Diels-Alder Reactions of Ethyl α-Bromoacrylate with Open-chain Dienes—Synthesis of Ethyl 1,3-/ 1,4-Cyclohexadienecarboxylates

Li, Yingjie[a](李颖杰) Wang, Quanrui*,[a](王全瑞) Andreas, Goeke*,[b](高安德)

[a] *Department of Chemistry, Fudan University, Shanghai 200433, China*
[b] *Shanghai Givaudan Ltd, 298 Li Shi-zhen Road, Shanghai 201203, China*

The Diels-Alder reactions of ethyl α-bromoacrylate **1** with open-chain dienes **2** were conducted under thermal or Lewis acid-catalysis conditions. In most cases, the cyclic adducts of 1-bromocyclohex-3-enecarboxylates **3** were formed in high yields with good regio- and stereoselectivity. Subsequent E2-elimination by treatment with DBU provided the corresponding 1,3- or 1,4-cyclohexadienecarboxylates depending on the relative configuration of the products. Starting from myrcene (7-methyl-3-methyleneocta-1,6-diene) the reaction sequence afforded the ester precursor of *Georgywood* with good yields.

Keywords Diels-Alder reaction, cyclohexadienecarboxylate, stereochemistry, *Georgywood* ester

Introduction

The Diels-Alder reaction represents an extremely versatile tool for the construction of six-membered rings. The search for novel dienes and dienophiles has been dominating a fundamental role in the development of synthetic utilities since its discovery. Recently, a set of α-halo-α,β-unsaturated carbonyl compounds, including aldehydes,[1] nitriles[2] and ketones,[3] have attracted much interest regarding the use as dienophiles because many types of further transformations can be envisioned due to this added halogen functional handle. We felt that the base-mediated dehydrohalogenation process to create functionalized 1,3- or 1,4-cyclohexadienes merits particular attention since these structural motifs widely occur in the synthesis of natural products and other important compounds and possess utility as valuable synthetic intermediates.[4] For example, in a recent work by Passacantilli toward the synthesis of several industrially significant fragrances, the Diels-Alder reaction of myrcene with 3-bromobut-3-en-2-one was performed under thermal or $SnCl_4$-catalysis conditions, leading to the formation of the 1-(1-bromocyclohex-3-enyl)ethanone adduct and the cycloaddition-cyclization product with a bromo-containing octahydronaphthalene skeleton, respectively. Both of them could be dehydrobrominated with DBU to give the respective cyclic dienone products.[5]

Recently, a reliable general procedure for the preparation of α-haloacrylate derivatives via dimethyl sulfoxide-mediated dehydrohalogenation of the dihalopropanoate derivatives has appeared.[6] Among them ethyl α-bromoacrylate **1** is proved to be more stable under ambient conditions, and less prone to undergo polymerization, thus rendering it to be a more appropriate dienophile. Remarkably, the potential of this bromo-containing ester as a dienophile component remains rarely touched.[7] In this work, we wish to unravel the Diels-Alder reaction between **1** and a series of open-chain dienes **2**, and to investigate the base-mediated elimination to provide the cyclohexadienecarboxylates.

Results and discussion

Our initial studies were focused on the use of myrcene **2a** as the diene moiety and two conditions were attempted. In the presence of 5 mol% of aluminum chloride the reaction of **1** with **2a** proceeded smoothly at low temperature (0 ℃) and went to completion in just 6 h. The reaction led to the high-yielding formation of a mixture of regioisomeric adducts **3a** and **4a**, with the "*para*" isomer **3a** highly predominated (Table 1, Entry 1).[9] We then carried out the same reaction under thermal conditions without using any catalyst. A much longer reaction time was required for completing the reaction and, expectedly, a much poorer "*para*/*meta*" regioselectivity was afforded despite of the slightly improved yield (Table 1, Entry 2). Apparently, under the catalytic influence of a Lewis acid like $AlCl_3$, the Diels-Alder reaction occurred under quite mild conditions without harming the sensitive bromo-acrylate. This was further verified by using isoprene **2b** as the diene (Table 1, En-

* E-mail: qrwang@fudan.edu.cn; andreas.goeke@givaudan.com
Received September 9, 2009; revised October 24, 2009; accepted November 13, 2009.
Project supported by the Discovery-Project (No. 04174) from the Givaudan AG, Switzerland.

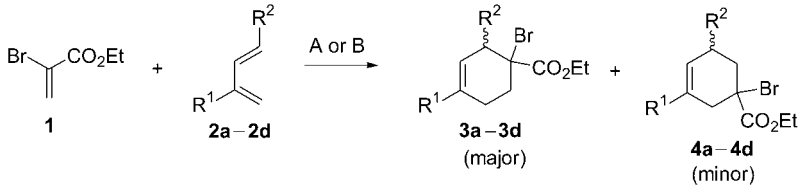
try 3). Furthermore, applying $AlCl_3$ as catalyst, the non-branched diene penta-1,3-diene **2c** reacted with **1** furnishing the "*ortho*" adduct **3c** with high yield, complete regioselectivity and high *endo*:*exo* diastereoselectivity (Table 1, Entry 4).

We then turned our attention to the reaction of homomyrcene with the bromo-containing dienophile **1**. It was found that both of the Lewis acid catalyzed and the thermal uncatalyzed conditions provided exclusively the tetrasubstituted "*para*" cyclohexadiene product **3d** as a mixture of stereoisomers. The ratio of the products seems to be in accordance with Alder's endo rule. Again, Lewis acid catalysis led to a more pronounced stereoselectivity (Table 1, Entry 5 vs. Entry 6).

An interesting cycloaddition/cyclization-domino sequence was observed for the reaction with myrcene **2a**. Under the Lewis acid-catalysis condition, the formation of the octahydronaphthalene product **5** was detected from the reaction mixture. Mechanistically, the outcome of the reaction can be accounted for by invoking the $AlCl_3$ catalyzed Diels-Alder reaction followed by an acid-mediated intramolecular cyclization of the 4-methylpent-3-enyl unit with the cyclohexene ring in **3a**. Compound **3a** could be completely transformed to **5** after refluxing in toluene with 1.1 equiv. of 62% sulfuric acid for 12 h. The direct formation of **5** is beneficial since the octahydronaphthalene skeleton becomes easily accessible.[10]

Next, endeavor was made to conduct the dehydrobromination of **5** to the bicyclic dienecarboxylate **6**, which is a potential precursor of the industrially important fragrance material *Georgywood*.[8] As we expected, the elimination reaction was efficiently performed by treatment of **5** with two equivalents of the hindered organic base DBU in CH_2Cl_2 at room temperature. Compound **6** was obtained as yellow oil in 80% yield.[11] Under the same conditions, elimination reaction of the 4-substituted 1-bromo-cyclohex-3-enecarboxylates **3a** and **3b** led to the 4-substituted cyclohexa-1,3-dienecarboxylates **7a** and **7b** in yields of 89% and 93%, respectively (Scheme 1).

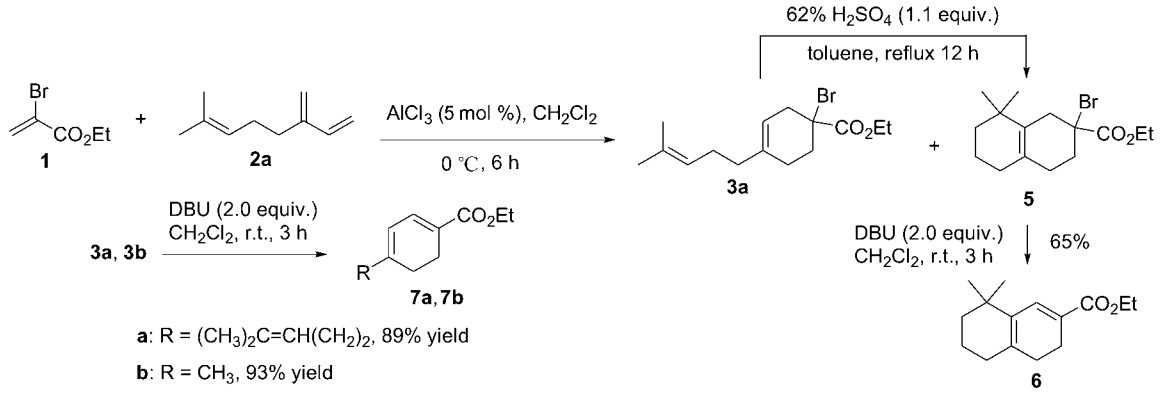
Table 1 The results of Diels-Alder reactions



Entry	**2**—**4**	R^1	R^2	Condition[a]	Yield[b]/%	**3** : **4**[c]	*Endo* : *Exo*[d]
1	**a**	$(CH_3)_2C{=}CH(CH_2)_2$	H	A	83	96 : 4	—
2	**a**	$(CH_3)_2C{=}CH(CH_2)_2$	H	B	87	69 : 31	—
3	**b**	CH_3	H	A	86	97 : 3	—
4	**c**	H	CH_3	A	83	100 : 0	93 : 7
5	**d**	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3	A	87	100 : 0	89 : 11
6	**d**	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3	B	56	100 : 0	76 : 24

[a] Condition: (A) $AlCl_3$ (5 mol%), CH_2Cl_2, 0 ℃, 6 h; (B) toluene, reflux, 24 h. [b] Isolated yields of all isomers which are inseparable. [c] Determined by GC. [d] Determined by ^1H NMR.

Scheme 1 Synthesis of ethyl cyclohexa-1,3-dienecarboxylates **6**, **7a**, **7b** via Diels-Alder reaction and elimination



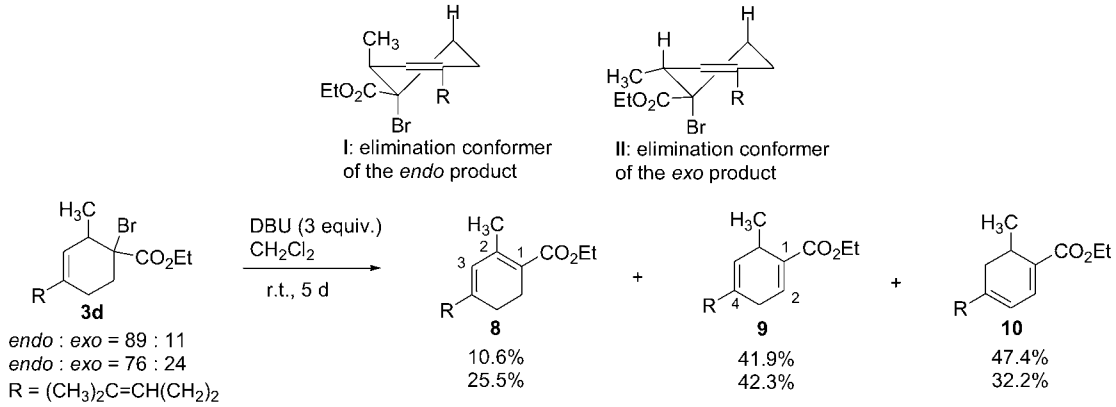
CHINESE JOURNAL OF CHEMISTRY

Finally, the outcome of the base-promoted dehydrohalogenation of the tetrasubstituted adducts **3d** proofed helpful to discriminate between the *endo*- and *exo*-Diels-Alder adducts. We expected *endo*-**3d** to be the major isomer of the mixture but the unambiguous assignment by NMR is difficult as an NOE between the bromo atom and the vicinal methyl group does not exist and other couplings in distorted cyclohexenes are not significant. However, since the DBU-promoted E2-elimination of a proton is supposed to proceed *anti* to the vicinal bromo substituent (conformer **I** in Scheme 2), dehydrohalogenation from the major isomer *endo*-**3d** is expected to result in the unconjugated compound **9**. On the other hand, the elimination of the allylic proton in conformer **II** of the minor adduct *exo*-**3d** can be assumed to generate conjugated cyclohexadienyl derivative **8**. Thus, after a long reaction time (4—5 d) a mixture of cyclohexadienecarboxylates **8**—**10** was obtained. The distribution corresponded well to the original diastereoisomeric *endo* : *exo* ratios of bromo compounds **3d** (Scheme 2). The formation of the thermodynamically more stable compound **10** via initially formed isomer **9** can be regarded as a secondary process.

Conclusion

In summary, we have demonstrated for the first time the dienophilicity of ethyl α-bromoacrylate with a set of linear dienes including myrcene and homomyrcene under thermal and Lewis acid ($AlCl_3$)-catalyzed Diels-Alder reactions. The bromo-containing cyclic adducts successfully undergo DBU-mediated dehydrobromination leading to 1,3- and/or 1,4-cyclohexadienecarboxylates, which are of synthetic significance.

Scheme 2 Dehydrobromination in **3d** (The ratio was determined by GC-MS. The structures of compounds **8**—**10** were assigned by NMR.)



References and notes

1 (a) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920.
(b) Fu, F.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2006**, *8*, 5999.
(c) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.

2 Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Tetrahedron* **1986**, *42*, 3097.

3 (a) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115.
(b) Rickerby, J.; Vallet, M.; Bernardinelli, G.; Viton, F.; Kuendig, E. P. *Chem. Eur. J.* **2007**, *13*, 3354.

4 Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

5 Bella, M.; Cianflone, M.; Montemurro, G.; Passacantilli, P.; Piancatelli, G. *Tetrahedron* **2004**, *60*, 4821.

6 Li, W.; Li, J.; Wan, Z.; Wu, J.; Massefski, W. *Org. Lett.* **2007**, *9*, 4607.

7 In one case, ethyl α-bromoacrylate was reacted with anthracene to give the adduct under $AlCl_3$-catalyzed condition, see Rachon, J.; Goedken, V.; Walborsky, H. M. *J. Org. Chem.* **1989**, *54*, 1006.

8 *Georgywood*® is a trademark of Givaudan SA. For a recent efficient synthesis of *β-Georgywood*, see Fráter, G.; Schröder, F. *J. Org. Chem.* **2007**, *72*, 1112 and references cited therein. See also: Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 1346.

9 Procedure for preparation of 1-bromo-4-(4-methylpent-3-enyl)cyclohex-3-enecarboxylic acid ethyl ester (**3a**): To a stirred suspension of $AlCl_3$ (67 mg, 0.5 mmol) in anhyd CH_2Cl_2 (100 mL) was added ethyl α-bromoacrylate **1** (1.79 g, 10 mmol) under cooling in an ice bath. The mixture was stirred for a couple of minutes, and then myrcene **2a** (1.63 g, 12 mmol) was slowly added dropwise. The mixture was stirred further for 6 h, and quenched with 10% HCl (20 mL). The phases were separated and the aqueous phase was extracted with additional CH_2Cl_2 (50 mL). The combined organic phases were sequentially washed with saturated aq. $NaHCO_3$ (50 mL×3), H_2O (50 mL) and saturated aq. NaCl (50 mL), dried over Na_2SO_4 and concentrated. The residue was subjected to vacuum distillation to afford 2.62 g of **3a** as colorless liquid (**3a**/**4a** ratio 96 : 4). Yield 83%, b.p. 131—134 ℃/15 Pa. IR (neat) ν: 2970, 2914, 1738, 1445, 1249, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.31 (t, J=7.2 Hz, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.95—2.35 (m, 8H, 4 CH_2), 2.74 (d, J=18 Hz, 1H, one H of

=CCH_2C(Br)), 2.93 (d, J=18 Hz, 1H, the other H of =CCH_2C(Br)), 4. 25 (q, J=7.2 Hz, 2H, OCH_2), 5.05—5.09 (m, 1H, CH=), 5.28—5.32 (m, 1H, CH=); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.86 (**C**H_3CH_2O), 17.68 (CH_3), 25.68 (CH_3), 26.20, 27.18, 33.93, 37.04, 37.60 (CH_2), 59.48 (CBr), 61.83 (CH_2O), 117. 33, 123.86 (CH=), 131.64, 137.01 (C=), 170.88 (C=O). HRMS (ESI) calcd for $C_{15}H_{23}BrO_2$: 314.0881, found 314.0877.

10 Procedure for conversion of **3a** to 2-bromo-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carboxylic acid ethyl ester (**5**): To a solution of **3a** (3.14 g, 10 mmol) in toluene (100 mL) was added dilute sulfuric acid (62%, 1.74 g, 11 mmol). The mixture was refluxed for 12 h. After cooling to r.t., the mixture was neutralized with aq. $NaHCO_3$. The phases were separated and the organic phase was washed with saturated aq. $NaHCO_3$ (50 mL), H_2O (50 mL) and saturated aq. NaCl (50 mL), dried over Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography (SiO_2, *n*-hexane/EtOAc, *V*/*V*, 100∶1). Compound **5** was obtained as pale yellow oil in 65% yield. IR (neat) v: 2959, 2931, 1737, 1463, 1206 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.97 (s, 6H, $(CH_3)_2C$), 1.29 (t, J=7.2 Hz, 3H, C**H**$_3CH_2O$), 1.44—2.37 (m, 10H, 5 CH_2), 2.64 (d, J=16.5 Hz, 1H, C(1)-H), 2.91 (d, J=16.5 Hz, 1.18, 1H, C(1)-H), 4.23 (q, J=7.2 Hz, 2H, CH_3C**H**$_2O$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.8 (**C**H_3CH_2), 19.0 (CH_2), 26.9, 27.3 ((**C**$H_3)_2C$), 29.9 (CH_2), 30.5 (CH_2), 33.7 ($(CH_3)_2$**C**), 34.3, 37.2, 39.2 (CH_2), 60.7 (CBr), 61.7 (OCH_2), 126.4 (C=), 132.4 (C=), 170.6 (C=O). HRMS (ESI) calcd for $C_{15}H_{23}BrO_2$ 314. 0881, found 314. 0869.

11 Detailed procedure for the preparation of 8,8-dimethyl-3,4,5,6,7,8-hexahydronaphthalene-2-carboxylic acid ethyl ester **(6)**: To a solution of **5** (3.14 g, 10 mmol) in anhydrous CH_2Cl_2 (100 mL) was added dropwise DBU (2.28 g, 15 mmol) under cooling in an ice bath. The solution was stirred at 0 ℃ for 6 h. The progress of the reaction was monitored by GC. The reaction mixture was diluted with H_2O (50 mL). The phases were separated and the aqueous phase was extracted with additional CH_2Cl_2 (30 mL×2). The combined organic phases were washed with aq. NH_4Cl (50 mL×3), aq. $NaHCO_3$ (50 mL), H_2O (50 mL) and saturated NaCl (50 mL), dried ($MgSO_4$) and concentrated. The residue obtained was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc, *V*/*V*, 100∶1) to give 1.99 g of compound **6** as pale yellow oil in 85% yield. IR (KBr) v: 2932, 1701, 1584, 1462, 1252, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.04 (s, 6H, $(CH_3)_2$), 1.31 (t, J=7.2 Hz, 3H, CH_3), 1.47—1.51 (m, 2H, CH_2), 1.61—1.65 (m, 2H, CH_2), 2.05—2.13 (m, 4H, $2CH_2$), 2.37 (t, J=9.6 Hz, 2H, CH_2), 4.21 (q, J=7.2 Hz, 2H, CH_2), 7.14 (s, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 137.3, 134.6, 134.4, 125.1, 60.1, 38.8, 32.4, 31.3, 29.3, 28.40 (2C), 21.4, 19.1, 14.4; HRMS (ESI) calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1615.

(E0908051 Cheng, F.; Lu, Z.)

