Tetrahedron Letters 55 (2014) 7002–7006

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diels–Alder reactions of five-membered heterocycles containing one heteroatom

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ARTICLE INFO

Article history:
Received 21 August 2014
Revised 14 October 2014
Accepted 21 October 2014
Available online 31 October 2014

Keywords:
Diels–Alder reactions
Dienes
Dienophiles
Acid-catalyzed reactions

ABSTRACT

Diels–Alder reactions of five-membered heterocycles containing one heteroatom with an *N*-arylmaleimide were studied. Cycloaddition of 2,5-dimethylfuran (**4**) with 2-(4-methylphenyl)maleimide (**3**) in toluene at 60 °C gave bicyclic adduct **5**. Cycloadditions of **3** with 2,5-dimethylthiophene (**11**) and 1,2,5-trimethylpyrrole (**14**) were also studied. Interestingly, the bicyclic compound **5** cleanly rearranged, with loss of water, when treated with *p*-toluenesulfonic acid in toluene at 80 °C to give 4,7-dimethyl-2-*p*-tolylisoindoline-1,3-dione (**6**).

We recently reported a screening campaign for type three secretion system (T3SS) inhibitors that identified differentiated hit compounds, which we grouped into three scaffolds.[1] One of these scaffolds was represented by the bicyclic compound **5**, and close analogs with different substituents in the phenyl ring.[1] Our first task was to prepare an authentic sample of compound **5** to confirm activity. We also wished to explore rearrangement chemistry that the bicyclic compound **5** might undergo, as we predicted may happen, upon treatment with acid. In addition, we explored the biological activity of similar compounds and synthesized compounds related to **5** with varied heteroatoms in the oxygen-containing bridge. The findings from these synthetic investigations are presented in this Letter.

The synthesis of hit compound **5** is presented in Scheme 1. Solutions of *p*-toluidine (**1**) and maleic anhydride (**2**) in tetrahydrofuran were combined, and after 15 minutes, the solvent was decanted and the remaining solid was treated with acetic anhydride and sodium acetate at 120 °C with microwave irradiation to produce 1-*p*-tolyl-1*H*-pyrrole-2,5-dione (**3**) in 62% yield.[2–4] Subsequent treatment of maleimide **3** with 2,5-dimethylfuran (**4**) in toluene at 80 °C gave the *exo* Diels–Alder adduct **5** in 50% yield. It is well-known that both furan[5,6] and 2,5-dimethylfuran[7–9] produce *exo* Diels–Alder adducts with maleimides under elevated temperature conditions, and that an *endo* product can be produced if the Diels–Alder reaction is done at room temperature and kept in the dark.

Interestingly, we were able to effect a very efficient, very clean conversion of bicyclic compound **5** to 4,7-dimethyl-2-(4-methylphenyl)phthalimide (**6**) in quantitative yield. This acid-catalyzed rearrangement proceeded in toluene at reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid. Although we could not find other examples of this exact conversion, we did find a somewhat related dehydrative rearrangement of a tricyclic dihydrofuran compound that produced a 2,3,6,7-tetrahydro-*as*-indacene-1,8-dione.[10] Also, there are reports of the preparation of phthalimides directly from 2,5-dimethylfuran (**4**) and maleimides, wherein the intermediate Diels–Alder adducts are not isolated but are presumably intermediates that rearrange in situ.[11,12] The mechanism that we propose for the conversion of **5**–**6** is shown in Scheme 2.

We prepared an authentic sample of phthalimide **6**, using a recently reported procedure,[4] to verify the structure. Treatment of commercially available 4,7-dimethylphthalimide (**7**) with *p*-toluidine (**1**) in dimethylformamide using microwave conditions (Scheme 1) produced an authentic sample of **6**, which was identical in every respect to the material produced from the very efficient, acid-catalyzed dehydrative rearrangement of *exo* adduct **5**.

Moreover, we were able to also produce the *endo* adduct from the Diels–Alder reaction of imide **3** with 2,5-dimethylfuran (**4**), when we used diethyl ether as the solvent at room temperature, as shown in Scheme 3. The distinguishing characteristic between the *exo* and *endo* regiochemistries in these adducts is the position of the bridgehead protons alpha to the carbonyl groups. These protons appear as a singlet at δ 2.97 ($CDCl_3$) for the *exo* adduct **5**, and at δ 3.37 ($CDCl_3$) for the *endo* adduct **10**. These assignments

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http://dx.doi.org/10.1016/j.tetlet.2014.10.114
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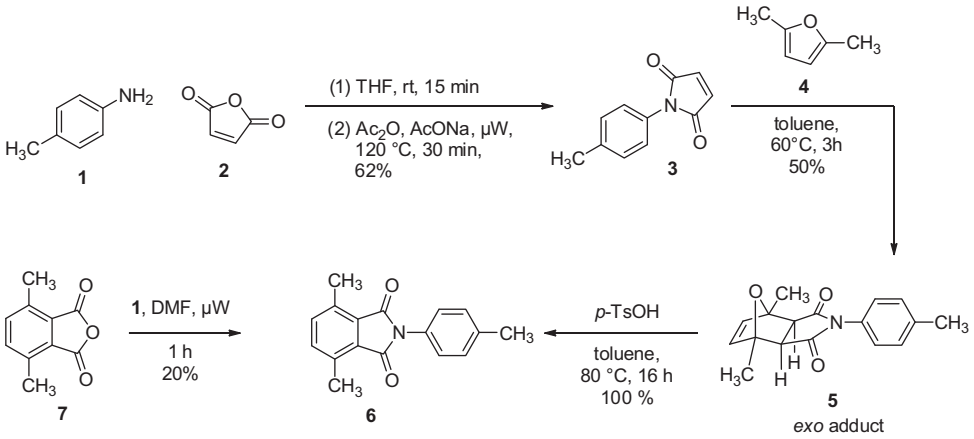
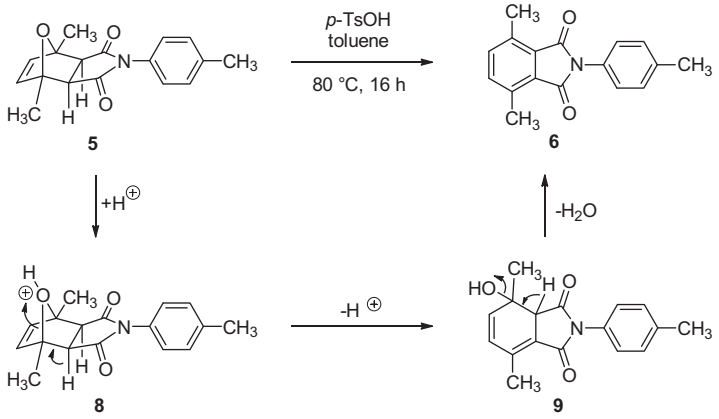
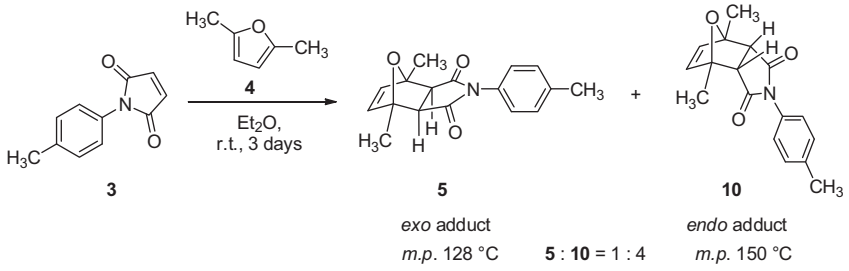


Scheme 1. Synthesis of bicyclic Diels–Alder adduct **5** and its conversion to phthalimide **6**.



Scheme 2. Proposed mechanism for the acid-catalyzed rearrangement of Diels–Alder adduct **5** to phthalimide **6**.

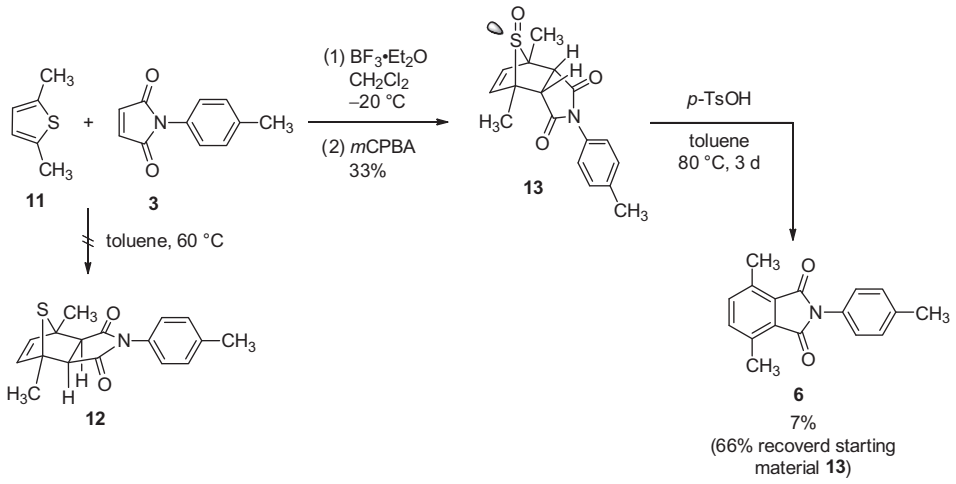


Scheme 3. Preparation of *endo* Diels–Alder adduct **10** from maleimide **3** and furan **4**.

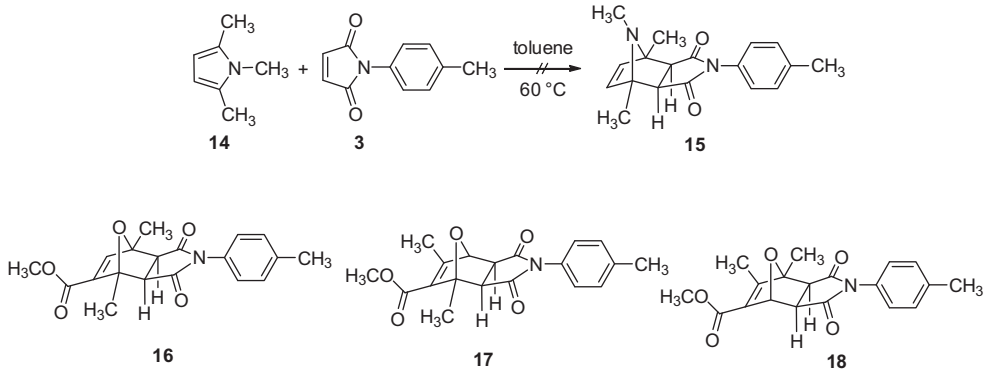
for *exo* and *endo* isomers for maleimide adducts with 2,5-dimethylfuran (**4**), where the *exo* bridgehead protons are consistently ca. δ 0.40 ppm upfield with respect to the *endo* isomer, are well-documented in the literature.[9,10]

We next explored the reactivity of imide **3** with 2,5-dimethylthiophene (**11**) as shown in Scheme 4. Although diene **11** was not reactive enough to undergo [2+4] cycloaddition with **3** in toluene at 60 °C, we were able to produce a cycloadduct in the presence of *m*-chloroperoxybenzoic acid, which converted thiophene **11** to its corresponding sulfoxide in situ to provide a more reactive diene. The structure of this adduct is the *endo* adduct **13**, which is completely analogous to another reported cycloadduct whose structure was confirmed by X-ray diffraction.[13,14] Interestingly, adduct **13** also underwent acid-catalyzed rearrangement with *p*-toluenesulfonic acid in toluene, albeit at a significantly slower rate than **6** was produced from **5**, to give phthalimide **6**.

We also attempted to prepare a Diels–Alder adduct between 1,2,5-trimethylpyrrole (**14**) and maleimide **3**. It is reported that cycloaddition reactions of pyrroles with alkenes are limited by the inherent thermodynamic instability of the cycloadducts wherein cycloreversion or retro-Mannich reactions (followed by rearomatization) are predominant.[15–17] When we treated pyrrole **14** with maleimide **3**, in toluene at 60 °C as shown in Scheme 5, we observed no cycloadducts from these reactants. However, we did obtain a small amount of adduct that arose from maleimide **3** and a furan-containing contaminant that was present in our commercial sample of **14**, which we determined to have an empirical formula of $C_{19}H_{19}NO_3$ from mass spectral analysis. We



Scheme 4. Preparation of thiophene sulfoxide Diels–Alder adduct **13** and its rearrangement to phthalimide **6.**



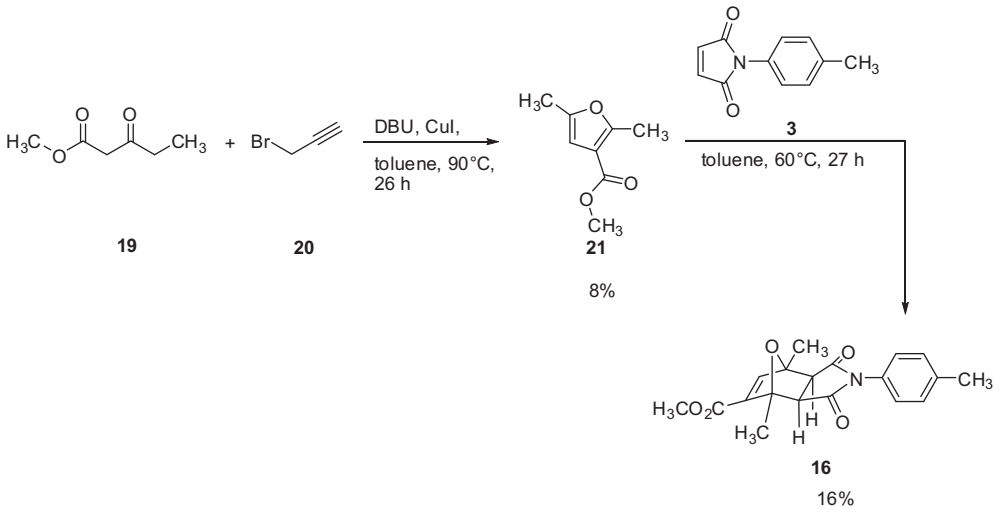
Scheme 5. Attempted preparation of a Diels–Alder adduct between 1,2,5-trimethylpyrrole (**14**) and maleimide **3**, and potential structures of the unknown product.

proposed, from NMR analysis, that this compound should have one of the structures shown at the bottom of Scheme 5, (i.e., structures **16**–**18**). We realized that three additional structures were theoretically possible, wherein the carbomethoxy group would reside at the bridgehead position next to the ether oxygen. However, we considered these structures less likely, since they would be products arising from a less reactive, more electron poor diene.[18]

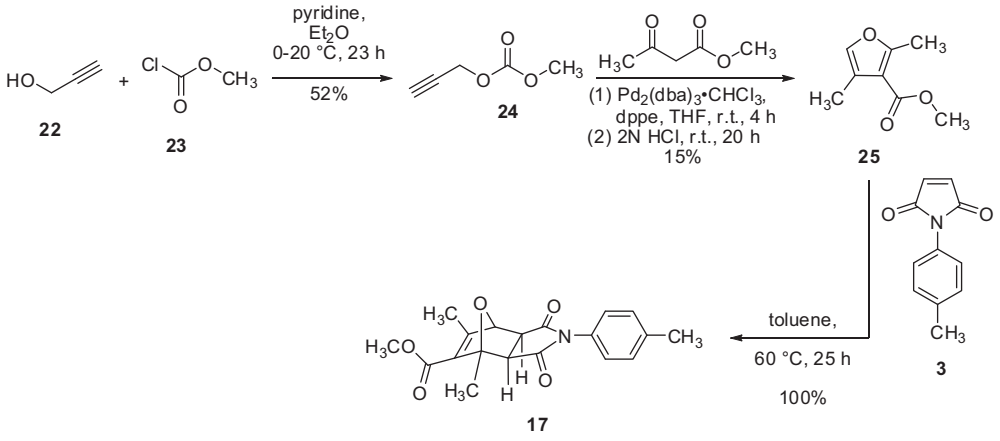
We first prepared an authentic sample of compound **16**, to determine whether this might be the material formed from maleimide **3** and a substituted furan impurity that was present in our commercial sample of **14**. As shown in Scheme 6, we treated methyl 3-oxovalerate (**19**) with propargyl bromide (**20**), in the presence of cuprous iodide and DBU in toluene at 90 °C for 26 h[19] to provide 2,5-dimethylfurancarboxylic acid methyl ester (**21**). Furan **21** underwent cycloaddition with maleimide **3** in modest yield to give the expected cycloadduct **16**. Although the spectral data for compound **16** were very similar to the spectral data gathered for the unknown compound, the two materials were distinct. For instance, the bridgehead protons for compound **16** appeared at δ 3.12 and δ 3.02 (coupling constant 6.3 Hz, $CHCl_3$), whereas these bridgehead protons appeared at δ 3.12 and δ 3.06 (coupling constant 6.6 Hz, $CHCl_3$) for the unknown compound. The biggest difference in the ^{1}H NMR spectra of these compounds was that the vinyl proton in compound **16** appeared as a singlet at δ 7.06, and this signal was not present in the unknown compound, but its counterpart signal was a singlet that appeared at δ 5.10. The ^{13}C position for the carbon atom bearing this proton in the unknown compound appeared at δ 84.34 ppm ($CHCl_3$), which we felt was upfield from where a vinyl carbon signal should appear. These data suggested that compounds **17** or **18** would better fit the data, as these compounds would have allylic protons in the δ 5 ppm range and would have an allylic bridgehead carbon signal downfield from δ 84.34 ppm. Thus, we next set out to prepare an authentic sample of compound **17**.

The synthesis of compound **17** is shown in Scheme 7. Propargyl alcohol (**22**) was acylated with methyl chloroformate (**23**) to give methyl prop-2-ynyl carbonate (**24**).[20] Treatment of carbonate **24** with methyl acetoacetate under palladium-catalyzed conditions, followed by treatment with 2 M aqueous hydrochloric acid gave a modest yield of 2,4-dimethylfuran-3-carboxylic acid methyl ester (**25**). Furan **25** underwent very clean and efficient cycloaddition with maleimide **3** in toluene at 60 °C to provide compound **17**, which was identical in every respect with the unknown cycloadduct that was isolated from the treatment of 1,2,5-trimethylpyrrole (**14**) with maleimide **3**.

The regiochemistry of *exo* adduct **17** is clearly demonstrated by examining the ^{1}H NMR spectrum, which displays coupling between the maleimide bridgehead protons (as previously described) and no observed coupling between the furan bridgehead proton and the adjacent maleimide bridgehead proton. Inspection of a structural model for this compound reveals that the dihedral angle defined by these two bridgehead protons and the carbons to which they are attached is close to 90°. Lack of observed coupling between protons configured with a dihedral angle of 90° is consistent with the prediction from the Karplus equation.[21,22] An *endo* regiochemistry, where the dihedral angle is ca. 60°, would clearly display coupling



Scheme 6. Synthesis of an authentic sample of compound **16**.



Scheme 7. Synthesis of an authentic sample of compound **17**.

between the furan bridgehead proton and the adjacent maleimide bridgehead proton of ca. 4.5 Hz.

It is not clear why our commercial sample of pyrrole **14** was contaminated with furan **25**.[23] The classic synthesis of 2,5-dimethylpyrrole involves the condensation of acetonylacetone with ammonium carbonate,[24] and this process produces pyrrole **14** if methylamine[25] or *N*-methylformamide[26] is substituted for ammonium carbonate. It is difficult to imagine the coproduction of furan **25** using these synthetic routes. Pyrroles are also commonly prepared using the Knorr pyrrole synthesis,[27–30] and it is conceivable that furan **25** might have been produced as a coproduct using this procedure. We felt it was important to spend the considerable effort that we did to establish the structure of cycloadduct **17** with the reactive maleimide **3**, since pyrrole **14** was completely unreactive with **3**, but **3** was very reactive with the minor component, furan **25.** Thus, this structural information is now available to others who might encounter similar difficulties in treating pyrrole **14** with additional dienophiles.

We did consider further studies with other pyrroles to effect cycloaddition products with maleimide **3**. However, as previously mentioned, cycloadducts of pyrroles with dienophiles are inherently thermodynamically unstable.[15–17] Osmium complexation of pyrroles has allowed the production of cycloadducts with maleimides and other dienophiles; however, decomplexation is not straightforward and stable cycloadducts can only be isolated after reduction of the resulting dihydropyrrole.[15] The greater aromatic character of pyrroles, as compared with furans or thiophenes, limits their reactivity toward cycloaddition reactions.[15]

Recent reports have described the preparation of phosphole-*N*-phenylmaleimide [4+2] cycloadducts as precursors to the preparation of nucleophilic phosphinidines,[31] secondary phosphine–borane complexes,[32] and dibromophosphines.[33] Interestingly, these cycloadducts are *endo* adducts, as shown by X-ray crystallography.[32] Thus, it is possible to perform [4+2] cycloadditions of *N*-phenylmaleimides with five-membered ring heterocycles containing one heteroatom, when that single heteroatom is oxygen, sulfur, nitrogen, or phosphorous.

In summary, we have investigated the cycloaddition reactions of *N*-arylmaleimide **3** with furans and thiophenes, and shown that the cycloadducts with 2,5-dimethylfuran (**4**) and 2,5-dimethylthiophene *S*-oxide undergo acid-catalyzed rearrangements to produce phthalimide **6**. Although 1,2,5-trimethylpyrrole (**14**) did not undergo cycloaddition with **3** under the conditions we employed, we isolated and characterized the interesting cycloadduct **17** that was produced from furan **25**, which was present as an impurity in the sample of **14** that we used.

Acknowledgements

This work was supported in part by DHHS/NIH Grant R43 AI-068185 from the National Institute of Allergy and Infectious Diseases (NIAID) NIH – United States.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.114.

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