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A Facile One-Pot Transformation of Baylis–Hillman Adducts into Unsymmetrical Disubstituted Maleimide and Maleic Anhydride Frameworks: A Facile Synthesis of Himanimide A

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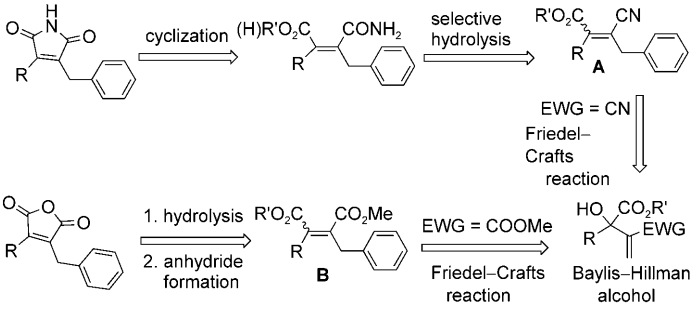
The development of efficient and convenient methodologies for the synthesis of 3,4-disubstituted maleimide and maleic anhydride derivatives has been, and continues to be, an attractive and challenging endeavor in organic and medicinal chemistry.[1,2] The importance of these targets is demonstrated by the presence of such frameworks in a number of bioactive natural products, such as himanimides A–D,[1g,i] polycitrins A and B,[1m] arcyriarubin-B,[1o,p] aspergillus acids A–D,[2a] lindenanolide E,[2f] chaetomellic acids A and B,[2g] tyromycin A,[2h] and tautomycetin.[2i] Furthermore, derivatives of 3,4-disubstituted maleimide and maleic anhydride have also been known to exhibit various biological activities, such as cytotoxicity,[1c] inhibition of cell death,[1d] inhibitors of CaMKIIδ (calmodulin-dependant protein kinase),[1a] angiogenesis,[1h] and vascular endothelial cell proliferation.[1j] In continuation of our ongoing research program in heterocyclic compounds,[3] we herein report a facile and convenient methodology for the synthesis of 3,4-disubstituted maleimide and maleic anhydride derivatives starting from the corresponding Baylis–Hillman (B–H) adducts (derived through the coupling of α-keto esters with acrylonitrile/methyl acrylate) in an operationally simple one-pot strategy. This one-pot procedure involves three reactions, that is, Friedel–Crafts reaction, selective hydrolysis, and cyclization, and employs methanesulfonic acid as an efficient reagent to perform all three steps. This strategy has been successfully extended to the synthesis of himanimide A, an important bioactive molecule.

In the last twenty years, the B–H reaction has grown exponentially and, in fact, has become a very popular carbon–carbon bond-forming reaction because it provides valuable classes of densely functionalized molecules.[4,5] Due to the proximity of functional groups in the products, the B–H adducts have also become attractive substrates in a number of reactions, such as Friedel–Crafts, Diels–Alder, Heck, Johnson–Claisen rearrangement, isomerization, and hydrogenation reactions.[4] Although the B–H (secondary) alcohols, derived from aldehydes, have been employed as valuable substrates for the Friedel–Crafts reaction,[6] to the best of our knowledge the B–H (tertiary) alcohols derived from α-keto esters have not been properly investigated as substrates in the Friedel–Crafts reaction.

Therefore, it occurred to us that the B–H adducts, derived from α-keto esters as electrophiles (and acrylonitrile/methyl acrylate as activated alkenes), could, in principle, serve as potential substrates for a Friedel–Crafts reaction with benzene to provide phenylated products, that is, tetrasubstituted alkenes **A** (Scheme 1), containing ester and cyano groups (in the case of adducts derived from acrylonitrile) and **B**, containing two ester groups (in the case of adducts derived from methyl acrylate), for the retrosynthetic strategy, see Scheme 1.

Upon selective hydrolysis and cyclization, these tetrasubstituted alkenes, **A** and **B**, would, respectively, provide disubstituted maleimide and maleic anhydride derivatives. It



Scheme 1. Retrosynthetic strategy for the synthesis of 3,4-disubstituted maleimide and maleic anhydride frameworks. EWG = electron-withdrawing group.

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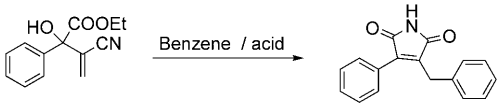
also occurred to us that it would be useful if all three steps could be performed in one pot and by a single reagent.

Accordingly, we first selected the B–H adduct 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**1a**),[7] obtained by the reaction of ethyl benzoylformate with acrylonitrile, as a substrate for treatment with benzene under the influence of various acids (Table 1). The best results were obtained when **1a** was treated with benzene in the presence of methanesulfonic acid at reflux for 4 h, thus, providing the desired 3-benzyl-4-phenyl-1*H*-pyrrole-2,5-dione (**2a**) in 79% yield after purification by column chromatography (Table 1, entry 4). We were pleased to note that methanesulfonic acid had successfully performed all three steps (i.e., Friedel–Crafts reaction, selective hydrolysis, and cyclization) in one pot.

Table 1. Optimization of reaction conditions: reaction of B–H alcohol (**1a**, 1 mmol) with benzene (6 mL) under the influence of acid (3 mmol) at reflux.

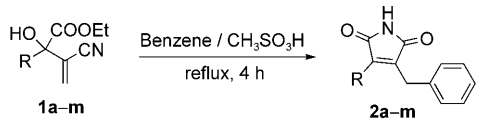


1a **2a**

Entry	Acid	*t* [h]	Yield[a] [%]
1	concd H_2SO_4	4	32
2	CF_3CO_2H (TFA)	4	–
3	*p*-TsOH	4	62
4	CH_3SO_3H	4	79
5	CF_3SO_3H	4	58
6	$TiCl_4$	4	–

[a] Yield of the isolated product.

Table 2. Synthesis of 3,4-disubstituted maleimides.[a]



1a–m **2a–m**

Entry	B–H alcohol	R	Product[b]	Yield [%][c]
1	**1a**	C_6H_5	**2a**[d]	79
2	**1b**	2-MeC_6H_4	**2b**	65
3	**1c**	2-$MeOC_6H_4$	**2c**	57
4	**1d**	3-MeC_6H_4	**2d**	76
5	**1e**	3-$MeOC_6H_4$	**2e**[d]	55
6	**1f**	4-MeC_6H_4	**2f**	70
7	**1g**	4-$MeOC_6H_4$	**2g**	63
8	**1h**	4-$EtOC_6H_4$	**2h**	54
9	**1i**	4-BrC_6H_4	**2i**	65
10	**1j**	4-ClC_6H_4	**2j**	61
11	**1k**	methyl	**2k**[d]	66
12	**1l**	ethyl	**2l**	62
13	**1m**	*n*-propyl	**2m**	58

[a] All of the reactions were carried out on a 1 mmol scale of the B–H alcohols (**1a–m**) with methanesulfonic acid (3 mmol) in benzene (6 mL) at reflux for 4 h.[7–9] [b] All of the compounds (**2a–m**)[8] were fully characterized (see the Supporting Information). [c] Yields of the isolated pure products based on the B–H alcohols.[9] [d] Structures of these molecules were also established from the single-crystal X-ray data (see the Supporting Information).[10]

Encouraged by this promising result, we transformed representative B–H alcohols (**1b–j**), obtained from aromatic α-keto esters and acrylonitrile, into the desired 3,4-disubstituted maleimides (**2b–j**) in 54–76% yield by treatment with benzene in the presence of CH_3SO_3H at reflux for 4 h (Table 2, entries 2–10). We also obtained single crystals for compounds **2a** and **2e** and further confirmed the structures by single-crystal X-ray data (Figure 1).[10]

With a view to understand the generality of this methodology, we employed the B–H alcohols (**1k–m**), obtained by the coupling of aliphatic α-keto esters and acrylonitrile, as substrates, which provided the desired 3,4-disubstituted maleimides (**2k–m**) in 58–66% yield (Table 2, entries 11–13). We obtained a single crystal for **2k** and further established its structure by single-crystal X-ray data (Figure 2).[10]

We successfully extended this strategy to the synthesis of himanimide A (**3**),[11] an important biologically active molecule, in 11.28% overall (unoptimized) yield in three steps starting from the α-keto ester **4** (Scheme 2).[12] Although the

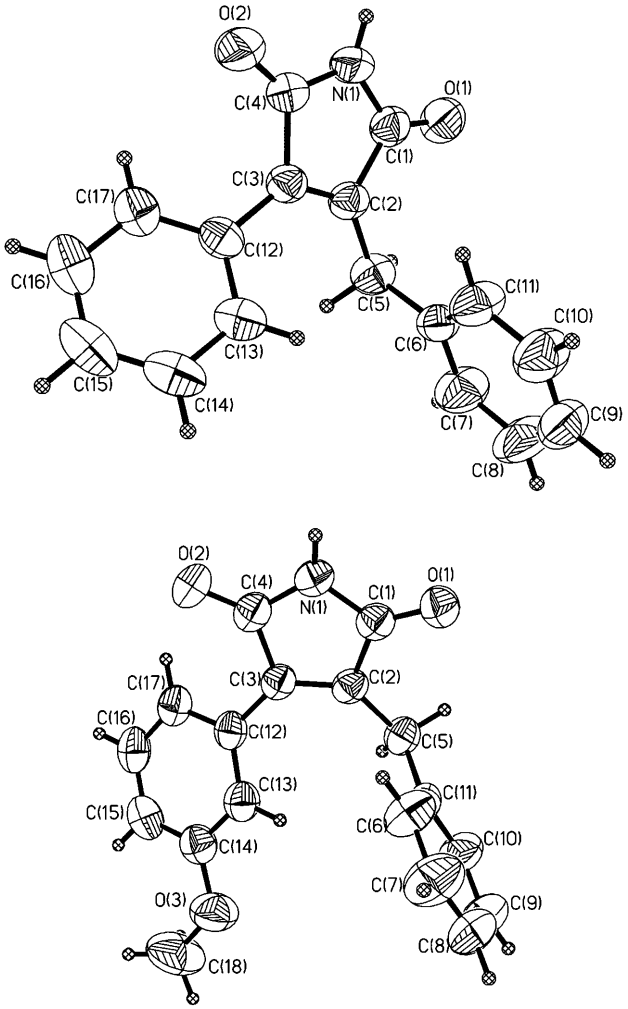


Figure 1. ORTEP diagrams of compounds **2a** and **2e**. Ellipsoids at 50% probability.

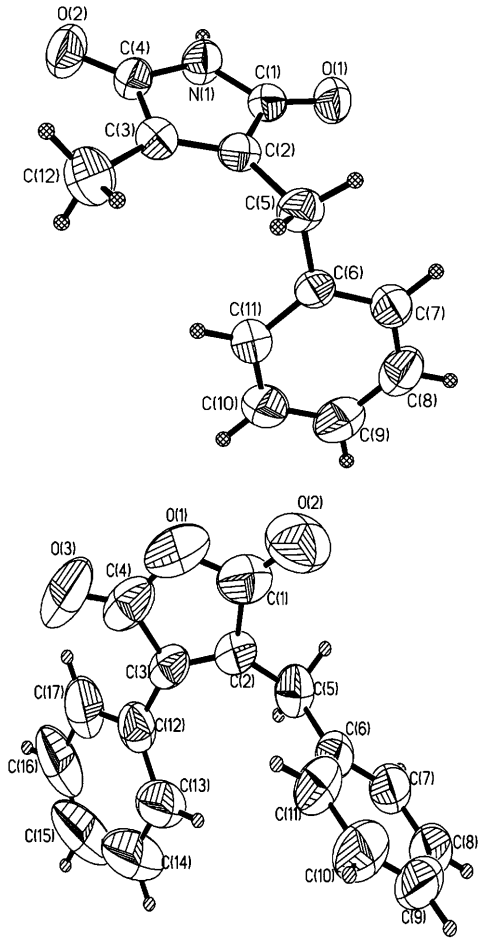
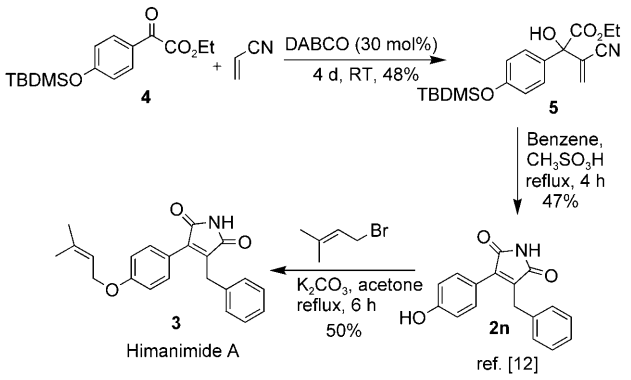


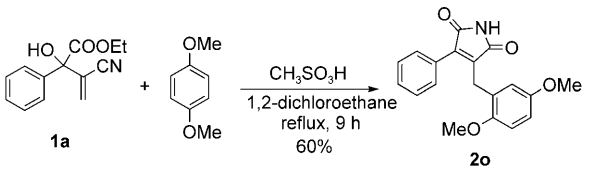
Figure 2. ORTEP diagrams of compounds **2k** and **7a**. Ellipsoids at 50% probability.



Scheme 2. Simple route for the synthesis of **3**.[11] DABCO = 1,4-diazabicyclo[2.2.2]octane, TBDMS = *tert*-butyldimethylsilyl.

yields are not high, this synthesis demonstrates the potential of the maleimide strategy in the synthesis of bioactive molecules.

We also used 1,4-dimethoxybenzene for a Friedel–Crafts reaction with **1a** in the place of benzene and obtained the corresponding maleimide derivative (**2o**) in 60% yield (Scheme 3). However, when toluene was used for the Friedel–Crafts reaction with **1a**, we obtained the corresponding maleimide derivative as a mixture of *ortho* and *para* products in 51% yield.

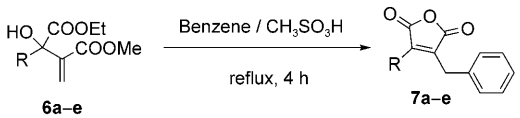


Scheme 3. Synthesis of 3,4-disubstituted maleimide derivatives by the reaction of **1a** with 1,4-dimethoxybenzene.

After developing a simple one-pot methodology for the synthesis of unsymmetrical 3,4-disubstituted maleimide derivatives, we directed our attention towards the synthesis of 3,4-disubstituted maleic anhydride derivatives, **7a–e**.[8] We first selected methyl 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanoate (**6a**), the B–H alcohol obtained by the coupling of ethyl benzoylformate with methyl acrylate, as a substrate. The best results were obtained when **6a** was treated with benzene in the presence of methanesulfonic acid at reflux for 4 h, providing the required 3-benzyl-4-phenylmaleic anhydride (**7a**) in 52% yield. Notably, compound **7a** is a natural product isolated from *Aspergillus nidulans*.[21]

To understand the generality of this reaction strategy, we subjected four more B–H alcohols, **6b–e**, to the reaction conditions to provide 3,4-disubstituted maleic anhydride derivatives (7**b–e**) in 40–56% yield (Table 3).[13] Although the yields are inferior when compared to the corresponding maleimides, this reaction is still interesting in the sense that this methodology offers a simple procedure for the synthesis of 3,4-disubsitituted maleic anhydride derivatives, yet another important structural motif. We obtained a single crystal for **7a** and further established its structure by single-crystal X-ray data (for the ORTEP diagram, see Figure 2).[10]

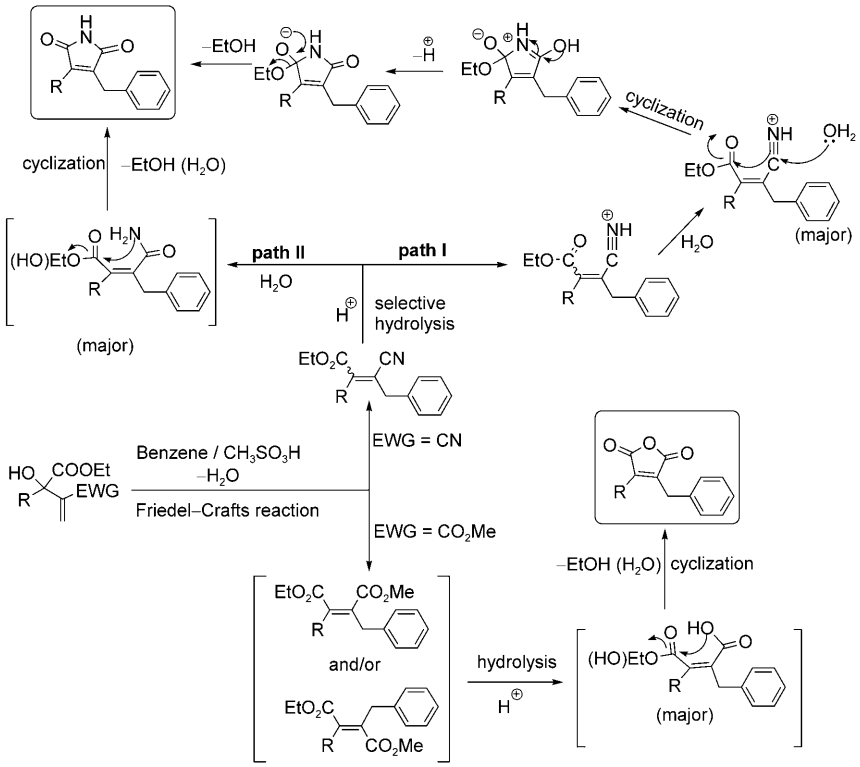
Table 3. Synthesis of 3,4-disubstituted maleic anhydrides.[a]



Entry	B–H alcohol	R	Product[b]	Yield [%][c]
1	**6a**	C_6H_5	**7a**[d]	52
2	**6b**	4-MeC_6H_4	**7b**	45
3	**6c**	4-$MeOC_6H_4$	**7c**[15]	40
4	**6d**	4-BrC_6H_4	**7d**	56
5	**6e**	4-ClC_6H_4	**7e**	49

[a] All of the reactions were carried out on a 1 mmol scale of the B–H alcohols (**6a–e**) with methanesulfonic acid (3 mmol) in benzene (6 mL) at reflux for 4 h.[7–9] [b] All of the compounds (**7a–e**) were obtained as colorless solids and fully characterized (see the Supporting Information). [c] Yields of the isolated pure products based on the B–H alcohols.[13] [d] The structure of this molecule was also established from single-crystal X-ray data (see the Supporting Information).[10,14]

A plausible mechanism for the formation of the maleimide and maleic anhydride frameworks from B–H adducts is presented in Scheme 4. The fact that the stereochemistry of the double bond in 3,4-disubstituted maleimide derivatives (Table 2) is *Z*, clearly indicates that the amide ester



Scheme 4. A plausible mechanism for the formation of 3,4-disubstituted maleimides and maleic anhydride frameworks.

(acid) generated in situ should have predominantly *Z* stereochemistry (Scheme 4, paths I & II). Whatever the course of the reaction may be, the products isolated clearly indicate that the transient intermediate before the cyclization step had *Z* stereochemistry. In the case of 3,4-disubstituted maleic anhydrides, we noticed that substantial amounts (15–25%) of starting material remain intact, as evidenced by TLC analysis of the reaction mixture (Scheme 4).[9,13] Hence, the resulting products were obtained in low yields. However, the results are still encouraging because the important 3,4-disubstituted maleic anhydride derivatives are synthesized in a one-pot operation from the B–H adducts in reasonably good yields. Studies are underway to understand the stereochemical course of the reaction.

In conclusion, we have developed a convenient, operationally simple, one-pot procedure for the synthesis of unsymmetrical 3,4-disubstituted maleimide and maleic anhydride derivatives from B–H alcohols derived from α-keto esters (as electrophiles). This strategy has been successfully employed to the synthesis of **3**, an important bioactive molecule.

Experimental Section

General experimental procedure: Methanesulfonic acid (3 mmol, 0.288 g, 0.2 mL) was added to a stirred solution of 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (1 mmol, 0.231 g) in benzene (6 mL) at RT and heated at reflux for 4 h. Then the reaction mixture was allowed to cool to RT and diluted with water (10 mL). Aqueous $NaHCO_3$ solution was added slowly to neutralize the acid and then it was extracted with diethyl ether (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 5% EtOAc in hexanes) to furnish the compound **2a** as a colorless solid (0.208 g, 79%).

All the experimental details, spectral data, ^1H and ^{13}C NMR spectra for all the compounds are available in the Supporting Information.

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Keywords: Friedel–Crafts reaction · heterocycles · himanimide A · natural products · synthetic methods

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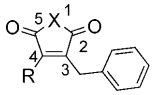
[8] These derivatives are named as 3,4-disubstituted maleimide and maleic anhydride derivatives according to the following numbering:



[9] We cannot completely rule out the formation of minor amounts of fumaric acid derivatives in these reactions, since the yields of maleimide are not quantitative and also the yields of maleic anhydride derivatives are low.

[10] Detailed X-ray crystallographic data for compounds **2a** (CCDC-687372), **2e** (CCDC-687373), **2k** (CCDC-687374), **7a** (CCDC-687375) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] Himanimide A is known in the literature; ^{1}H and ^{13}C NMR spectral data are reported. Our data is in agreement with that of the literature data.[1i] This compound was isolated as a liquid.[1i] We obtained this compound **3** as a solid (m.p. 108–110 °C decomp).

[12] During the course of the Friedel–Crafts reaction, the *t*-butyldimethylsilyl protecting group was cleaved to provide the corresponding phenol derivative (**2n**).

[13] We also noticed that longer reaction times gave a mixture of products as evidenced by TLC examination.

[14] This compound is known in the literature (it was isolated from *Aspergillus nidulans* and its melting point, ^{1}H and ^{13}C NMR spectral data are reported. Our data is in agreement with that of the literature data).[2i]

[15] This compound is known in the literature, the synthesis (by a non-B–H route), ^{1}H and ^{13}C NMR spectral data of which are reported. Our spectral data is in agreement with that of the literature data.[1g]

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