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Selective and Environmentally Friendly Methodologies Based on the Use of Electrochemistry for Fine Chemical Preparation: An Efficient Synthesis of N,N′-Disubstituted Ureas

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Abstract: A novel efficient synthesis of N,N′-disubstituted ureas has been developed. Aromatic and aliphatic primary amines undergo oxidative carbonylation under atmospheric pressure of carbon monoxide using Pd(II) catalyst in combination with its anodic recycling at a graphite electrode.

Substituted ureas have been of recent interest due to the appearance of this functionality in drug candidates such as HIV protease inhibitors;[1,2] in addition, ureas have found widespread use as agricultural chemicals, resin precursors, dyes, and additives to petroleum compounds and polymers.[3]

For these reasons, many efforts have been made to find new efficient syntheses of ureas to replace the classical reactions of amines with phosgene[4] or related compounds (isocyanates,[5] carbonyldiimidazole,[6] or disuccinimmide carbonate[7]).

The synthesis of symmetrical ureas from amines can be accomplished by oxidative carbonylation of amines by means of carbon monoxide and a transition-metal catalyst (W,[8] Ni,[9] Mn,[10] Co,[11] Rh,[12] Ru,[13] and Pd[14]). Among them, the most commonly used is Pd.

The reaction with a Pd catalyst implies the use of a reoxidant reagent in stoichiometric amount to transform Pd(0) (that results from the reaction) into Pd(II) (the reactive species of the catalyst); usually, high pressures of CO and O_2 are necessary, sometimes in combination with I_2;[15] alternatively, CO, O_2, and copper salts can be used.[16]

Electrochemistry has also been used as reoxidizing system: recently Deng and co-workers have applied electrochemistry to the synthesis of symmetrical dialkyl ureas using $Pd(PPh_3)_2Cl_2$ as catalyst and $Cu(OAc)_2$ as co-catalyst, instead of high pressure of CO/O_2. In this case, it is proved that $Cu(OAc)_2$ "acted as not only an electron transfer agent but also a catalyst".[17]

In all these syntheses of ureas, a side reaction of either double carbonylation to oxamides takes place or the formation of isocyanates probably by amine-elimination reaction from urea. It is therefore important to find a synthesis with high selectivity to minimize the side reactions.

In the course of our studies aimed at the use of electrochemistry as a selective and environmentally friendly tool in organic synthesis, we have developed a new methodology for palladium(II) catalyst recycling by means of its anodic oxidation at a graphite electrode in the absence of any other cocatalyst or stoichimetric oxidant. This methodology was applied to the synthesis of methyl acetylencarboxylates starting from alkynes, carbon monoxide, and methanol[18] and oxazolidin-2-ones starting from 2-amino-1-alkanols and carbon monoxide, obtaining these heterocyclic compounds in very good yields.[19] In this paper, we want to extend this new procedure in order to obtain an efficient synthesis of N,N′-disubstituted ureas starting from amines and carbon monoxide.

The advantage of the anodic recycling at a graphite electrode of Pd(II) is that it proceeds efficiently under atmospheric pressure of carbon monoxide and avoids the use of copper or halide ions and high pressure of O_2 gas, which also implies the formation of water and causes undesired side reactions;[17] this way, the performances of the catalysts should be enhanced.

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TABLE 1. Electrochemical Synthesis of *N,N*-Dibenzylurea Using Different Pd(II) Complexes as Catalyst

entry	catalyst	base	ligand	reaction time (h)	urea 2, yield[a] (%)	oxamide 3, yield[a] (%)	current yield (%)
1	Pd(OAc)$_2$	AcONa		3	62	12	81
2	Pd(OAc)$_2$	AcONa	TFP[b]	3	32	2	68
3	Pd(OAc)$_2$	AcONa	PPh$_3$	3	59	10	73
4	Pd(OAc)$_2$	AcONa	dppp[c]	9	57	16	85
5	Pd$_2$(dba)$_3$[d]	AcONa		4	67	5	90
6	Pd(PPh$_3$)$_4$	AcONa		4	83	10	86
7	PdCl$_2$(PPh$_3$)$_2$	AcONa		4	73	6	81
8	PdCl$_2$	AcONa		5	48	<1	99
9	PdCl$_2$	NEt$_3$		7	50	6	77

[a] Yields determined by HPLC, yields relative to starting 1. [b] TFP = tri-2-furylphosphine. [c] dppp = 1,3-bis(diphenylphosphino)propane. [d] Tris(dibenzylideneacetone)dipalladium(0).

Aromatic and aliphatic primary amines undergo oxidative carbonylation to give N,N′-disubstituted ureas; the process is outlined in the following reaction (eq 1):

$$R\text{—}NH_2 \; + \; CO \; \xrightarrow[\text{+ 0.4 V } vs \text{ SCE}]{\text{Pd cat}}$$

(eq. 1)
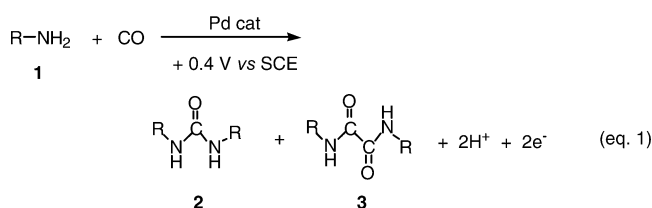
The following general procedure was used: in a cell with three separated compartments, kept at 50.0 ± 0.1 °C, the electrolysis was carried out on a solution of amine (0.50 mmol), in 30 mL of CH$_3$CN containing *n*-Bu$_4$NBF$_4$ (0.20 mol L^{-1}) as supporting electrolyte, in the presence of Pd(OAc)$_2$ (0.05 mmol) and NaOAc (2.00 mmol), under 1 atm of CO at +0.4 V vs SCE.[20] A graphite electrode, of apparent area of 3 cm^2, was used as working electrode. The counter-electrode was a Pt wire, and the reference was a saturated calomel electrode (SCE). The electrolysis was stopped when the current reached the value recorded at the end of the preelectrolysis.

Benzylamine was used as a model compound to study the influence of catalyst and ligands. The effect of different catalytic systems on the carbonylation of benzylamine is presented in Table 1.

Among the examined catalytic systems, Pd$_2$(dba)$_3$ exhibited good selectivity to afford the urea in 67% and oxamide in 5% yields, whereas the best yield in urea (83%) was obtained using Pd(PPh$_3$)$_4$ as catalyst. This suggests that the palladium(0) complexes, such as Pd(PPh$_3$)$_4$ and Pd$_2$(dba)$_3$, are good catalytic systems in this transformation. From the electrochemical point of view, the most efficient catalytic system was PdCl$_2$ as it appears from the current yield (99%) and from the selectivity of this reaction, but the reaction resulted very slow. The use of a base is necessary to avoid the formation of HPd(II)(L)$_2^+$ or of HPd(II)$^+$, which do not react in this transformation.[21] In the presence of PdCl$_2$ as catalyst, the use of NEt$_3$, instead of AcONa, seems to decrease the electrocatalytic system; in fact, the current yield affords 77% in the presence of NEt$_3$, with respect to 99% in the presence of AcONa.

TABLE 2. Electrochemical Synthesis of Aliphatic and Aromatic Ureas Using Palladium Catalyst[a]

entry	amine 1, R	catalyst[b]	reaction time (h)	urea 2, yield[c] (%)	oxamide 3, yield[c] (%)	current yield (%)
1	4-MeOPh	A	5	10	0	10
2	4-MeOPh	B	6	41	0	38
3	4-ClPh	A	7	20	0	46
4	4-ClPh	B	6	31	0	30
5	Ph	A	5	49	0	99
6	Ph	B	6	57	0	84
7	PhCH$_2$	A	4	83	10	86
8	PhCH$_2$	B	3	62	12	81
9	2-Py	A	5	30	0	99
10	2-Py	B	6	21	0	30
11	C$_6$H$_{11}$	A	3	57	0	66
12	C$_6$H$_{11}$	B	6	71	0	73
13	C$_5$H$_9$	A	5	35	1	44
14	C$_5$H$_9$	B	5	37	1	76
15	Bu	A	3	70	3	99
16	Bu	B	3	71	0	94

[a] General procedure: the same described in the text. [b] A, Pd(PPh$_3$)$_4$; B, Pd(OAc)$_2$. [c] Yields determined by HPLC, yields relative to starting 1.

To test its applicability, this electrochemical synthesis, using two different catalytic systems, a complex of Pd(0), i.e., Pd(PPh$_3$)$_4$, and a complex of Pd(II), i.e., Pd(OAc)$_2$, were applied to a variety of primary aliphatic and aromatic amines. The preparative results are summarized in Table 2.[22]

The yields in urea and the selectivity with respect to the formation of oxamide (side product) depend both on the structure of the starting amine and on the kind of catalyst system: the aromatic amines seem less reactive than the aliphatic ones, while the best catalyst seems to be a complex of Pd(II). In all cases (except benzylamine, entries 7 and 8), the selectivity was very high and oxamide was formed only in a very small amount or it was totally absent. It is to be underlined that in no case isocyanate was evidenced, so only two products were formed during the electrocatalytic carbonylation: diaryl or dialkylurea and oxamide.

The choice of solvent also appeared to be significant; among the solvents used in the electrocarbonyla-

(20) The working potential was slightly more positive than the oxidation peak potential of Pd(0): Carelli, I.; Chiarotto, I.; Cacchi, S.; Pace, P.; Amatore, C.; Jutand, A.; Meyer, G. *Eur. J. Org. Chem.* **1999**, 1471–1473.

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(22) Amines were purchased from commercial sources and were purified prior to use. Standard of disubstituted ureas and oxamides synthesized in this paper, are commercially available. The ureas and oxamides were characterized by comparison of infrared, nuclear magnetic resonance, and mass spectra with those for authentic materials and literature data.

tion, CH₃CN gave the best yields of urea and easiness in the electrolysis work up. Changing the solvent to THF or DMF resulted in a change in the carbonylation products and selectivity (no urea could be evidenced), and further studies are in progress to understand the influence of those solvents on the selectivity of the product.[23]

In conclusion, the electrochemical methodology permits a mild, selective and environmental friendly reoxidation of Pd(0) into Pd(II) in oxidative carbonylation of amines to ureas. The reaction is very selective (in most cases, no side product is formed), and good yields in ureas are obtained from aliphatic amines.

Supporting Information Available: Spectral data of ureas and oxamides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The HPLC analysis of the electrolysis carried out in DMF solvent showed the presence of both isocyanate and carbammic acid, but no qualitative analysis was possible because carbammic acid can be also produced, by hydrolysis of isocyanate, in the HPLC column.