Synthesis of Various N-carbamylamic Acids

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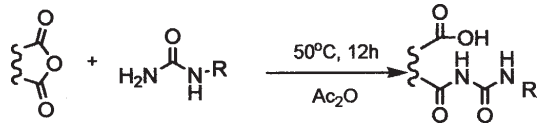
Some N-carbamylamic acids were obtained when cyclic anhydrides derived from succinic, maleic and phthalic acids were treated with un- or monosubstituted ureas in new conditions with the advantage that the time necessary to reactions is reduced significantly. Products were characterized by melting point, IR spectroscopy and ^{1}H- and ^{13}C-NMR spectrometry

Keywords: N-carbamylsuccinamic acids, N-carbamylmaleamic acids, N-carbamylphtalamic acids, ureas, nitrobenzene

Obtaining of N-carbamylamic acids (also called uric acids), better known as maleuric acids by fusing cyclic anhydrides with urea or monosubstituted ureas in glacial acetic acid at 50-60°C, for 12 h is the method described in the literature [1,2].



Scheme 1

These uric acids are important because they can cyclise to *N*-carbamylimides which easily decompose to isocyanates [1,3]. For this reason the *N*-carbamylimides could potentially be used as reagents for synthesis isocyanates by a new phosgene-free route [4]. Our research group's project is to find less toxic reagents able to replace phosgene in its reactions, and it has published suggestive results towards this [5].

Preliminary studies made of the reaction between succinic anhydride and N-methylurea in various conditions were recently reported [6]. It was found that the desired product, N-methylcarbamylsuccinamic acid has been finally obtained in nitrobenzene at 80°C in just 3h, but in 30% yield after recrystallization from ethyl acetate.

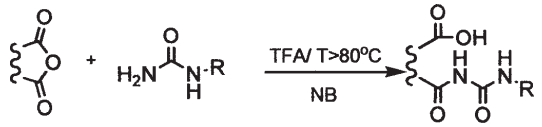
In the case of uric acids synthesis described in the literature [1,2] the authors noticed that the yield is greatly improved by using the mother liquor from a previous preparation of the same compound. They demonstrated that this improvement of the reaction yield is not due to saturation of the solution with uric acid being formed or its catalytic activity: the maleic anhydride and urea do not react sufficiently faster in fresh solvent (acetic acid) saturated with pure N-carbamylmaleamic acid and the results are poor. For this reason they suppose that the improvement in yield could be due to catalysis by impurities in the reactants, solvent and/or to by-products formed in small amount in the reaction [2].

In this paper we report some uric acids obtained in the conditions established for *N*-methylcarbamylsuccinamic acid synthesis [6].

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, maleic and phthalic anhydrides, urea, *N*-methyl urea and *N*-ethyl urea were purchased from chemical suppliers and used without further purification. Aromatic ureas were prepared according to literature data [7] and *N-tert*-butyl urea was prepared according to literature data [8].

General procedure for the preparation of N-carbamylamic acids (uric acids):



To a solution of cyclic anhydride (10 mmol) in 25 mL nitrobenzene, un- or monosubstituted urea (10 mmol) was added. The reaction mixture was maintained at 80°C for 3 hours and the solid crystalline precipitate formed was filtered and recrystallized from ethyl acetate.

***N*-methylcarbamylsuccinamic acid (1):**

The product was obtained (0.21g, 30%) as a white precipitate. When the reaction was repeated in mother liquor from the first synthesis the yield was 91%. The characterization of the product has been previously described [6].

***N*-carbamylsuccinamic acid (2)**

There are obtained 1.264 g (η = 79%) of white product. When the reaction was repeated in mother liquor from the previous synthesis 1.44g (90%) compound were obtained. **M.p.** 210-211°C (Lit. 211-211, 5°C[2]); **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1705, 1655; **^{1}H-NMR** (200 MHz; DMSO-d_6, ppm): 2.45(s, 4H), 7.09(s, NH, H_a), 7.79(s, NH, H_b), 10.23(s, NH), 12.25(s, OH);**^{13}C-NMR** (50 MHz; DMSO-d_6, ppm) 28, 30.5, 153.9, 173.5, 173.6.

***N*-ethylcarbamylsuccinamic acid (3)**

1.222 g (η= 65%) of white product was obtained. When the reaction was repeated in mother liquor from the previous synthesis 1.75g (93%) compound was obtained. **M.p.**190-192°C; **^{1}H- NMR** (80 MHz; $CDCl_3$-DMSO-d_6, ppm): 1.17 (t, 3H), 2.61(s, 4H), 3.33 (c, 2H), 8.36(s, NH_{amid}), 10.21(s, NH_{imid});

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No.	Anhydride	Ureas	Temp. (°C)	CAA	η (%)
1.	succinic	urea	80	**2**	79
2.					90[1]
3.		*N*-methylurea	80	**1**	57
4.					91[1]
5.		*N*-ethylurea	80	**3**	65
6.					93[1]
7.		N-(o-methoxyphenyl)urea	80	**4**	50
8.					89[1]
9.	maleic	urea	50	**5**	52
10.			80		57
11.					95[1]
12.		*N*-methylurea	80	**6**	72
13.					93[1]
14.		*N-tert*-butylurea	80	**7**	65
15.					91[1]
16.		*N*-phenylurea	80	**8**	50
17.					90[1]
18.	phthalic	*N*-methylurea	80	**9**	50
19.					88[1]

[1] Yield obtained when the mother liquor of previous synthesis was used

Table 1
OBTAINING OF N-CARBAMYLAMIC ACIDS (CAA)

***N*-(o-methoxyfenyl)carbamylsuccinamic acid (4)**

1.33 g (η = 50%) of white product was obtained. When the reaction was repeated in mother liquor from the previous synthesis 2.368 g (89%) compound was obtained. **^{1}H-NMR** (80 MHz; $CDCl_3$-DMSO-d_6, ppm) 2.66(s, 4H), 3.94(s, 3H), 6.99(m, 3H, H_{Ar}), 8.24 (d, 1H, H_{Ar}), 8.57(s, NH), 10.83(s, NH);

***N*-carbamylmaleamic acid (5)**

0.9 g (η = 57%) of white product was obtained. When the reaction was repeated in mother liquor from the previous synthesis 1.5g (95%) compound was obtained. **M.p.** 160-162°C (Lit. 161-162°C[1,2]); **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1710, 1672, 1634; **^{1}H-NMR** (200 MHz; DMSO-d_6, ppm): 6.37(s, 2H), 7.24(s, NH, H_a), 7.78(s, NH, H_b), 10.54(s, NH), 11.3(s, OH); **^{13}C-NMR** (50 MHz; DMSO-d_6, ppm) 130, 131.5, 161, 166, 167.

***N*-methylcarbamylmaleamic acid (6)**

1.238 g (η= 72%) of white product was obtained. When the reaction was repeated in mother liquor from the previous synthesis 1.6g (93%) compound was obtained. **M.p.** 173-175°C; **^{1}H-NMR** (80 MHz; DMSO-d_6, ppm) 2.82(d, 3H), 6.30 (d, 4H), 8.157(s, NH), 10.59(s, NH)

***N-tert*-butylcarbamylmaleamic acid (7)**

1.39 g (η = 65%) of white product was obtained. When the reaction was repeated in mother liquor from the previous synthesis 1.947g (91%) compound was obtained. **M.p.** 151-153°C(Lit. 151.5-153.5 [2]); **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1706, 1632; **^{1}H-NMR** (200 MHz; DMSO-d_6, ppm) 1.32 (s, 9H), 6.36(s, 2H), 8.26(s, NH), 10.44(s, NH);**^{13}C-NMR** (50 MHz; DMSO-d_6, ppm) 28.5, 49.9, 128.7, 132.3, 157.4, 166.1, 167.1 .

***N*-Phenylcarbamylmaleamic acid (8)**

1.17 g (η = 50%) of white product was obtained. When the reaction was repeated in mother liquor from the previous synthesis 2.1g (90%) compound was obtained. **M.p.** 183-185°C (Lit. 162-163°C[1,2]);**^{1}H-NMR** (200 MHz; DMSO-d_6, ppm) 6.39(m, 4H), 7.08(t, 1H), 7.32(t, 2H), 7.72 (d, 2H), 8.20(s, NH), 8.52(s, NH), 10.46(s, NH, H-5); **^{13}C-NMR** (50 MHz; DMSO-d_6, ppm) 119.5, 123.7, 128.7, 130.5, 131.6, 135.5, 138.4, 165.3, 167.7 .

***N*-methylcarbamylphthalamic acid (9)**

1.11 g (η = 50%) product was obtained. When the reaction was repeated in mother liquor from the previous synthesis 1.954g (88%) compound was obtained. **IR**(KBr pellet, cm^{-1}) $\nu_{C=O}$ = 1701, 1673; **^{1}H-NMR** (200 MHz; DMSO-d_6, ppm) 2.80(d, 3H), 7.47(d, 1H), 7.55 (t, 1H), 7.68(t, 1H), 7.90(d, 1H), 8.33(s, NH), 10.70(s, NH), 13.33(s, OH); **^{13}C-NMR** (50 MHz; DMSO-d_6, ppm) 25.9, 127.5, 129.5, 129.7, 131.65, 132.83, 153.9, 167.0, 170.8 .

Results and discussion.

First, we repeated the reaction between succinic anhidride and *N*-methylurea in nitrobenzene using the mother liquor from the synthesis previously described [6]. The product was isolated after recrystallization from ethyl acetate in 91 % yield.

The optimized procedure for the synthesis of *N*-methyl carbamoyl succinamic acid was also applied for the obtaining of other carbamoyl amic acids, derived from succinic, maleic and phthalic anhydride and un- and mono-substituted urea.

The reaction between succinic anhydride and urea known in the literature [2] was repeated in our conditions (nitrobenzene as solvent, 3 h , 80°C) and the product, *N*-carbamoylsuccinic acid, was successfully obtained and isolated with 79% yield after recrystallization from ethyl acetate (table 2). Repeating the synthesis using the mother liquor from the previous synthesis led to an increase of the yield to 90%. Good results were also obtained when *N*-ethyl urea and *N*-(o-methoxyphenyl) urea have been used. The results are presented in (table 1, entries 5-8)

Maleic anhydride is the most studied anhydride among other cyclic anhydrides and several *N*-carbamoylmaleamic acids are known. Studies regarding the influence of the temperature on the reaction between maleic anhydride and urea have shown that at room temperature the reaction

occurs slowly, requiring an excess of solvent in order to dissolve the entire amount of urea and also showed that at temperatures around 80°C the yield is much affected by the side reactions that occur at double bond C=C. For this reason, the authors [1] suggested that the reaction should be carried out at temperatures around 50°C.

The synthesis described above was achieved in nitrobenzene at both 80 and 50°C and it was observed that maleic anhydride reacted already at 50°C giving the corresponding *N*-carbamoylamic acid while at higher temperatures (80°C), side products were not observed. Instead, as we have already mentioned, succinic anhydride does not react with urea at temperatures below 80°C.

The almost all obtained products (table 1, entries 9-17) are known, but they have not been characterized through spectroscopic methods until now. With the help of IR spectroscopy and NMR spectrometry we confirmed their structure.

In the case of the reaction between the phthalic anhydride and various substituted ureas, Smith and Cavallitto [9] mentioned that *N*-carbamylphthalamic acids are obtained as intermediates, but these products were not isolated from the reaction mixture being further used in the cyclization reaction (when phthalyl urea is obtained). Instead, when the synthesis has occurred in nitrobenzene, at 80°C, *N*-methylcarbamylphthalamic acid was obtained and isolated (table 1, entries 18 and 19) and has for the first time been characterized by melting point, IR spectroscopy and NMR spectrometry.

Conclusions

N-carbamylamic acids derived from succinic, maleic and phthalic acids have been obtained by a new method.

Synthesis in nitrobenzene has the advantage that the reaction time is reduced from 12 to 3 h, and the additional advantage of the solvent being less polar than the acetic acid, used in the published method, is more easily removed, thus diminishing the likelihood of its entrapment in the crystal structure of the uric acid products due to hydrogen bond formation.

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