Reactions of N,N'-carbonyldisuccinimide with Nitrogen-containing Nucleophiles

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N,N'-Carbonyldisuccinimide can react with aliphatic amines by two pathways depending upon reaction conditions. Thus, in non-polar solvents, new compounds of the N-alkyl-4(3-alkyl-ureido)-4-oxo-butyramide type are obtained, whereas in polar solvents N,N'-carbonyldisuccinimide can be used as a substitute for phosgene, in which case symmetrically disubstituted ureas are obtained.

Key words: N,N'-Carbonyldisuccinimide, amines, ureas, N-alkyl-4(3-alkyl-ureido)-4-oxo-butyramide

N,N'-Carbonyldisuccinimide was obtained for the first time by our research group from triphosgene and succinimide, the reaction taking place in dichloromethane in the presence of trimethylamine [1]. Our search for this compound arose from literature reports about carboxylic acids derivatives of succinimide which manifested enhanced reactivity with nitrogen- and oxygen-containing nucleophiles [2].

N,N'-carbonyldisuccinimide has become a focus of interest for our research group in recent years because carbonic acid derivatives of enhanced reactivity [3] can be used in place of phosgene. This paper describes results obtained from studies on the reaction behaviour of *N,N'*-carbonyldisuccinimide with aliphatic amines under various conditions.

Experimental part

Melting points were determined on Boetius apparatus (Carl Zeiss Jena). The IR spectra were recorded in KBr pellet for the solid compounds with a Jasco FT/IR-430 instrument. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX 200 MHz NMR spectrometer (200- and 50 MHz, respectively). Mass spectra were recorded on a MS Varian MAT 212 (MI). N,N'-Carbonyldisuccinimide **1** was obtained by the method described [1]. All reagents and solvents were purchased from chemical suppliers and used without further purification.

Preparation of N-alkyl-4(3-alkyl-ureido)-4-oxo-butyramide 2a-b. General Procedure

To a suspension of *N,N'*-carbonyldisuccinimide (0.2 g, 0.89 mmole) in 10 ml dichloromethane was added a solution of primary amine (2.67 mmole) in 5 mL dichloromethane. The reaction mixture is kept agitated at room temperature for a specified period after which the newly-formed precipitate is filtered and washed with excess solvent.

N-cyclohexyl-4(3-cyclohexyl-ureido)-4-oxo-butyramide **(2a)** After 8 h 0.23g white product was obtained (yield 80%) with m.p. 205-207°C; ν_{max} (cm^{-1}) 3289.9m, 2934m, 2854m, 1688.4i, 1639.2i, 1556.2i, 1219m; δ_H(200 MHz; $CDCl_3$) 9(s, 1H, NH H-5), 8.2(d, 1H, NH, H-2) , 5.5(d, 1H, NH, H-6), 3.7(m, 2H, H-1), 2.6 (t, 2H, J= 12.2 Hz, H-3), 2.4(t, 2H, J=12.1 Hz, H-4), 1.64(m, 8H,), 1.2(m, 12H); δ_C(50 MHz; $CDCl_3$) 173.7($C{=}O_{amidic}$), 169.8($C{=}O_{amidic}$), 152.6($C{=}O_{ureic}$), 48.4 (CH), 33, 32.8, 32.2, 30.7, 30, 25.4, 24.7, 24.5 (CH_2); *m/z* 54(50), 98(44), 182(38), 100(100), 323 (1.03,M^+)

N-benzyl-4(3-benzyl-ureido)-4-oxo-butyramide **(2b)** After 10 h 0.284g white product was obtained (yield 93%) with m.p. 210- 212°C; ν_{max} (cm^{-1}) 3307i, 1703.8i, 1682.5i, 1638.2i, 1223m; δ_H(200 MHz; DMSO-d_6) 10.4(s,1H, NH, H-6), 8.7(t, 1H, NH, H-3), 8.3(t, 1H, NH, H-7), 7.29-7.24(m, 10H, arom.), 4.38(d, 2H, J = 5.8Hz, H-2), 4.26(d, 2H, J = 5.7Hz, H-8), 2.56(t, 2H, J = 6.2Hz, H-4), 2.45(t, 2H, J = 5.96Hz, H-5); δ_C(50 MHz; DMSO-d_6) 175($C{=}O_{amidic}$), 171($C{=}O_{amidic}$), 164($C{=}O_{ureic}$), 134.5(C), 128.2, 127.1, 126.6 (CH), 42.5, 42.0(CH_2-N), 30.9, 29.1(CH_2-C=O); *m/z* 78(35), 92(100), 106(87), 189(58), 339(4, M^+)

Preparation of symmetrical N,N'- dialkyl ureas 3a-b. General Procedure

To a solution of *N,N'*-carbonyldisuccinimide (0.17 g, 0.75 mmole) in 7 mL acetonitrile was added a solution of the primary amine (2.1 equivalents, 1.59 mmole) in 3 mL acetonitrile. The reaction mixture was maintained under reflux for 4 h, after which the product was isolated from the cooled solution.

N,N'-Dicyclohexyl urea **(3a)** 0.133 g white crystalline product (yield 78.5%) was isolated from the reaction mass by filtration. M.p. 232-234°C (Lit. 228°C [4]; 229-230°C[5]); $\nu_{C=O}$(cm^{-1})= 1624 (Lit. 1635 [4]); δ_H(200 MHz; DMSO-d_6) 1.3(m, 12H), 1.8(m, 8H), 3.6(m, 2H), 6(s, 2NH); δ_C(50 MHz; DMSO-d_6) 24.3($4CH_2$), 25.2($2CH_2$), 33.3($4CH_2$), 47.4(2CH), 156.5(C=O). *m/z* = 224

N,N'-Dibenzyl urea **(3b)** 0.153g white product (yield 85%) was obtained by separation using silica gel column chromatography, eluting with CH_2Cl_2: MeOH = 10:1. M.p. 166-167°C; $\nu_{C=O}$(cm^{-1})= 1626; δ_H(200 MHz; $CDCl_3$) 4.22(d, 4H), 6.5(t, 2NH), 7.3 (m; 10H); δ_C(50 MHz; $CDCl_3$) 43($2CH_2$), 126.7(CH), 127.1(4CH), 128.4(4CH), 141(2C), 158.3(C=O). *m/z* = 240

Results and discussion

N,N'-carbonyldisuccinimide (**1**) was initially treated with cyclohexylamine for the purpose of obtaining *N,N'*-dicyclohexylurea (**3a,** scheme 1). The reaction was studied in conditions similar to the reactions of *bis*(*o*-nitrophenyl)carbonate with aliphatic amines [6] working

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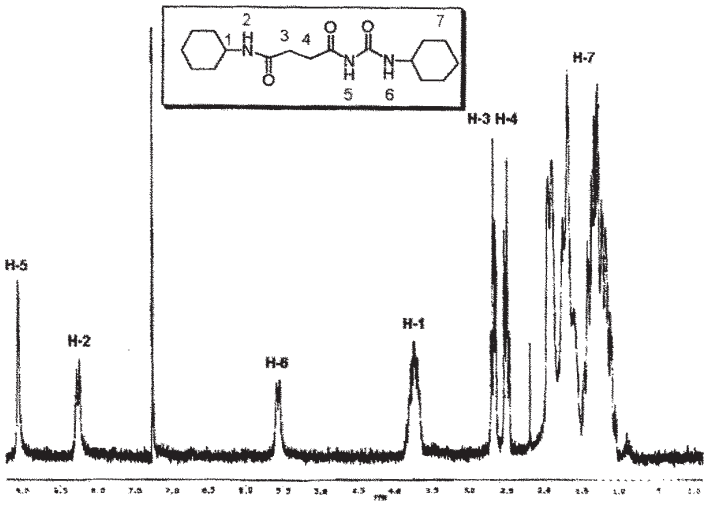


Fig. 1. ^{1}H-NMR spectrum of *N*-cyclohexyl-4(3-cyclohexyl-ureido)-4-oxo-butyramide (2a).

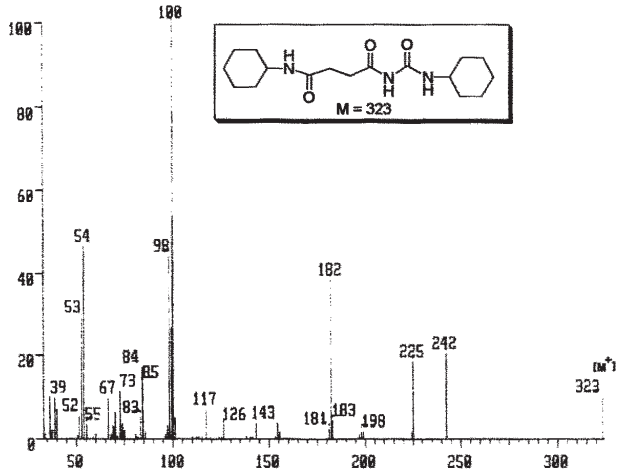
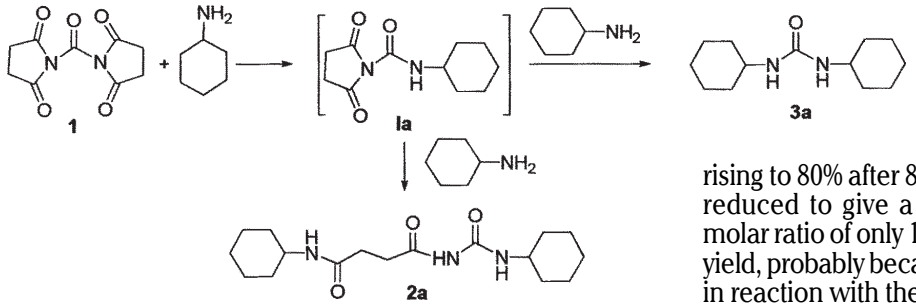


Fig. 2. Mass spectrum for *N*-cyclohexyl-4(3-cyclohexyl-ureido)-4-oxo-butyramide (2a)



Scheme 1

in dichloromethane at room temperature, at a molar reaction ratio of *N,N'*-carbonyldisuccinimide: amine = 1:3. The precipitate formed after 30 min from the combination of the reactants in the reaction medium was analysed by ^{1}H-NMR spectrometry (fig. 1), the spectrum showing a chemical shift corresponding to a novel compound, *N*-cyclohexyl-4(3-cyclohexyl-ureido)-4-oxo-butyramide (**2a,** scheme 1): a singlet for a proton at 9 ppm, associated with the NH group connected with two C=O groups (H-5), a doublet at 8.2 ppm and another at 5.5 ppm, associated with the other NH group (H-2 and H-6 respectively), a multiplet at 3.7 ppm for the two protons specific to CH groups in the two cyclohexyl rings (H-1), two triplets at 2.4 ppm and at 2.6 ppm, which are specific for the two CH_2 groups (H-3, H-4) (and which indicate the cleavage of the succinimide ring) and multiples at 1.64 ppm and 1.2 ppm which are specific to cyclohexyl groups (H-7).

In addition mass spectrometry analysis yielded a molecular peak at 323 D. This peak corresponds to the molecular mass of *N*-cyclohexyl-4(3-cyclohexyl-ureido)-4-oxo-butyramide (**2a**).

This product results from nucleophilic attack by the amine group both on the urea carbonyl group and on the carbonyl group in the succinimide ring. It is known from the literature that succinimide can react with amine forming N-substituted succinimide with the result that the imide ring is broken [7]. In this case it appears that the first-formed intermediate is N-cyclohexyl-N-carbamoyl-succinimide (**Ia,** scheme 1), which then in the presence of excess amine undergoes a cleavage of the succinimide ring with the final formation of *N*-cyclohexyl-4(3-cyclohexyl-ureido)-4-oxo-butyramide (**2a,** scheme 1).

Reaction yield under these conditions was 10%. If the reaction time was increased to 2h the yield reached 28%, rising to 80% after 8 h (table 1). If the excess of amine was reduced to give a *N,N'*-carbonyldisuccinimide : amine molar ratio of only 1 : 2.1 product **2a** was obtained in lower yield, probably because some of the amide was consumed in reaction with the succinimide eliminated following the formation of the intermediate. The intermediate N-cyclohexyl-N-carbamoylsuccinimide (**Ia**) was not identified in the reaction medium.

The synthesis was repeated in acetonitrile partly from the consideration that *N,N'*-carbonyldisuccinimide is readily soluble in this solvent and partly because it allows the use of more energetic reaction conditions. The first reaction carried out at room temperature in this solvent led to the formation of N,N'-dicyclohexylurea (**3a**) in a yield of 63% after 4h. Increasing the reaction time did not increase the yield, but if carried out under reflux the urea product was formed in 78% yield after 4h (table 1).

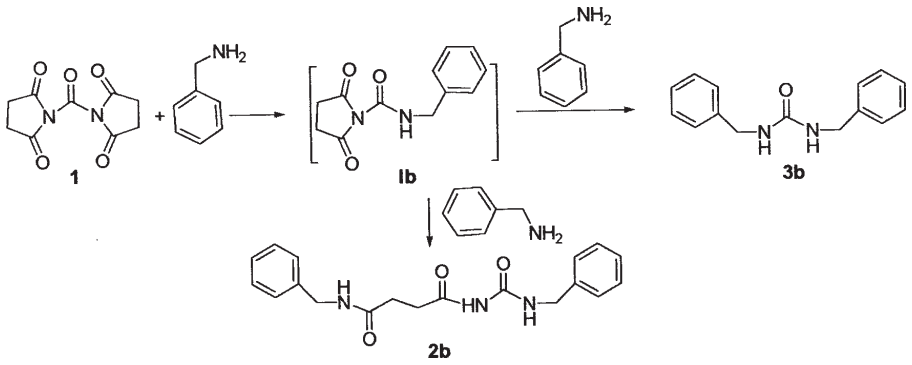
Table 1
REACTION CONDITIONS *N,N'*-CARBONYLDISUCCINIMIDE (CDS) WITH CYCLOHEXYLAMINE (A)

Molar ratio CDS:A	Solvent	Time, conditions	Product	Yield (%)
1: 3	CH_2Cl_2	30 min r.t.	**2a**	10
		2h		28
		8h		80
1: 2.1		24h		50
1: 2.1	CH_3CN	4h, r.t.	**3a**	62.6
		4h, reflux.		78.5

r.t. = room temperature

The study was extended to the reaction of *N,N'*-carbonyldisuccinimide with benzylamine under the same conditions as described in scheme 2.

N-benzyl-4(3-benzyl-ureido)-4-oxo-butyramide (**2b,** scheme 2) was isolated by precipitation from the reaction medium in high yield (93%) at room temperature when the working solvent was dichloromethane and the *N,N'*-



Scheme 2

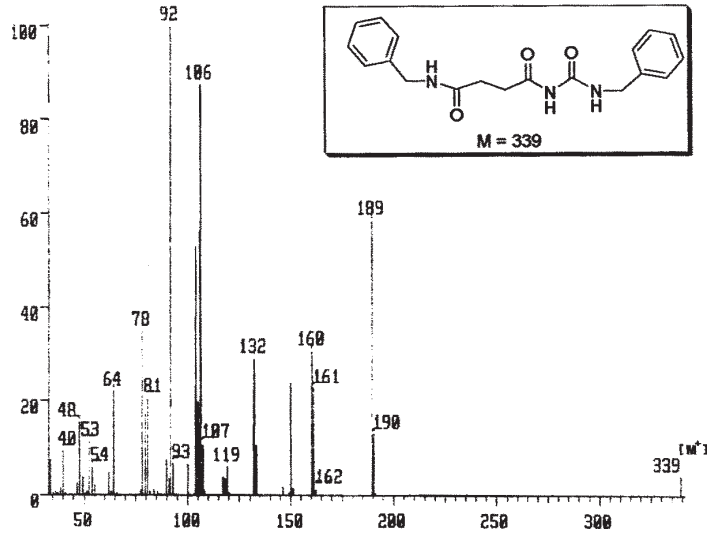


Fig. 3. Mass spectrum of *N*-benzyl-4(3-benzyl-ureido)-4-oxo-butyramide (2b)

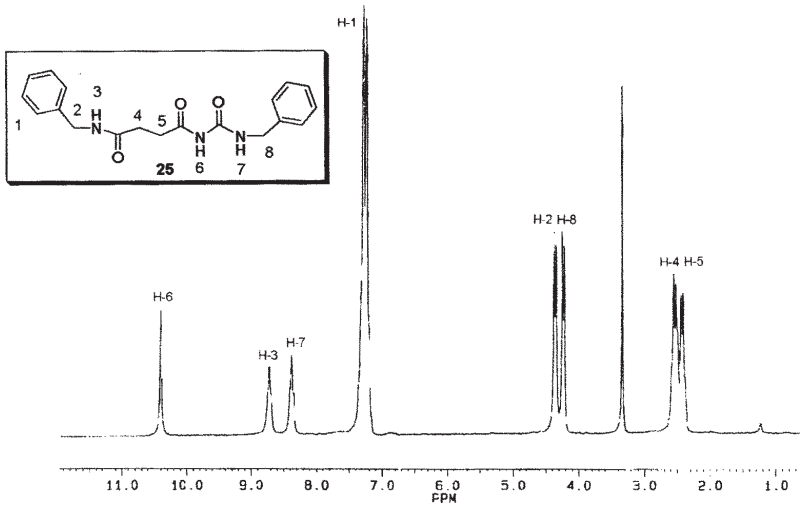


Fig. 4. ^{1}H-NMR spectrum of *N*-benzyl-4(3-benzyl-ureido)-4-oxo-butyramide (2b)

carbonyldisuccinimide: benzylamine molar ratio was 1: 3 (table 2).

The mass spectrum of the product shows a molecular peak at 339 D corresponding to the molecular mass of *N*-benzyl-4(3-benzyl-ureido)-4-oxo-butyramide (**2b**) (fig. 3), while the ^{1}H-NMR spectrum confirms the structure of this compound in showing chemical shift of protons within the molecule (fig. 4): a proton singlet at 10.4 ppm which belongs to the NH group connected to the two C=O groups (H-6), two triplets at 8.7 ppm and 8.3 ppm, which belong to the other two NH groups (H-3 and H-7), a multiplet at 7.29 ppm for the ten aromatic protons (H-1), two doublets at 4.3 ppm and 4.2 ppm for the two CH_2 groups bonded to the aromatic nucleus (H-2, H-8) and two triplets and 2.5 ppm and 2.4 ppm for the two succinic CH_2 groups (H-4, H-5).

When the synthesis was carried out in acetonitrile, whether at room temperature or under reflux, *N*-benzyl-4(3-benzyl-ureido)-4-oxo-butyramide was obtained (**2b**) but in lower yield (table 2). The symmetrical urea N,N'-dibenzylurea (**3b**), was also obtained in this situation, but, being soluble in acetonitrile, remains in the filtrate alongside the secondary product succimimide. It was isolated in 85% yield by column chromatography with **2b** being obtained in the lowest amount (table 2).

Table 2
REACTION CONDITIONS FOR THE REACTION OF *N,N'*-CARBONYLDISUCCINIMIDE (CDS) WITH BENZYLAMINE (A)

molar ratio CDS:A	Solvent	Time, conditions	Product	Yield (%)
1: 3	CH_2Cl_2	1h, r.t.	**2b**	47.7
		10h, r.t.		93.16
1: 2.1	CH_3CN	4h, r.t.	**2b** (3b)*	42
1: 2.1	CH_3CN	4h, reflux.	**2b** (3b)*	14.7

* Compound **2b** precipitates in cold acetonitrile whereas *N,N'*-dibenzylurea **(3b)** remains in solution. (r.t. = room temperature)

Conclusions

N,N'-carbonyldisuccinimide has been shown to be a compound with double application: in reaction with aliphatic amines, depending on the reaction conditions employed, it can either be used as a replacement for phosgene, leading to the formation of symmetrically disubstituted ureas, or for the obtaining of new compounds of the N-alkyl-4(3-alkyl-ureido)-4-oxo-butyramide family following attack by amine, present in excess, on the carbonyl group in the succinimide ring of N-alkyl-N-carbamoylsuccinimide, which is formed as an intermediate by succinimide elimination. In this way two new compounds have been obtained and a new method of obtaining some already-characterised ureas has been established.

References

1.SIMON, M., CSUNDERLIK, C., JONES, P. G., NEDA, I., FISCHER, A. K., Acta Cryst., **E 59**, 2003, p. 0686-7.

2.KATRITZKY, A. R., YANG, B., QIU, G., ZHANG, Z., Synthesis, **1**, 1999, p.55

3.a) SIMON, M., CSUNDERLIK, C., TIRNĂVEANU, A., Rev. Chim. (Bucharest), **52**, nr. 7-8, 2001 p. 371; b) SIMON, M., CSUNDERLIK, C., MEDELEANU, M., DINACHE, A., Rev. Chim.(Bucharest), **53**, nr. 7, 2002, p. 535; c) SIMON, M., CSUNDERLIK, C., JONES, P. G., NEDA, I., FISCHER, A. K., Acta Cryst., **E 59**, 2003, p. 0688; d) SIMON, M., CSUNDERLIK, C., JONES, P. G., NEDA, I., FISCHER, A. K., Acta Cryst. **E 59,** 2003, p. 0691; e) SIMON, M., CSUNDERLIK, C., JONES, P. G., NEDA, I., TARTA-MICLE, ANDREEA., Acta Cryst. **E 59,** 2003, p. 0683-0685; f) SIMON, M., CSUNDERLIK, C., MEDELEANU, M., Rev. Chim.(Bucharest), **54**, nr. 4, 2003, p. 325; g) SIMON, M., CSUNDERLIK, C., COTARCĂ, L., CĂPROIU, M.T., NEDA, I., TUROCZI, M. C., VOLPICELLI, R., Synth Commun., **35**, nr. 11, 2005, p.1471; h) SEGNEANU, A., MILEA, M., PINTEA, B., SIMON, M., CSUNDERLIK, C. Rev. Chim.(Bucharest), **57**, nr. 7, 2006 p. 739-42; i) SIMON, M., MICLE, A., ARMEANU, I., MEDELEANU, M., CSUNDERLIK, C. Rev. Chim.(Bucharest), **57**, nr. 11, 2006 p.1115-8; j) SIMON, M., MICLE, A., TUROCZI, M. C., BADEA, V., CSUNDERLIK, C., Rev. Chim.(Bucharest), **57**, nr. 4, 2006, p. 383; k) TUROCZI, M.-C., SIMON, M., BADEA, V., CSUNDERLIK, C. Molecules **13**, 2008, p. 3192; l) SIMON, M., MICLE, A., BADEA, V., CSUNDERLIK, C. Synth Commun., **39**, nr. 15, 2009, p. 2633

4.IZDEBSKI, J., PAWLAK, D. Synthesis 1989 p. 423

5.SKITA, A., ROLFES, H., Ber. Dtsch. Chem. Ges., **53**, 1920, p.1242

6.SIMON, M., TUROCZI, M. C., BADEA, V., CSUNDERLIK, C., Rev. Chim.(Bucharest), 2009, in press

7.SHEREMETEVA, T. V., GUSINKAYA, V. A., KUDRYAVTSEV, V. V., Russian Chem. Bull., 12, nr. 10, 1963, p. 1670-2

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