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A Convenient Synthesis of Bisindolylmaleimides

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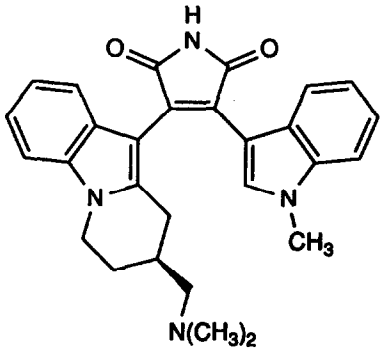
Abstract: A mild and flexible method for the preparation of bisindolylmaleimides from the corresponding indoles and indole-3-acetimidate esters is described.

The protein kinase C (PKC) isoenzyme family is believed to play an essential role in many signal transduction pathways[1] and is implicated in a wide range of physiological processes. Inappropriate activation of PKC is thought to occur in a number of pathological states.[2] Recently, bisindolylmaleimides (e.g. **1**), have been shown to be highly selective inhibitors[3] of PKC and show promise as a novel potential therapy for autoimmune diseases, such as rheumatoid arthritis.[4]

During the course of our work on substituted maleimides we required a high yielding, mild approach to these systems that would allow the synthesis of a wide range of analogues. Early syntheses of bisindolylmaleimides from indolyl Grignard reagents[5] or indolylacetic acid trianions[6] were neither mild nor selective enough for our purposes. Subsequently a mild method for the synthesis of disubstituted maleic anhydrides[7] and a process for conversion into the corresponding maleimides[8] have been described. The modest yields obtained in this coupling reaction however were not compatible with larger scale preparative work and a new efficient route to bisindolylmaleimides was sought.



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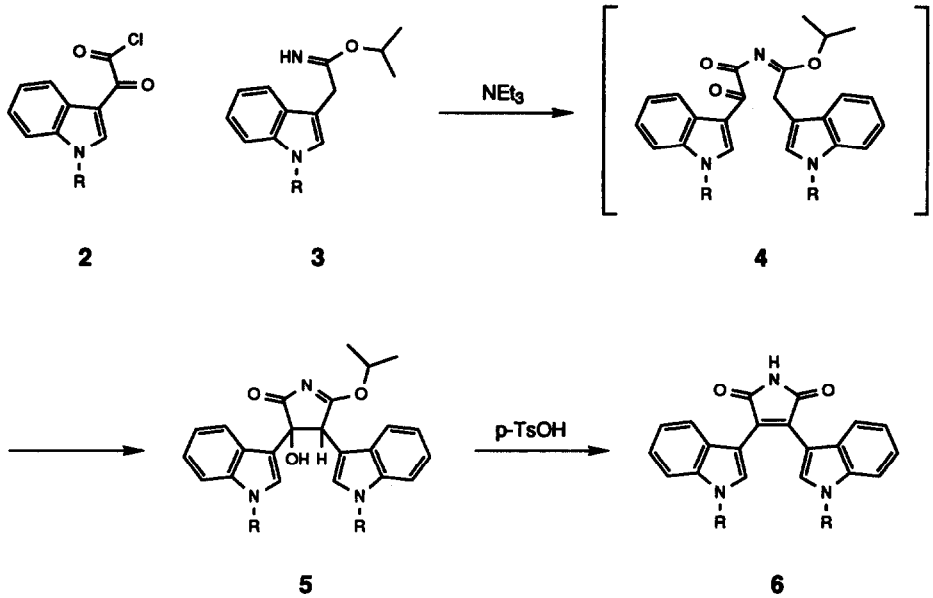

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We have now developed a new coupling reaction which allows direct access to the bisindolylmaleimide system in good yield. At the outset, we envisaged that an indolyl-3-glyoxylyl chloride **2** when treated with an appropriately substituted indolyl-3-acetimidate **3** and a suitable base should afford the corresponding acylimidate **4** which, in the presence of excess base, should undergo cyclisation to give hydroxyadduct **5**. Dehydration and hydrolysis of this hydroxypyrroline would then yield the desired bisindolylmaleimide **6**. This was indeed found to be the case and treatment of 1-methylindole-3-glyoxylyl chloride (**2**, R=CH_3) with imidate **3** (R=CH_3) in the presence of excess triethylamine led directly to hydroxypyrroline **5** (R=CH_3), which upon treatment with p-toluenesulphonic acid underwent dehydration and hydrolysis to give the desired imide **6** (R=CH_3) in good yield (table). A small amount of acyclic imide **8** (<5%) can usually be isolated, possibly arising from hydrolysis of acylimidate **7** which does not have the correct geometry for cyclisation to occur.

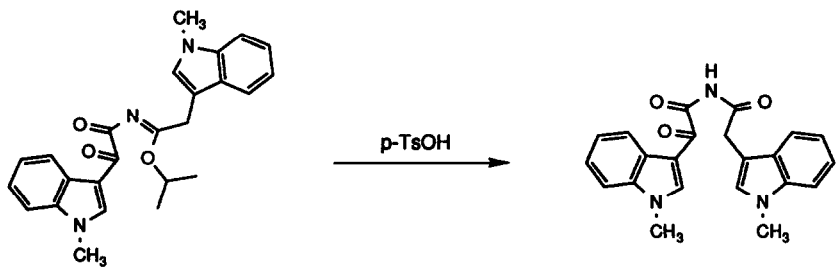

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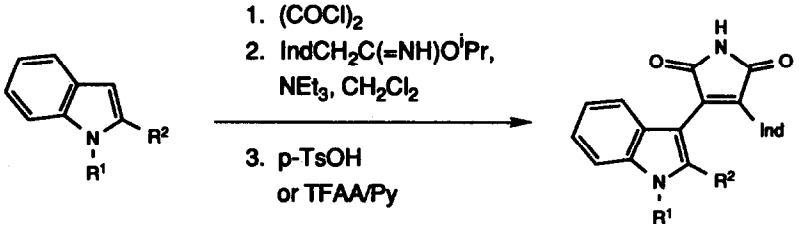
Table. Preparation of Bisindolylmaleimides



R^1	R^2	Ind	Yield (%)[a]
CH_3	CH_3	1-methyl-3-indolyl	70[b]
CH_3	H	1-methyl-3-indolyl	75[b]
CH_3	H	3-indolyl	56[b]
CH_3	H	1-acetyl-3-indolyl	48[b]
(S)-$(CH_2)_2CH(CH_2OAc)CH_2$		1-methyl-3-indolyl	64[b]
(S)-$(CH_2)_2CH(CH_2OAc)CH_2$		1-methyl-3-indolyl	68[c]
(S)-$(CH_2)_2CH(CH_2NHBOC)CH_2$		1-methyl-3-indolyl	42[c]
$(CH_2)_3OAc$	H	1-methyl-3-indolyl	48[c]

a Yields are unoptimised and based on starting indole. b Intermediate hydroxypyrroline was treated with 1 equivalent of p-TsOH to afford final product. c Intermediate hydroxypyrroline was treated with 1.05 equivalents of TFAA in pyridine to afford final product.

For acid sensitive groups an alternative method was developed for promoting the dehydration and hydrolysis of the intermediate hydroxypyrroline. Thus, treatment of **5b** with 1.05 equivalents of trifluoroacetic anhydride in pyridine also affords the desired maleimides in good yield.

In contrast to the the coupling of indolylglyoxylyl chlorides with indolylacetic acids this coupling will tolerate a free indole NH (table) and abrogates the need for protection. This reaction therefore constitutes a novel, convenient, mild and flexible synthesis of bisindolylmaleimides which is compatible with large scale preparations. Further work is underway to optimise and explore the scope of this methodology for the development of a general synthesis of substituted maleimides.

(S)-3-[8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl]-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione

Oxalyl chloride (3.95ml, 45mmol) was added to a stirred, ice cooled solution of (S)-8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole[3] (10g, 41mmol) in diethyl ether (100ml). After 15 minutes the suspension was filtered and the solid washed with diethyl ether (2x25ml). The solid was dissolved in dichloromethane and treated with 1-methylindole-3-acetimidic acid isopropyl ester hydrochloride[9] (10.97g, 41mmol). The stirred solution was cooled to 0°C and treated dropwise with triethylamine (23ml, 166mmol). After stirring for 4h. at room temperature under nitrogen the solution was washed with water (300ml) and 0.5M hydrochloric acid (300ml). The organic extract was dried (Na_2SO_4), filtered and evaporated. The residue in toluene (150ml) was treated with p-toluenesulphonic acid (7.8g, 41mmol). The mixture obtained was stirred at room temperature for 2.5h., washed with water (200ml), saturated $NaHCO_3$ solution (250ml), brine (250ml), dried (Na_2SO_4) and evaporated to give a brown solid. Trituration with methanol (100ml) gave 12.3g (64%) of (S)-3-[8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl]-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione. A sample was crystallised from dichloromethane/methanol to give an orange solid of melting point 238-241°C. $[\alpha]_D$= -54.3° (c=0.05% in $CHCl_3$ at 20°C); δ(300MHz, d_6-DMSO, 80°C) 1.3-1.7(2H, bm), 1.7-2.1(2H, bm), 1.9(3H, s, OAc), 2.5-2.7(1H, bm), 3.65-3.9(3H, bm), 3.85(3H, s, NCH_3), 4.2-4.3(1H, m), 6.35(1H, d, J=7Hz, indole-H), 6.6(1H, t, J=7Hz, indole-H), 6.95(1H, t, indole-H), 7.0-7.15(2H, m, indole-H), 7.3-7.45(3H, m, indole-H), 7.93(1H, s, indole-2H), 10.6(1H, bs, NH); m/z 467(M^+); calculated for $C_{28}H_{25}N_3O_4$ (467.525) C:71.93; H:5.39; N:8.99%; found C:71.58; H:5.39; N:8.96%.

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9. Prepared by bubbling HCl through a stirred solution of 7.5g (44mmol) of 1-methylindole-3-acetonitrile in isopropanol (100 ml). After 4h the solvent was removed under reduced pressure and the residue triturated with ether to give 5.2g of imidate, mp. 133°C.

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