



Contents lists available at ScienceDirect

Tetrahedron

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

DMAP-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone and methyleneindolinones for the synthesis of spirocyclic oxindoles

Ming-Qiang Zhou^{a,b}, Jian-Qiang Zhao^{a,b}, Yong You^{a,b}, Xiao-Ying Xu^a, Xiao-Mei Zhang^a, Wei-Cheng Yuan^{a,*}

^a National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China

^b University of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:

Received 4 February 2015

Received in revised form 8 April 2015

Accepted 11 April 2015

Available online xxx

Keywords:

Diels–Alder reaction

3-Hydroxy-2-pyrone

Methyleneindolinones

Spirocyclic oxindoles

4-Dimethylaminopyridine

ABSTRACT

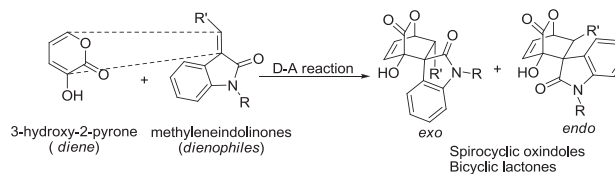
An efficient Diels–Alder reaction of 3-hydroxy-2-pyrone with a wide range of methyleneindolinones has been developed by employing 4-dimethylaminopyridine as a catalyst under mild reaction conditions. This process provides a promising method for the construction of structurally diverse spirocyclic oxindoles containing bicyclic lactone motif with moderate diastereoselectivities and good to excellent yields.

© 2015 Published by Elsevier Ltd.

1. Introduction

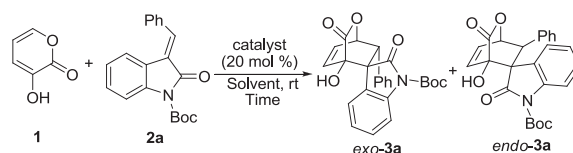
The Diels–Alder reaction is one of the most versatile reactions for the construction of structurally diverse and complex molecules containing carbocyclic skeletons in a single step.¹ Impressive advances have been documented for the realization of various Diels–Alder reactions.^{1,2} Among them, the Diels–Alder reaction of 3-hydroxy-2-pyrone with various dienophiles belongs to an interesting method to prepare highly functionalized bicyclic lactone derivatives, which are attractive and important building blocks for the synthesis of biological active natural products and their analogs.³ Consequently, a variety of protocols have been developed for generating structurally and stereochemically rich bicyclic lactone compounds by the cycloaddition of 3-hydroxy-2-pyrone and different dienophiles.⁴ Despite the advances made thus far, to the best of our knowledge, there is no report involving 3-hydroxy-2-pyrone as diene reacting with suitable dienophiles for the construction of spirocyclic compounds, which have occupied a key place among the various classes of organic molecules due to their highly remarkable biological activities.⁵ In this context, developing new and efficient methods for the direct construction of spirocyclic compounds with 3-hydroxy-2-pyrone as diene is very important.

Spirocyclic oxindole scaffolds are extensively found in a number of biologically active synthetic and natural molecules.⁶ A variety of strategies for the synthesis of structurally diverse spirocyclic oxindoles have been developed in the past few decades.⁷ In particular, methyleneindolinones have been used as highly reactive substrates for yielding spirocyclic oxindole derivatives.⁸ Additionally, our group have been working on developing creative methods to access diverse spirocyclic oxindoles with complex structures, and a series of new protocols have been achieved.⁹ Encouraged by these results, as our continuous interest in developing new synthetic strategies, we envisioned that spirocyclic oxindole compounds with bicyclic lactone motifs could be constructed through Diels–Alder reactions between 3-hydroxy-2-pyrone and methyleneindolinones (Scheme 1). Herein, we hope to report the successful implementation of this strategy with 4-dimethylaminopyridine (DMAP) as a catalyst to provide structurally diverse and complex spirocyclic



Scheme 1. The construction of spirocyclic oxindole scaffolds with bicyclic lactone motifs via Diels–Alder reactions.

* Corresponding author. E-mail address: yuanwc@cioc.ac.cn (W.-C. Yuan).

Table 1
Optimization of reaction conditions^a


Entry	Solvent	Catalyst	Time (h)	dr (<i>exo/endo</i>) ^b	Yield ^c (%)
1	DCE	Et ₃ N	22	31/69	82
2	DCE	DABCO	22	30/70	85
3	DCE	DBU	18	26/74	85
4	DCE	Piperidine	10	33/67	67
5	DCE	DMAP	16	27/73	91
6	DCE	K ₂ CO ₃	10	—	Trace
7	EtOAc	DMAP	32	32/68	73
8	Toluene	DMAP	18	—	nd
9	THF	DMAP	18	—	nd
10	Et ₂ O	DMAP	18	—	nd

^a The reactions were carried out with **1** (0.2 mmol), **2a** (0.22 mmol) and catalyst (20 mol %) in 0.5 mL solvent at room temperature. nd=not determined.

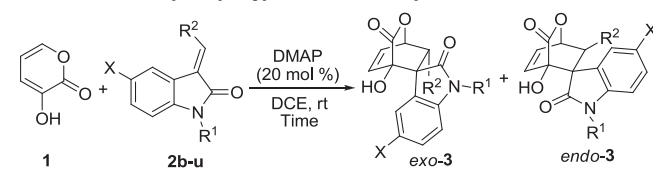
^b Determined by ¹H NMR analysis of the crude products.


^c Yield of isolated product as a diastereoisomeric mixture.

oxindole compounds under mild reaction conditions that had not been previously explored.

2. Results and discussion

Guided by the above speculation, we investigated the possibility of Diels–Alder reaction between 3-hydroxy-2-pyrone (**1**) and methyleneindolinone **2a** with various bases as catalysts. As summarized in Table 1, when the reaction was carried out in 1,2-dichloroethane (DCE) in the presence of 20 mol % Et₃N at room temperature, the desired spirocyclic oxindole **3a** could be obtained in 82% yield with 31/69 diastereoselectivity (*exo/endo*) after 22 h

Table 2
Substrate scope for DMAP-catalyzed Diels–Alder reactions of 3-hydroxy-2-pyrone **1** with methyleneindolinones **2b–u**^a


Entry	2	Time (h)	3	dr (<i>exo/endo</i>) ^b	Yield ^c (%)
1	X, R ¹ , R ² =H, Boc, 2-FC ₆ H ₄ (2b)	62	3b	60/40	98
2	X, R ¹ , R ² =H, Boc, 4-FC ₆ H ₄ (2c)	16	3c	32/68	98
3	X, R ¹ , R ² =H, Boc, 2-ClC ₆ H ₄ (2d)	72	3d	60/40	89
4	X, R ¹ , R ² =H, Boc, 4-ClC ₆ H ₄ (2e)	16	3e	31/69	96
5	X, R ¹ , R ² =H, Boc, 2-BrC ₆ H ₄ (2f)	144	3f	57/43	65
6	X, R ¹ , R ² =H, Boc, 4-BrC ₆ H ₄ (2g)	16	3g	33/67	97
7	X, R ¹ , R ² =H, Boc, 3-NO ₂ C ₆ H ₄ (2h)	12	3h	45/55	99
8	X, R ¹ , R ² =H, Boc, 4-CNC ₆ H ₄ (2i)	12	3i	48/52	99
9	X, R ¹ , R ² =H, Boc, 2-MeOC ₆ H ₄ (2j)	72	3j	58/42	75
10	X, R ¹ , R ² =H, Boc, 3-MeOC ₆ H ₄ (2k)	72	3k	32/68	74
11	X, R ¹ , R ² =H, Boc, 2,3-(MeO) ₂ C ₆ H ₃ (2l)	48	3l	60/40	71
12	X, R ¹ , R ² =H, Boc,  (2m)	18	3m	29/71	93
13	X, R ¹ , R ² =H, Boc, 1-naphthyl (2n)	96	3n	45/55	59
14	X, R ¹ , R ² =H, Boc, 2-furyl (2o)	120	3o	57/43	81
15	X, R ¹ , R ² =H, Boc, 2-thienyl (2p)	120	3p	27/73	83
16	X, R ¹ , R ² =H, Boc, n-C ₃ H ₇ (2q)	20	3q	58/42	99
17	X, R ¹ , R ² =H, Boc, CO ₂ Et (2r)	12	3r	48/52	99
18	X, R ¹ , R ² =Br, Boc, Ph (2s)	10	3s	34/66	90
19	X, R ¹ , R ² =H, Me, Ph (2t)	72	3t	31/69	85
20	X, R ¹ , R ² =H, CO ₂ Et, Ph (2u)	24	3u	29/71	97

^a Unless otherwise noted, the reactions were carried out with 3-hydroxy-2-pyrone **1** (0.2 mmol), methyleneindolinones **2** (0.22 mmol) and 20 mol % DMAP in 0.5 mL 1,2-dichloroethane at room temperature for the specified reaction time.

^b Determined by ¹H NMR analysis of the crude products.

^c Yield of isolated product as a diastereoisomeric mixture.

(Table 1, entry 1). Then, with 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalysts, respectively, the similar results for product **3a** were observed (Table 1, entries 2 and 3). Piperidine was also investigated, giving **3a** in 67% yield with 33/67 dr (Table 1, entry 4). Delightedly, the reaction proceeded smoothly and delivered **3a** in 91% yield with 27/73 dr with 20 mol % 4-dimethylaminopyridine (DMAP) (Table 1, entry 5). However, the reaction gave the product with only a trace amount when using K₂CO₃ as a catalyst (Table 1, entry 6). Consequently, these results suggest that DMAP is the relatively suitable base for the Diels–Alder reaction of 3-hydroxy-2-pyrone (**1**) and methyleneindolinone **2a**. Ultimately, to further find the optimal conditions for the reaction, a series of screenings were performed with different solvents (Table 1, entries 7–10). Unfortunately, not only no significant improvement was obtained by comparing with the results in entry 5, but also the reaction could hardly occur in toluene, THF, and ethyl ether (Table 1, entries 8–10).

Having the optimized reaction conditions in hand, the generality of the methodology was evaluated with the reactions of **1** and a series of methyleneindolinones **2b–u** bearing various substituents at the carbon–carbon double bond (Table 2). Firstly, for the benzylideneindolinone substrates containing different electron-withdrawing groups at the benzylidene moiety, such as fluorine, chlorine, bromine, nitro, and nitrile substituents, no matter what the position of these substituents on the aromatic ring, we found that these substrates **2b–i** reacted smoothly with 3-hydroxy-2-pyrone (**1**) under the standard reaction conditions, giving the Diels–Alder reactions products **3b–i** in 65–99% yields and moderate diastereoselectivity (*exo/endo*) (Table 2, entries 1–8). On the other hand, the similar reactivity and diastereoselectivity were also observed for those benzylideneindolinone substrates **2j–m** bearing different electron-donating groups at the benzylidene moiety, giving the corresponding spirocyclic oxindoles **3j–m** (Table 2, entries 9–12). Nevertheless, the naphthyl moiety was tolerated in the

Download English Version:

<https://daneshyari.com/en/article/5215101>

Download Persian Version:

<https://daneshyari.com/article/5215101>

[Daneshyari.com](https://daneshyari.com)