

Synthesis of Several New N-Substitutedmaleisoimides and Phthalisoimides Using Different Dehydrating Agents

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ABSTRACT. Several new members of N-substitutedmaleisoimides and phthalisoimides are prepared. Four of these compounds are N-arylphthalisoimides, three are N-arylisomaleimides, and one is N-cyclopropylmaleisoimides. The yields of N(2-ethylphenyl) phthalisoimide and other isoimides were compared when the dehydration of the corresponding amic acids performed using trifluoroacetic anhydride (TFAA), ethyl chloroformate (ECF), and N,N-dicyclohexylcarbodiimide(DCC). Structure determination of the new compounds were based on IR,NMR and isomerization of the isoimides to the corresponding imides.

Although numerous reports about the synthesis of maleimides and phthalisoimides are found in literature (Roderick and Bhatia 1963, Cotter *et al.* 1961, and Pyriadi and Harwood 1971), we could not locate many synthesis of their isoimide isomers. This may be partly because of the difficulties encountered during the preparation of the isoimides in general. Their low yields and lack of stabilities on one hand and the difficulties in their purification from the isomeric imide contaminants on the other hand could be some of those reasons.

We wish to report here the synthesis of several new members of N-substitutedmaleisoimides and Phthalisoimides prepared by the dehydration of the corresponding amic acids using three different dehydrating systems namely, TFAA- triethylamine, ECF -triethylamine, and DCC. Reactivities and utilities of the above dehydrating systems were also compared.

Experimental

Preparation of Amic Acids

Literature procedures (Liwschitz *et al.* 1956) were followed in the preparation of the N-substituted maleamic and phthalamic acids. Their percent yields, and

melting points are listed in Table 1, while their proton NMR are presented in Table 2.

Table 1. Percent yields, melting points, and code numbers of the prepared amic acids

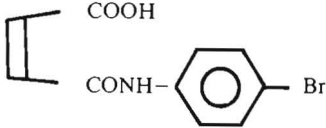
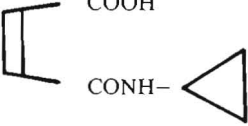
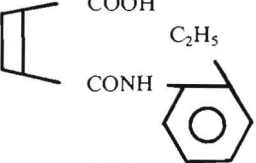
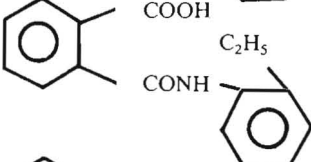
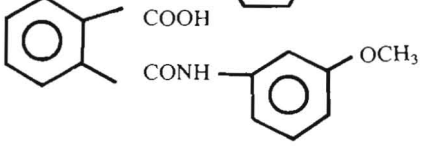
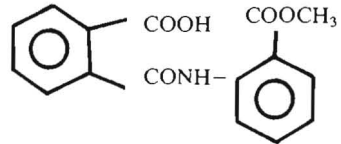
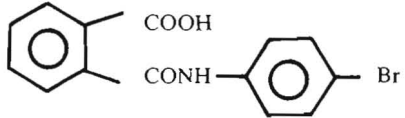


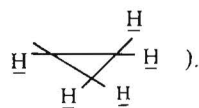

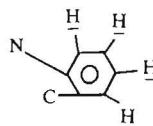
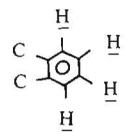
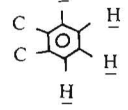
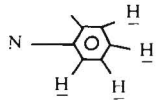
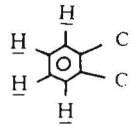
Code #	Amic acids structure	% yield	Melting point °C
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2	 <chem>OC(=O)C=C(NC(=O)C1CC1)C(=O)O</chem>	85	156-157
3	 <chem>OC(=O)C=C(NC(=O)c1ccccc1C)C(=O)O</chem>	94	102-103
4	 <chem>OC(=O)C=C(NC(=O)c1ccccc1C)C(=O)O</chem>	90.5	160-161
5	 <chem>OC(=O)C=C(NC(=O)c1cccc(OC)c1)C(=O)O</chem>	95	172-173
6	 <chem>OC(=O)C=C(NC(=O)c1cccc(C(=O)OC)c1)C(=O)O</chem>	75	150-151
7	 <chem>OC(=O)C=C(NC(=O)c1ccc(Br)cc1)C(=O)O</chem>	75	129-130

Table 2. Proton NMR^a of the prepared N-substituted amic acids in DMSO_{d6}

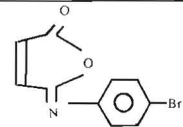
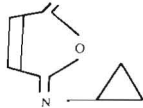
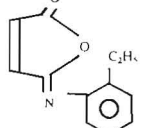
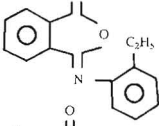
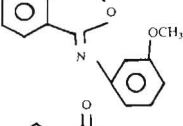
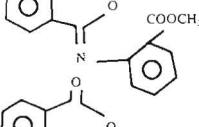
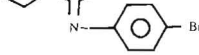
Amic acid code #	Nuclear magnetic resonance chemical shifts in delta units
1	δ 10.00 (s, 1H, OH); δ 7.60 (s, 1H, NH); δ 7.31 (m, 4H, C ₆ H ₄ -); δ 6.21 (d, 2H, C=C). 
2	δ 9.20 (s, 1H, OH); δ 6.50 (s, 1H, NH); δ 6.34 (d, 2H, C=C);  δ 0.50-0.81 (m, 5H, ).
3	δ 9.18 (s, 1H, OH); δ 7.35 (s, 1H, NH); δ 7.17 (m, 4H, C ₆ H ₄); δ 6.23-6.75 (q, 2H, -C=C); δ 2.62 (q, 2H, CH ₂); δ 1.17 (t, 3H, CH ₃). 
4	δ 9.46 (s, 1H, OH); δ 7.64 (s, 1H, NH); δ 7.40 (m, 4H, ); δ 7.00 ^b  (m, 4H, ); δ 2.61 (q, 2H, CH ₂); δ 1.16 (t, 3H, CH ₃).
5	δ 10.22 (s, 1H, OH); δ 7.75 (s, 1H, NH); δ 7.60 (m, 4H, C ₆ H ₄); δ 7.20 (m, 4H, C ₆ H ₄); δ 3.71 (s, 3H, CH ₃).
6	δ 10.90 (s, 1H, OH); δ 8.31 (s, 1H, NH); δ 7.70-7.94 (m, 4H, ); δ 7.58 (m, 4H, ); δ 3.77 (s, 3H, CH ₃).
7	δ 10.13 (s, 1H, OH); δ 7.70 (s, 1H, NH); δ 7.40 (m, 8H, 2 C ₆ H ₄).

^a A varian 80 MHz NMR spectrometer was used

Preparation of N-Substitutedmaleisoimides and Phthalisoimides

The procedure of Cotter *et al.* 1961) was used for the dehydration of the amic acids of Table 1. The three dehydrating systems mentioned above were carefully tested to dehydrate N-(2-ethylphenyl) phthalamic acid, and other amic acids. However, DCC was used mostly for the preparation of the isoimides since it gave the purest product (see the discussion part). Melting points, yields, IR data and elemental analysis of the products of dehydrations are listed in Table 3. Table 4

Table 3. Some physical properties of the prepared isoimides

Structure of the isoimide	Cm ⁻¹ C=O	Cm ⁻¹ C=N	M.P °C	Elemental analysis (calcd./found)			% Yield
				C	H	N	
1 	1790	1680	99	47.63 47.61	2.38 2.44	5.55 5.43	79.5
2 	1782	1675	61	61.37 61.01	5.22 5.10	10.11 9.98	60
3 	1790	1685	66	71.64 71.22	5.47 5.56	6.96 6.98	63
4 	1745	1680	96	76.49 76.38	5.17 5.07	5.57 5.45	80
5 	1786	1705	69	75.94 75.91	4.64 4.55	5.90 5.82	69
6 	1763	1700	88	68.32 68.11	3.91 3.55	4.98 4.42	85
7 	1802	1703	157	75.67 75.48	3.60 3.53	6.30 6.21	60

contains NMR spectral data of the prepared isoimides, while Table 5 lists the conditions of the dehydrations.

Table 4. NMR spectral data of the prepared isoimides

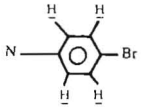



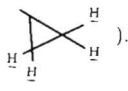
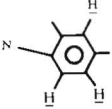
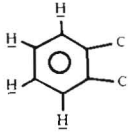
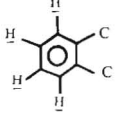
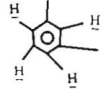
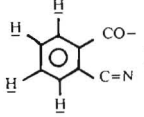
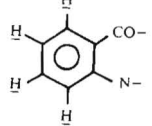
Isoimide code #	Nuclear magnetic resonance chemical shifts in delta units
1	δ 7.00-7.45 (m, 4H, ); δ 6.51 (d, 2H, ).
2	δ 6.82 (center of two doublets, 2H, ); δ 3.45 (m, 1H, ); δ 1.00 (m, 4H, ).
4	δ 7.60-8.00 (m, 4H, ); δ 7.17 (s, 4H, ); δ 2.70 (q, 2H, $-\text{CH}_2-\text{O}$); δ 1.13 (3H, CH_3)
5	δ 7.81-8.21 (m, 4H, ); δ 6.82-7.77 (m, 4H., ); δ 3.85 (s, 3H, CH_3).
6	δ 7.81-8.23 (m, 4H, ); δ 7.00-7.82 (m, 4H., ); δ 3.89 (s, 3H, CH_3).
7	δ 8.00 and 7.32 (two multiple complexes representing two aromating ring protons)

Table 5. Reaction conditions and results of dehydration of N-(2-ethylphenyl) phthalamic acid using TFAA, DCC, and ECF

Dehydrating agent	Moles of triethylamine used	% Yield	Melting point of product
TFAA	1	40.5	90-91
TFAA	2	75	90-91
ECF	1	80	89-90
DCC	—	68.6	95-96

Isomerization of N-Substitutedmaleisoimides and Phthalisoimides to the Corresponding Imides

Each isoimide product prepared (Table 3) was isomerized to the corresponding imide by refluxing a certain amount of the isoimide with 5% anhydrous sodium acetate in dry benzene similar to the procedure of Cotter *et al.* (1961).

Results and Discussion

Two main difficulties seem to have accompanied the preparations of the present maleisoimides and phthalisoimides. First was the difficulty of purification of the products from the isomeric imides which often forms in small quantities and second was the low yields of such products. Although dehydration of N-(2-ethylphenyl) phthalamic acid with DCC gave moderate yields of the corresponding phthalisoimide than when TFAA plus two moles of triethylamine or, ECF - triethylamine systems were employed, the quality of the product was purer, and the only impurity in the product when using DCC was some of N,N-dicyclohexylurea (DCU) that dissolved in the organic solvent. On the other hand dehydration of N-(2-ethylphenyl) phthalamic acid with TFAA plus one mole of triethylamine produced the lowest yields of the corresponding isoimide. The highest yield of the above isoimide was obtained when using one mole of triethylamine with a mole of ECF. Table 5 contains the experimental conditions, and results of the above dehydration reactions. Recrystallization of the dehydration products in order to get rid of the contaminant imides was not effective. The only effective method was to use column chromatography technique using Florisil which did absorb the imides and leaving the isoimides to pass through with excess eluting solvent, benzene. The triethylamine used with TFAA, and with ECF had actually two advantages. First was to convert the carboxyl group of the amic acid to the corresponding salt, and thus it would enhance the cyclization process. The second advantage was its combining with the liberated acetic acid or trifluoroacetic acid which otherwise might hydrolyze the produced isoimide. When two moles of ET_3N were used with

one mole of amic acid, the yield of the isoimide increased from 40.5% to 75%. This result supports our early rationalization (Pyriadi and Harwood 1971) of such reactions. Structures of the new isoimides (Table 3) were proved not only from their I.R. and NMR spectra, but also by their isomerization to the corresponding imides. Refluxing the isoimides in dry benzene containing catalytic amounts of anhydrous sodium acetate caused their complete isomerization to the corresponding imides. All the corresponding imides were also prepared in order to correlate and compare the melting points and spectral data.

The prepared isoimides showed the characteristic absorption of $-C=N-$ around $1675-1705\text{ cm}^{-1}$ in their I.R. spectra. In addition, the carbonyl absorptions showed in the ranges of $1745-1802\text{ cm}^{-1}$ (see Table 3).

References

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- Liwschitz, Y., Pfeffermann, and Lapidoth, Y. (1956) Synthesis of aspartic acid derivatives. II. N-alkylated alpha-and beta asparagines, *J. Am. Chem. Soc.* **78**: 3069-3072.
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- Roderick, W.R. and Bahatia, P.L. (1963) Action of trifluoroacetic anhydride on N-substituted amic acids, *J. Org. Chem.* **28**: 2018-2024.

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تحضير بعض المال آيسو أميدات والفثال آيسو أميدات المعوضة نتروجينياً باستخدام عوامل مختلفة مزيلة للماء

ذنون محمد بريادي و قاسم سعيد هادي

قسم الكيمياء - كلية العلوم - جامعة بغداد - بغداد - العراق

تم تحضير عدد جديد من المال آيسو أميدات المعوضة نتروجينياً والآيسو فثال أميدات . هذه المركبات هي آيسو فثال أميدات معوضة بالأريل ، وواحد هو آيسو مال أميد معوض بالسايكلوبروبيل . كما قورنت مقادير الناتج من الفثال آيسو أميد المعوض 2 - أثيل - فنيل وذلك عند تحضير المادة أعلاه باستخدام كل من ثلاثي فلور حامض الخليك اللامائي (TFAA) أو أثيل كلوروفورمات (ECF) أو N,N - ثنائي سايكلو هكسيل كاربوداي أميد (ECF) . وقد تم تحديد تراكيب الآيسو أميدات الجديدة بواسطة ال IR وال NMR علاوة على ترتيبها إلى الأميدات المقابلة .