Stereoselective Aza Diels−Alder Reaction on Solid Phase: A Facile Synthesis of Hexahydrocinnoline Derivatives

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As part of our continuing studies of polymer-supported pericyclic reactions for preparing biologically interesting heterocyclic compounds, we have introduced a traceless solid-phase synthesis of hexahydrocinnolines. We developed a method in which mild reaction conditions can be used for the hetero-Diels−Alder reactions on a polymeric support. The dienoic 3-vinyl-2-cyclohexenol attached to a Wang resin through an ether linkage undergoes [4 + 2] cycloaddition reaction with several azadienophiles. The highly stereoselective Diels−Alder reaction showed preferential formation of a single cycloadduct resulting from an anti attack of the dienophile on the polymer-bound diene. Trifluoroacetic acid-mediated cleavage of the polymer-bound cycloadducts yields fused nonaromatic hexahydrocinnolines in moderate yields in three steps.

Introduction

The simultaneous development of multiple stereocenters with a high degree of regioselectivity and stereoselectivity makes the Diels−Alder reaction one of the most advantageous carbon−carbon bond-forming reactions in synthetic organic chemistry.[1] In the hetero-Diels−Alder reaction, various heteroatoms can be incorporated in both the dienoic and dienophilic components.[2] This methodology has been employed successfully for constructing various heterocyclic moieties that constitute the structural skeleton of a large number of natural products and pharmacologically active compounds.[3] The development of solid-phase organic synthesis (SPOS) has progressed rapidly during recent years, and many examples of polymer-supported [4 + 2] cycloaddition reactions have been reported in the literature.[4] As part of our continuing interest in polymer-supported [4 + 2]-cycloaddition reactions[5] for the preparation of pharmacologically interesting heterocyclic compounds, we report the solid-phase synthesis of hexahydrocinnolines. The cinnoline structure and its various derivatives can be found in several pharmaceutically interesting compounds (Figure 1). Cintazone for example is a nonsteroidal anti-inflammatory agent.[6] Cinoxacin is a synthetic antimicrobial agent related to oxolinic and nalidixic acids and is used to treat urinary tract infections.[7] Certain cinnoline-related compounds are useful as antianxiety[8] and antihypertensive agents.[9] Recently, two groups have demonstrated the usefulness of the epoxyquinol scaffold in the synthesis of a structurally diverse chemical library.[10,11] Some members of these libraries (Figure 1), structurally similar to our hexahydro-1,2,4-triazolocinnoline-3,5-diones, inhibit the growth of human small-cell lung carcinoma (A549) and induction of heatshock protein (HSP 72). Hence, the procedures and methods for efficiently synthesizing and screening these types of heterocycles are of considerable importance.

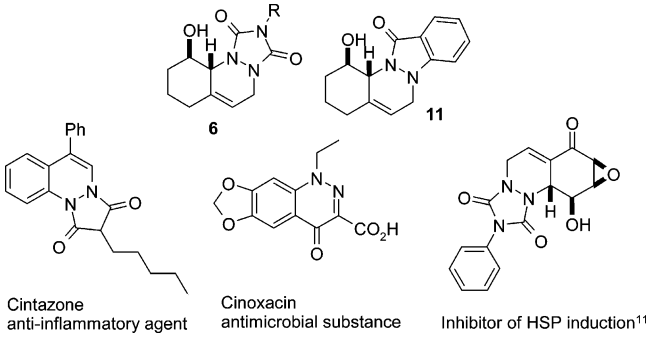

Figure 1. Some of the synthesized hexahydrocinnolines and examples of biologically active cinnoline derivatives.

The main aim of this study was to develop a practical synthetic method in which the Diels−Alder reaction between the polymer-bound semicyclic diene and N═N-azadienophiles could be performed in parallel mode. 1,2,4-Triazole-3,5-diones (TADs) and other carbonylazo compounds are known to be powerful dienophiles in [4 + 2]-cycloaddition reactions.[3,12] The lower LUMO energy of the N═N bond in contrast to the corresponding C═C bond in alkenes[13] allows reactions to proceed more rapidly and often at ambient temperatures without the need for drastic thermal conditions. Therefore, these types of dienophiles would be useful in solid-phase cycloadditions as demonstrated by Boldi et al.[14] in the synthesis of a triazolopyridazine library. Dienol system **1** (Scheme 1) is a valuable building block in the synthesis of natural products via [4 + 2]-cycloaddition reactions.[15] These studies have shown that heteroatomic substitutions[16,17]

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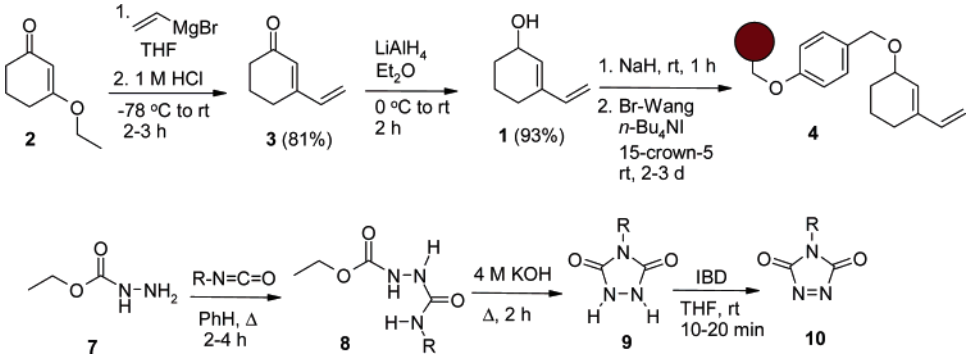
Scheme 1. Preparation of Diene and Dienophiles: Synthesis of Polymer-bound 3-Vinyl-2-cyclohexen-1-ol **4** and 1,2,4-Triazole-3,5-diones **10**.



and steric effects[17] at the allylic position can control diastereoselectivity in the Diels−Alder transition states of semicyclic dienes. Therefore, immobilization of the hydroxy functionality in **1** to a bulky polymeric moiety could promote better diastereoselectivity and provide a protective group for the allylic alcohol. Here we report our study of the intermolecular hetero-Diels−Alder reactions between the electron-deficient azadienophiles and the Wang resin-bound semicyclic diene.

Results and Discussion

The synthesis of diene **1**[18] (Scheme 1) commences with the facile Grignard reaction of readily available 3-ethoxy-cyclohex-2-enone **2** and vinylmagnesium bromide, affording a good yield (81%) of 3-vinylcyclohex-2-enone **3**[19] after purification by vacuum distillation. Reduction of the ketone **3** with $LiAlH_4$ in diethyl ether resulted in the allylic alcohol **1** (93%). Curiously, the same reduction step in tetrahydrofuran, as a solvent, afforded a mixture of **1** and partially reduced double bond-containing products. The hydroxy group of **1** was used as an anchor for coupling with the polymeric support.

Deprotonation of secondary alcohol **1** was accomplished by treatment with sodium hydride. The resulting anion was linked with the commercially available bromo-Wang resin[20] in the presence of tetra-*n*-butylammonium iodide (Scheme 1). A catalytic amount of 15-crown-5 in THF secured effective loading.[21] The commercial availability of the additional azadienophilic precursors (Table 1), urazoles, is usually restricted. However, preparation of urazoles by condensing *N*-alkyl or *N*-aryl isocyanates and ethyl hydrazinecarboxylate **7**, followed by cyclization of intermediate **8** in a basic medium (KOH/H_2O) is straightforward, as demonstrated by Cookson et al.[22] (Scheme 1, Table 1). Purification by recrystallization conveniently afforded N-substituted urazoles **9d**−**o** as stable azadienophile precursors. Several oxidizing agents, including fuming nitric acid, lead peroxide, manganese dioxide, lead(IV) acetate, *tert*-butyl hypochlorite, and dinitrogen tetroxide, have been used for the generation of N-substituted TADs.[23] However, all of these reagents, except dinitrogen tetraoxide, form byproducts that are difficult to remove or are too reactive toward sensitive azo compounds. Hypervalent iodine oxidation with iodobenzene diacetate (IBD) was reported to be a mild and nonacidic way for formation of TADs.[23] Intensive and rapid color change of the urazoles **9a**−**m** (from colorless to dark red/violet) during IBD oxidation in situ indicates formation of highly reactive dienophiles **10a**−**m**, followed by the hetero-Diels−Alder reaction with polymer-bound diene **4**.

Table 1. Diels−Alder Reaction between the Polymer-Bound Diene **4** and Various Azadienophiles

entry	dienophile precursor	R	cycloadduct (yield, %)[b]
1	**9a**[a]	H	**6a** (26)
2	**9b**[a]	Me	**6b** (35)
3	**9c**[a]	Ph	**6c** (42)[c]
4	**9d**[25]	cyclohexyl	**6d** (30)
5	**9e**[22]	*t*-Bu	**6e** (30)
6	9f	3-$MeOC_6H_4$	**6f** (33)
7	**9g**[26]	benzyl	**6g** (53)
8	9h	4-FC_6H_4	**6h** (40)
9	9i	3-$NO_2C_6H_4$	**6i** (30)
10	9j	5-indanyl	**6j** (51)
11	9k	5-benzo-1,3- dioxolyl	**6k** (49)
12	**9l**[27]	4-ClC_6H_4	**6l** (35)
13	**9m**[28]	1-naphthyl	**6m**[d] (49)
14	**9n**	2-furanylmethyl	
15	**9o**[29]	4-tosyl	
16	indazolinone[a]		**11** (30)
17	maleic hydrazide[a]		**12** (8)
18	phthalhydrazide[a]		**13** (19)
19	pyrazolidine-3,5-dione[30]		

[a] Commercially available. [b] Isolated yields of the purified cycloadducts are based on the initial loading of the bromo-Wang resin and are not optimized. [c] Reaction carried out at −78 °C to room temp. [d] Inseparable mixture of atropisomers.

Commercially available *N*-phenyl-1,2,4-triazole-3,5-dione participated effectively in the hetero-Diels−Alder reaction with polymer-bound diene **4** at low temperature (−78 °C, Table 1, entry 3). The [4 + 2]-cycloaddition reaction was monitored by FT-IR spectroscopy. Appearance of a strong characteristic carbonyl band at 1710 cm^{-1} in **5** revealed formation of the cycloadduct. Trifluoroacetic acid treatment of polymer **5** resulted in a traceless cleavage of the benzylic ether bond, affording a satisfying yield of racemic tricyclic alcohol **6c**[17] after chromatographic purification (42%, over three steps). Good purity (65−98%, HPLC) and formation of single diastereomeric cycloadducts were observed as judged by TLC and HPLC analyses of the aliquots of the cleaved crude products **6a**−**m**. The use of a higher reaction temperature (−10 °C vs −78 °C) did not affect the stereoselectivity of the Diels−Alder reaction, and tricyclic

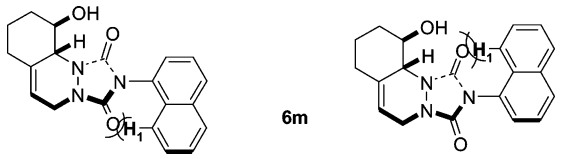


Figure 2. Lack of free rotation of the *N*-naphth-1-yl moiety results in atropisomerism in cycloadduct **6m**.

alcohols **6a**−**m** were isolated as single diastereomers[24] with moderate yields (Table 1). *N*-Aryl TADs gave slightly better yields (30−53%) compared to the *N*-alkyl TADs generated in situ from the corresponding *N*-alkyl urazoles (26−35%). No color change was observed, and no hexahydrocinnolines were isolated upon oxidation of urazoles **9n**−**o**. The presence of an electron-rich furan ring in **9n** could have led to [4 + 2] cycloaddition within the reactive azadienophile part and resulted in the formation of oligomerized starting material that was isolated as a pale orange, insoluble solid. Interestingly, compound **6m** with a large naphthyl moiety was obtained as an inseparable mixture of two diastereomers distinguished by ^{1}H and ^{13}C NMR. This can be explained by hindered rotation about the naphthyl C−N bond in **6m** (Figure 2). This results in two atropisomeric forms of compound **6m**.

The stereochemistry of isolated cycloadducts **6a**−**m** was determined by ^{1}H NMR studies, which showed that allylic proton H_b resonates as a doublet ($^{3}J_{H_a-H_b} = 8-10$ Hz). This, together with a broad ddd of homoallylic methine proton H_a indicates that protons H_a and H_b are *trans* to each other (Scheme 2), as was reported previously for the corresponding solution-phase reaction.[17]

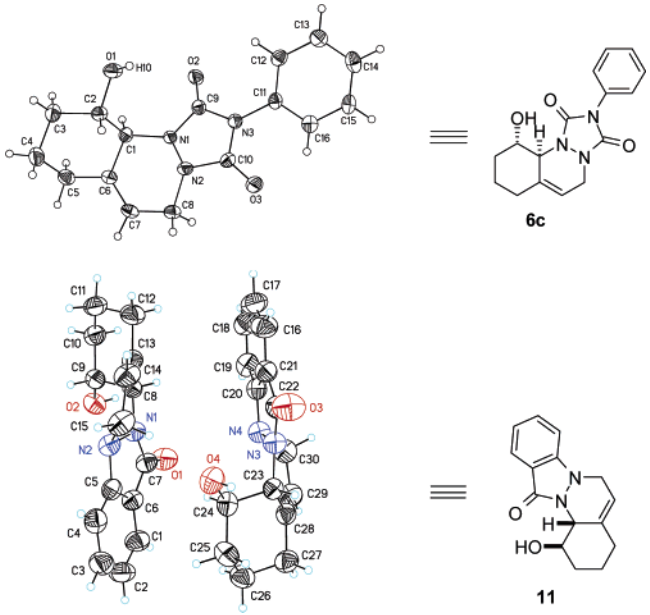
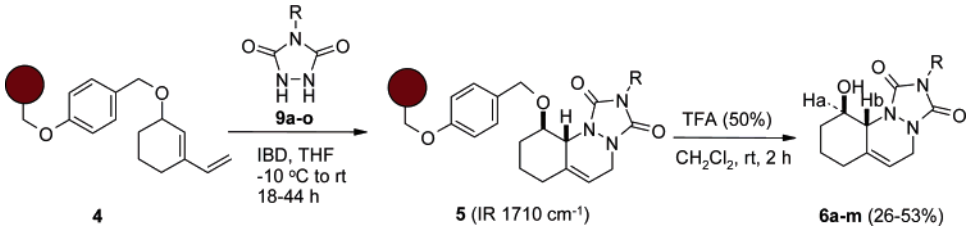


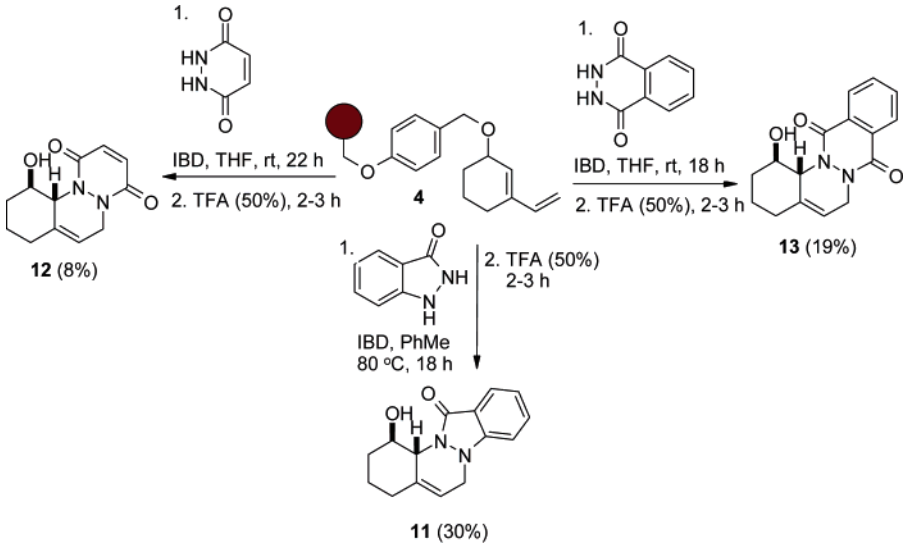
Figure 3. X-ray crystal structure of **6c** and the molecular structure of the two crystallographically independent molecules of **11**.

The X-ray crystal structure of cycloadduct **6c** (Figure 3) confirmed the assignment. After successful reactions with TADs **10**, we examined the scope of the method by testing other types of cyclic azadienophiles. Indazolinone, maleic hydrazide, phthalhydrazide, and pyrazolidine-3,5-dione were oxidized by IBD or lead(IV) acetate to the corresponding aza compounds and allowed to react with polymer-supported diene **4**. The heterocycles formed (**11**−**13**) were released from the resin as the corresponding alcohols by treatment

Scheme 2. Solid-Phase Synthesis of Hexahydro-1,2,4-triazolo[1,2-a]cinnoline-1,3-diones **6a**−**m**.



Scheme 3. Hetero-Diels−Alder Reaction between Polymer **4** and Carbonylazo Dienophiles.



with TFA (Scheme 3, Table 1). The stereochemistry of cycloadducts **11**−**13** was the same as that observed with the reactions that produced **6a**−**m** (^{1}H NMR). Curiously, compound **11** obtained from a reaction between indazolinone and polymer-bound diene **4** was isolated as a single regio- and stereoisomer. The carbonyl group of the indazolone moiety was located on the same side as the hydroxy group of the cyclohexanol ring. This was proven by X-ray crystallographic structural analyses of heterocyclic **11** (Figure 2). Reaction with pyrazolidine-3,5-dione and polymer-supported diene **4** did not generate detectable amounts of the cycloaddition product.

Conclusions

In summary, we developed a parallel method for the solid-phase hetero-Diels−Alder reaction between semicylic diene and carbonylazo compounds. The cycloadducts reported herein possess the hexahydrocinnoline moiety that could show potential as a pharmacophoric group in medicinal chemistry. Although this study used racemic starting materials, the methodology could lead to enantiopure products if optically pure 3-vinyl-2-cyclohexen-1-ol **1** was used. We are currently using the resulting heterocycloadducts as templates to diversify their chemical structures. These transformations are likely to provide access to even more functionalized heterocyclic compounds, and the method developed can be used for the synthesis of structurally diverse cycloadduct libraries.

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Supporting Information Available. Experimental and characterization data for all new compounds and X-ray data for compounds **6c** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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