Synthesis of *N*-carbamylimides by a New More Efficient Method

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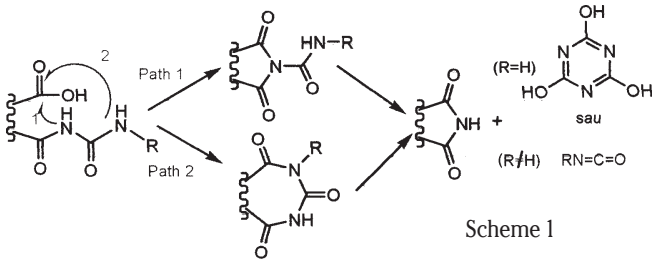
Cyclization of N-carbamylamic acids in nitrobenzene in the presence of trifluoracetic acid at 90-95°C gave N-carbamylimides. Products were characterized by melting point, IR spectroscopy and ^{1}H- and ^{13}C-NMR spectrometry.

Keywords: N-carbamylamic acids, N-methylcarbamylsuccinamic acid, N-carbamylimides, N-methylcarbamylsuccinimide, nitrobenzene, trifluoracetic acid

N-carbamylamic acids (uric acids) can cyclise through nucleophilic attack on the carbon atom of the carboxyl group by the two nitrogen atoms: one from the imidic group (Path 1, scheme 1) and another from the amidic group (Path 2, scheme 2). Taking into account the nucleophilicity of the two nitrogen atoms, the attack of the amidic nitrogen atom is more likely to occur because it has a pronounced nucleophilic character, its lone pair of electrons being involved in conjugation with only one carbonyl group. This attack leads to the obtaining, in most known cases (5-membered cycle, namely succinic, maleic and phthalic anhydrides) of 7-membered cycle (Path 2) which is less stable than the 5-membered cycle, obtained when nucleophilic attack of imidic nitrogen atom occurs (Path 1).

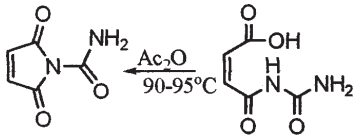


Scheme 1

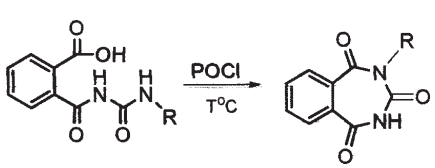
Literature data confirm that the above-mentioned reaction may occur both by Path 1 and Path 2. If the reaction follows Path 1, *N*-carbamylimides are obtained; in the case of Path 2, 7-membered cyclic ureas are obtained.

Thus, heating maleuric acids[1,2] at temperatures of 90-95°C in acetic anhydride led to the formation of *N*-carbamylmaleinimides [2,3] (scheme 2). Uric acids obtained from succinic, itaconic and citraconic anhydrides and urea cyclised similarly to corresponding *N*-carbamylimides [1,3].

Instead, phthaluric acids (also called ureides of phthalic acid [4,5]) when heated in the presence of phosphorus oxychloride gave phthalyl ureas[4] (scheme 3).



Scheme 2



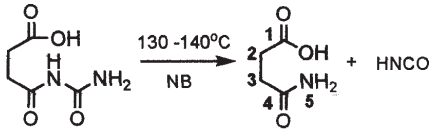
Scheme 3

As far as we know, no information about the synthesis of *N*-carbamylphthalimides (involving phtaluric acids to cyclization following Path 1) nor about the obtaining of succinyl or maleimyl ureas (that is the corresponding uric acids to cyclicize following Path 2) has been previously published.

In this paper we report the cyclization in new conditions of *N*-carbamylamic acids (uric acids) recently obtained from succinic, maleic and phthalic anhydrides and various ureas [6,7].

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 AC 200 MHz NMR spectrometer (200 and 50 MHz, respectively). Nitrobenzene was distilled before use. N-carbamylamic acids were prepared according to literature data [6,7]. Succinic anhydride, urea, N-methyl urea and trifluoracetic acid were purchased from chemical suppliers and used without further purification.

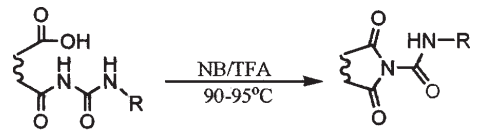


1a **2**

Scheme 4

*Decomposition of N-carbamylsuccinamic acid (**1a**) in succinamic acid (**2**)*

10 mmol (1.6 g) *N*-Carbamylsuccinamic acid was added to 25 mL nitrobenzene. The reaction mixture was heated to 130-140 °C and maintained for 40 min. During this time the *N*-carbamylsuccinamic acid dissolved. The solution was cooled and the solid crystalline precipitate formed was filtered (1.05g) and analyzed proving to be succinamic acid (η=90%). IR (KBr pellet, cm^{-1}): 1727, 1708, 1648 (Lit. 1726, 1709, 1651[8]); ^{1}H-NMR(200 MHz, DMSO-d$_6$): δ 2.35 (dd, 4H); 6.7 (s, 1H, NH); 7.23 (s, 1H, NH); ^{13}C-NMR(50 MHz, DMSO-d$_6$): δ 29 (C-2); 29.7 (C-3); 173.1 (C-4); 173.8 (C-1).



1a-f Scheme 5 **3a-f**

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General procedure for the preparation of N-carbamylimides

To a mixture of *N*-carbamylamic acid (10 mmol) in 10 mL nitrobenzene, TFA (0.1eq) was added. The reaction mixture was heated to 90-95°C and maintained for 35-40 min, in which time the solid dissolved. On cooling the solid crystalline precipitate formed was filtered and washed with acetone. When the reaction was repeated in mother liquor from the first cyclization the yield increased significantly.

***N*-carbamylsuccinimide (3a)**

1.136 g (η = 80%) of white product was obtained. M.p. 136-138UCC (Lit. 90-110°C[2]); **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1703, 1658; **^{1}H-NMR**(200 MHz; DMSO-d_6, ppm): 2.68(s, 4H), 7.69(s, NH), 7.91(s, NH); **^{13}C-NMR**(50 MHz; DMSO-d_6, ppm) 28.5, 149(C=O ureic), 175.3(2 x C=O amidic)

***N*-methylcarbamylsuccinimide (3b)**

1.40 g (η = 90%) of white product was obtained. M.p. 157-160°C; **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1794, 1741, 1691; **^{1}H-NMR**(200 MHz; DMSO-d_6, ppm): 2.69(s, 4H), 2.72(d, 3H), 8.33(s, NH); **^{13}C-NMR** (50 MHz; DMSO-d_6, ppm) 26.7, 29.1, 148.7(C=O), 175.1(C=C)

***N*-carbamylmaleimide (3c)**

1.232 g (η = 88%) of white product was obtained. M.p. 156-158°C (Lit. 157-158°C[2]); **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1811, 1790, 1740; **^{1}H-NMR**(200 MHz; DMSO-d_6, ppm): 7.08(s, 2H), 7.35(s, NH), 7.7(s, NH); **^{13}C-NMR**(50 MHz; DMSO-d_6, ppm) 135.4, 148, 169.

***N*-methylcarbamylmaleimide (3d)**

1.263 g (η = 82%) of white product was obtained. M.p. 140-143°C ; **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1795.4, 1737; **^{1}H-NMR**(200 MHz; DMSO-d_6, ppm): 2.74(d, 3H), 7.12 (s, 2H), 8.08(s, NH); **^{13}C-NMR**(50 MHz; DMSO-d_6, ppm) 26.7, 135.2, 147.7, 168.5

***N-terţ*-butylcarbamylmaleimide (3e)**

1.27 g (η = 65%) of white product was obtained. M.p. 106-108°C(106-107.5°C[2]); **^{1}H-NMR**(200 MHz; DMSO-d_6, ppm): 1.35(s, 9H), 6.92 (s, 2H), 7.45(s, NH);

***N*-methylcarbamylphthalimide (3f)**

1.61 g (η = 79%) of product was obtained. M.p. 173-175°C; **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1703, 1674; **^{1}H-NMR**(200 MHz; DMSO-d_6, ppm): 2.81(d, 3H), 7.94 (s, 4H), 8.38(s, NH); **^{13}C-NMR**(50 MHz; DMSO-d_6, ppm) 26.8, 123.7, 130.9 135.2, 148, 165.3

*Preparation of N-methylcarbamylsuccinimide (**3b**) directly from succinic anhydride and N-methyl urea*

To a solution of succinic anhydride (0.5 g, 5 mmol) in 10 mL solvent, *N*-methyl urea (0.3 g, 4 mmol) and trifluoroacetic acid (0.1 equiv) were added. The reaction mixture was maintained at 95°C for 4h and the solid crystalline precipitate formed was filtered and washed with acetone. The product was obtained in 50% yield (0.312g). When the reaction was repeated in mother liquor from the first synthesis the yield increased to 85%. Characteristics of the product are the same as those obtained through *N*-methylcarbamylsuccinamic acid cyclisation.

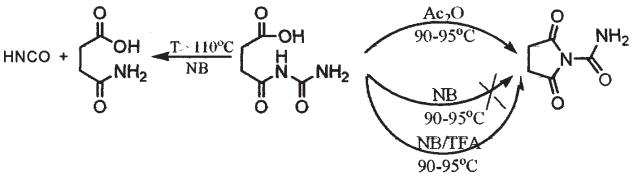
Results and discussion.

Because we succeeded in obtaining of some *N*-carbamylamic acids in nitrobenzene at a temperature below 80°C [6,7], and were aware of published statements that they can cyclize to *N*-carbamylimides at 95-100 °C in acetic anhydride [2,3], we attempted to extend our method to cyclization, using the same solvent, nitrobenzene, but at a higher temperature. The advantages of this method consist in the possibility of directly obtaining *N*-carbamylimides, by heating at higher temperatures the ureas together with the corresponding cyclic anhydrides without the isolation of the intermediates, *N*-carbamylamic acids.

A study of the cyclization of *N*-carbamylsuccinamic acid [7] in nitrobenzene at different temperatures was performed by analyzing the ^{1}H-NMR spectra of precipitate obtained on cooling of the reaction mixture. Thus, a mixture of *N*-carbamylsuccinamic acid and nitrobenzene was heated at 90-95°C. After one hour, the reaction mixture was cooled, but the collected product was the raw material, *N*-carbamylsuccinamic acid (fig. 1a). The reaction temperature was increased to 110-115°C and after one hour, a mixture of raw material and succinamic acid was obtained (fig. 1c). When the *N*-carbamylsuccinamic acid was heated in nitrobenzene to130-140°C, only the succinamic acid precipitated (fig. 1b). As a consequence, it may be said that the *N*-carbamylsuccinamic acid (succinuric acid) decomposes in succinamic acid and cyanic acid, when heated in nitrobenzene at temperatures above 110°C (scheme 6).

The obtaining of succinamic acid is confirmed by NMR spectrometry, by the disappearance of the signal corresponding to the imidic proton from 10.2 ppm (fig. 1a vs. fig. 1b). The signals corresponding to the H-2 and H-3 protons of the methylene groups appear as singlet for succinamic acid and as doublet of doublets for succinuric acid. The signals of the amidic protons appear at higher fields (chemical shifts of 7.3 and 6.8 ppm towards 7.8 and 7.1 ppm, as is characteristic for succinuric acid).

The synthesis was repeated at temperatures of 90-95°C, by adding 0.1eq trifluoroacetic acid and the desired product, *N*-carbamylsuccinimide, was obtained in 80% yield.



2 **1a** **3a**

Scheme 6

Other *N*-carbamylimides have been obtained in the same conditions and the results are presented in Table1.

Concerning the *N*-carbamylphthalamic acid, published reports mention that cyclization occurs via the attack of the amidic nitrogen atom on the carboxylic group, leading to a 7-membered cyclic urea (phthalyl urea) [4].

In the ^{1}H-NMR spectrum of any *N*-carbamylamic acid, the amidic protons have chemical shifts around 8 ppm, and the imidic protons around 10 ppm (fig. 2a).

If the cyclization occurs through nucleophilic attack of amidic nitrogen, the product will have protons bonded to imidic nitrogen which means that in the ^{1}H-NMR spectrum should appear signals around 10 ppm.

On heating *N*-methylcarbamylphthalamic acid in nitrobenzene at 95 °C in the presence of the trifluoracetic acid, cyclization took place through nucleophilic attack of the imidic nitrogen giving *N*-methylcarbamylphthalimide rather than *N*-methylphthalyl urea, in ^{1}H-NMR spectrum (fig. 2b) the signal appearing at 8.37 ppm. This fact proves that the cyclization occurred, similarly to previous cases, through nucleophilic attack of the imidic rather than amidic nitrogen.

Because in nitrobenzene we achieved both the synthesis of *N*-carbamylamic acids[6,7] and also their cyclization to *N*-carbamylimedes, we tried to reobtain these last compounds directly from cyclic anhydride and ureas. Previous results show that the first stage of the reaction,

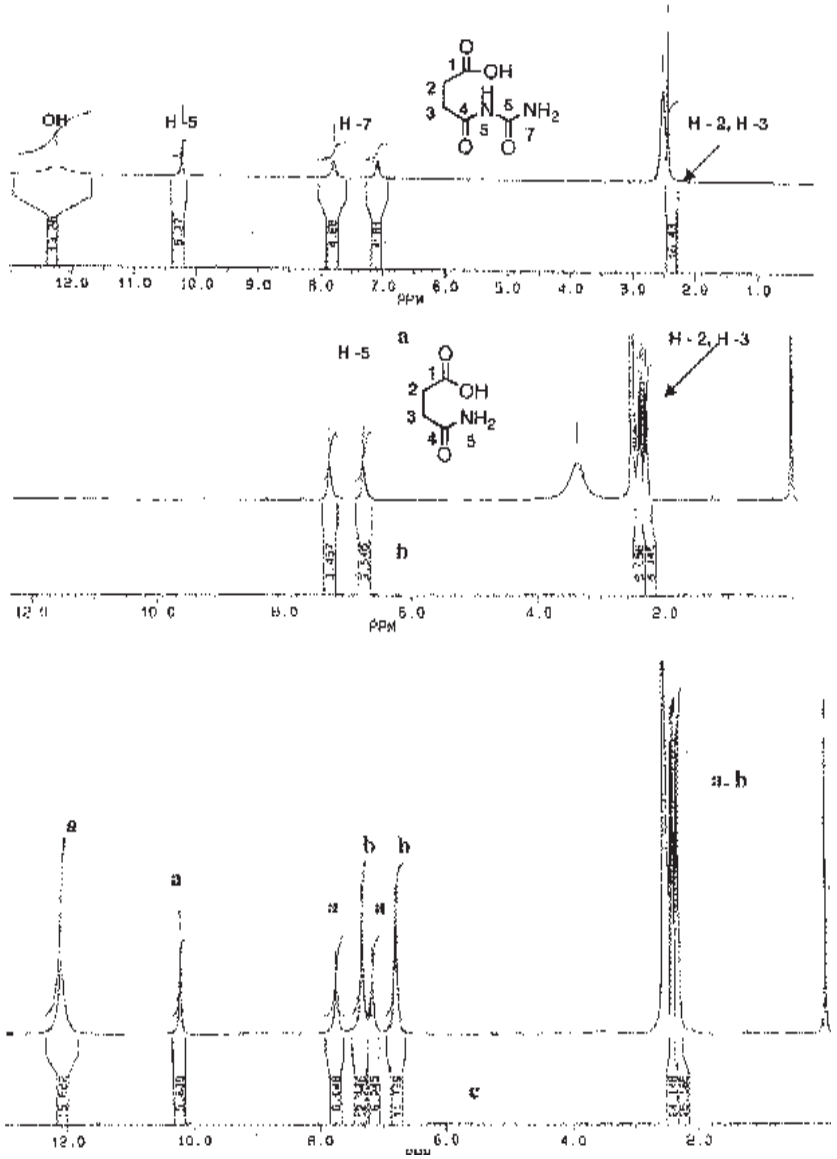


Fig. 1. ^{1}H-NMR spectra of precipitates obtained after the heating at different temperatures of *N*-carbamylsuccinamic acid in nitrobenzene: a) 90-95°C- *N*-carbamylsuccinamic acid; b) 130-140°C - Succinamic acid; c) 110-115°C-Mixture of a) and b)

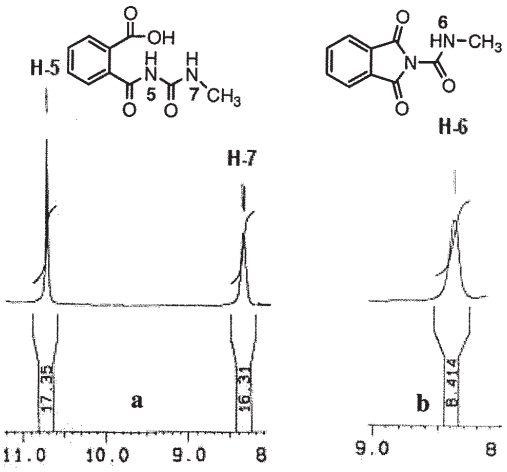


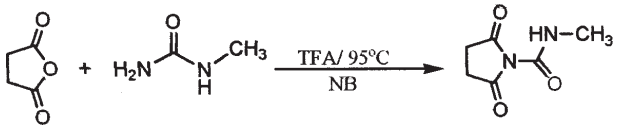
Fig. 2. Chemical shifts of the protons bonded to nitrogen from *N*-methylcarbamyl-phthalamic acid (a) and *N*-methylcarbamylphthalimide respectively (b)

Table1
CYCLIZATION OF *N*-CARBAMILAMIC ACID (CAA) TO *N*-CARBAMYLIMIDE (NCI)

Nr. crt.	CAA	NCI	η (%)
1.	**1a**	**3a**	80
2.	**1b**	**3b**	90
3.	**1c**	**3c**	88
4.	**1d**	**3d**	82
5.	**1e**	**3e**	65
6.	**1f**	**3f**	79

synthesis of *N*-carbamylamic acids, requires temperatures of 50-80°C and may be carried out both in presence or absence of trifluoroacetic acid acting as a catalyst[6]. The second stage of the reaction requires temperatures above 95°C and a catalyst. Synthesis of *N*-methylcarbamyl-succinamic acid has been achieved by treating succinic anhydride and *N*-methyl urea in nitrobenzene at 95°C in the presence of 0.1 equivalents trifluoroacetic acid (scheme 7). The reaction mixture was heated for 4 h at 95°C and cooled. The precipitate obtained, *N*-methylcarbamylsuccinimide, was isolated from the

reaction mixture in 50% yield (in the case of first synthesis) and in 85% yield when the second synthesis was performed using the mother liquor from the first synthesis as solvent.



Scheme 7

Conclusions

N-carbamylimides have been obtained through cyclization of *N*-carbamylamic acids in new conditions which employed nitrobenzene as a solvent, trifluoracetic acid as a catalyst and temperatures of 90-95°C. As with the synthesis of *N*-carbamylamic acids the use of mother liquor from the previous synthesis resulted in a significant increase in the yield.

N-methylcarbamylsuccinimide was succesfully obtained directly from succinic anhydride and *N*-methyl urea without isolation of the intermediate, *N*-methylcarbamylsuccinamic acid, the synthesis taking place in nitrobenzene in the presence of trifluoroacetic acid at 95 °C.

N-carbamylimides readily decompose to produce isocyanates, a property which suggests them as useful reagents for synthesis of isocyanates.

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