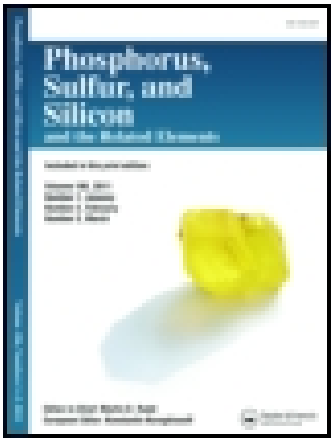

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

CHLOROSULFONATION OF N-ARYLMALEIMIDES

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Published online: 23 Sep 2006.

To cite this article: Augusto C. Tomé, José A. S. Cavaleiro, Fernando M. J. Domingues & Richard J. Cremlyn (1993) CHLOROSULFONATION OF N-ARYLMALEIMIDES, Phosphorus, Sulfur, and Silicon and the Related Elements, 79:1-4, 187-194, DOI: 10.1080/10426509308034412

To link to this article: http://dx.doi.org/10.1080/10426509308034412

Phosphorus, Sulfur, and Silicon, 1993, Vol. 79, pp. 187–194
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CHLOROSULFONATION OF *N*-ARYLMALEIMIDES

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(Received October 19, 1992; in final form January 5, 1993)

N-phenylmaleimides, *o*-, *m*- and *p*- substituted (**1**) reacted with excess chlorosulfonic acid to give the corresponding sulphonyl chlorides (**2–5**). These were condensed with amines and phenols to give derivatives (**7–29**) which underwent hydrolysis or ammonolysis to give respectively the sulfamoyl maleamic acids (**31–34**) and sulfamoyl maleamides (**35–39**).

Key words: N-arylmaleimides; chlorosulfonation.

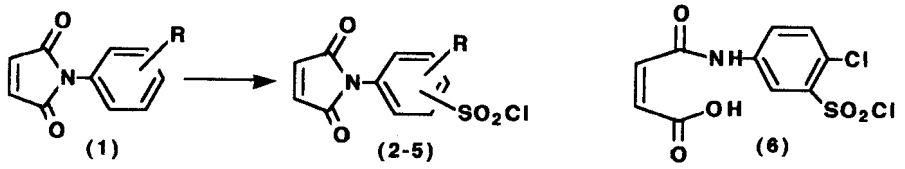
INTRODUCTION

The pharmacological and fungicidal activity of imides is well established.[1] In this group of compounds, the maleimides are very important and several of them are pattented for their biological properties.[2–5] In addition, sulfonyl compounds (namely sulfonamides, sulfonylureas, and sulfonylhydrazides) have well-established antibacterial,[6] antifungal,[7] and herbicidal[8] activities. With this in mind, and as an extension of the previous work on this subject,[9] we decided to synthesise some new sulfonated *N*-arylmaleimide derivatives as potentially bioactive compounds.

RESULTS AND DISCUSSION

The *N*-arylmaleimides (**1**) used throughout this work were prepared in good yields following a modification of the method described by Cava *et al.*[10]

The sulfonyl chlorides (**2–5**) were obtained by reacting the corresponding *N*-arylmaleimides with an excess (6 equiv.) of chlorosulfonic acid[9] (Scheme I, Table I). This reaction is strongly influenced by the substituents on the aromatic ring. While with *N*-phenylmaleimide (**1**, R = H) the reaction with chlorosulfonic acid, at room temperature, is slow, with activated *N*-arylmaleimides (**1**, R = Me or MeO) the chlorosulfonation is extremely fast, even at 0°C. With deactivated *N*-arylmaleimides (**1**, R = Cl), the reaction will proceed only under forcing con-



Scheme I Chlorosulfonation of *N*-Arylmaleimides

TABLE I

N-Arylmaleimide Sulfonyl Chlorides

Comp.	R	SO_2Cl	Yield (%)	M.P. (°C)
2	2-MeO	5-SO_2Cl	98	117-118
3	3-MeO	6-SO_2Cl	69	148-149
4	4-MeO	3-SO_2Cl	74	129-130
5	4-Me	3-SO_2Cl	83	149-151

ditions. For instance, after treating *N*-(4-chlorophenyl)maleimide (**1**, R = 4-Cl) with 6 equiv. of chlorosulfonic acid, for 5 hours at 90°C, the substrate was recovered unchanged. Under more vigorous conditions (5 hours at 130°C) the reaction only afforded water-soluble products but if the reaction was allowed to proceed for 48 hours at 105–110°C a chlorosulfonated product was isolated which was identified as the sulfonated maleamic acid (**6**) from NMR and MS data.

The chlorosulfonation reaction is highly regioselective* and the site of sulfonation is controlled by the position of the activating group on the aromatic ring. When the methoxy group is in position 2, (**1**, R = 2-MeO), as a result of the *ortho/para* directing effect, the chlorosulfonyl group goes in to the *para* position (position 5) which is also the less sterically hindered position. Evidence for this arises from the ^{1}H-NMR spectra of the chlorosulfonyl maleimide (**2**) and their sulfonamide derivatives, where *ortho* coupling between protons Ha and Hb and long range *meta* coupling between Hb and Hc is visible, thus excluding the possibility of *ortho* substitution relative to the methoxy group (Figure 1A).

With the activating group in position 4, (**1**, R = 4-Me or 4-MeO), chlorosulfonation occurs *ortho* to the methoxy or methyl group. This is also evident from the ^{1}H-NMR spectra of the sulfonated derivatives with a similar pattern for protons Ha, Hb and Hc (Figure 1B).

With aromatic rings substituted in position 3, (**1**, R = 3-MeO) orientation of chlorosulfonation is not so predictable as one could assume, in principle, that *ortho* and *para* substitution would be similarly favoured. Besides the two regioisomers would result in a similar pattern for the ^{1}H-NMR spectra of protons Ha, Hb and Hc (Figure 1C) and (Figure 1D). The problem was solved with a NOE difference spectra of sulfonamide (**11**). Irradiation of the methoxy group resulted in an increase on the intensity of the signal of protons Hc and Hb, thus confirming that the sulfonyl group is in the *para* position relative to the methoxy group.

We tried, unsuccessfully, to prepare a bis-sulfonyl chloride by reacting the *N*-(3-methoxyphenyl)maleimide (**1**, R = 3-MeO) with 12 equiv. of $ClSO_3H$ at 130°C but no definite product could be isolated; only water-soluble compounds were formed.

The sulfonyl chlorides (**2–5**) are stable compounds and, after crystallization, can be stored for months without decomposition.

Careful addition of a primary or secondary amine to ice cooled solutions of the sulfonyl chlorides (**2–5**) in acetonitrile, resulted in the formation of the corre-

*The TLC and ^{1}H-NMR spectroscopic data of the chlorosulfonyl maleimides and their derivatives indicated that only one of the possible regioisomers was present.

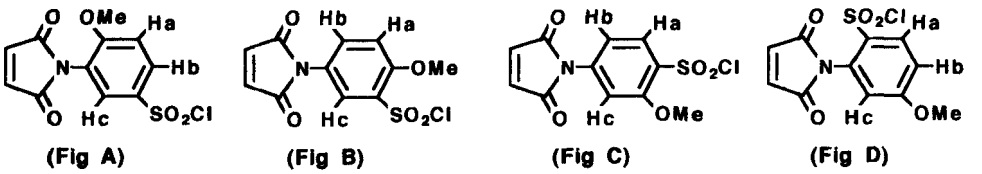
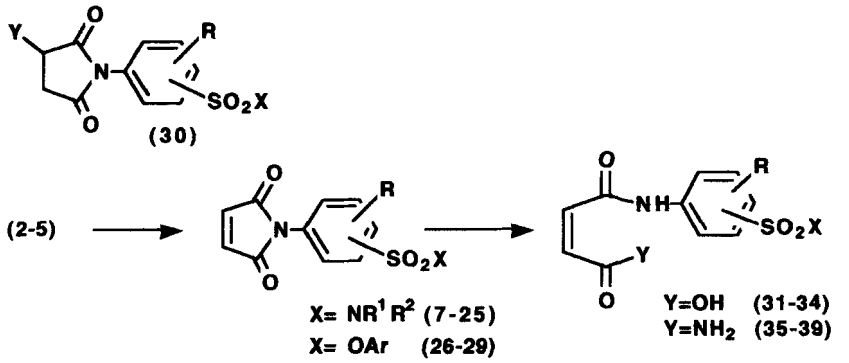


FIGURE 1



Scheme II Synthesis of *N*-Arylmaleimidosulfonyl derivatives

TABLE II

N-Arylmaleimidosulfonamides

Comp.	R	SO_2X	Comp.	R	SO_2X
7	2-MeO	5-SO_2NMe_2	**19**	4-MeO	3-$SO_2NHCH_2CH_2OH$
8	2-MeO	5-SO_2NEt_2	**20**	4-MeO	3-SO_2-Piperidino
9	2-MeO	5-SO_2NH^iPr	**21**	4-Me	3-SO_2NMe_2
10	2-MeO	5-SO_2NHPh	**22**	4-Me	3-SO_2NEt_2
11	3-MeO	6-SO_2NMe_2	**23**	4-Me	3-SO_2NH^iPr
12	3-MeO	6-SO_2NEt_2	**24**	4-Me	3-SO_2NHPh
13	3-MeO	6-SO_2NH^iPr	**25**	4-Me	3-$SO_2NHCH_2CH_2OH$
14	3-MeO	6-SO_2NHPh	**26**	4-MeO	3-$SO_2OC_6H_4$-3-NO_2
15	4-MeO	3-SO_2NMe_2	**27**	4-MeO	3-$SO_2OC_6H_4$-4-NO_2
16	4-MeO	3-SO_2NEt_2	**28**	4-MeO	3-$SO_2OC_6H_4$-4-Cl
17	4-MeO	3-SO_2NH^iPr	**29**	4-MeO	3-$SO_2OC_6Cl_5$
18	4-MeO	3-SO_2NHPh			

sponding maleimides (**7–25**) (Scheme II, Table II) and small amounts of the succinimide derivatives (**30a**, X = Y = NR^1R^2) as a result of the Michael addition of the amine to the double bond of the imino ring.[11] The maleimides were separated from the corresponding succinimides by column chromatography on silica gel. The succinimide analogues (**30b**, X = OC_6H_4Cl-p, Y = Piperidyl) and (**30c**, X = NEt_2, Y = NHC_6H_4Me-p) were obtained by reacting the corresponding sulfonated maleimides with different amines.

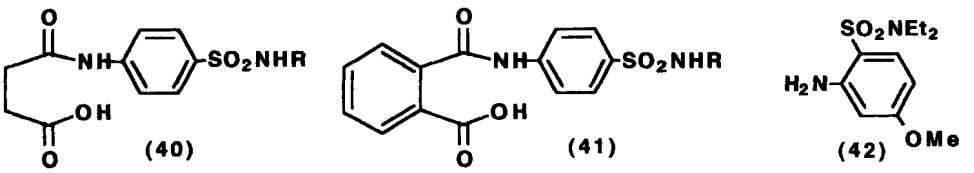


FIGURE 2

TABLE III
Maleamic Acids and Maleamides

Comp	R	SO_2X	Yield (%)	M.P. (°C)
31	2-MeO	5-SO_2NEt_2	38	71-74
32	3-MeO	6-SO_2NMe_2	76	142-143
33	4-MeO	3-SO_2NEt_2	68	149-150
34	4-MeO	3-$SO_3C_6H_4$-3-NO_2	56	155-156
35	2-MeO	5-SO_2NEt_2	69	113-114
36	3-MeO	6-SO_2NMe_2	73	156-158
37	3-MeO	6-SO_2NEt_2	68	181-186
38	4-MeO	3-SO_2NEt_2	64	144-145
39	4-MeO	3-$SO_3C_6H_4$-3-NO_2	56	168-169

The reaction of the sulfonyl chloride (**4**) with phenols, in the presence of triethylamine, gave good yields of the arylsulfonates (**26–29**) (Table II).

Compounds of type (**40**) and (**41**) have found extensive use in the treatment of certain intestinal infections.[6b] Since these compounds are very poorly absorbed and rapidly excreted, large doses can be administered orally without danger of toxic effects (Figure 2).

We have prepared unsaturated analogues of compounds (**40**) by opening the imino ring of the sulfonated *N*-arylmaleimides. This was achieved by treatment of the sulfonated maleimides with aqueous sodium or potassium hydroxide solutions or with ammonia, at room temperature; the maleamic acid derivatives (**31–34**) and the maleamides (**35–39**), respectively, were obtained (Scheme II, Table III). Surprisingly with the maleimide (**12**) similar conditions (treatment with aqueous sodium hydroxide solution at room temperature) gave the corresponding sulfonated aniline (**42**) as the main product.

CHARACTERIZATION OF THE COMPOUNDS

All the new compounds were characterized by their NMR and IR spectra and some of the key compounds were also characterized by microanalysis or mass spectrometry.

In the ^{1}H-NMR spectra of the maleimide derivatives (**7–29**), the singlet at δ 6.8–7.0 ppm is the most characteristic signal and is attributed to the two equivalent vinylic protons. The protons in the tri-substituted aromatic rings clearly show two

doublets with coupling constants 2.5 and 8.5 Hz, respectively and a double doublet. When the imido ring is opened to obtain the maleamic acid derivatives (**31–39**), the two vinylic protons are no longer equivalent and give raise to two doublets with a coupling constant of approximately 13 Hz. This relatively high coupling constant for *cis* vinylic protons is characteristic of the maleamic acid derivatives. The NMR spectra of the compounds (**31–39**) show a broad signal at δ 10–12.5 ppm which is attributed to the NH proton. The frequency of this signal clearly indicates that the NH proton is involved in a hydrogen bonding.

Another interesting feature in the ^{1}H-NMR spectra of compounds (**31–39**) is the high downfield shift observed in the signal of the aromatic protons *ortho* to the nitrogen when compared with the corresponding cyclic imides (ca. 1.3 ppm for proton Hc in the 2- and 3-methoxy derivatives, and 0.5 and 0.3 ppm, respectively for protons Hb and Hc in the 4-methoxy derivatives), which arises from the anisotropic effect of the carbonyl group adjacent to the aromatic ring.

The IR spectra of the sulfonated maleimides show the characteristic absorption pattern for the carbonyl group in the cyclic imides (a strong band at 1710 and a weak band at 1770 cm^{-1}) and for the sulfonyl group (1170 and 1370 cm^{-1}). As expected, the IR spectra of the maleamic acids (**29–32**) and the maleamides (**33–37**) differ considerably from the IR spectra of the corresponding maleimides, specially in the range of 1600–1800 cm^{-1}. In contrast with the very strong absorption at 1710 cm^{-1} for the maleimides, the maleamic acids show two medium intensity absorptions at 1700 (CO_2H) and 1635 cm^{-1} (CONHAr). The maleamides show two medium intensity absorptions at 1620 ($CONH_2$) and 1650 cm^{-1} (CONHAr).

EXPERIMENTAL

Melting points were determined with a Reinch Termovar electric apparatus and are uncorrected. NMR spectra were recorded on Varian XL 200, Brucker AC-200 and Brucker AMX 300, using tetramethylsilane as internal standard and $CDCl_3$ unless otherwise stated. MS were recorded on a VG AutoSpec-Q instrument and IR spectra were measured as KBr pellets on a Perkin-Elmer 683 Infrared Spectrophotometer. Microanalysis were carried by courtesy of Shell Research Ltd, Sittingbourne, Kent, England.

Yields, melting points and microanalysis or MS data of selected compounds are presented in Table IV.

Synthesis of the N-*Arylmaleimides*

N-(4-methoxyphenyl)maleimide (**1**, R = 4-MeO). To a suspension of maleic anhydride (20.1 g; 0.21 mol) in diethyl ether (250 ml), a suspension of p-anisidine (24.6 g; 0.2 mol) in diethyl ether (300 ml) was added dropwise. A suspension formed which was stirred overnight at room temperature. The solid was then filtered through a sintered glass funnel, washed with diethyl ether and dried in the oven at 100°C. The *N*-(4-methoxyphenyl)maleamic acid was obtained as a cream powder (44.0 g; 99.4%), m.p. 181–182°C. A mixture of the maleamic acid (44.0 g; 0.2 mol), fused sodium acetate (10 g) and freshly distilled acetic anhydride (125 ml) was heated in an oil bath at 95–100°C for 1.5 hours. After cooling down to room temperature, the suspension was added to cold water, the solid filtered off and washed with water. The solid was then dissolved in dichloromethane (120 ml), washed with water and dried over anhydrous sodium sulphate. After concentration, the compound was recrystallized from cyclohexane. A first crop of 31 g of the maleimide (m.p. 149–150°C) was obtained. The mother liquor was concentrated and purified by silica column chromatography. A second crop of the maleimide (2.7 g) was eluted with dichloromethane/petroleum ether (3/2) along with some unreacted maleamic acid (6.0 g). The combined yield, based on consumed maleamic acid, was 97%.

The other *N*-arylmaleimides used throughout this work were prepared following the same method. (R, Yield, m.p. °C): (2-OCH_3, 95, 122–123); (3-OCH_3, 90, 66–67.5); (4-CH_3, 97, 149–150.5); (4-Cl, 94, 115–116.5).

TABLE IV

Physical data for the compounds **7** to **29**

Comp	Yield (%)	M. P. (°C)	Molecular Formula	Microanalysis or MS Found (Calc.) % C	H	N
7	41	186-187	$C_{13}H_{14}N_2O_5S$	50.24(50.32)	4.53(4.55)	8.93(9.03)
8	55	146-147	$C_{15}H_{18}N_2O_5S$	53.52(53.24)	5.42(5.36)	8.28(8.28)
9	59	155-156	$C_{14}H_{16}N_2O_5S$	51.91(51.84)	4.97(4.97)	8.57(8.64)
10	60	195-196	$C_{17}H_{14}N_2O_5S$	56.45(56.98)	3.86(3.94)	7.66(7.82)
11	56	143-144	$C_{13}H_{14}N_2O_5S$	310(M^+), 266, 203, 202, 174, 159		
12	86	oil	$C_{15}H_{18}N_2O_5S$	338(M^+), 266, 203, 202, 174, 159		
13	80	138-140	$C_{14}H_{16}N_2O_5S$	51.09(51.84)	4.89(4.97)	8.34(8.64)
14	98	184-185	$C_{17}H_{14}N_2O_5S$	57.43(56.98)	3.99(3.94)	7.77(7.82)
15	37	188-189	$C_{13}H_{14}N_2O_5S$	50.17(50.31)	4.49(4.55)	8.97(9.03)
16	87	139-140	$C_{15}H_{18}N_2O_5S$	53.34(53.24)	5.39(5.36)	8.32(8.28)
17	78	198-199	$C_{14}H_{16}N_2O_5S$	51.45(51.84)	4.94(4.97)	8.52(8.64)
18	96	199-200	$C_{17}H_{14}N_2O_5S$	358(M^+), 263, 202, 187, 172		
19	76	128-130	$C_{13}H_{14}N_2O_5S$	47.41(47.85)	4.29(4.32)	8.35(8.58)
20	73	177-179	$C_{16}H_{18}N_2O_5S$	54.99(54.85)	5.23(5.18)	7.94(7.99)
21	42	139-140	$C_{13}H_{14}N_2O_4S$	53.20(53.05)	4.79(4.79)	9.43 (9.52)
22	80	81-83	$C_{15}H_{18}N_2O_4S$	322(M^+), 307, 250, 186, 158		
23	68	177-179	$C_{14}H_{16}N_2O_4S$	54.57(54.53)	5.26(5.23)	9.02(9.08)
24	80	158-159	$C_{17}H_{14}N_2O_4S$	59.92(59.64)	4.35(4.12)	8.17(8.18)
25	72	133-135	$C_{13}H_{14}N_2O_5S$	49.91(50.32)	4.53(4.55)	8.89(9.03)
26	90	201-202	$C_{17}H_{12}N_2O_8S$	404(M^+), 266, 202, 187, 172		
27	94	164-165	$C_{17}H_{12}N_2O_8S$	50.31(50.50)	2.91(2.99)	6.87(6.93)
28	91	121-122	$C_{17}H_{12}ClNO_6S$	393(M^+), 266, 202, 187, 172		
29	88	273-275	$C_{17}H_8Cl_5NO_6S$	38.69(38.41)	1.49(1.52)	2.62(2.63)

Chlorosulfonation of the N-*Arylmaleimides*

N-*(3-chlorosulfonyl-4-methoxyphenyl)maleimide* (**4**). The N-*(4-methoxyphenyl)maleimide* (**1**, R = 4-MeO) (10.16 g; 0.05 mol) was slowly added to ice-cold chlorosulfonic acid (20.0 ml; 0.3 mol) with constant stirring. As HCl evolved from the reaction mixture this was allowed to warm up to room temperature and left for two hours. The mixture was then slowly and carefully poured onto crushed ice, with stirring. The precipitate was filtered off and washed with cold water. After drying in a vacuum desiccator, the product (11.2 g; 74%) was used in the subsequent reactions without further purification.

A small sample was dissolved in chloroform, the organic solution washed with water, dried (Na_2SO_4) and concentrated, and the pure product precipitated with petroleum ether. Cream powder, m.p. 129–130°C, ^{1}H-NMR 4.10 (s, 3H, OCH_3), 6.87 (s, 2H, HC=CH), 7.22 (d, 1H, H^5, J = 8.2), 7.67–7.73 (dd, 1H, H^6), 7.99 (d, 1H, H^2, J = 2.8)

N-*(3-chlorosulfonyl-4-chlorophenyl)maleamic acid* (**6**). Chlorosulfonic acid (5.0 ml, 75 mmol) was added to *N*-(4-chlorophenyl)maleimide (**1**, R = 4-Cl) (2.08 g, 10 mmol) and the red solution was stirred for 48 hr at 105–110°C, protected from moisture with a silica gel tube. The mixture was then carefully poured onto crushed ice, with stirring. The yellow precipitate was filtered off, washed with water and

dissolved in $CHCl_3$. The organic solution was washed again with water, dried over sodium sulfate and, after concentration, the product was precipitated by addition of hexane. The maleamic acid was filtered, washed with hexane and dried to give a yellow powder (0.34 g, 10.5%), m.p. 149–151°C. ^{1}H NMR (D_6 acetone) 6.39 (d, 1H, HO_2CCH=$\underline{CH}$NR, J = 12.42), 6.66 (d, 1H, $HO_2C\underline{CH}$=CHNR, J = 12.42), 7.83 (d, 1H, $\underline{H}^5$, J = 8.76), 8.10–8.14 (dd, 1H, $\underline{H}^6$), 8.69 (d, 1H, $\underline{H}^2$, J = 2.58), 10.54 (br, 1H, $\underline{NH}$)

MS: 323 (M^+), 305, 225, 206, 126, 99

Reaction of the Sulfonyl Chlorides with Amines

N-*(3-diethylsulfamoyl-4-methoxyphenyl)maleimide* (**16**). Diethylamine (2.1 ml; 0.02 mol) was slowly added to a solution of the sulfonyl chloride (**4**) (3.02 g; 0.01 mol) in acetonitrile (25 ml) at 0°C, and the mixture was stirred at this temperature for two hours. The diethylamine hydrochloride precipitate was filtered off with suction, washed with cold acetonitrile (10 ml), and discarded. The combined acetonitrile solutions were evaporated under reduced pressure. The solid residue was dissolved in dichloromethane and purified by silica column chromatography, using dichloromethane as eluent. The pure sulphonamide was recrystallized from dichloromethane/petroleum ether or from methanol. Yellow crystals (2.95 g; 87%), m.p. 139–140°C. ^{1}H-NMR 1.13 (t, 6H, $CH_2\underline{CH_3}$), 3.36 (q, 4H, $\underline{CH_2}CH_3$), 3.96 (s, 3H, $O\underline{CH_3}$), 6.86 (s, 2H, $\underline{HC}$=$\underline{CH}$), 7.07 (d, 1H, $\underline{H}^5$, J = 8.6), 7.44–7.49 (dd, 1H, $\underline{H}^6$), 7.90 (d, 1H, $\underline{H}^2$, J = 3.0)

Reaction of the Sulfonyl Chlorides with Phenols

N-*(3-(4-nitrophenylsulfonate)-4-methoxyphenyl)maleimide* (**27**). A stirred mixture of the sulfonyl chloride (**4**) (3.02; 0.01 mol) and 4-nitrophenol (1.39 g; 0.01 mol) in acetonitrile (25 ml) was left for one hour at 55–60°C. Triethylamine (1.4 ml; 0.01 mol) was then added dropwise to the reaction mixture and the reaction allowed to proceed for a further 45 minutes at this temperature. After cooling to room temperature, the solid triethylamine hydrochloride was filtered off with suction, washed with cold acetonitrile and discarded. The combined solutions were evaporated under reduced pressure. The solid residue was dissolved in a small amount of dichloromethane and purified by chromatography on a silica column, using dichloromethane as eluent. The solvent was evaporated and the residue was recrystallized from ethanol. Yellow crystals (3.78; 94%), m.p. 164–165°C. ^{1}H-NMR (D_6-acetone) 4.07 (s, 3H, $O\underline{CH_3}$), 7.03 (s, 2H, $\underline{HC}$=$\underline{CH}$), 7.46–7.50 (m, 3H, $\underline{H}^5$ + $\underline{H}^{2'}$ + $\underline{H}^{6'}$), 7.76–7.81 (dd, 1H, $\underline{H}^6$), 7.87 (d, 1H, $\underline{H}^2$, J = 2.5), 8.27–8.31 (m, 2H, $\underline{H}^{3'}$ + $\underline{H}^{5'}$)

Hydrolisis of the N-*Arylmaleimide Derivatives*

Synthesis of the maleamic acid (**33**). To a solution of the diethylsulfamoylarylmaleimide (**16**) (1.02 g; 3.0 mmol) in acetonitrile (20 ml) 10% aqueous NaOH (2.0 ml) was added and the mixture stirred at room temperature for three hours. The sodium salt of the maleamic acid (**33**) precipitated out and was filtered off and washed with acetonitrile. The solid was dissolved in water and the solution acidified with 10% HCl. The resultant suspension was extracted with chloroform and the combined organic extracts were concentrated and dried over sodium sulfate. Removal of the solvent under vacuum afforded a white solid which was recrystallized from chloroform/petroleum ether. White crystals (0.73 g; 68%), m.p. 149–150°C. ^{1}H-NMR (D_6-acetone) 1.05 (t, 6H, $CH_2\underline{CH_3}$), 3.33 (q, 4H, $\underline{CH_2}CH_3$), 3.96 (s, 3H, $O\underline{CH_3}$), 6.37 (d, 1H, $\underline{HC}$=CHR, J = 12.75), 6.69 (d, 1H, HC=$\underline{CHR}$, J = 12.75), 7.24 (d, 1H, $\underline{H}^5$, J = 9.02), 7.95–8.01 (dd, 1H, $\underline{H}^6$), 8.15 (d, 1H, $\underline{H}^2$, J = 2.71), 10.38 (br, 1H, $\underline{NH}$)

Ammonolisis of the N-*Arylmaleimide Derivatives*

Synthesis of the maleamide (**38**). Ammonia (25%, 1.5 ml) was added to a solution of the diethylsulfamoylarylmaleimide (**16**) (1.02 g; 3.0 mmol) in acetonitrile (20 ml) and the mixture stirred at room temperature for four hours. The solvent was evaporated under vacuum at room temperature. The residue was dissolved in chloroform and purified by silica column chromatography, using a gradient of chloroform/acetone mixture as eluent. A first fraction containing some of the starting material was isolated. The second fraction contained the pure maleamide, which after concentration, was precipitated by addition of dichloromethane. Yellow crystals (0.68 g; 64%), m.p. 144–145°C. ^{1}H-NMR (D_6-acetone) 1.06 (t, 6H, $CH_2\underline{CH_3}$), 3.33 (q, 4H, $\underline{CH_2}CH_3$), 3.93 (s, 3H, $O\underline{CH_3}$), 6.26 (d, 1H, $\underline{HC}$=CHR, J = 13.37), 6.40 (d, 1H, HC=$\underline{CHR}$, J = 13.37), 7.17 (d, 1H, $\underline{H}^5$, J = 8.97), 7.91–7.97 (dd, 1H, $\underline{H}^6$), 8.17 (d, 1H, $\underline{H}^2$, J = 2.65), 12.40 (br, 1H, $\underline{NH}$)

Microanalysis: Found (Calc.) % C, 50.77 (50.69); H, 6.00 (5.96); N, 11.78 (11.82)

Synthesis of Succinimide (**30b**). To a solution of maleimide (**28**) (0.39 g; 1 mmol) in acetonitrile (8 ml) piperidine (0.3 ml; 3 mmol) was added. The mixture was left overnight at room temperature, with stirring. The reaction mixture was then diluted with $CHCl_3$ and washed with dilute hydrochloric acid. After concentration, the product was purified by TLC using $CHCl_3$ as eluent. The succinimide was obtained as a colorless oil (0.37 g; 77%) which on standing turned into a low melting solid.

^{1}H-NMR 1.48–1.67 (m, 6H piper.), 2.49–2.56 (m, 2H, piper.), 2.77–2.85 (m, 2H, piper.), 2.77–2.85 (dd, 1H, COCH(R)C$\underline{H}_2$CO, J = 4.9 and J = 18.7), 2.96–3.05 (dd, 1H, COCHRC$\underline{H}_2$CO, J = 9.1 and J = 18.7), 3.90–3.95 (dd, 1H, CO$\underline{C}$HRCH$_2$CO, J = 4.9 and J = 9.1), 4.01 (s, 3H, O$\underline{C}$H$_3$), 7.04–7.31 (AB, 4H, *p*-Cl-C$_6\underline{H}_4$O), 7.15 (d, 1H, $\underline{H}^5$, J = 8.9), 7.54–7.58 (dd, 1H, $\underline{H}^6$, J = 2.6 and J = 8.9), 7.78 (d, 1H, $\underline{H}^2$, J = 2.6).

MS: 478 (M^+), 393, 266, 202, 187, 172, 111

Synthesis of Succinimide (**30c**). To a solution of maleimide (**16**) (0.68 g; 2 mmol) in acetonitrile (10 ml) *p*-toluidine (0.32 g, 3 mmol) was added. The solution was refluxed for 6 hours, and then diluted with $CHCl_3$ and washed with dilute hydrochloric acid. After concentration, the mixture was purified by TLC using $CHCl_3$ as eluent. Some of the starting maleimide (0.12 g, 17.7%) was recovered. The succinimide (0.68 g, 93% based on consumed maleimide) was recrystallized from ethanol, to yield a cream powder, m.p. 146–147°C.

^{1}H-NMR 1.13 (t, 6H, CH$\underline{C}$H), 2.27 (s, 3H, Ar$\underline{C}$H$_3$, 2.77–2.85 (dd, 1H, COCHCR$\underline{C}$H$_2$CO, J = 5.2 and J = 18.0), 3.31–3.43 (m, 5H, $\underline{C}$H$_2$CH$_3$ and COCHCR$\underline{C}$H$_2$CO), 3.95 (s, 3H, ArO$\underline{C}$H$_3$), 4.44–4.47 (m, 2H, CO$\underline{C}$HCRCH$_2$CO and $\underline{N}$H), 6.58–7.08 (AB, 4H, Me-C$_6\underline{H}_4$-NHR), 7.06 (d, 1H, $\underline{H}^5$, J = 8.8), 7.43–7.47 (dd, 1H, $\underline{H}^6$, J = 2.6 and J = 8.8), 7.91 (d, 1H, $\underline{H}^2$, J = 2.6)

MS: 445 (M+), 430, 338, 323, 309, 266, 133

ACKNOWLEDGEMENT

This work was supported by the Instituto Nacional de Investigação Científica and the University of Aveiro, Portugal. Thanks are due to Mr. R. H. Davis of Shell Research Ltd (Sittingbourne Research Center) Sittingbourne, Kent, England, for microanalysis and to the Mass Spectrometry Group of the University of Aveiro for MS data.

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