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A New One Step Synthesis of Maleimides by Condensation of Glyoxylate Esters with Acetamides

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Abstract: Bisphenyl, bisheteroaryl, indolylaryl and indolylcycloalkyl maleimides are prepared in one step and 67-99% yield by condensation of glyoxylate esters with acetamides using a 1.0 *M* solution of potassium *tert*-butoxide in THF. The mechanism of the reaction is discussed.

Maleimides are generally prepared from the corresponding maleic anhydrides by treatment with ammonia or an ammonium source (NH_4OAc, NH_4OH, HMDS/MeOH).[1] Although symmetrical maleic anhydrides can be prepared by condensation of two molecules of a carboxylic acid with a dehydrating agent (e.g acetic anhydride, trifluoroacetic anhydride, DCC), this approach is unsuccessful for the preparation of unsymmmetrical anhydrides, which generally undergo disproportionation to the two simple anhydrides when heated.[2] A related procedure, involving reaction of glyoxylic acids with acetic acids in acetic anhydride, has been employed for the synthesis of bisphenyl[3] and indolylaryl[4] maleic anhydrides albeit in 45% and 22% yield respectively. The most general method available for the synthesis of unsymmetrical maleic anhydrides involves condensation of an acyl halide with an acetic acid salt (e.g. Na, K, Ag, Tl, Et_3N, pyridine) in a suitable organic solvent. This approach has been applied to the synthesis of indolylaryl maleic anhydrides in 23-43% yield, by condensation of *N*-methyl indole-3-glyoxylate chloride with aryl (Ph, *p*-MeOPh, 1-naphthyl and 1-thienyl) acetic acids using Et_3N in CH_2Cl_2, however for this approach to be successful substitution on the indole nitrogen was required.[4] Although the ammonolysis reaction to convert maleic anhydrides into maleimides is generally high yielding, no general method to prepare maleimides, directly in one step, from readily available starting materials previously existed.

We recently reported a new method for the synthesis of bisindolylmaleimides in 84-100% yield by condensation of indole-3-acetamides with methyl indole-3-glyoxylates using potassium *tert*-butoxide in THF.[5] To further expand the scope of this reaction we were interested in determining if it could be developed into a general method for the synthesis of bisphenyl, bisheteroaryl and arylalkyl maleimides. This manuscript describes the results of this work and our development of a new method for the synthesis of this class of compounds.

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Our initial efforts focused on the synthesis of indolylaryl and indolylheteroaryl substituted maleimides **3a-j** (eq 1, Table 1, entries 1-10). Condensation of either methyl indole-3-glyoxylate **1a**[5] or methyl *N*-methyl indole-3-glyoxylate **1b**[5] with acetamides **2a-e** using a 1.0 *M* solution of potassium *tert*-butoxide in THF afforded maleimides **3a-j** in >86% yield, demonstrating that the reaction is successful independent of substitution on the indole nitrogen. Maleimides **3a-e** were isolated directly from the reaction and required no additional purification. Maleimides **3f-j** were purified by trituration from Et_2O. The yield of maleimide was independent of which partner was employed as the acetamide, since condensation of methyl benzoyl formate **1c** with *N*-methyl indole-3-acetamide **2g** afforded maleimide **3f** in 93% yield (Table 1, entry 12), comparable to the

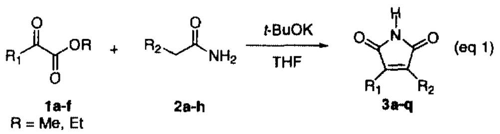


Table 1: Synthesis of Maleimides (eq 1)[6]

entry	1	R_1	2	R_2	3	Yield, %
1	**a**	3-indolyl	**a**	Ph	**a**	99[a, b]
2	**a**	3-indolyl	**b**	*p*-BrPh	**b**	95[a]
3	**a**	3-indolyl	**c**	*p*-MeOPh	**c**	98[a]
4	**a**	3-indolyl	**d**	1-naphthyl	**d**	95[a]
5	**a**	3-indolyl	**e**	3-benzo[*b*]-thienyl[d]	**e**	97[a]
6	**b**	*N*-methyl-3-indolyl	**a**	Ph	**f**	89[c]
7	**b**	*N*-methyl-3-indolyl	**b**	*p*-BrPh	**g**	89[c]
8	**b**	*N*-methyl-3-indolyl	**c**	*p*-MeOPh	**h**	91[c]
9	**b**	*N*-methyl-3-indolyl	**d**	1-naphthyl	**i**	90[c]
10	**b**	*N*-methyl-3-indolyl	**e**	3-benzo[*b*]-thienyl[d]	**j**	86[c]
11	**b**	*N*-methyl-3-indolyl	**f**	cyclohexyl	**k**	81
12	**c**	Ph	**g**	*N*-methyl-3-indolyl	**f**	93
13	**c**	Ph	**a**	Ph	**l**	90[a, e]
14	**d**	2-thienyl	**h**	3-indolyl	**m**	89[f]
15	**d**	2-thienyl	**a**	Ph	**n**	67[b, e]
16	**e**	2-furanyl	**a**	Ph	**o**	70[b, e]
17	**e**	2-furanyl	**e**	3-benzo[*b*]-thienyl	**p**	73[b, e]
18	**f**	isopropyl	**d**	*N*-methyl-3-indolyl	**q**	8

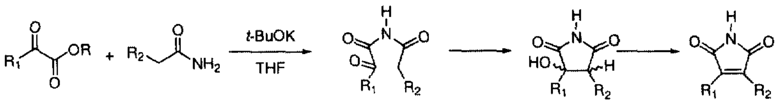
[a] Yield of maleimides obtained directly from the reaction. [b] Reaction performed using 2.0 equiv. of glyoxylate **1**. [c] Yield of maleimide after trituration from Et_2O. [d] Prepared from thianaphthene-3-acetonitrile by hydrolysis with KOH (8 equiv.) in *tert*-BuOH. [e] Purified by column chromatography. [f] Elimination of hydroxyimides performed using DMAP/Im_2CO in acetonitrile.

89% yield obtained when methyl *N*-methyl indole-3-glyoxylate **1b** and phenylacetamide **2a** were employed (Table 1, entry 6). The reaction was also successful with cyclohexylacetamide **2f**[7] which afforded maleimide **3k** in 81% yield upon condensation with methyl *N*-methyl indole-3-glyoxylate **1b** (Table 1, entry 11). However, ethyl isopropylglyoxylate **1f** afforded only a 8% yield of maleimide **3q** upon condensation with *N*-methyl indolyl-3-acetamide **2d** (Table 1, entry 16). The low yield observed with **1f** was due to the difficulty in effecting elimination of the intermediate hydroxyimide **5q** which was isolated in 60% yield.

Having demonstrated the reaction to be successful for indole-3-glyoxylate esters, other glyoxylate esters were evaluated. Condensation of methyl benzoyl formate **1c** with phenylacetamide **2a** afforded bisphenylmaleimide **3l** in 90% yield after trituration from Et_2O (Table 1, entry 13), a significant improvement over the previously published procedure. Ethyl 2-thienyl glyoxylate **1d** was converted into maleimides **3m** and **3n** in 67% and 89% yield upon condensation with phenylacetamide **1a** and indole-3-acetamide **1h** respectively (Table 1, entries 14 and 15). Condensation of ethyl 2-furanyl glyoxylate **1e**, prepared in 75% yield by esterification of 2-furanyl glyoxylic acid, with phenylacetamide **2a** and 3-benzo[*b*]-thienylacetamide **2e** provided maleimides **3o** and **3p** in 70% and 73% yield. The results obtained demonstrate that this reaction is successful with a variety of aryl and heteroaryl derivatives. The ready availability of acetamides and glyoxylic esters[8] should make this a general method for the synthesis of this class of compounds.

All reactions were performed by addition of a 1.0 *M* solution of potassium *tert*-butoxide (3.0 or 4.5 equiv.) in THF into a slurry of acetamide (1.0 equiv.) and glyoxylate ester in THF at 0 °C. In most cases the reactions were successful using 1.2 equiv. of the glyoxylate ester. However, for reactions using methyl indole-3-glyoxylate **1a** (Table 1, entries 1-5) 2.0 equiv. of the ester was required due to competing decomposition of indole-3-glyoxylate ester to the corresponding indolyl-3-glyoxylic acid under the reaction conditions. Although the glyoxylic acid was readily removed during work-up by base extraction with $NaHCO_3$, unreacted acetamide (observed when <2.0 equiv. of ester were employed) was extremely difficult to remove, due to the low solubility of maleimides **3a-e** in organic solvents which made chromatographic purification difficult.

Scheme 1



1a-f
R = Me, Et
2a-h
4a-q
5a-q
3a-q

In analogy with our mechanistic work on the synthesis of bisindolylmaleimides, we believe that the reaction proceeds by initial acylation of the acetamide to generated the short lived tricarbonyl intermediate **4**. This cyclizes rapidly to hydroxyimides **5**, which, upon dehydration, generate maleimides **3a-p** (Scheme 1). Dehydration of **5** is believed to be the rate determining step. In most of the reactions studied, hydroxyimides **5** were observed but eliminated to product under the basic reaction conditions. An exception to this was observed during formation of 3-indolyl, 2-thienyl maleimide **3m** (Table 1, entry 14). In this reaction dehydration of **5** was slow, in fact formation of **3m** was only achieved after isolation and subsequent elimination of the hydroxyimides with DMAP/Im_2CO in acetonitrile.

In summary, we have developed a new one pot synthesis of bisphenyl, bisheteroaryl, indolylaryl and indolylcycloalkyl maleimides in 67-99% yield by condensation of glyoxylate esters with acetamides using potassium *tert*-butoxide in THF. The reaction represents a significant improvement over previous methods which proceed by a two step process involving formation of the maleic anhydride followed by ammonolysis. The ready availability of acetamides and glyoxylate esters should allow this method to become a general approach to the synthesis of this class of compounds.

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