Acta Chemica Scandinavica, 1999: 53: 928–931
Printed in UK. All rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904-213X

Electrochemical Reduction of *N*-Acylureas

M. Gloria Quintanilla,* Guillermo Montero, Angel G. Hierro, Jose M. Díaz and Silvina Bassani

Department of Organic Chemistry, University of Alcalá, 28871 Alcala de Henares, Madrid, Spain

Dedicated to Professor Henning Lund on the occasion of his 70th birthday.

Quintanilla, M. G., Montero, G., Hierro, A. G., Díaz, J. M. and Bassani, S., 1999. Electrochemical Reduction of *N*-Acylureas. Acta Chem. Scand. 53: 928–931. © Acta Chemica Scandinavica 1999.

The cathodic reduction of *N*-acylureas with the structure R–NH–CO–N(COR')–R in an aprotic medium gives *N*-alkylamides (R'–CO–NH–R) and amines (R–NH_2) in a selective cleavage process. The structure of the R' group is a significant factor of the electrochemical process.

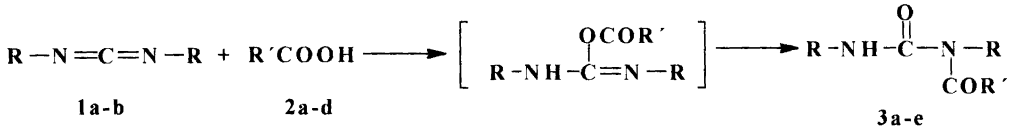
Carbodiimides, and especially dicyclohexylcarbodiimide (DCC) are well known[1] as the most useful reagents for coupling acids and alcohols to form esters or amino acids in peptide synthesis. A number of experiments have also been done on the reaction between carboxylic acids and carbodiimides in the absence of an added nucleophile. The product is often the anhydride, which means that the acid couples with itself, but the corresponding urea and *N*-acylurea are also obtained in amounts varying with the conditions of the reaction, the mechanism of which has been widely described in the literature.[1–4]

The most important factors affecting the final products are type of carbodiimide, strength of the acid, kind of solvent and other active compounds present in the reaction medium.

The first step in the mechanism was postulated as a 1,2-addition of the carboxylic acid to the carbodiimide function, producing an *O*-acylisourea (Scheme 1), which can then act as an acylating agent or rearrange to the commonly obtained *N*-acylurea, as has been often discussed.[4]

Moreover, the stability of the rearranged products has been studied.[3] *N*-Acylureas formed from aromatic carbodiimides dissociate into isocyanates and amides at temperatures above 60 °C, whereas *N*-acylureas formed from aliphatic carbodiimides have proved to be more stable, being dissociated only between 120 and 160 °C. Amides and carbamates have also been obtained by treatment of *N*-acylureas with sodium isopropoxide in isopropyl alcohol or sodium *tert*-butoxide in *tert*-butyl alcohol.[5]

In the present work several *N*-acylureas (compounds **3a–e**, Scheme 1) have been obtained in order to study the electrochemical behaviour of these kinds of com-



R	Comp.
$-CH(CH_3)_2$	**1a**
$-C_6H_{11}$	**1b**

R'	Comp.
-Ph	**2a**
$-CH_2$-Ph	**2b**
$-CHPh-CH_2-CH_3$	**2c**
3,5-$(CH_3)_2$-Ph-	**2d**

R	R'	Comp.
$-CH(CH_3)_2$	-Ph	**3a**
$-C_6H_{11}$	-Ph	**3b**
$-C_6H_{11}$	$-CH_2$-Ph	**3c**
$-C_6H_{11}$	$-CHPh-CH_2-CH_3$	**3d**
$-C_6H_{11}$	3,5-$(CH_3)_2$-Ph	**3e**

Scheme 1.

* To whom correspondence should be addressed.

pound. The outcome of their cathodic reduction depends on the *N*-acyl group employed.

Results and discussion

The reaction of diisopropylcarbodiimide with benzoic acid at room temperature yielded *N*-benzoyl-*N,N'*-diisopropylurea (**3a**) via the quantitative rearrangement of the presumably initially formed *O*-acylisourea, as shown in Scheme 1. Since the products obtained in the reaction between carboxylic acids and carbodiimides are strongly influenced by the solvent employed, as mentioned above,[2] we carried out the process in dry tetrahydrofuran (THF), where the main product obtained was the desired *N*-acylurea and none of the anhydride was found. IR and NMR spectral data confirmed these results.

The reduction of **3a** at a mercury cathode (attempts to perform the reaction on glassy-carbon were unsuccessful) in *N,N*-dimethylformamide (DMF)–$LiClO_4$ under an argon atmosphere gave *N*-isopropylbenzamide and isopropylamine as the only products.

When the electrochemical reduction begins the solution becomes intensely emerald green. This colour slowly disappeared in about two hours when the reaction medium was kept under an argon atmosphere, and in a few minutes when the reaction medium was allowed to stay in contact with the air. It also disappeared when treated with dilute mineral acid or iodine solution in carbon tetrachloride.

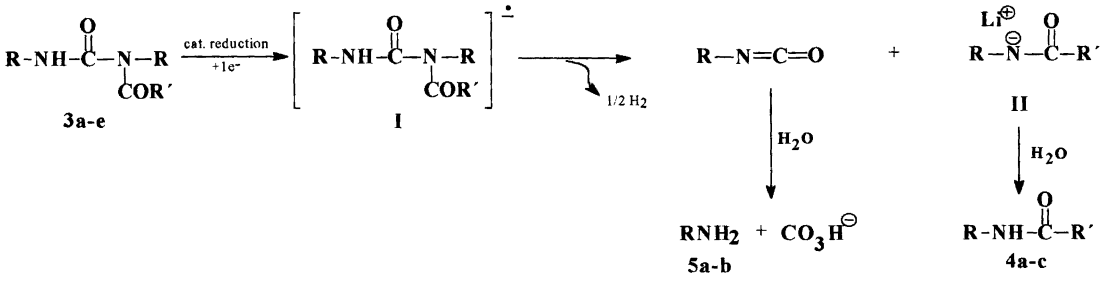
A posible route for the reaction is summarised in Scheme 2. *N*-Acylurea **3a** was reduced upon consumption of 1 F mol^{-1}. The amide **4a** was obtained by protonation during the work-up of the anion **II** produced. The hydrolysis of isopropyl isocyanate yielded isopropylamine **5a**. Alternatively the cleavage of the N–COPh bond in **3a** could lead to the formation of diisopropylurea, but none of this compound was detected. The selective cleavage of **3a** can be explained by resonance stabilization of the amidic anion **II** formed, caused by the presence of the aromatic group.

In order to prove that the corresponding urea is not formed, *N*-benzoyl-*N,N'*-dicyclohexylurea (**3b**) was prepared, since dicyclohexylurea is a very insoluble product and its formation would compete with the formation of the amide. Cathodic reduction of **3b** was performed as described above and again an emerald green colouration appeared, yielding *N*-cyclohexylbenzamide (**4b**) and cyclohexylamine (**5b**), but not dicyclohexylurea.

To check whether the aromatic group present is involved in the reduction process, *N*-phenylacetyl- and *N*-(α-phenyl)butanoyl-*N,N'*-dicyclohexylurea (**3c**, **3d**) (both systems in which the CO group is not conjugated to the aromatic ring) as well as *N*-(3,5-dimethylbenzoyl)-*N,N'*-dicyclohexylurea (**3e**) (containing again an aromatic group conjugated with the carbonyl group) were prepared.

In the cathodic reduction of **3e**, the green colouration appeared (and disappeared upon treatment of drops of the reaction medium with a dilute solution of iodine in carbon tetrachloride) but changed to brown before the reaction ended. As before, the corresponding *N*-cyclohexyl-3,5-dimethylbenzamide (**4c**) and cyclohexylamine (**5b**) were obtained.

However, the cathodic reduction of compounds **3c** and **3d** could not be carried out since their reduction potential appeared to be more negative than that of the SSE (solvent-supporting electrolyte) employed. This fact might be explained by the electron-withdrawing effect of the aroyl group in *N*-acylureas **3a**, **3b** and **3e**, whereas in compounds **3c** and **3d** the aliphatic chain avoids this effect, presumably causing the increased reduction poten-



R	Comp.
$-CH(CH_3)_2$	**5a**
$-C_6H_{11}$	**5b**

R	R'	Comp.
$-CH(CH_3)_2$	-Ph	**4a**
$-C_6H_{11}$	-Ph	**4b**
$-C_6H_{11}$	$3,5-(CH_3)_2$-Ph-	**4c**

Scheme 2.

tials. In conclusion, only *N*-acylureas with aromatic groups conjugated with the carbonyl group can be reduced in the SSE employed, and they undergo selective cleavage as described above.

Experiments were performed with equimolecular amount of sodium amalgam in THF for **3a** and in DMF for **3b** and the emerald green colouration appeared again. The corresponding amides (**4a**, **4b**) and amines (**5a**, **5b**), as in the electrochemical process, were obtained.

Experimental

The electrolysis was carried out using an Amel potentiostat Model 552 with an electronic integrator Amel Model 721. Mass spectra (EI, ionizing voltage 70 eV) were determined using a Hewlett-Packard Model 5988A mass-selective detector equipped with a Hewlett-Packard MS ChemStation. IR spectra were obtained for dispersions in KBr, on a Perkin-Elmer Model 883 spectrometer. ^{1}H NMR (300 MHz) spectra were recorded on a Varian Unity 300 apparatus with deuteriochloroform as an internal standard. The chemical shifts are given in ppm. Melting points were determined on a Reichter Thermovar micro-hot-stage apparatus, and are uncorrected. Polarography and cyclic voltammetry were carried out on a Metrohm apparatus Model 663 VA Stand and a Scanner 626 Polarecord. The potential values are given in V vs. the calomel electrode. Analytical HPLC was performed on a Hewlett-Packard 5033 instrument, using a reversed-phase column and 80% methanol–water as the eluent.

General procedure for N-*acylureas* (**3a–d**). To a solution of diisopropyl- (**1a**) or dicyclohexyl-carbodiimide (**1b**) (0.02 mol) in dry THF (20 ml) placed in a 50 ml two-necked round-bottomed flask equipped with magnetic stirrer, calcium chloride tube and septum, were added at room temperature with a syringe 0.02 mol of benzoic acid (**2a**), phenylacetic acid (**2b**), α-phenylbutyric acid (**2c**) or 3,5-dimethylbenzoic acid (**2d**) dissolved in 20 ml of dry THF. Immediate reaction took place and the corresponding urea precipitated. The mixture was allowed to stand overnight at room temperature and then the urea was filtered off and washed with more THF. The filtrates were evaporated under reduced pressure and then the residue recrystallized to give the *N*-acylurea (**3a–e**).

N-*Benzoyl*-N,N′-*diisopropylurea*[6] (**3a**). Starting from **1a** and **2a**, 2.9 g (0.012 mol, 62% yield) of **3a** were obtained. M.p. (petroleum ether–ethanol): 110–112 °C. IR (KBr): 3303, 2976, 2877, 1675, 1644, 1545 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, 2 H, J=7 Hz), 7.66 (t, 1 H), 7.50 (t, 2 H), 6.65 (s, 1 H,), 4.38 (septet, 1 H, J= 6 Hz), 3.58 (septet, 1 H, J=6 Hz), 1.40 (d, 6 H), 0.95 (d, 6 H). MS *m/z* (%): 248 (4), 162 (16), 148 (32), 105 (100), 77 (35).

N-*Benzoyl*-N,N′-*dicyclohexylurea*[3] (**3b**). Starting from **1b** and **2a**, 4.26 g (0.013 mol, 68% yield) of **3b** were obtained. M.p. (ethanol): 162–167 °C. IR (KBr): 3302, 2933, 2855, 1697, 1649, 1544 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, 2 H, J=7 Hz), 7.49–7.33 (m, 3 H), 6.13 (d, 1 H), 4.06 (quintet, 1 H), 3.44 (quintet, 1 H), 2.13–0.78 (m, 20 H). MS *m/z* (%): 328 (2), 247 (20), 202 (9), 105 (100), 77 (55).

N-*Phenylacetyl*-N,N′-*dicyclohexylurea*[7] (**3c**). Starting from **1b** and **2b**, 5.14 g (0.015 mol, 79% yield) of **3c** were obtained. M.p. (ethanol): 115–118 °C. IR (KBr): 3344, 2934, 2858, 1704, 1652, 1522 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.23 (m, 5 H), 4.05–395 (m, 1 H), 3.7 (s, 2 H), 2.0–1.1 (m, 20 H). MS *m/z* (%): 342 (8), 217 (23), 118 (21), 91 (100), 83 (53).

N-*(α-Phenyl)butyryl*-N,N′-*dicyclohexylurea* (**3d**). Starting from **1b** and **2c**, 3.79 g (0.010 mol, 52% yield) of **3d** were obtained. M.p. (ethanol): 150–152 °C. IR (KBr): 3295, 2928, 2856, 1699, 1655, 1535 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3–7.25 (m, 5 H), 4.1–4.01 (m, 1 H), 3.62 (t, 1 H), 3.21–3.15 (m, 1 H), 2.07 (quintet, 2 H), 1.92–1.09 (m, 20 H), 0.84 (t, 3 H). MS *m/z* (%): 370 (5), 245 (18), 120 (35), 91 (73), 83 (100).

N-*(3,5-Dimethyl)benzoyl*-N,N′-*dicyclohexylurea* (**3e**). Starting from **1b** and **2d**, 5.24 g (0.014 mol, 77% yield) of **3e** were obtained. M.p. (ethanol): 167–168 °C. IR (KBr): 3314, 2927, 2857, 1697, 1649, 1542 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7,10 (s, 2 H), 7.05 (s, 1 H), 6.22 (br s, 1 H), 4.17–4.0 (m, 1 H), 3.1–3.23 (m, 1 H), 2.29 (s, 6 H), 2.06–1.14 (m, 20 H). MS *m/z* (%): 356 (0.1), 282 (5), 133 (100), 105 (16), 77 (7).

General procedure for the electrochemical reduction of compounds **3a–e**. Reference electrode: saturated calomel electrode (SCE); anode: platinum; anolyte: lithium perchlorate (4×10^{-3} mol) in dry *N,N*-dimethylformamide (DMF) (30 ml); cathode: mercury pool; catholyte: lithium perchlorate (5×10^{-3} mol) in 40 ml dry DMF and 3×10^{-3} mol of compound **3a–e**; electrolysis cell: divided cell, containing a piece of glass tubing with a glass of medium porosity at one end (anode compartment), thermostatted at 15 °C, equipped with magnetic stirrer. The cell top was fitted with O-ring sealed ports for the working electrode, reference electrode and argon connection (bubbling through for 10 min before the reaction started and then sweeping smoothly over the solution in the cell throughout the whole process). Solid potassium carbonate (2.0 g) was added to the anode compartment to neutralise the perchloric acid generated. In the cathodic compartment a light solid was formed during the process (presumably the lithium salt of anion **II**). The cathodic solution was poured over ice–water, and a white solid precipitated, which was identified as the corresponding amide (**4a–c**). The solution was treated with 5% HCl solution and extracted with

dichloromethane to remove the *N*,*N*-dimethylformamide. The acidic solution was basified and extracted again with the same solvent. In the organic extracts the corresponding amine (**5a**, **b**) was identified by HPLC and mass spectrometry.

Cathodic reduction of **3a**. CV measurements showed a reduction peak at −2.1 V. A constant cathodic potential between −2.1 and −2.2 V was applied. An emerald green colouration appeared. The end of the process was controlled by TLC. The charge consumption in that moment was 1 F mol^{-1}, although the decrease in the current could not be properly observed, since the working potential was too close to the SSE reduction potential. *N*-Isopropylbenzamide **4a** (1.8 mmol, 60% yield) was obtained (m.p. 95–97 °C) and identified by its spectroscopic data. IR (KBr): 3342, 2969, 2877, 1624, 1577 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 2 H), 7.43–7.40 (m, 3 H), 5.90 (s, 1 H), 4.25 (septet, 1 H), 1.25 (d, 3 H). MS *m/z* (%): 163 (23), 142 (6), 105 (100), 77 (31).

Cathodic reduction of **3b**. CV measurements showed a reduction peak at −2 V. A cathodic potential between −1.9 and −2.1 V was applied. In this case the decrease in the current could be observed, so the charge consumption could be clearly measured as 1 F mol^{-1}. Again the green colouration appeared and remained until the work-up. *N*-Cyclohexylbenzamide **4b** (2.6 mmol, 86% yield) was obtained (m.p. 138–140 °C) and identified by its spectroscopic data. IR (KBr): 3322, 2931, 2854, 1627, 1574, 1533 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2 H), 7.50–7.39 (m, 3 H), 5.96 (br s, 1 H), 3.99–3.96 (m, 1 H), 2.05–1.14 (m, 10 H). MS *m/z* (%): 224 (0.6), 203 (38), 122 (72), 105 (100), 77 (41).

Cathodic reduction of **3c** *and* **3d**. CV measurements showed no reduction peaks below the potential limit for the SSE employed. Nevertheless the experiment was performed. The current flow began only when the applied potential achieved the value of −2.3 or −2.4 V (potential limit for the SSE), but no green colouration appeared. A charge consumption of 2 F mol^{-1} was allowed to pass. However, the starting material was recovered untransformed after work-up (the reaction was also monitored by TLC during the electrolysis).

Cathodic reduction of **3e**. CV measurements showed a reduction peak at −1.9 V. A constant cathodic potential between −1.9 and −2.1 V was applied. The initial green colour of the reaction medium changed to brown, a colour which remained until work-up. As before the charge consumption was of 1 F mol^{-1} and *N*-cyclohexyl-3,5-dimethylbenzamide **4c** (2.2×10^{-3} mol, 75% yield) was obtained (m.p. 140–142 °C). IR (KBr): 3350, 3285, 2927, 2856, 1626, 1601, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (s, 2 H), 7.08 (s, 1 H), 5.91 (br s, 1 H), 3.99–3.84 (m, 1 H), 2.33 (s, 6 H), 2.03–1.01 (m, 20 H). MS *m/z* (%): 231 (19), 150 (46), 133 (100), 105 (24), 77 (11).

Acknowledgements. This study was financed by the Spanish Ministry of Education and Culture through project PB97-0753 of which Prof. F. Barba is the main respondent.

References

1. Khorana, H. G. *Chem. Rev. 53* (1953) 145.
2. Mikolajczyk, M. and Kielbasinski, P. *Tetrahedron Lett. 37* (1981) 233.
3. Schotman, A. H. M. *Recl. Trav. Chim. Pays-Bas 110* (1991) 319.
4. Jacobs, A. *Understanding Organic Reaction Mechanisms*, Cambridge University Press, Cambridge 1997.
5. Hajos, Z. G., Parrish, D. R. and Goldberg, M. W. *J. Org. Chem. 30* (1965) 2849.
6. Palau, E. and Hartke, K. *Rev. Real Acad. Cienc. Exactas Fis. Natur. Madrid 62* (1968) 155.
7. Palau, E. and Hartke, K. *Chem. Ber. 99* (1966) 3155.

Received December 28, 1998.