Study of the N-methylcarbamylsuccinamic Acid Synthesis

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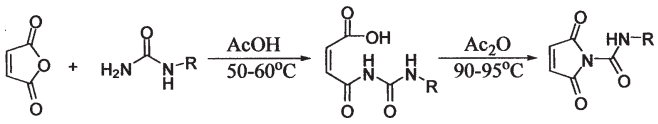
The synthesis of N-methylcarbamylsuccinamic acid from succinic anhydride and N-methyl urea in various conditions was studied. When nitrobenzene was employed as solvent the desired product was obtained. The reaction was followed using FTIR spectroscopy and the new final product was characterized by melting point, IR spectroscopy and ^{1}H- and ^{13}C-NMR spectrometry

Keywords: N-methylcarbamylsuccinamic acid, succinic anhydride, N-methyl urea, nitrobenzene

A successful condensation of maleic anhydride with urea or monosubstituted ureas has been reported in literature [1]. The reactions took place in two steps obtaining first maleuric acids which cyclize to *N*-carbamylmaleimides (scheme 1). The reactions were performed in glacial acetic acid at 50-60°C in 12 h to obtain the maleuric acids, while the cyclization is accomplished by heating to 90-95°C in acetic anhydride.



Scheme 1

Other *N*-carbamylamic acids derived from various anhydrides and monosubstituted ureas were prepared in a similar manner [2]. Some of them are used after oxidation with hydrogen peroxide for bleaching, oxidizing or disinfecting purpose [3,4] and others, after cyclization are good precursors of izocyanates [1,5]

Taking into account that our research area is oriented towards the carbonic acid derivatives [6] and it is mainly focused on finding new, less toxic reagents [7] that may successfully replace phosgene [8] in a series of reactions, it may be said that synthesis of these carbamylamic acids shows great importance. This is due to the subsequent cyclization of the carbamylic acids that led to the obtaining of *N*-carbamylamides, potential reagents for isocyanates synthesis by a new method.

The current paper presents a study regarding the influence of different reaction parameters on the synthesis of *N*-methylcarbamylsuccinamic acid (*N*-methylsuccinuric acid).

Experimental part

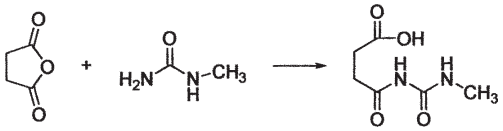
Melting points were determined on Boetius apparatus (Carl Zeiss Jena). *The IR spectra* were recorded in KBr pellet for the solid compounds with a Jasco FT/IR-430 instrument. *The ^{1}H-NMR* and *^{13}C-NMR spectra* were recorded on a Bruker DPX 200 MHz NMR spectrometer (200 and 50 MHz, respectively). Nitrobenzene was distilled before use. Succinic anhydride, *N*-methyl urea, glacial acetic acid, acetone and trifluoroacetic acid were purchased from chemical suppliers and used without further purification

General procedure for the preparation of N-methylcarbamylsuccinamic acid:

To a solution of succinic anhydride (0.5 g, 5 mmol) in 10 mL solvent, *N*-methyl urea (0.3 g, 4 mmol) and sometimes strifluoroacetic acid (0.1 equiv) were added. The reaction mixture was maintained at a specific temperature for a determined time period and the solid crystalline precipitate formed was filtered and recrystallized from ethyl acetate. The product was obtained (0.21g, 30%) as a white precipitate with m.p. 198-200°C; $\nu_{C=O}$(cm^{-1}) = 1719, 1676; δ_H(200 MHz; DMSO-d_6, ppm) 2.50 (s, 4H), 2.71 (d, 3H), 8.17(s, NH), 10.27 (s, NH), 12.11 (s, OH); δ_C(50 MHz; DMSO-d_6, ppm) 25.6 (CH_3), 28.1 (CH_2), 30.5 (CH_2), 153.6(C=O), 173.5(C=O), 173.6(C=O) .

Results and discussions

Initially we tried to obtain *N*-methylcarbamylsuccinamic acid under the same conditions employed in the literature for the preparation of *N*-carbamylmaleamic acids [1]. Therefore succinic anhydride was treated with *N*-methyl urea in glacial acetic acid at 50°C (scheme 2). Because succinic anhydride has a low solubility in glacial acetic acid we had to use five times the amount of solvent used in the literature to solubilize the entire amount of anhydride (synthesis 1). After 12 h at 50°C we did not obtain any precipitate. The solvent was then evaporated and the residue was analyzed by IR spectroscopy (fig. 1, spectrum 3) and ^{1}H-NMR spectrometry.



Scheme 2

The IR spectrum (fig. 1, spectrum 3) shows the appearance of a new carbonylic stretching band at 1699 cm-1 different from those presented in the reactants: 1647 cm^{-1} in N-methyl urea (fig. 1, spectrum 1) and 1878 cm^{-1} and 1784 cm^{-1} in succinic anhydride (fig. 1, spectrum 2). From the 1H-NMR spectrometry data it resulted that the only species presented in the reaction residue are N-methyl urea (MeU) and succinic acid (SA).

We repeated the synthesis using the same amount of solvent (synthesis 2) as in literature [1], even though the

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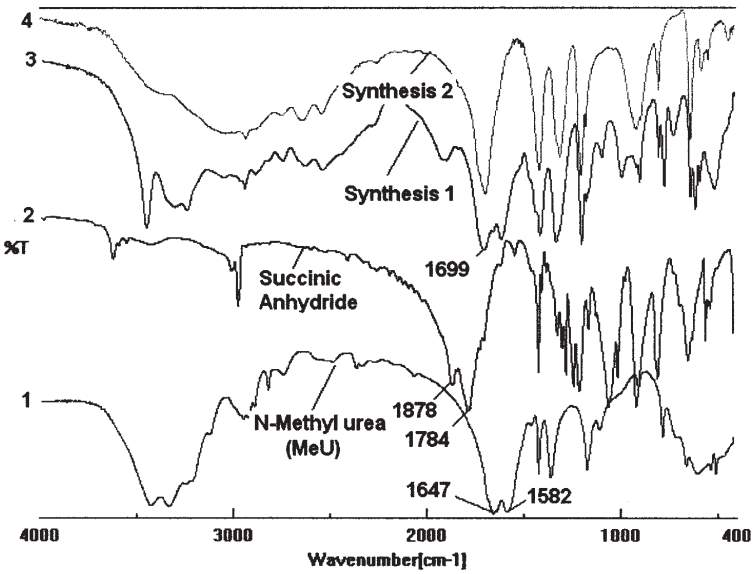
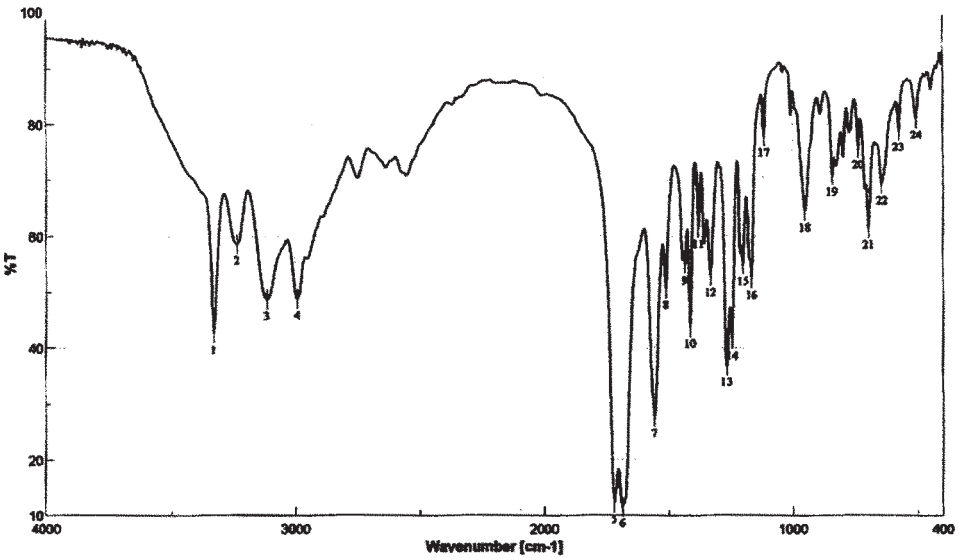


Fig. 1. Reaction of succinic anhydride with *N*-methyl urea in glacial acetic acid. 1- IR spectrum of *N*-methyl urea; 2- IR spectrum of succinic anhydride; 3- IR spectrum of the residue obtained in synthesis 1; 4- IR spectrum of the precipitate obtained in synthesis 2

Table 1
REACTION OF SUCCINIC ANHYDRIDE (SAn) WITH N-METHYL UREA (MeU) IN NITROBENZENE UNDER VARIOUS CONDITIONS

No.	Temp[°C]	SAn : MeU: TFA	Products
1	25	1 : 1.25	SA, MeU
2	25	1 : 1.25 : 0.1	SA, MeU
3	50	1 : 1.25	SA, MeU
4	50	1 : 1.25 : 0.1	SA, MeU
5	80	1 : 1.25	SA, MeU, NMCSA
6	80	1 : 1.25 : 0.1	SA, MeU, NMCSA
7	100	1 : 1.25	SA, MeU, NMCSA
8	100	1 : 1.25 : 0.1	SA, MeU , NMCSA



Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1:	3326.61	42.8454	2:	3235.00	58.6554	3:	3113.51	48.6804	4:	2992.02	48.8223
5:	1718.26	12.3143	6:	1685.48	11.5744	7:	1556.27	27.5987	8:	1509.99	50.7179
9:	1431.89	55.0504	10:	1410.67	43.7201	11:	1378.85	61.5290	12:	1330.64	52.9061
13:	1265.07	36.8436	14:	1243.86	41.5480	15:	1200.47	54.8799	16:	1165.76	52.3617
17:	1115.82	77.7432	18:	951.70	64.4819	19:	842.74	70.7963	20:	736.67	75.6556
21:	696.11	81.4451	22:	645.07	69.3027	23:	576.61	78.7777	24:	507.19	80.9940

Fig. 2. IR spectrum of *N*-methylcarbamylsuccinamic acid

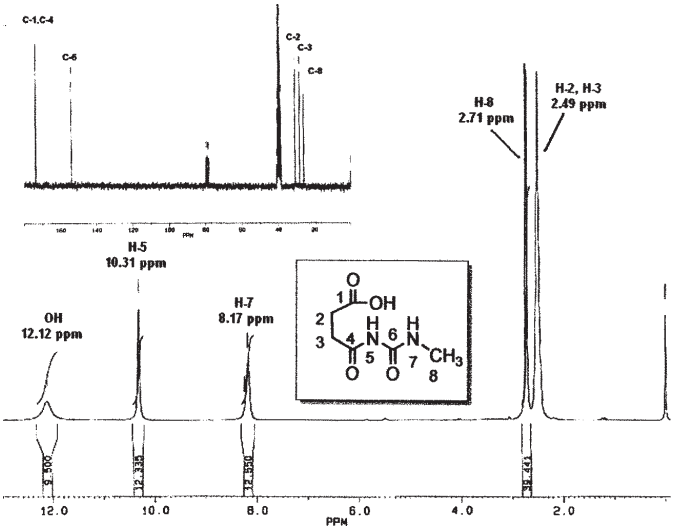


Fig. 3. ^{1}H-NMR and ^{13}C-NMR spectra (200 MHz, DMSO-d_6) of *N*-methylcarbamylsuccinamic acid

succinic anhydride is not completely dissolved. During the reaction we noticed that the succinic anhydride was consumed (the initial insoluble solid was finally dissolved) and after 12 h at 50°C, a new precipitate appeared. It was isolated and analysed by IR spectroscopy (fig. 1, spectrum 4), which demonstrated that it was succinic acid with the carbonylic stretching band at 1699 cm^{-1}.

Next, we performed the synthesis using acetone as solvent. The reason for this choice was that both reactants possess good solubility in acetone and the solvent can be easily removed. The reaction did not occur in these conditions. To facilitate the reaction, trifluoroacetic acid [9] was used as catalyst, but, as in the previous cases, the product we finally obtained was succinic acid.

Further the synthesis was performed in nitrobenzene at various temperatures, with or without catalyst (table 1). At low temperature the reaction did not occur while at temperature of at least 80°C, N-methylcarbamyl-succinamic acid, (NMCSA) the desired product, was identified in the reaction mixture, whatever if the catalyst, trifluoroacetic acid (TFA) was or not added. The product was isolated from reaction mixture after 3 h by filtration and was recrystallized from ethyl acetate being obtained in high purity but only in 30 % yield. The IR (fig. 2) and NMR (fig. 3) spectra prove that the product obtained is N-methyl-carbamylsuccinamic acid.

Conclusions

In summary, we obtained a new product, *N*-methylcarbamylsuccinamic acid, by the reaction of succinic anhydride with *N*-methyl urea in nitrobenzene at 80°C. This compound opens new opportunities for the synthesis of isocyanates which can be easily obtained by thermal decomposition of *N*-carbamylimides.

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