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# A MILD CONVERSION OF MALEIC ANHYDRIDES INTO MALEIMIDES

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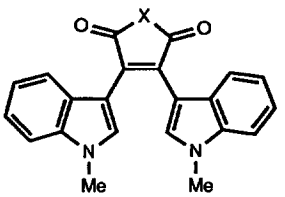
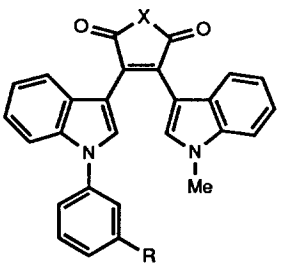
*Summary: Maleic anhydrides are converted into maleimides, at room temperature and in excellent yield, by treatment with a mixture of methanol and hexamethyldisilazane. Esters and nitriles are unaffected under these conditions.*

Maleimides are of interest as potent and selective inhibitors of protein kinase C[1]. Bis-indolyl maleimides are also valuable intermediates in the synthesis of the aglycones of indolocarbazole alkaloids such as staurosporine[2,3] and rebeccamycin[4]. Since bis-indolyl- and other indolyl-aryl- maleic anhydrides are available in one step from indoles[5], we have investigated their conversion into maleimides.

Simple bisaryl maleimides may be prepared from the readily available anhydrides by the standard method[6] of heating at high temperature in the presence of ammonia or an ammonia source. For example bisindolyl maleimide **1** was formed in 80% yield by heating anhydride **2** in DMF with aqueous ammonia in a sealed vessel at 140°C. However these conditions are neither convenient nor mild and were not applicable to maleimides containing sensitive functionality; the nitrile in anhydride **3** was converted into the amidine **4** during imide formation and the ester **5** gave a mixture of ester **6**, amide **7** and acid **8**. The N-substituted indole **9** gave a mixture of products containing little or none of the desired imide **10**.

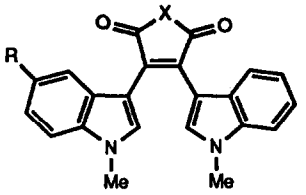



**1** X = NH
**2** X = O

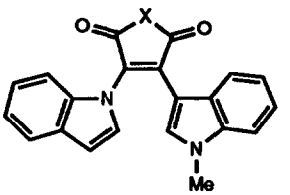



**3** X = O R = CN
**4** X = NH R = $C(NH)NH_2$

The reaction of cyclic acid anhydrides with ammonia proceeds via the amic acids (eg. maleamic acid **11**), which are largely deprotonated in the presence of excess ammonia. At the reactant concentrations employed, the second step (the cyclisation of the amic acid) is generally slow and rate-limiting. A common strategy therefore, is to isolate the amic acid and cyclise these to the imides in a separate reaction by treatment with activators such as acetic anhydride or phosphorus pentoxide[7]. However this strategy is not easily applicable to maleic anhydrides having bulky substituents on the 2 and 3 positions since the amic acids are unstable towards reversion into the anhydrides[8].

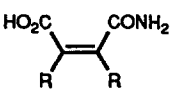


5 X = O R = $CO_2Me$
6 X = NH R = $CO_2Me$
7 X = NH R = $CONH_2$
8 X = NH R = $CO_2H$

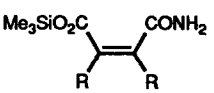


9 X = O
10 X = NH

Our strategy was to activate the amic acid by conversion into the silyl ester **12** *in situ* . This conversion should be possible in the presence of ammonia due to the greater strength of the Si-O bond *vs.* the Si-N bond. A reagent was therefore developed which contained both ammonia and silylating agent : addition of methanol (0.5 molar equivalents) to hexamethyldisilazane (HMDS) gave a mixture containing methoxytrimethylsilane, ammonia and residual HMDS as shown by GC/MS and NMR ($^1H$ and $^{13}C$). The reaction was about 50% complete after 1h and essentially complete after standing 16h. In practice, however, the reagent may be used immediately; similar results were obtained with freshly prepared mixtures and mixtures which had stood overnight. No aminotrimethylsilane was detected in the mixture, even in the presence of excess HMDS, due either to preferential reaction of methanol with aminotrimethylsilane as it is formed or to the tendency of this substance to disproportionate into ammonia and HMDS[9].



**11**



**12**

When DMF solutions of maleic anhydrides were treated with HMDS/methanol reagent, at room temperature for 16h, the imides were formed in excellent yields (Table). In contrast to the conventional conditions, the nitrile in anhydride **3** and the ester in anhydride **5** were unaffected. Furthermore, the imide **10**, which was not readily accessible by standard procedures, was produced smoothly from anhydride **9**. The reaction was not limited to bisarylmaleic anhydrides; 2,3-dimethylmaleic anhydride **14** gave 2,3-dimethylmaleimide **15** in good yield. Maleic anhydride itself, however, did not undergo a satisfactory conversion into the imide under these conditions.

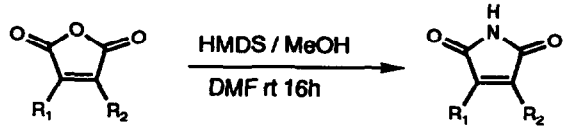
The reaction may also be performed in acetonitrile at reflux. Thus 2,3-diphenylmaleic anhydride **16** was converted into 2,3-diphenylmaleimide **17** in 97% yield in 3h.

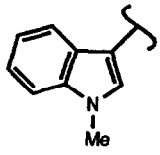
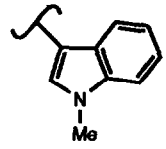
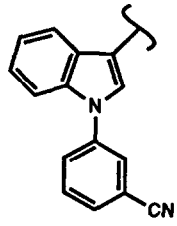
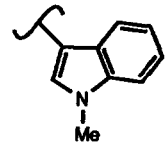
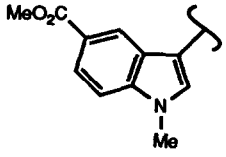
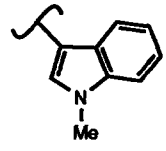
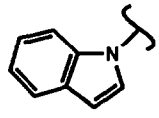
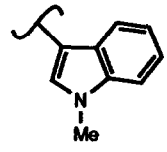
**Typical Procedures**

A. Reaction in DMF: 2,3-bis(1-methyl-3-indolyl)maleimide (**1**)

A solution of bis(1-methyl-3-indolyl)maleic anhydride (**2**, 356mg, 1mmol) in DMF (4ml) was treated with a mixture of 1,1,1,3,3,3-hexamethyldisilazane (1.61g, 10mmol) and methanol (0.16g, 5 mmol). After 16h at room

**Table: Preparation of maleimides from maleic anhydrides**




| Anhydride | $R_1$ | $R_2$ | Imide | Yield % |
|---|---|---|---|---|
| 2 |  |  | 1 | 95 |
| 3 |  |  | 13 | 97 |
| 5 |  |  | 6 | 90 |
| 9 |  |  | 10 | 98 |
| 14 | Me | Me | 15 | 93 |
| 16 |  |  | 17 | 94 |

temperature the mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed well with water and dried ($MgSO_4$).Removal of solvent under reduced pressure gave 2,3-bis(1-methyl-3-indolyl)maleimide as a red solid (337mg, 95%). m.p.>300°C. NMR (300MHz, $d_6$-DMSO, δppm/TMS): 10.92, s, 1H (NH), 7.81, s, 2H (indole C2 protons), 7.42, d, (J=7.5Hz), 2H (indole C7 protons), 7.03, t, (J=7.5Hz), 2H (indole C6 protons) ,6.77, d, (J=7.5 Hz), 2H , (indole C4 protons), 6.65, t, (J=7.5Hz), 2H (indole C5 protons), 3.88, s, 6H (NMe).IR (nujol) 1705 (vs) $cm^{-1}$. Accurate Mass: measured 355.1301 ,calculated for $C_{22}H_{17}N_3O_2$ 355.1320.

B. Reaction in acetonitrile: 2,3-diphenylmaleimide (17)

A solution of 2,3-diphenylmaleic anhydride (16, 250mg, 1mmol) in acetonitrile (30ml) was treated with a mixture of 1,1,1,3,3,3-hexamethyldisilazane (1.61g, 10mmol) and methanol (0.16g, 5mmol) and the solution heated at reflux for 3h. Methanol (10ml) was added and heating continued for 5 minutes. Solvents were removed under reduced pressure to give 2,3-diphenylmaleimide as a yellow solid (242mg, 97%).mp. 216-217°C (lit.[10] 217°C).NMR (300MHz, $d_6$-DMSO, δppm/TMS): 11.25, s , 1H (NH), 7.30-7.45, complex signal , 10H, (aromatics). IR (nujol) 1706 (vs) $cm^{-1}$. Accurate Mass: measured 249.0782, calculated for $C_{16}H_{11}NO_2$ 249.0789. Analysis: calculated for $C_{16}H_{11}NO_2$ C 77.17% H 4.45% N 5.63% found C 76.96% H 4.37% N 5.35%.

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