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Novel products arising from bisarylmaleimide synthesis

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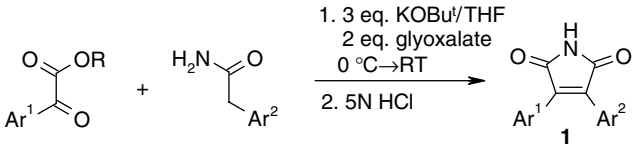
Abstract—The reaction of a 2-methoxyarylglyoxalate with a 2,3,6-trifluorophenylacetamide yielded a novel 2-hydroxyaryl substituted bisarylmaleimide (**5h**). We propose based on X-ray crystallographic evidence that this transformation occurs via formation of a previously undescribed tricyclic ring system (**6h**). The reactivity of the 2-halo analogues of the arylacetamide **(3h)** indicated that 2,6-disubstitution facilitated conversion compared to other substitution patterns.

As part of our investigation of maleimides[1,2] as templates for inhibitors of the protein kinase Glycogen Synthase Kinase 3 (GSK-3),[3,4] a route for the parallel synthesis of bisarylmaleimides **1** was required (Scheme 1). The condensation of glyoxalate esters with aryl acetamides[5] (synthesised from aryl Grignards[6] and aryl acetic acids, respectively) proved efficient, generally giving moderate to good yields of the required product.

In the reaction between 2-methoxyphenylglyoxalate **2** and 2-(2,3,6-trifluorophenyl)acetamide **3h** the expected product **4h** was not obtained as the major component but instead two additional products were formed (Scheme 2); bisarylmaleimide **5h** (8%) where the 2-fluoro-substituent has been displaced by a hydroxy group and the tricyclic derivative **6h** (30%). The structure and



Scheme 1.

relative configuration of this racemic compound was subsequently confirmed using single crystal X-ray diffraction techniques[7] (Fig. 1). To the best of our knowledge this constitutes a novel tricyclic ring system.

The formation of these new products can be rationalised by an alternative reaction path becoming available to the intermediate dianion **7h**, which Faul et al.[5] proposed would normally be dehydrated under the basic reaction conditions to give the expected bisarylmaleimide product **4h**. Instead the displacement of the *ortho*-fluoro-substituent by the hydroxy anion in an S_NAr process (Scheme 3) yields an isolable (*cis*)-tricyclic ring system **6h**, the dianion of which can react via two possible routes to give the *ortho*-hydroxy maleimide **5h** under the reaction conditions or during workup:

- deprotonation of the bridgehead methine proton followed by β-elimination;
- activation of the ether oxygen under acidic conditions during workup by protonation of the oxygen atom and then β-elimination.

When the tricyclic entity was subjected to both basic (3 equiv KO^{t}Bu in THF) and acidic (5 N HCl) conditions, maleimide was observed only under the basic conditions, suggesting that its formation occurs via deprotonation of the methine proton.

During the course of our structure activity relationship studies a range of halogenated phenylacetamides and phenylglyoxalates were used, leading to various

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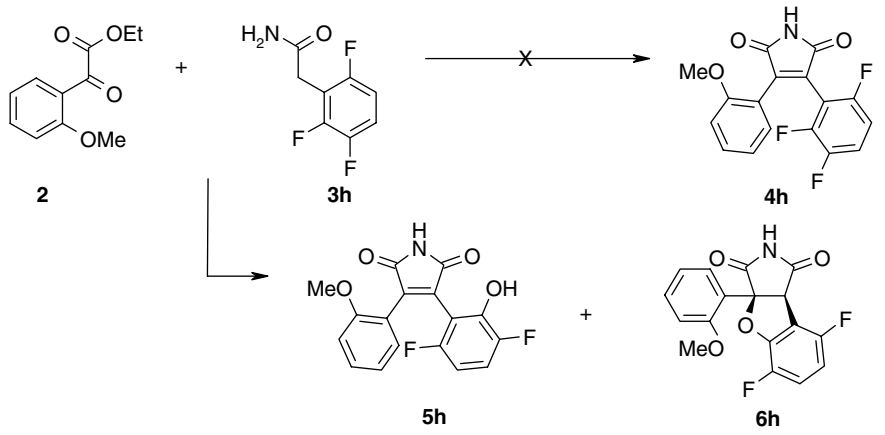


Scheme 2.

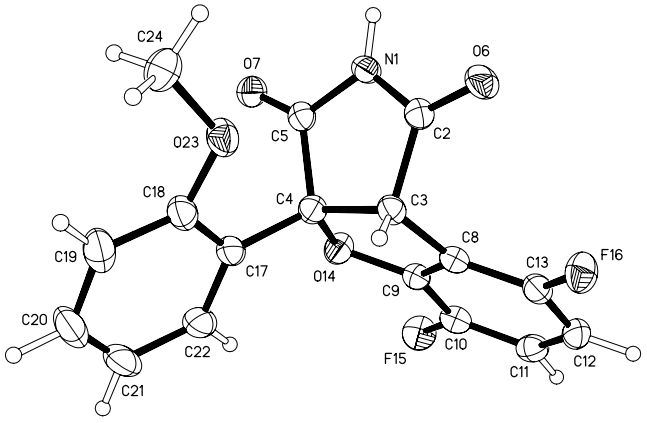
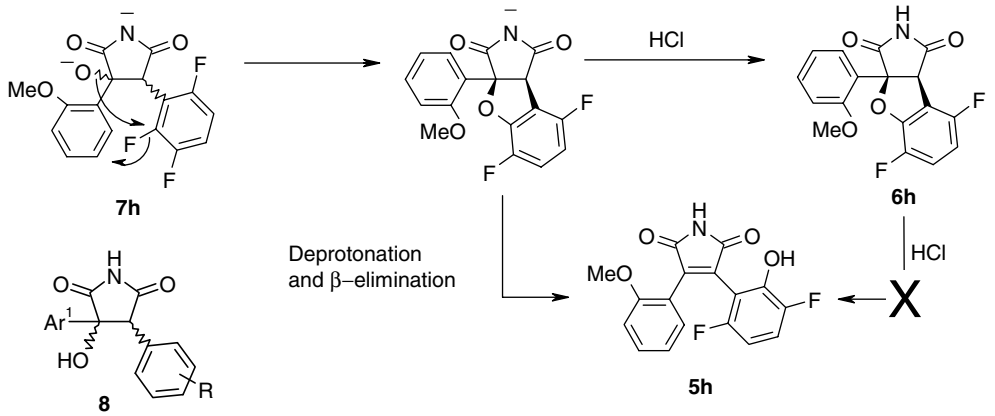


Figure 1. An atomic displacement plot of one of the two independent molecules in the asymmetric unit of the **6h** crystal structure. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

mixtures of maleimide and tricyclic derivatives. Selected data are shown in Table 1. In several cases the hydroxysuccinimide derivative **8** arising from protonation of the intermediate dianion was also formed as a byproduct.

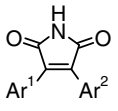
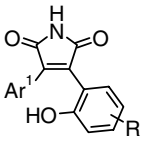
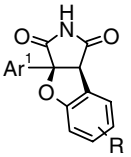
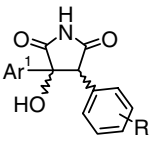
The data suggest that intermediates of type **8** form first and can either lead to products **4** or undergo displacement to give intermediates **6**, which subsequently lead to ring opened products **5**. In our hands the 2-fluoro analogue (**a**) did not lead to any tricyclic product. This is also true for the 2,4-difluoro substitution pattern (**d**) indicating that a *meta* relationship alone does not facilitate the alternative reaction pathway. With a 2,6-*meta* relationship such as with the 2,6-difluoro (**b**), 2-fluoro-6-chloro (**e**) and 2-fluoro-6-trifluoromethyl (**g**) cases, the 2-fluoro substituent becomes sufficiently activated to allow displacement to occur. This suggests that the twisting induced by the 6-substituent of the aromatic ring Ar^2 relative to Ar^1 directly relates to the degree of cyclisation that occurs. Substitution of a chlorine atom can also occur as noted with 2,6-dichloroacetamide **3f** to give **5f** in addition to the expected product **4f**, although the fluorine atom is displaced, as anticipated, in preference to chlorine atom when both groups are present **3e**.

The occurrence of the cyclisation reaction with 3,5-dimethylphenylglyoxalate giving **6j** demonstrates that the *ortho*-methoxy group is not essential for the substitution process to occur, although in this case the ring opened product **5j** was not observed, indicating that subtle Ar^1



Scheme 3.

Table 1.

Ph-acetamide Ar^2 substituent		 **4**	 **5**	 **6**	 **8**
2-F	(**a**)	47%[a]			34%
2,6-DiF	(**b**)		22%	32%	
2,3-DiF	(**c**)	65%		5%	
2,4-DiF[b]	(**d**)	45%			Trace
2-F-6-Cl	(**e**)	Trace	15%[c]	55%[c]	
2,6-DiCl	(**f**)	10%	17%		
2-F,6-CF_3[b]	(**g**)			17%	5%
2,3,6-TriF	(**h**)		8%	30%	
2,3,6-TriF[b]	(**i**)	11%	7%		
2,4,6-TriF[b]	(**j**)			25%	Trace

[a] All yields are unoptimised after chromatography.
[b] Ar^1 = 3,5-dimethylphenyl, otherwise 2-methoxyphenyl.
[c] Compounds show fluoro displacement only.

substituent effects were involved. When 2,3,6-trifluorophenylacetamide **3i** was reacted with 3,5-dimethylphenylglyoxalate both the expected bisaryl- maleimide **4i** and the hydroxybisarylmaleimide **5i** products were isolated in contrast to the results described earlier for 2-methoxyphenylglyoxalate **2** where only tricyclic **6** and phenolic **5** products were observed. This supports the hypothesis that the degree of nucleophilic substitution is influenced by the geometry of the 2-halo-bearing aryl ring.

The only example of displacement without an Ar^2 six-substituent being present occurred with 2-(2,3-difluorophenyl)acetamide **2c** where the adjacent fluorine atom activates the 2-fluorine sufficiently to allow some (5%) of the tricyclic product **6c** to be formed along with the formation of the expected bisarylmaleimide **4c** (65%).

In conclusion we have reported the formation of a novel tricyclic system, an intermediate generated during the formation of bisarylmaleimides, and highlighted the requirements for these derivatives to be generated.

Typical procedure: 2,3,6-Trifluoroacetamide **3h** (95 mg, 0.5 mmol) was added to 2-methoxyglyoxalate **2** (208 mg, 1 mmol) followed by anhydrous THF (1 mL). The stirring mixture was cooled to 0 °C and potassium *tert*-butoxide (1.0 M in THF, 1.5 mmol) was added. After 15 min the mixture was allowed to warm to ambient temperature and stirred for a further 4 h. 5 N HCl (1.5 mL) was added and the mixture was then extracted with dichloromethane and washed with aqueous saturated sodium bicarbonate solution. The combined organic layers were evaporated in vacuo and the residue purified by silica gel chromatography eluting with a 1–30% diethyl ether in dichloromethane gradient. Evaporation of appropriate fractions gave product **6h** as a solid.

^{1}H NMR (400 MHz, DMSO-d_6); δ 3.80 (s, 3H), 4.94 (s, 1H), 6.90 (m, 1H), 7.06 (td, $J = 1.9$, 0.2 Hz, 1H), 7.14 (d, $J = 2.0$ Hz, 1H), 7.35 (m, 1H), 7.42 (m, 1H), 7.48 (dd, $J = 1.9$, 0.4 Hz, 1H). MS: m/z calcd for $C_{17}H_{12}NO_4F_2$ (M^+H^+): 332.0734; found, 332.0745.

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