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Application of γ -valerolactone as an alternative biomass-based medium for aminocarbonylation reactions

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Abstract: γ -Valerolactone was proposed as a renewable, non-toxic reaction medium having negligible vapor pressure for homogeneous Pd-catalyzed aminocarbonylation reactions. Iodobenzene as a model substrate and its 4-substituted derivatives were converted to the corresponding 2-ketocarboxamides with high conversion and chemoselectivities in γ -valerolactone. The effect of carbon monoxide pressure and reaction temperature on the conversion and selectivities were studied in the range of 1–50 bar and 25–100 °C, respectively. The highest conversion and selectivity was achieved at 25 bar and 50 °C for iodobenzene in GVL for 24 h.

Introduction

The chemical industry, which produces enormous amount of value-added chemicals highly depends on fossil based resources. The integrated processing of crude oil continuously provides bulk chemicals including conventional organic solvents for both petrochemical and fine chemical industries. Although, it is hard to estimate the depletion of crude oil, the environmental and sustainability issues have increased attentions toward the identifications and applications of alternative resources and renewable building blocks from which the selection of appropriate solvents is also highly desired. The rapidly expanding research activity on biomass conversion, as the most preferred alternative solution has identified several renewable platform chemicals that could replace fossil based ones as well as could act as a part of alternative solvents. The industrial activities involving solvents result in the release of volatile organic compounds (VOCs) including conventional solvents into the environment for example for EU28 over 7 million tons annually.^[1] Some of them have been leading to serious environmental concerns, moreover, economic issues. According to FDA guidelines^[2] utilization of several "classic" organic solvents must be avoided (e.g. benzene and chlorinated hydrocarbons) or limited (e.g. toluene), just to name a few. Focusing on the development of environmentally benign chemical transformations, several alternative solvents e.g water,^[3] fluorous⁴ and ionic liquids (IL),⁵ and supercritical carbon dioxide^[6] have been successfully introduced in the homogeneous catalysis. For the last decades, trends have been moved towards to identification of bio-based reaction media for organic synthesis and catalysis for example glycerol^[7] and its derivatives,^[8] or ethyl lactate.^[9] Consequently, in the development of alternative, non fossil-based strategies to produce value-added chemicals in the future, the selection of solvents having environmental friendly properties, *i.e.* low vapor pressure and toxicity is fundamentally important and even could be a key part of cleaner and greener chemical processes.

Among the recently characterized biomass-based platform molecules, $^{[10]}\ensuremath{\gamma}\xspace$ valerolactone (GVL) has been received an ever increasing interest since it was firstly proposed as a sustainable liquid by Horváth in 2008.^[11] Due to its attractive physical and chemical properties, several applications of GVL were demonstrated in the last few years. It can be produced from cellulose^[12] and used for the production of alkanes and alkenes,^[13] transportation fuels,^[14] fine chemicals,^[15] illuminating and lighter fluid, [16] etc. GVL is liquid in wide temperature range and has negligible vapor pressure^[17] avoiding its emission to the atmosphere. It occurs in fruits and wines,^[18] non-toxic and has been utilized by food industry. Recently, the utilization of GVL as a biomass-based solvent has received an increasing attention, as well. We have shown that it can be a reaction medium for selective hydrogenation of levulinic acid to 4-hydroxyvaleric acid.[19] Horváth et al. demonstrated that the dehydration of various carbohydrates could be performed in GVL under strong acidic environment in temperature range 70-170 °C.[20] It was recently shown that GVL with co-solvents can form as an efficient media for dissolution of various lignins at moderate temperature (40-70 °C)^[21] as well as enhance the hydrolysis of monosaccharides and lignocellulosic biomass over 120 °C. [22] Dumesic revealed that the levulinic acid and GVL can be produces from cellulose in a GVL-based biphasic system operating high temperatures (> 180 °C).^[23] Vaccaro and coworkers showed that it could be an excellent solvent for heterogeneous coupling reactions operating in wide temperature range (50-150 °C).^[24,25,26] The Pt-catalyzed enantioselective hydroformylation of styrene was also successfully carried out in GVL in a range of 40-130 °C without significant changes of enantiomeric excess.[27]

The carbonylation reactions have indisputable role in homogeneous transition metal catalysis and serve as a facile method for carbon-carbon bond formation.^[28] Among carbonylations, alkoxy- and aminocarbonylation has gained a special importance. Since the early discovery of Heck et al^[29] on the Pd-catalyzed carbonylation of haloarenes, hundreds of examples were published describing structure-reactivity, structure-selectivity correlations and demonstrating synthetic applications.^[30] Various structures were functionalized using a

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broad variety of alcohols and amines as O- and N-nucleophiles, respectively. In this way, esters and carboxamides that are not available by using conventional synthetic routes have been synthesized representing a diversity of products in both laboratory and industrial requirements. As one of the principal side-reaction of carboxamide formation, the seminal work of Yamamoto *et al* on double carbonylation in the presence of amines, *i.e.* the formation of 2-ketocarboxamides has to be highlighted. ^[31] Thus, aminocarbonylation is of utmost importance in the synthesis of carboxamides and ketocarboxamides.

 $\ensuremath{\text{Table 1.}}$ Table 1. Toxicity data and solvatochromic parameters of solvents used for aminocarbonylation reactions.

Q = h = = = + [a]	Toxicity data	Kamlet-Taft Parameters ^[32]		
Solvent	LD ₅₀ oral rat (mg/kg)	$\alpha^{[a]}$	$\beta^{[b]}$	π* ^[c]
DMF	2800 ^[33]	0.00	0.69	0.88
Toluene	5000 ^[34]	0.00	0.11	0.54
1,4-dioxane	5200 ^[35]	0.00	0.37	0.55
acetonitrile	175 ^[36]	0.19	0.40	0.75
2-butanone	2900 ^[37]	0.06	0.48	0.67
THF	1650 ^[33]	0.00	0.55	0.58
GVL	8800 ^[11]	0.00	0.60	0.83

[a] hydrogen-bond donating ability (acidity), [b] hydrogen-bond accepting ability (basicity), [c] polarity/polarizability

Although, the aminocarbonylation reactions are routinely performed in conventional organic solvents such as N,Ndimethylformamide (DMF),^[38] toluene,^[39] 1,4-dioxane,^[40] 2butanone,^[41] acetonitrile^[42] and tetrahydrofurane (THF),^[43] DMF has been identified as best medium for Pd-catalyzed reactions. However, the toxicity of the conventional solvents is significantly higher compared to biomass-based alternative γ -valerolactone (Table 1.). The oral LD_{50} value of GVL measured on rat is ca. three times higher that that of DMF. In addition, GVL does not form any measurable amount of peroxide during its storage under air for weeks,^[11,44] which is also crucial safety issue for handling and laboratory use. We selected solvatochromic Kamlet-Taft parameters concerning hydrogen-bond donating ability (acidity, α), hydrogen-bond accepting ability (basicity, β) and polarity (π^*) to compare (Table 1.) the various solvents utilized for aminocarbonylation. It shows that GVL has similar solvatochromic properties to DMF. Both β and π^* parameters are very close to each other. It has to be also emphasized that to the best of our knowledge, no carbonylation reactions in GVL as a solvent has been demonstrated yet.

We report here the application of GVL as a proposed nontoxic, polar and renewable reaction medium for palladiumcatalyzed aminocarbonylation of iodobenzene and its derivatives at different pressures and temperatures. We do think that this utilization of GVL opens a greener alternative way in carbonylation reactions.

Results and Discussion

The vapor pressure as a key property of a volatile organic compound (VOC)^[45] is crucial for application of a substance as a solvent. In comparison the temperature dependence of vapor pressure of solvents that commonly used for aminocarbonylation reactions to GVL's, it can be stated that the replacement of these media with GVL could result in an environmental benign catalytic system. The vapor pressures of GVL in the temperature range of aminocarbonylation reactions are two orders of magnitude less than DMF or toluene (Figure 1).^[46]

In order to demonstrate the applicability of GVL as a reaction medium for Pd-catalyzed aminocarbonylation of iodobenzene and its derivatives in the presence of Et₃N as a base, we applied *t*BuNH₂ as a nucleophile. Firstly, iodobenzene (Scheme 1, **1a**, 1 mmol) was carbonylated in the presence of catalyst *in situ* formed from 0.025 mmol of Pd(OAc)₂ and 0.05 mmol of PPh₃, and 0.5 mL of Et₃N in 10 mL of DMF as a reference reaction at 50 °C. When 1 bar of CO was applied,



Figure 1. Vapor pressures of commonly used solvents and GVL.



X = H (a), NH₂ (b), OH (c), tBu (d), CH₃ (e), *i*Pr (f), Ph (g), F (h), Cl (i) Br (j), COOCH₃ (k), C(O)CH₃ (l), CF₃ (m), CN (n)

Scheme 1. Aminocarbonylation of 4-substituted iodobenzenes with *tert*butylamine in GVL.

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Table 2. Aminocarbonylation of iodobenzene (1a) in the presence of Pd(OAc)₂/2 PPh₃ in situ catalyst using tert-butylamine as an N-nucleophile in conventional organic solvents and GVL^[a]

		Conversion ^[b]			Ratio of the carbonylated products ^[b]				
#	Solvent	Pco		Cart	ooxamide (2a)	Ketoca	Ketocarboxamide (3a)		
		1 bar	10 bar	1 bar	10 bar	1 bar	10 bar		
1	DMF	98	96	42	30	58	70		
2	Toluene	13	99	56	0	44	100		
3	Acetonitrile	44	86	43	0	57	100		
4	1,4-dioxane	21	99	68	2	32	98		
5	2-butanol ^[c]	0	84	0	0	0	11		
6	GVL	78	93	30	6	70	94		

[a] Reaction conditions: 1 mmol iodobenzene, 3 mmol of $tBuNH_2$, 0.025 mmol of Pd(OAc)₂, 0.05 mmol of PPh₃, 0.5 mL of Et₃N, solvent: 10 mL, T = 50 °C, t = 24 h [b] determined by GC-MS. [c]: The main product (89%) was 2-butyl benzoate.

98% conversion was achieved with 42% selectivity of carboxamide (2a) (58 % 2-ketocarboxamide (3a)) for 24 h. By increasing the carbon monoxide pressure to 10 bar 96% conversion was observed under identical conditions. However, the selectivity of carboxamide decreased to 30% indicating that the double carbon monoxide insertion leading to 3a was slightly favoured upon an increased carbon monoxide pressure. (Table 2, entry 1). In order to compare the commonly used reaction media to GVL, the reaction was repeated in conventional organic solvents generally utilized for aminocarbonylation (Table 2, entries 2-5). The conversions were moderate at atmospheric pressure; however, when 10 bar CO was applied comparable values were achieved. It should be noted that outstanding selectivity was obtained in toluene and acetonitrile under 10 bar of CO. Expectedly, in 2-butanol as O-nucleophile the main product was 2-butyl benzoate as alkoxycarbonylated product (Table 2, entry 5). By replacing the solvent to GVL, a slightly lower conversion (78 %) with comparable selectivity were obtained for iodobenzene (1a) at atmospheric pressure of CO for 24 h. However, the conversion of (1a) and chemoselectivity to 2-ketocarboxamide (2a) was increased enormously providing almost perfect selectivity to the double carbonylated product 3a when 10 bar CO pressure was applied. (Table 2, entry 6 and Table 3, entry 1). It should be noted that iodobenzene (1a) can be completely converted to 2a and 3a in up to 72 h even under mild conditions without significant changes in selectivity (Table 3, entry 2).

GVL proved to be excellent solvent also for the conversion of series of 4-substituted iodobenzenes (Scheme 1, **1b-1n**) to the corresponding 4-substituted carboxamide (Scheme 1, Table 3, **2b-2n**) and ketocarboxamide (Scheme 1, **3b-3n**). With the exception of 4-iodoaniline (**1b**) and 4-iodophenol (**1c**) good to excellent activities were observed, *i.e.*, iodoarenes were converted to the corresponding aminocarbonylated products in high yields. The reaction is highly selective concerning iodoarene carbonylations showing good functional group tolerance. No side-reactions could be observed using either **1b**, **1c** or the halide substituted substrates (**1h-1j**). It is remarkable that no 1,4-dicarboxamide formation was detected even with 4bromoiodobenzene (1j) possessing bromoarene functionality as well. This reaction might be of synthetic importance since the 4bromocarboxamide (2j) and the 4-bromoketocarboxamide (3j) products can be further reacted towards 1,4-functionalized Mixtures of carboxamides (2b-2n) derivatives. and ketocarboxamides (3b-3n) were formed in most cases. It should be emphasized that 2-ketocarboxamides, formed in double CO insertion, prevailed in all cases. Interestingly, while the chemoselectivities towards 2-ketocarboxamides at 10 bar CO could be supported by electron-releasing groups (see, for instance, entries 1, 3, 6), the opposite trend can be observed in case of electron-withdrawing groups (see, for instance entries 19, 21). These two cases can be exemplified by the methyl group (σ_p = -0.17) and the trifluoromethyl group (σ_p = +0.54), where the chemoselectivity towards the corresponding ketocarboxamides (3e and 3m) was increased from 83% to 97%, and decreased from 82% to 63%, respectively. However, when 1k and 1n were carbonylated, the formation of ketokarboxamide was favored at 10 bar.

The high ketocarboxamide selectivity obtained under mild conditions could substantially be further improved by increasing CO pressure. Accordingly, the effect of carbon monoxide pressure on the conversion and selectivity was investigated in the range of $p_{CO} = 1-50$ bar by reacting of 1 mmol iodobenzene (1a) and 3 mmol of tBuNH₂ in the presence of catalyst formed in situ from 0.025 mmol of Pd(OAc)₂ and 0.05 mmol of PPh₃ in a mixture of 0.5 mL of Et₃N and 10 mL of GVL at 50 °C (Figure 2.). Both conversion of 1a and selectivity of ketocarboxamide were slowly increased by increasing of CO pressure reaching a maximum at ca. 25 bar. Working above 25 bar the conversion decreased significantly at higher pressures. It can be assumed that the higher CO concentration could increase the number of coordinated carbonyl ligand on Pd center resulting in lower concentration of coordinatively unsaturated catalytically active species. Similar observations were reported for SILP-Pd assisted aminocarbonylation of iodobenzene and synthesis of ferrocene amides.^[47,48] Selectivities towards the formation of the

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Table 3. Aminocarbonylation of 4-substituted iodobenzenes (1a-1n) in the presence of Pd(OAc)₂/2 PPh₃ in situ catalyst using tert-butylamine as an Nnucleophile in GVL ^[a]

	Sub	strate (1)		Conv	version ^[b]	Ratio of the carbonylated products ^[b]			
#			Time (h)	Рсо		Carboxamide (2)		Ketocarboxamide (3)	
	Code	X		1 bar	10 bar	1 bar	10 bar	1 bar	10 bar
1	а	Н	24	78	93	30 (2a)	6 (2a)	70 (3a)	94 (3a)
2	а	н	72	100	-	39 (2a)		61(3a)	
3	b	NH_2	24	38	62	11 (2b)	2 (2b)	89 (3b)	98 (3b)
4	с	ОН	24	15	19	14 (2c)	3 (2c)	86 (3c)	97 (3b)
5	d	<i>t</i> Bu	24	20	26	0 (2d)	0 (2d)	100 (3d)	100 (3d)
6	е	CH₃	24	68	94	17 (2e)	3 (2e)	83 (3e)	97 (3e)
7	е	CH ₃	96	91	-	26 (2e)		74 (3e)	
8	f	<i>i</i> Pr	24	16	59	10 (2f)	4 (2f)	90 (3f)	96 (3 f)
9	g	Ph	24	74	90	20 (2g)	16 (2g)	80 (3g)	84 (3g)
10	g	Ph	48	98	-	31 (2g)		69 (3g)	
11	h	F	24	58	92	9 (2h)	2 (2h)	91 (3h)	98 (3h)
12	h	F	48	93	-	22 (2h)		78 (3h)	
13	i	CI	24	74	76	8 (2i)	20 (2i)	92 (3i)	80 (3i)
14	i	CI	48	100	-	13 (2i)		87 (3i)	
15	j	Br	24	73	95	16 (2j)	3 (2 j)	84 (3j)	97 (3j)
16	j	Br	48	100	-	26 (2j)		74 (3j)	
17	k	COOCH ₃	24	91	100	17 (2k)	7 (2k)	83 (3k)	93 (3k)
18	k	$COOCH_3$	48	100	-	17 (2k)		83 (3k)	
19	I	C(O)CH ₃	24	91	99.8	20 (2I)	35 (2I)	80 (3I)	65 (3I)
20	I	C(O)CH ₃	48	100	-	24 (2I)		76 (3I)	
21	m	CF_3	24	74	73	18 (2m)	37 (2m)	82 (3m)	63 (3m)
22	m	CF ₃	48	94	-	21 (2m)		79 (3m)	
23	n	CN	24	87	100	39 (2n)	19 (2n)	61 (3n)	81 (3n)
24	n	CN	48	100	-	31 (2n)		69 (2n)	

[a] Reaction conditions (unless otherwise stated): 1 mmol substrate (1a-1n), 3 mmol of $tBuNH_2$, 0.025 mmol of Pd(OAc)₂, 0.05 mmol of PPh₃, 0.5 mL of Et₃N, 10 mL of GVL, T = 50 °C. [b] determined by GC-MS.

corresponding ketocarboxamides were also increased; however, its decreasing was not detected at higher pressures.

The effect of reaction temperature on the conversion and selectivity was also investigated in the range of 25–100 °C. While, the almost complete conversion could be achieved at 75 °C for 24 h, the selectivity towards formation of keto-carboxamide started to decrease over 50 °C (Figure 3.). It is in good agreement with observation reported for conversion iodoferrocene under 40 bar of CO at different temperatures.^[48] It

is important to emphasize that the thermal stability of GVL is limited by its ring-opening to form 3-pentenoic acids, which can undergo further isomerization. However, these reactions as well as the formation of α -angelicalactone could take place at high temperatures (> 160 °C).^[13b, 49] Expectedly, our GC-MS and NMR analysis did not indicate any degradation of GVL in the temperature range used for aminocarbonylation reactions.

The reproducibility of catalytic conversions was confirmed by repeating the experiment under 10 bar of CO using

iodobenzene (**1a**) as a substrate at 50 °C (Table 2, entry 1.). Conversion of 92 % with same selectivities was achieved in the repeated measurement.



Figure 2. Effect of carbon monoxide pressure on the conversion of iodobenzene.



Figure 3. Effect of reaction temperature on the conversion of iodobenzene. Reaction conditions: 1 mmol iodobenzene (1a), 3 mmol of $tBuNH_2$, 0.025 mmol of Pd(OAc)₂, 0.05 mmol of PPh₃, 0.5 mL of Et₃N, 10 mL of GVL, p_{CO} = 25 bar.

Conclusions

We demonstrated that GVL as a non-toxic and renewable platform chemical can be used as alternative solvent for palladium-catalyzed aminocarbonylation reactions opening a greener procedure for this synthetically relevant transformation. Various 4-substituted iodobenzenes were converted to the corresponding 2-ketocarboxamides of synthetic importance in GVL.

Experimental Section

lodobenzene and its derivatives (**1b-1n**), DMF, toluene, and GVL were obtained from Sigma-Aldrich Kft., Budapest, Hungary. GC analyses were performed on a HP 5890N instrument with HP-5 capillary column (15 m x 0.25 μ m) using H₂ as a carrier gas. For the analysis, 10 μ L of reaction mixture was dissolved in 1 mL of methylene chloride followed by the addition of 10 μ L toluene as internal standard. GVL was purified by distillation at reduced pressure (4–5 Hgmm) at 75–80 °C^[17] and stored on a molecular sieve under N₂.

In a typical carbonylation reaction performed at atmospheric carbon monoxide pressure $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.2 mg, 0.05 mmol), 4-substituted iodobenzene (1.00 mmol), *tert*-butylamine (0.315 mL, 3.00 mmol), and triethylamine (0.5 mL) were dissolved in the corresponding solvent (10 mL) (except GVL) under argon in a 100 mL three-necked bottle with a reflux condenser connected to a balloon on the top of it. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time (Table 3) upon stirring at 50 °C. The reaction mixture was analysed by TLC as well as by GC and GC-MS. The solvent was evaporated under reduced pressure. The waxy residue was dissolved in chloroform (20 mL), then washed with water (20 mL), twice with 5% aq HCI (20mL), satd aq NaHCO₃ (20mL) and satd. aq. brine (20mL). The organic phase was dried over Na₂SO₄, filtered and evaporated to a solid material.

To the reaction mixtures dissolved in GVL, 50 mL of hexane and 100 mL of water was added. The hexane phase was separated and washed with water (100 mL). The organic phase was dried over Na_2SO_4 , filtered and evaporated to a solid material.

All compounds were subjected to column chromatography (Silicagel 60 (Merck), 0.063-0.200 mm), EtOAc/CHCl₃ or hexane/EtOAc/CHCl₃ eluent mixtures. Isolated yields from 5% (**2f**) to 20% (**2a**) and from 33% (**3n**) to 68% (**3d**) (not optimized, based on amount of the substrate used in atmospheric experiments) were obtained for carboxamides and ketocarboxamides, respectively. The compounds gave identical analytical data with those synthesized in conventional procedure.^[50]

In a typical high-pressure carbonylation experiment, the 25 mL high-pressure Hastelloy-C reactor (4742, Parr Inst. IL USA) equipped with manometer, safety relief and magnetic stirring bar using external heating (oil bath) was charged with 1 mmol substrate, 3 mmol of $tBuNH_2$, 0.025 mmol of Pd(OAc)₂ as a catalyst precursor, 0.05 mmol of PPh₃, 0.5 mL of Et₃N, and 10 mL of corresponding solvent resulting in a straw yellow solution. The reaction mixture was pressurized with carbon monoxide (99.9%) gas then heated up to 50 °C and stirred at 350 RPM. After given reaction time, the reaction mixture was cooled down to room temperature and the pressure was released in a well-ventilated hood. The product mixture was analyzed by a GC or GC-MS. The work-up of the reaction mixture containing GVL solvent was identical to that described for atmospheric experiments.

The single and double carbonylated products (**2a-n** and **3a-n**, respectively) show identical spectra with those obtained in conventional aminocarbonylation.^[50]

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Keywords: green solvent • gamma-valerolactone • homogeneous catalysis • carbonylation

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Entry for the Table of Contents

FULL PAPER

It was demonstrated that GVL as a non-toxic and renewable platform chemical can be used as alternative solvent for palladium-catalyzed aminocarbonylation reactions opening a greener procedure for this synthetically relevant transformation.



Diána Marosvölgyi-Haskó, Blanka Lengyel, József M. Tukacs, László Kollár, László T. Mika*

Page No. – Page No.

Application of γ -valerolactone as an alternative biomass-based medium for aminocarbonylation reactions