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Note

A facile synthesis of *N*-substituted maleimides

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A simple and efficient method for the synthesis of *N*-substituted maleimides from the corresponding maleamic acids under the phase transfer catalysis has been described.

Keywords: Maleamic acids, phase transfer catalysis, maleimides, synthesis

N-Substituted maleimides find significant applications in synthetic chemistry[1] particularly as a source of functionalized β-lactams[2], as Diels-Alder dienophiles[3] and as Michael acceptors[2,3]. Incorporation of maleimide unit has been found to be economical in polymer industry as thermal stabilizers[4]. Several nice synthetic methods to design maleimides are well established[4-8]. In the present communication we report yet another a simple and efficient approach to *N*-substituted maleimides taking the advantage of phase transfer catalysis (**Scheme I**).

Results and Discussion

Maleamic acids **1a-g** were prepared quantitatively by reacting equimolar amounts of amines and maleic anhydride in CH_2Cl_2 at RT. During the esterification of maleamic acids **1a-g** in the presence of dimethyl sulphate, sodium carbonate and tetrabutylammonium bromide (TBAB), direct formation of maleimides **3a-g** in very good to excellent yields (**Scheme I, Table I**) was observed. The reaction progress was monitored by TLC, which revealed that the corresponding esters can be the probable intermediates. This was later proved separately by transforming the *N*-(α)-methylbenzylmaleamic acid methyl ester **2a** to the corresponding maleimide **3a** in the presence of TBAB and Na_2CO_3 (**Scheme I**). The presence of TBAB for the conversion of **1a** to **3a** is necessary, as in its absence the sole product obtained was the methyl ester **2a**. In the absence of dimethyl sulfate most of the starting acid was recovered, which also supports the methyl ester **2a** as the most probable intermediate.

The scope of the reaction was further evaluated in presence of various bases (**Scheme I**, **Table II**).The best results were obtained in presence of sodium carbonate. When a strong base like NaOH was used, reaction was not complete even at prolonged duration, instead ester was hydrolysed to maleamic acid. This indicates that the two reactions *viz.* cyclisation of the ester to the corresponding maleimide and its hydrolysis to starting acid are competing with each other.

Conclusion

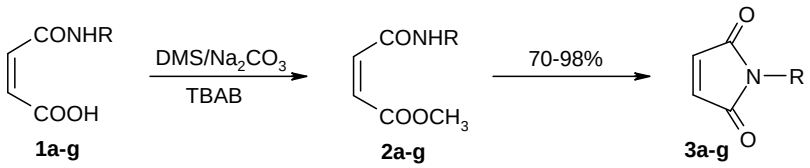
In conclusion, a general efficient method for the synthesis of *N*-substituted maleimides by using the phase transfer catalysis is demonstrated.

Experimental Section

Materials were obtained from commercial suppliers and were used without further purification. Column chromatographic purifications were done on silica gel (60-120 mesh). Products obtained as solids or thick oils were dried under high vacuum. TLC was performed on pre-coated silica plates (Merck F_{254}, 0.25 mm thickness); compounds were visualized under UV light. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200 MHz) NMR spectrometer. IR spectra were recorded on a Shimadzu FT-IR spectrophotometer and elemental analyses were carried out on a Thermo Finnigan Flash EA 1112 series analyzer. Melting points are uncorrected.

General procedure for the synthesis of *N*-substituted maleimides 3a-g

To the mixture of maleamic acid **1** (215 mg, 1.00 mmole), sodium carbonate (159 mg, 1.20 mmole), tetrabutylammonium bromide (20 mg, 0.26 mmole) and 1:1 EDC/water (10 mL) was added dimethyl sulfate (0.13 mL, 1.50 mmole) at RT. The reaction-mixture was stirred at RT for 8 hr and the reaction progress was followed by TLC. The separated organic layer was washed successively with saturated $NaHCO_3$ solution, brine, dried over sodium sulfate and concentrated *in vacuo* to furnish maleimide **3**.



1a-g **2a-g** **3a-g**

Scheme I

Table I — Phase transfer catalysed synthesis of *N*-substituted maleimides **3a-g**

Product	R	Time (hr)	Yield (%)	m.p. (°C, Lit.)
3a	-$CH(CH_3)C_6H_5$	8	93	Colourless liquid[7]
3b	- $CH_2C_6H_5$	7	98	68 (69-70, ref 7)
3c	-C_6H_4-*p*-CH_3	8	92	150 (149-50, ref. 6)
3d	-C_6H_4-*p*-NO_2	10	70	169 (167-68, ref.5)
3e	-C_6H_4-*p*-OCH_3	10	85	157 (157, ref. 6)
3f	-Cyclohexyl	7	91	88 (87-90, ref. 4)
3g	-(*S*)-$CH(CH_3)C_6H_5$	8	94	Colourless liquid[5]

Table II — Phase transfer catalysed synthesis of *N*-benzylmaleimide **3b** from *N*-benzyl maleamate **2b** in presence of various bases.

Reagents	Time (hr)	Yield of **3b** (%)	Recovered acid **1b** (%)
TBAB + Na_2CO_3	2	95	nil
TBAB + $NaHCO_3$	4	95	nil
TBAB + CH_3COONa	100	10	80
TBAB + NaOH	1	50	50
Tetrabutyl ammonium hydroxide	8	90	nil

***N*-(α)-Methylbenzylmaleimide, 3a**: IR (neat): 1706, 1633, 831, 763, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.83 (d, *J* = 8 Hz, 3H), 5.36 (q, *J* = 8 Hz, 1H), 6.63 (s, 2H), 7.2 0-7.45 (m, 5H).

***N*-Benzylmaleimide, 3b**: m.p. 68°C; IR (nujol): 1712, 1496, 842, 723, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.65 (s, 2H), 6.68 (s, 2H), 7.30 (bs, 5H).

***N*-*p*-Tolylmaleimide, 3c**: m.p.150°C; IR (nujol): 1716, 1515, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.40 (s, 3H), 6.85 (s, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H).

***N*-*p*-Nitrophenylmaleimide, 3d**: m.p. 169°C; IR (nujol): 1724, 1523, 1507, 857, 698, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.92 (s, 2H), 7.68 (d, *J* = 8 Hz, 2H), 8.33 (d, *J* = 8 Hz, 2H).

***N*-*p*-Methoxyphenylmaleimide, 3e**: m.p. 157°C; IR (nujol): 1706, 1510, 1247, 1027, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.83 (s, 3H), 6.91 (s, 2H), 7.03-7.27 (m, 4H).

***N*-Cyclohexylmaleimde, 3f**: m.p. 88-90°C; IR (nujol): 1706, 827, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25-2.05 (m, 10H), 3.90 (m, 1H), 6.60 (s, 2H).

(*S*)-*N*-(α)-Methylbenzylmaleimide, 3g: colourless liquid; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.83 (d, *J* = 8 Hz, 3H), 5.36 (q, *J* = 8 Hz, 1H), 6.63 (s, 2H) 7.2 0-7.45 (m, 5H); $[\alpha]_{25}^{D}$ -85° ($CHCl_3$), Lit. $[\alpha]_{22}^{D}$ - 89.3° ($CHCl_3$, ref. 5).

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