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Electronic effects in the acid-promoted deprotection of *N*-2,4-dimethoxybenzyl maleimides

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Abstract—Cleavage of several 2,4-dimethoxybenzylmaleimides could be performed employing TFA in anisole. Electronic effects exemplified by varying the substitution present on the maleimide resulted in a variation in the rate of the deprotection. In contrast, 2,4-dimethoxybenzylsuccinimides were inert to the conditions.

Efforts toward the syntheses of the indolocarbazole aglycone and closely related bisindolylmaleimide families of natural products have been examined by a large number of synthetic groups in academia and in the pharmaceutical industry due to their interesting, diverse and extraordinary biological activities.[1] Most routes to these classes of natural products required masking the maleimide nitrogen with either a methyl, phenyl or benzyl functionality. The free maleimide was revealed in a stepwise fashion via the anhydride by hydrolysis and reintroduction of the nitrogen.[2] Our research sought to find an alternative protecting group that could be cleaved to provide directly the maleimide natural product. Danishefsky et al.[3] have reported the use of benzyloxymethyl (BOM) as a protecting group, but this is introduced by alkylation of the corresponding maleimide. A more convenient source of protected maleimides is from the one step combination of an anhydride and amine bearing a cleavable group. It has been reported by a number of groups that 2,4-dimethoxybenzyl (DMB) and paramethoxybenzyl (PMB) protected amides,[4] lactams[5] and uridines[6] may be cleaved through treatment with trifluoroacetic acid or $AlCl_3$ and anisole under mild conditions. In addition, mild oxidative deprotections of PMB and DMB amides and lactams have been performed using DDQ, CAN, Na/NH_3 and $K_2S_2O_6/KH_2PO_4$.[4c,7] However, to our knowledge, there are no previous reports describing the use of DMB groups in the maleimide family of natural products.

In our investigations toward an indolocarbazole target, we made an interesting observation. Bisindolylmaleimide **2a** could be deprotected employing TFA in anisole or thioanisole. The corresponding indoloindoline **7a**, however, was unreactive to the same conditions. We postulated that the electron density of the nitrogens on the indoles increased the electronegativity of the carbonyl oxygens through conjugation, thus facilitating the acid catalyzed cleavage of the DMB protecting group. There is no such effect in indoloindoline **7a** due to the absence of the double bond. Therefore a number of DMB protected maleimide derivatives were prepared[8] to investigate the scope of this observation.

From our results, one observes a noticeable trend whereby the absence of conjugation as present in the succinimide DMB protected derivatives **7a** and **8a** results in no deprotection. It also appears that electron-donating substituents in conjugation with the carbonyl oxygens on the imide facilitate the cleavage of the DMB group under acidic conditions. Carbazole **3a** undergoes facile cleavage of the DMB protecting group at 90°C to provide the unprotected imide **3b** in 96% yield. Electron-withdrawing groups as in the case of dichloride **9a** and dibromide **10a**, on the other hand, attenuate the basicity of the carbonyl oxygen and thus prevent the deprotection. Prolonged heating of **9a** and **10a** (>60 h) gave no acid promoted cleavage of the DMB group. Deprotection of bisindolylmaleimide **1a** proceeds at 60°C in 8 h to provide the desired imide **1b** in 44% yield. Higher temperature resulted in an undesirable side product. The presence of electron-withdrawing fluorines in the indole portion shown in

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maleimide **2a** reduced the rate of deprotection. Deprotection of disulfide **4a** with TFA was complete after 15 h at 90°C. After replacing the sulfur substituents with methyl groups a dramatic decrease in reactivity was visible. Even less reactive was the diphenyl substituted DMB imide **6a** which required almost 4 days at 90°C to completely deprotect. In all cases yields are good and the general trend of reaction rate is consistent with the predicted electron density mapping for the charge of the carbonyl oxygens.[9] One unexpected result was that phalthimide derivative **11a** was not deprotected employing these conditions. Failure to deprotect **11a** indicated that electron delocalization of the carbonyl oxygens by *endo*-conjugation of benzene is much more profound than that from the *exo*-conjugation by diphenyl groups **6a** (Table 1).

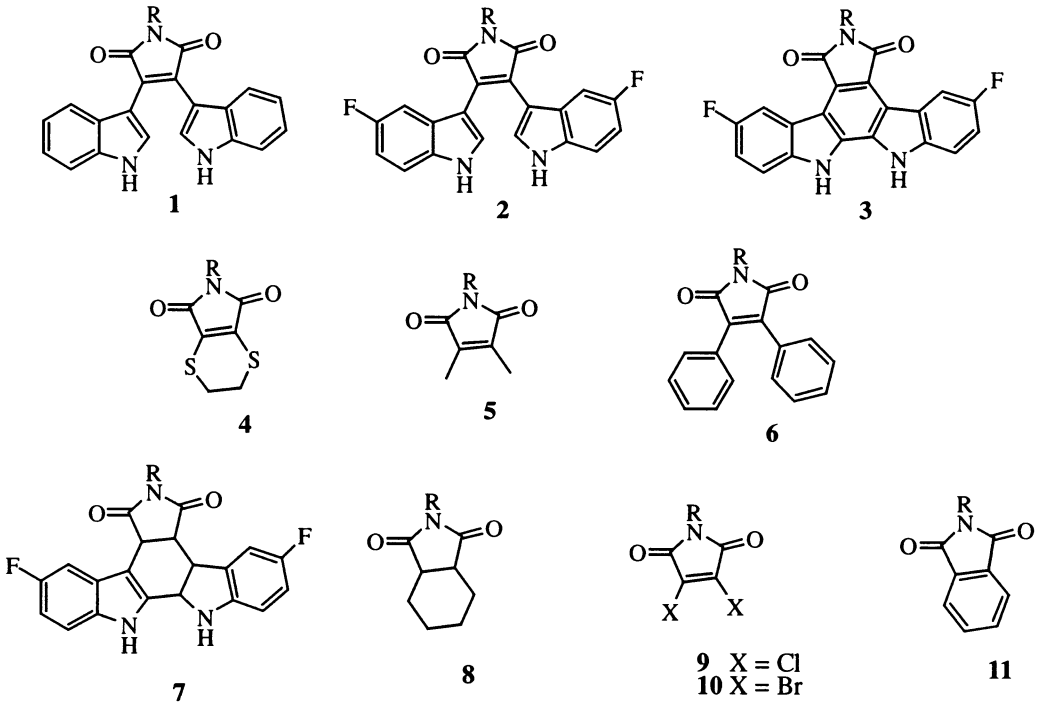
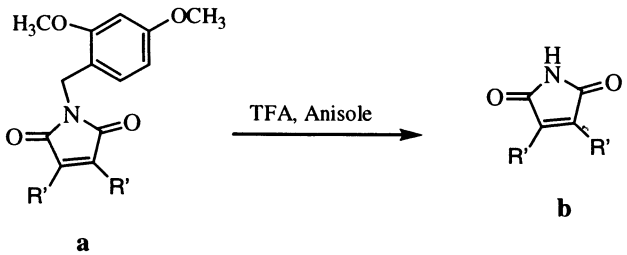


Table 1.



Entry	Substrate R = DMB	Reaction time (h)	Temperature (°C)	Product[10] R = H	Yield (% isolated)
A	**1a**	8	60	**1b**[11]	44
B	**2a**	5	90	**2b**	85
C	**3a**	12	90	**3b**	96
D	**4a**	15	90	**4b**	87
E	**5a**	44	90	**5b**	68
F	**6a**	92	90	**6b**	79
G	**7a**	–	90	**7b**	NR
H	**8a**	–	90	**8b**	NR
I	**9a**	–	90	**9b**	NR
J	**10a**	–	90	**10b**	NR
K	**11a**	–	90	**11b**	NR

NR = no reaction after an extended period of time.

The mechanism is thought to proceed through an acid catalyzed pathway. However, TFA has been reported to be an effective one-electron oxidant[12] and thus a possible radical cation induced deprotection should also be considered. To address the mechanistic pathway we performed experiments with acids varying in pK_a.[13] Bisindolylmaleimide **2a** was inert to phosphoric acid (H_3PO_4, $pK_a = 2.1$). Cleavage occurred with trichloroacetic acid ($pK_a = -0.5$) at 90°C but at a much slower rate compared to TFA ($pK_a = -0.6$). The stronger acid, methane sulfonic acid (MSA, $pK_a = -1.9$) cleaved the DMB group at room temperature employing only 2 equiv. in anisole. The yield of the product decreased due to its instability with the stronger acid. Maleimides **4a**, **5a** and **6a** were also deprotected employing MSA although higher temperatures were required while **8a** and **10a** did not undergo deprotection. Phalthimide **11a** was slowly deprotected using MSA in anisole, however, the reaction was sluggish (50% conversion after 3 days at 90°C). Although the MSA promoted reaction proceeds using fewer equivalents of acid, it is only suitable if the product is stable to the strongly acidic conditions. It has also been reported in the literature that MSA has been used to cleave a 2,4-dimethoxbenzyl protected electron rich uridine moiety[14] which complements our findings.

In conclusion, we have demonstrated a protecting group strategy for the preparation of the indolocarbazole natural products whereby it is unnecessary for a hydrolysis/aminolysis sequence to incorporate the maleimide. In addition, we have shown that electron-donating groups present on the 2,4-dimethoxybenzyl maleimides serve to assist the acid promoted deprotection whereas electron-withdrawing groups prevent the reaction.

General procedure for the deprotection of 2,4-dimethoxybenzylimides

To 2,4-dimethoxybenzyl maleimide **4a** (200 mg, 0.59 mmol) in anisole (3.22 mL, 0.03 mol) was added TFA (2.28 mL, 0.03 mol) in a dropwise fashion under nitrogen at room temperature. The mixture was heated to 90°C for 15 h and then cooled to ambient temperature. TFA was removed in vacuo and then hexanes were added and the resulting precipitate filtered, washed with hexanes and dried in a vacuum oven at 40°C for 3–5 h. The desired product **4b** was obtained as a yellow crystalline solid (94.3 mg, 85%).[10]

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8. Substrates **1a**, **2a**, **3a**, **7a, 9a** and **10a**: manuscript in preparation. Substrates **4a**, **5a**, **6a**, **8a** and **11a**: prepared from the anhydride according to: (a) Schweiger, M. J.; Ederer, T.; Sünkel, K.; Beck, W. *J. Organomet. Chem.* **1997**, *545*, 17; (b) Andricopulo, A. D.; Willain-Filho, A.; Corrêa, R.; Santos, A. R. S.; Nunes, R. J.; Yunes, R. A.; Cechinel-Filho, V. *Pharmazie* **1998**, *53*, 493.
9. Theoretical calculations employing a PC Sparton Pro and utilizing the pBP/DN** theory with Mulliken charge analysis predicted an increasing negative charge on the carbonyl oxygens which correlated to the increasing reactivity observed experimentally. Note: in all examples, the dimethoxybenzyl group was replaced with a methyl group to provide simplicity in the calculations. It must also be noted that this is a basic calculation theory and not always reliant for prediction of reactivity but merely serves as a guide.
10. Spectral data for deprotected imides. **2b**: ^{1}H NMR (300 MHz, CD_3CN): δ 9.89 (bs, 2H), 8.55 (bs, 1H), 7.86 (d, $J = 3.0$ Hz), 7.42 (dd, 2H, $J = 6.0$ and 9.0 Hz), 6.83 (td, 2H, $J = 3.0$, 9.0 and 18.0 Hz), 6.45 (dd, 2H, $J = 3.0$ and 12.0 Hz); ^{13}C NMR (75 MHz, CD_3CN): δ 173.00, 159.68, 156.59, 133.37, 131.43, 128.88, 127.24, 127.09, 121.31, 113.52, 113.39, 111.19, 110.84, 107.12, 106.62, 106.29; IR (cm^{-1}, KBr) 3342, 1698; exact mass calcd for $C_{20}H_{11}F_2N_3O_2$ 364.0898, found 364.0889. **3b**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.01 (bs, 2H), 11.02 (bs, 1H), 8.60 (bd, 2H, $J = 1$ Hz), 7.76 (bs, 2H), 7.38 (bs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.9, 159.1, 156.1, 137.4, 130.7, 122.6, 122.5, 120.6, 115.8, 115.6 and 115.2, 113.9, 109.9 and 109.6; IR (cm^{-1}, THF, thin film) 3233, 1702, 1477; MS: $(M-H)^+$ 360.11. **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.3 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 131.2, 26.2; IR (cm^{-1}, KBr) 3249, 1764, 1709; exact mass calcd for $C_6H_5NO_2S_2$ 185.9769, found 185.9752. **5b**: ^{1}H N MR (300 MHz, $CDCl_3$): δ 7.43 (bs, 1H), 1.97 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.86, 138.35, 8.63; IR (cm^{-1}, CH_2Cl_2, thin film) 3217, 1702. **6b** ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.35–7.47 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.50, 137.05, 129.98, 129.85, 128.59, 128.31; IR (cm^{-1}, KBr) 3178, 3061, 1712; exact mass calcd for $C_{16}H_{11}NO_2$ 250.0868, found 250.0863.

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