. [b]Conversion (*X*) of **2** and selectivity (*S*) for *N*-palmitoylpyroglutamic acid methyl ester (**4**) determined by GC-FID and GC-MS. [c]Methyl palmitate (5.8 mmol) was used instead of **3**. [d]Selectivity towards the methyl and propyl ester of *N*-palmitoylpyroglutamic acid.

Both the catalyst and the Dean-Stark system for water removal are essential to produce *N*-palmitoylpyroglutamic acid methyl ester (**4**) under these mild conditions, otherwise the reaction did not proceed (Entry 1). For the titanium-based catalyst, the conversion was limited to 16% (Entry 2), presumably because Ti alkoxides are generally highly sensitive to degradation, e.g. by hydrolysis or by reaction with the carboxylic acid. *N*-Pyroglutamoylpyroglutamic acid methyl ester was observed as the major side product, as a result of the self-condensation of **2**. In an attempt to prevent catalyst degradation, the carboxylic acid **3** was substituted with its methyl ester derivative, which also has a slightly better leaving group (-OMe *vs*. -OH), but the yield of **4** could not be improved (Entry 3). Among the other catalysts tested in the *N*-acylation of **2**, boron-, tin- and lanthanum-based catalysts appeared to be nearly inactive (Entries 4-6). Higher activities were observed for several zirconium-based catalysts: Zr(propoxide)$_4$, Zr(acac)$_4$ and $ZrOCl_2$•$8H_2O$ produced **4** in > 60% yield (Entries 8, 10 and 12), whereas $Zr(SO_4)_2$•$4H_2O$ and $ZrO(NO_3)_2$ were far less active (Entries 13-14). These observations can be explained by the higher solubility of homogeneous zirconium catalysts with organic ligands in the apolar reaction medium. Moreover, the presence of basic ligands such as alkoxides or enolates in the coordination sphere of zirconium could assist in lactam deprotonation, making it more susceptible towards nucleophilic attack on the carboxylic acid. Addition of a strong base such as sodium methoxide was however not beneficial to increasing the extent of *N*-acylation (Entries 9 and 11). Rather than increasing the nucleophilic character of the lactam moiety in **2**, sodium methoxide reacted with the carboxylic acid **3** or with water to produce sodium palmitate or sodium hydroxide. The latter may also facilitate hydrolysis of the methyl ester moiety in **2**, which promotes the formation of *N*-pyroglutamoylpyroglutamic acid methyl ester and hence reduces the selectivity towards **4**. Finally, the commercially available solid ZrO_2 catalyst was completely inactive (Entry 15), because the Lewis acidity was much less pronounced compared to the other homogeneous catalysts and only zirconium atoms that are exposed at the catalyst's surface were able to participate in the reaction.

Next, the catalytic system was optimized in terms of temperature by performing the *N*-acylation of **2** with Zr(propoxide)$_4$ and $ZrOCl_2$•$8H_2O$ in other high-boiling solvents (Table 2). The selection was limited to non-halogenated aromatic solvents to enable the azeotropic removal of water from the reaction medium. In the case of Zr(propoxide)$_4$, the conversion of **2** increased to 97% by using mesitylene at reflux, *viz.* 165 °C (Entry 5). Also for $ZrOCl_2$•$8H_2O$ the conversion increased to 78% in mesitylene, while maintaining the selectivity at > 99% (Entry 7).

Table 2. Catalyst and solvent screening in the *N*-acylation of pyroglutamic acid methyl ester (**2**) with palmitic acid (**3**)[a]



Entry	Catalyst	Solvent	Temp. (°C)	X (%)[b]	S (%)[b]
1	-	Toluene	110	< 1	-
2	Zr(propoxide)$_4$	Toluene	110	78	94[c]
3	Zr(propoxide)$_4$	Toluene/ xylene (1:1)	130	73	91[c]
4	Zr(propoxide)$_4$	Xylene	144	93	93[c]
5	Zr(propoxide)$_4$	Mesitylene	165	97	94[c]
6	$ZrOCl_2$.$8H_2O$	Toluene	110	63	> 99
7	$ZrOCl_2$.8H2O	Mesitylene	165	78	> 99

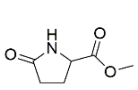
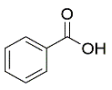
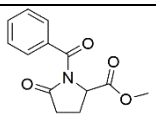
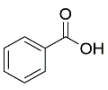
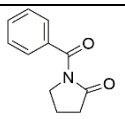
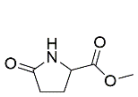
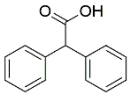
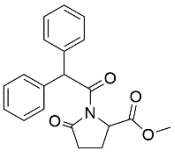
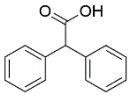
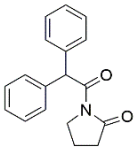
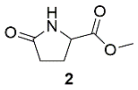
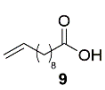
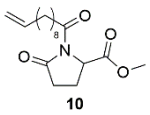
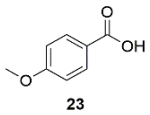
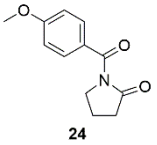
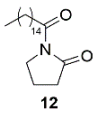
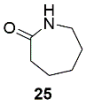
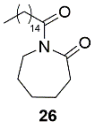
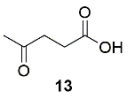
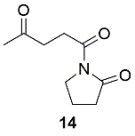
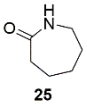
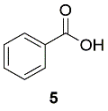
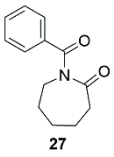
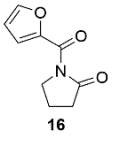
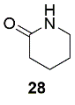
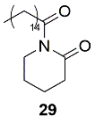
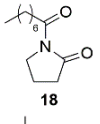
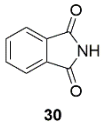
[a]Reagents and conditions: **2** (5.8 mmol), **3** (5.8 mmol), catalyst (0.58 mmol), solvent (20 mL), reflux, 18 h, water removal using a Dean-Stark apparatus. [b]Conversion (*X*) of **2** and selectivity (*S*) for *N*-palmitoylpyroglutamic acid methyl ester (**4**) determined by GC-FID and GC-MS. [c]Selectivity towards the methyl and propyl ester of *N*-palmitoylpyroglutamic acid.

The long-term stability of active catalysts such as Zr(propoxide)$_4$ and Zr(acac)$_4$ might be an issue, because substantial discoloration of the reaction medium was observed. Moreover, in the presence of Zr(propoxide)$_4$ a complex product mixture was obtained due to (trans)esterification of the substrates and the product. On the other hand, $ZrOCl_2$•$8H_2O$ represents an already hydrolyzed zirconium compound and therefore is expected to be more stable. Furthermore, $ZrOCl_2$•$8H_2O$ has low toxicity ($LD_{50,\ oral\ rat}$ = 2950 mg/kg),[13] is commercially available, inexpensive and air stable,[14] making it a practical and easily manageable catalyst.

2.2. Substrate scope

After having identified $ZrOCl_2 \cdot 8H_2O$ as a stable catalyst for the *N*-acylation of pyroglutamic acid methyl ester (**2**) with palmitic acid (**3**), the substrate scope was investigated by variation of both the lactam and the carboxylic acid (Table 3). The *N*-acylation of **2** did not proceed with benzoic acid (**5**) or diphenylacetic acid (**7**) as acylating agents, likely as a result of steric hindrance (Entries 1-2). On the other hand, the *N*-acylated lactam derived from 10-undecenoic acid (**9**) and **2** was obtained in 57% yield and the unsaturated C-C double bond remained unaffected (Entry 3). The *N*-acylation of 2-pyrrolidone (**11**) with carboxylic acids generally proceeded more easily, because this lactam displays a higher solubility in mesitylene. Moreover, the absence of a carboxylic ester group increases the nucleophilicity of the lactam moiety, and has a beneficial effect on the selectivity. *N*-Acylated lactams derived from **11** and various carboxylic acids such as **3**, **5** and octanoic acid (**17**) were obtained in 81-97% yield (Entries 4, 7 and 9). The conversion was limited with **7**, pivalic acid (**19**), 2-furoic acid (**15**) and levulinic acid (**13**) as acylating agents (Entries 5, 6, 8 and 10), as a result of steric hindrance in the carboxylic acid reagent, solubility issues, or interactions between the acid and the catalyst, for example possibly between Zr and the ketone moiety in **13**.[15] The solubility of the carboxylic acid could be tremendously improved by switching to other solvents: for example, the *N*-acylation of **11** with *p*-anisic acid (**23**) was unsuccessful in mesitylene, but *N*-anisoyl-2-pyrrolidone (aniracetam, **24**) was obtained in 79 and 84% yield in chlorobenzene as determined by isolated yield or GC-measurement, respectively (Entry 11). The latter compound is an established anxiolytic and nootropic agent, which is commercially available and has applications as a memory enhancer and neuroprotective drug in various central nervous system disorders.[2,16] Data regarding the annual production of **24** are not available, but the structurally related 2-oxo-1-pyrrolidine acetamide (piracetam), a less potent nootropic drug, is produced on an annual thousand ton scale.[17] Furthermore, *N*-acylated lactams derived from δ-valerolactam (**25**) or ε-caprolactam (**28**) were obtained in 73-89% yield (Entries 12-14). However, imides such as phthalimide (**30**) and succinimide (**32**) were inert towards *N*-acylation in this catalytic system (Entries 15-16). These compounds are too sterically hindered and lack the nucleophilicity required to participate in the reaction.

Table 3. *N*-Acylation of lactams and imides with various carboxylic acids: substrate scope[a]

Entry	Substrate	Acid	Product	Yield (%)[b]	Entry	Substrate	Acid	Product	Yield (%[b])
1	 **2**	 **5**	 **6**	3	9	 **11**	 **5**	 **21**	81
2	 **2**	 **7**	 **8**	0	10	 **11**	 **7**	 **22**	1
3	 **2**	 **9**	 **10**	57	11	 **11**	 **23**	 **24**	79-84[c]
4	 **11**	 **3**	 **12**	97	12	 **25**	 **3**	 **26**	80
5	 **11**	 **13**	 **14**	8	13	 **25**	 **5**	 **27**	73
6	 **11**	 **15**	 **16**	6	14	 **28**	 **3**	 **29**	89
7	 **11**	 **17**	 **18**	90	15	 **30**	**3**	**31**	0
8	**11**	**19**	**20**	4	16	**32**	**3**	**33**	0

[a]Reagents and conditions: lactam or imide (5.8 mmol), carboxylic acid (5.8 mmol), $ZrOCl_2 \cdot 8H_2O$ (0.58 mmol), mesitylene (20 mL), reflux (165 °C), water removal using a Dean-Stark apparatus. [b]Yield determined by GC-FID and GC-MS. [c]Reaction in chlorobenzene at reflux (131 °C), isolated yield 79%, GC-yield: 84%.

2.3. Reaction course

Selected *N*-acylation reactions were studied in greater detail to elucidate the reaction course. First, a kinetic study was performed for the *N*-acylation of 2-pyrrolidone (**11**) with palmitic acid (**3**) (Figure. 1).

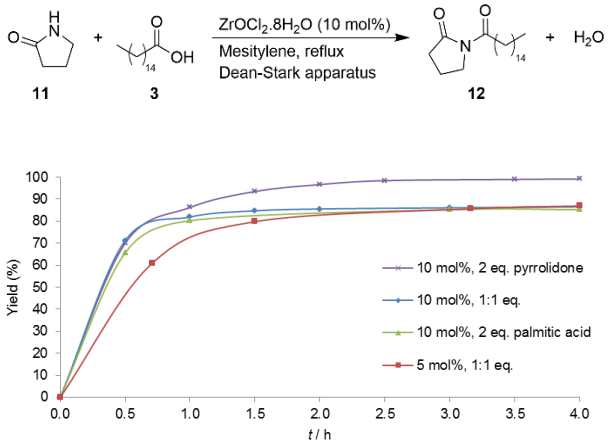
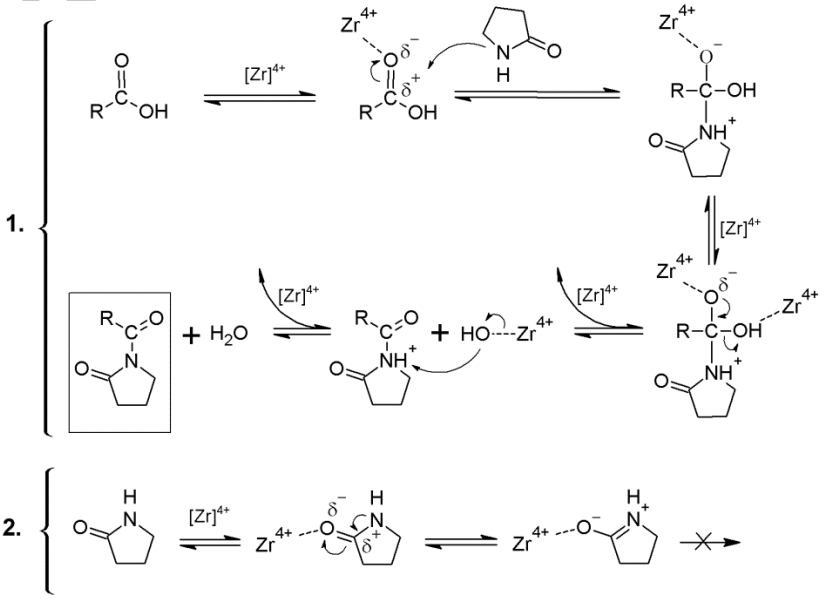


Figure. 1. Kinetic study of the *N*-acylation of 2-pyrrolidone (**11**) with palmitic acid (**3**) to *N*-palmitoyl-2-pyrrolidone (**12**). Reagents and conditions: **11** (6-12 mmol), **3** (6-12 mmol), $ZrOCl_2$•$8H_2O$ (0.6-1.2 mmol), mesitylene (20 mL), reflux (165 °C), water removal using a Dean-Stark apparatus.

Both reactants were combined in various ratios (e.g. 1:1, 2:1 and 1:2) and the catalyst loading was varied between 5 and 10 mol%. High conversions were obtained within 2 h with the equimolar mixture and 10 mol% $ZrOCl_2$•$8H_2O$; the yield of **12** levels off at 87%. Although the reaction proceeded more slowly when the catalyst loading was reduced to 5 mol%, **12** was still obtained in 86% yield after 3 h. An excess of the carboxylic acid reactant has almost no influence on the reaction rate, but an excess of the lactam reactant resulted in an increased yield of **12** (> 99%). The *N*-acylation of pyroglutamic acid methyl ester (**2**) with palmitic acid (**3**) as well as the synthesis of aniracetam (**24**) from 2-pyrrolidone (**11**) and *p*-anisic acid (**23**) required much longer reaction times; in both cases the product was obtained in only 15% yield after 5 h (ESI, Fig. S1-S2). Moreover, a slight induction phase was observed for the former reaction. *In situ* catalytic formation of anhydrides was ruled out following an experiment using palmitic acid (6 mmol) and $ZrOCl_2$•$8H_2O$ (0.6 mmol) in mesitylene at reflux with a Dean-Stark for water removal; no water formation was observed.

Based on previous observations, a plausible catalytic mechanism is proposed (Scheme 3). First, palmitic acid is activated by ligand exchange on the catalytically active, Lewis acidic $Zr_4(OH)_8(H_2O)_{16}^{8+}$ cluster of zirconyl chloride, thereby displacing water molecules in the coordination sphere of the metal.[13] Afterwards, 2-pyrrolidone undergoes nucleophilic attack on the activated carboxylic acid and *N*-palmitoyl-2-pyrrolidone is obtained after rearrangement (Route 1). Water removal is necessary because otherwise generation of the active complex is inhibited. However, 2-pyrrolidone can also form a complex with $ZrOCl_2$•$8H_2O$; previous research has demonstrated that amides such as *N*,*N*-dimethylformamide can interact *via* their carbonyl group with highly oxophilic zirconium species.[15] Indeed, when an 8:1-mixture of 2-pyrrolidone and $ZrOCl_2$•$8H_2O$ was heated at 130 °C for 18 h in a typical reaction set-up, the lactam remained stable according to ^{1}H NMR analysis, but 3.2 equivalents of water were collected in the Dean-Stark bridge. 2-Pyrrolidone is probably deactivated towards *N*-acylation by the generation of an inactive –NH^+-R moiety upon interaction with the catalyst (Route 2).[13] This might explain why the conversion reached a plateau in the equimolar tests, whereas nearly quantitative yields were reached with excess lactam (Figure. 1).



Scheme 3. Plausible mechanism for the *N*-acylation of 2-pyrrolidone (Route 1) and the deactivation of 2-pyrrolidone (Route 2) in the presence of zirconium catalysts.

3. Conclusion

The *N*-acylation of lactams with unactivated carboxylic acids is catalyzed by various zirconium compounds and $ZrOCl_2 \cdot 8H_2O$ was identified as the most stable catalyst. Continuous removal of water from the reaction medium is essential to drive the condensation and assists in increasing the accessibility of the zirconium cluster. The mechanism is based on activation of the carboxylic acid by interaction with the zirconium cluster. The reaction should be performed with a slight excess of the lactam, because this reagent can be partially deactivated by interaction with the catalyst. The productivity of the system depends mainly on the nucleophilicity of the lactam, the solubility of the reactants in the solvent and the steric hindrance of both reactants. The procedure has been successfully applied to the synthesis of aniracetam from 2-pyrrolidone and *p*-anisic acid. This zirconium-based *N*-acylation method may open new routes for the less expensive, greener production of aniracetam and *N*-acylated lactam derivatives.

Acknowledgements

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Graphical Abstract

Zirconium-catalysed *N*-acylation of lactams using unactivated carboxylic acids

Joris Hulsbosch, Laurens Claes and Dirk E. De Vos

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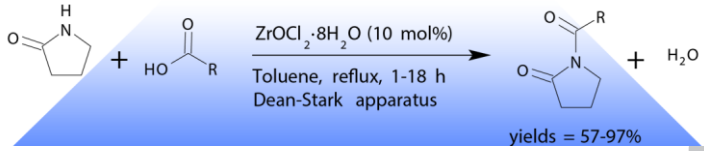

- New method for the catalytic *N*-acylation of lactams with carboxylic acids.
- Screening of Lewis acid catalysts for *N*-acylation of pyroglutamic acid methyl ester.
- Yields up to 97% were reached with 10 mol% $Zr(propoxide)_4$.
- Substrate scope was investigated; with 57-97% yield achieved.
- The drug aniracetam can be produced in 84% yield.