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The Diels−Alder Reaction between Deactivated Dienes and Electron-Deficient Dienophiles on Solid Support: Stereoselective Synthesis of Hexahydro-1,3-dioxoisoindoles

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The Diels−Alder reaction has been seen as a major focus for the development of new synthesis methods. As part of our continuing studies of polymer-supported pericyclic reactions for preparing pharmacologically interesting heterocyclic compounds, we embarked on the solid-phase synthesis of hexahydro-1,3-dioxoisoindoles. We have developed a new method which enables us to carry out in mild conditions the [4 + 2] cycloaddition reactions between deactivated dienes and electron-poor dienophiles, a reaction usually only performed with difficulty. We have immobilized commercially available dienoic carboxylic acids on Wang resin through an ester linkage and allowed them to react with N-substituted maleimides, typically by heating in toluene or at room temperature in a low solvent volume. The fused hexahydro-1,3-dioxoisoindoles are formed stereoselectively via a [4 + 2] cycloaddition reaction in moderate to good yields.

Introduction

The Diels−Alder reaction, a concerted [4 + 2] cycloaddition reaction of a conjugated diene with a dienophile, provides several pathways toward the construction of substituted six-membered rings with a high degree of regioselectivity, diastereoselectivity and enantioselectivity. The Diels−Alder reaction is one of the most important carbon−carbon bond-forming cycloaddition reactions in synthetic organic chemistry.[1] In addition, the Diels−Alder reaction displays interesting physicochemical properties and mechanistic aspects. In view of its utility, the Diels−Alder reaction has been seen as a major focus for the development of new solid-phase synthesis methods. Hence, it is not surprising that examples of polymer-supported [4 + 2] cycloaddition reactions have been reported in recent literature.[2]

As a part of our continuing studies of polymer-supported pericyclic reactions for preparing pharmacologically active heterocyclic compounds, we embarked on the solid-phase synthesis of hexahydro-1,3-dioxoisoindoles. The hexahydroisoindole moiety occurs in certain cytochalasin-related compounds that induce binucleation in human lymphocytes.[3] Certain hexahydroisoindole-related pyrrolophthalimides are useful in the treatment of thrombocytopenia to increase the blood platelet count.[4] Some quinolonecarboxylic acid derivatives that incorporate the hexahydroisoindole structure are useful as antibiotics against *Staphylococcus aureus*.[5] Furthermore, some of the hexahydroisoindole cycloadducts, in turn, structurally resemble *N*-arylphthalimides that possess anticonvulsant activity.[6] Hence, procedures and methods for efficiently synthesizing and screening these types of cycloadducts are of considerable importance.

The main objective of this study was to develop a facile synthesis method whereby the [4 + 2] cycloaddition reactions between deactivated dienes and electron-poor dienophiles could be executed by solid-phase chemistry. So far, there are only a few reports about these types of disfavored Diels−Alder reactions in solution[7] and, to date, only one report about the reaction that has been carried out on solid support. Sun and Murray[8] studied the intramolecular solid-phase Diels−Alder reaction of amino acid triene in which the Wang resin-bound acrylate-type dienophile was coupled via an amide linkage to the dienophilic sorbic acid moiety. This intramolecular cycloaddition gave a mixture of the functionalized hexahydroisoindoles in a yield of 38% after cleavage from the resin. Consequently, there is a need for additional studies which can extend the scope of the disfavored Diels−Alder reactions on solid supports from intramolecular to *intermolecular* cycloadditions. Herein, we wish to report our study of the intermolecular Diels−Alder reactions between electron-poor dienophiles and the Wang resin-bound deactivated dienes.

Results and Discussion

The synthetic routes presented in Schemes 1−3 were used for the solid-phase synthesis of various hexahydro-1,3-dioxoisoindoles. First, the electronically deactivated dienoic carboxylic acids were coupled to 4-(bromomethyl)-phenoxymethyl polystyrene or Wang brominated resin in the presence of Hünig's base and cesium iodide in DMF at room temperature to give the resin-bound dienes **1**, **4**, and **6**.[9] The coupling of the conjugated dienes to the resins proceeded smoothly on the basis of the FT-IR assays of the resin beads.

N-Substituted maleimides **2a**−**h** were found to be sufficiently reactive dienophiles to participate in [4 + 2] cycloaddition reactions with the polymer-bound dienes **1**, **4**, and **6**, even at room temperature. Three structurally different resin-bound dienes, namely, the acyclic **1**, carbocycloaromatic **4**, and heterocycloaromatic **6** dienoic carboxylic acids, were subjected to the cycloaddition conditions in the presence of N-substituted maleimides. We found that the cycloaddition of the resin-bound 1,3-butadiene-1-carboxylic acid **1** with N-substituted maleimides **2a**−**h** occurs under mild thermal conditions (method A), yielding the cycload-

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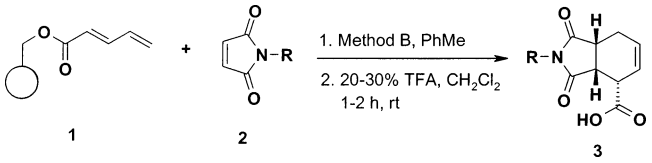
Table 1. Solid-Phase Synthesis of Hexahydro-1,3-dioxoisoindoles **3a**−**h**[a]

entry	compd	R	isolated yield(%)[b]
1	**3a**	H	30
2	**3b**	Me	29
3	**3c**	Et	40
4	**3d**	*tert*-Bu	46
5	**3e**	Chx	23
6	**3f**	Ph	33
7	**3g**	Bn	32
8	**3h**	4-Br−Ph	35

[a] Method B: PhMe 400−1200 μL, rt, 30−70 h. [b] Refers to combined yield over the coupling, cycloaddition, and cleavage steps. Yields are based on the initial loading of the resin and are not optimized.

Scheme 1



ducts **3a**−**h** after cleavage from Wang resin (Scheme 1, Table 1). The Morphy group has recently reported a very interesting observation that the use of extremely low solvent volumes in solid-phase reactions results in increases in yield both for the Diels−Alder and Heck reactions.[10] In our solid-phase cycloaddition reactions between the resin-bound diene **1** and N-substituted maleimides **2b**−**h (**method B**)**, we obtained similar or slightly better yields using only 1−2 μL of solvent/mg of resin, as compared to the conventional high-dilution techniques. However, in the case of the maleimide **2a**, a slightly better yield (40%) was obtained at heating in toluene (method A). A higher diastereoselectivity was achieved under room temperature and low-solvent volume conditions (method B). TLC, ^{1}H NMR, and ^{13}C NMR analyses of the crude products showed that only a single diastereomer was formed during the cycloaddition. On the other hand, in the case of using mild thermal conditions (method A), we found that both solid- and solution-phase[11] reactions gave a mixture of two diastereomers, as observed in the ^{1}H NMR spectra of the crude products. The low-solvent volume reactions (1.0−2.0 μL toluene/mg of resin, method B) were carried out in a sealed tube at room temperature, and prolonged reaction times were needed (40−70 h) to complete the cycloaddition (Table 1). The change of the solvent from the initially used CH_2Cl_2 or 1,2-dichloroethane to toluene resulted in a remarkable increase in yields of the cycloadducts **3a**−**h**. Additionally, the yields of the observed byproducts, such as dimerized pentadienoic acid[12] (GC/MS *m*/*z* 224, dimeric adduct as dimethyl ester) and aromatized or rearranged products arising from the intermediate cycloadducts **3a**−**h** were significantly decreased. The maleimide dienophiles **2h** (R = 4-Br−Ph), **2c** (R = Et) and **2d** (R = *tert*-Bu) gave the highest yields of 35, 40 and, 46% respectively, over the coupling, cycloaddition, and cleavage steps. The cycloaddition between the polymer-bound anthracene-9-carboxylic acid **4** and **2b** gave the best overall yield (63%) in our study.

The stereochemistry of the cycloadduct **3h** was determined by single-crystal X-ray diffraction, and it is shown in

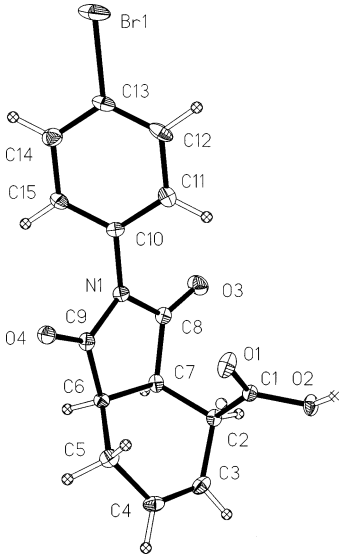


Figure 1. View of the molecule **3h**. Thermal ellipsoids have been drawn at 30% probability level.

Scheme 2

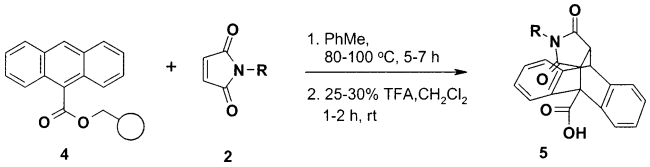


Figure 1. The cycloadduct was formed via the endo transition state. The endo selectivity has previously been reported in an intramolecular solid-phase Diels−Alder reaction by the Murray group.[8] In addition, the solution-phase Diels−Alder reaction between electron-deficient butadiene-tricarbonyliron and *N*-methylmaleimide has been reported to proceed via the endo transition state.[13]

The isolated and purified cycloadducts **3a**−**h** were initially analyzed as the O- and N-methylated derivatives by means of gas chromatography/mass spectrometry. For the methyl ester formation, an ethereal solution of diazomethane[14] was used as a derivatization agent. The GC/MS chromatographs and spectra of the methyl esters regularly showed the presence of 3−4 isomers with the same molecular weight by different ratios on compounds **3a**−**h**, although in the ^{1}H NMR spectra of the crude products, only one (method B) or one to two (method A) cycloadducts were observed.[15] The subsequent HPLC analyses of the free acids **3a**−**h** finally proved that only one diastereomer of the cycloadduct was formed when reactions were carried out under low solvent volume (method B) conditions. However, when three randomly selected cycloadducts **3a**, **3c**, and **3h** were methylated with diazomethane, two closely eluting isomers (with equal *m*/*z* values) were observed in their HPLC chromatographs.

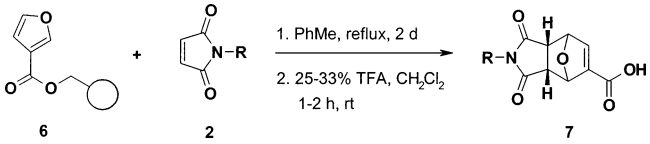
The polymer-bound anthracene-9-carboxylic acid **4** was found to be the most efficient diene in our study of the [4 + 2] cycloaddition reaction using randomly selected N-substituted maleimides **2a**, **2b**, and **2f** as dienophiles (Scheme 2, Table 2). The Diels−Alder reactions were carried out in toluene (85−100 °C, 5−7 h).[16] After cleavage from the Wang resin, the crude products were purified by SiO_2 column chromatography to give the pentacyclic cycloadducts **5a**−**c**

Table 2. Solid-Phase Synthesis of Hexahydro-1,3-dioxoisoindoles **5a**−**c** and **7a**−**b**

entry	compd	R	reaction conditions[a]	isolated yield (%)[b]
9	**5a**	H	C	57
10	**5b**	Me	C	63
11	**5c**	Ph	C[c]	55
12	**7a**	H	D	16
13	**7b**	Ph	D	24

[a] C: toluene, 85−100 °C, 5−7 h. D: toluene, reflux, 2 d. [b] Refers to combined yield over the coupling, cycloaddition and cleavage steps. Yields are based on the initial loading of resin and are not optimized. [c] Toluene, 100 °C, 18 h.

Scheme 3



in good overall yields (57, 63, and 55%, respectively) and as single isomers by ^{1}H NMR and GC/MS (**5c** by LC/MS) analyses.

The polymer-bound furan-2-carboxylic acid and thiophene-3-carboxylic acid were found to be inert toward [4 + 2] cycloaddition with electron-poor dienophiles in our study (refluxing toluene, 2 d). The highly aromatic thiophene ring is known to be a poor diene in the Diels−Alder reactions, and therefore, thiophenes react only with very reactive dienophiles, usually under harsh conditions.[17] However, the Wang resin-bound furan-3-carboxylic acid **6** was found to undergo Diels−Alder cycloaddition with randomly selected N-substituted maleimides **2a** and **2f** (Scheme 3, Table 2). After cleavage from the Wang resin, the crude products were purified by column chromatography on SiO_2 to yield the tricyclic products **7a** and **7b** as single isomers (by ^{1}H NMR and LC/MS) in moderate yields of 16 and 24%, respectively. Harsher reaction conditions were needed to execute these reactions, because the aromatic system of the furan ring is destroyed during the cycloaddition reaction.

Conclusions

In conclusion, we believe that the intermolecular cycloaddition protocol presented herein will find application in the polymer-supported disfavored Diels−Alder reactions between deactivated dienes and electron-deficient dienophiles. Finally, the cycloadducts reported herein possess the common pharmacophoric hexahydro-1,3-dioxoisoindole moiety that could have great potential in medicinal chemistry.

We are presently studying the extension of the molecular diversity and reaction optimization because this transformation is likely to provide an access to even more functionalized heterocyclic compounds, and it can be combinatorialized for the synthesis of cycloadduct libraries. The results of our studies will be published in due course.

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Supporting Information Available. Experimental details and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) A more detailed description is presented in the Supporting Information (Solution-Phase Model Reaction).

(12) The dimerized pentadienoic acid is presumably formed via the [4 + 2] cycloaddition, pentadienoic acid acting both as a diene and a dienophile. The analysis was carried out by means of GC/MS after derivatization with diazomethane; *m*/*z* 224 (dimeric adduct as a dimethyl ester).

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(14) Diazomethane was prepared as described in the Aldrich Technical Bulletin AL-180, Diazald, MNNG and Diazomethane Generators.

(15) Our tentative proposal is that diazomethane might be capable of acting as a weak base and epimerizing the cycloadducts **3a**−**h** by means of abstraction of the acidic α-protons from **3a**−**h**, enolization, and reprotonation of the enolate in the course of the diazomethane-assisted methylation.

(16) The low-dilution method was not used with dienes **4** and **6**. Heating in toluene at 85−100 °C renders this method inconvenient, because the small solvent volume evaporates easily from the reaction mixture.

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