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Note

A Facile Synthesis of Bridged-tricyclic Skeletons via Intramolecular Diels-Alder Reaction of Cyclic 1,3-Dienes Containing an α,β-Unsaturated Ester

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Intramolecular Diels-Alder reaction (IMDA) precursors are easily available starting from addition of ester functionalized zinc-copper reagents to cyclohexadienyl- and cycloheptadienylirontricarbonyl cation salts. The resulting cyclic 1,3-dienes containing an α,β-unsaturated ester functionality underwent smoothly IMDA reaction to afford bridged tricyclic compounds. Bridged heterotricyclic skeletons were also available via IMDA reaction of cyclic 1,3-dienes bearing an imine or aldehyde functionality.

Keywords: Cyclic 1,3-diene; Intramolecular Diels-Alder reaction; Bridged-tricyclic compound.

INTRODUCTION

Intramolecular Diels-Alder (IMDA) reaction has been widely utilized as one of the most powerful tools to construct fairly complex carbocycles in organic synthesis.[1] The 4+2 reaction creates two new carbon-carbon bonds and generates bicyclic compounds from a substrate having two separate functional groups, diene and dienophile. Two types of IMDA reaction are of great interest. When the diene and dienophile are joined at the C-1 position of the diene, the reaction leads to fused bicyclic compounds (type 1 IMDA),[2] whereas the type 2 variant of IMDA provides an access to bridged bicyclic molecules in one step from the substrates with a dienophile at the C-2 position of the diene.[3] These two types of IMDA reactions can further be extended to the synthesis of tricyclic skeletons by employing a system wherein a dienophile is directly incorporated into a cyclic diene moiety. Surprisingly, reports on the IMDA reaction of conjugated cyclic dienes with a dienophile at the C-5 position of the rings are rare.[4,5] Herein we report that cyclohexa- and cyclohepta-1,3-diene-tethered α,β-unsaturated esters undergo IMDA reaction in refluxing *n*-butyl ether to give a variety of bridged tricyclic skeletons. Moreover, IMDA reaction of cyclic 1,3-dienes with an imine or aldehyde moiety furnished bridged heterotricyclic compounds.

RESULTS AND DISCUSSION

Cyclohexa- and cyclohepta-1,3-dienes containing an α,β-unsaturated ester can be synthesized using the method developed in these laboratories. As shown in Scheme I, IMDA reaction precursors, **2a**-**b**, were prepared starting from addition of ester functionalized zinc-copper reagents RCu(CN)ZnI to (η^5-cyclohexadienyl)tricarbonyliron cation salt in THF according to literature procedures.[6] Decomplexation of the resulting complexes with cerium ammonium nitrate (CAN) in acetone followed by reduction with diisobutylaluminum hydride (DIBAL) at -78 °C afforded cyclohexa-1,3-dienals **1a**-**b**. Treatment of the dienals with the Horner-Wadsworth-Emmons reagent[7] (Ph_3PCHCO_2Et) in CH_2Cl_2 at 30 °C for 4 h furnished **2a**-**b**, with an *E* stereochemistry at the double bond. Cycloheptadiene analogs **2c**-**d** were synthesized using a similar approach starting from cycloheptadienylirontricarbonyl cation salt and ester functionalized zinc-copper reagents (Scheme I).

Our IMDA reaction study began with **2a**. Substrate **2a** (0.33 g, 1.60 mmol) was added to a round-bottom flask containing 100 mL of anhydrous *n*-butyl ether under nitrogen. The dilute solution was stirred at 150 °C for 2 h and led to a 60% yield of tricyclo[4.3.1.0^{3,7}]dec-8-ene-2-carboxylic acid ethyl ester (**3**) as the only stereoisomer isolated after chro-

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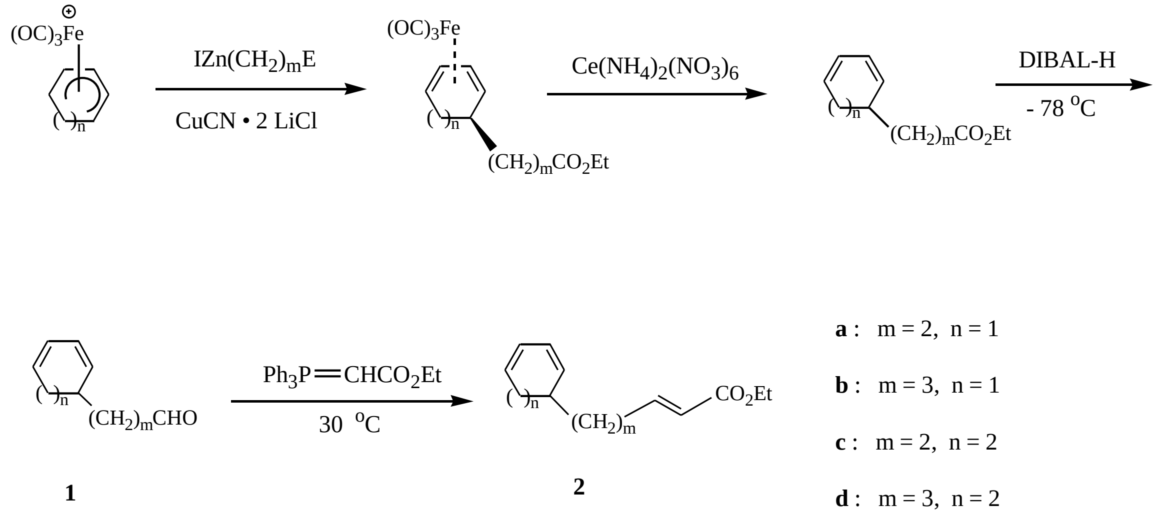
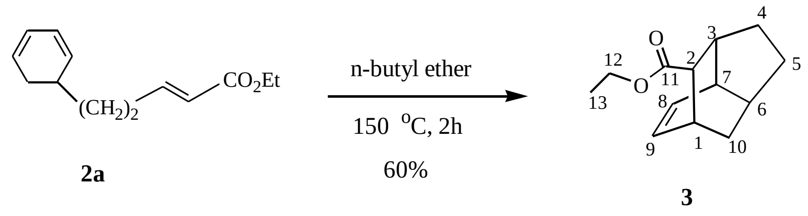
Scheme I

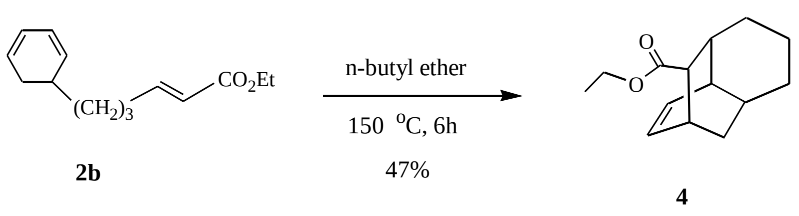


matographic purification (eq 1). Of particular note is the use of a readily available C-5 functionalized cyclohexa-1,3-diene derivative **2a** to control the relative stereochemistry of the five contiguous asymmetric centers. NMR studies provided the initial evidence for support of the structural assignments. The resonances of a multiplet at δ 6.20 for **3** were due to vinyl protons at C-8 and C-9. A quartet, centered at δ 4.08 was assigned to the methylene protons at C-12; a multiplet, centered at δ 2.86 was assigned to the methine proton at C-1 and a multiplet, centered at δ 2.45 was assigned to the methine proton at C-7. The C-13 NMR spectrum exhibited a signal at δ 174.7 assigned to C-11 (carbonyl); two signals at δ 132.5 and 131.4 assigned to two vinyl carbons (C-8 and C-9); and a signal at δ 60.2 assigned to C-12. The relative configuration of five contiguous stereogenic centers as depicted is fixed by syn-endo addition of the dienophile to the diene. This stereochemistry is generally governed by the steric and/or orbital requirements, as is often the case for the IMDA reaction.[8] The substrate with an additional methylene group at the tether, **2b**, also underwent IMDA reaction to afford tricyclo[5.3.1.$0^{3,8}$]-undec-9-ene-2-carboxylic acid ethyl ester (**4**) as the only stereomer in 47% isolated yield (eq 2). However, the IMDA reaction of seven-membered ring substrate, **2c**, was more sluggish and led to a 64% yield of tricyclo[4.3.2,$0^{3,7}$]undec-8-ene-2-carboxylic acid ethyl ester (**5**) after refluxing **2c** in *n*-butyl ether for 6 days (eq 3). Attempted IMDA reaction of **2d** failed to provide the desired product **6** (eq 4).

In order to further utilize the above method for synthesis of bridged heterotricyclic skeletons we set out to exam the IMDA reaction of the benzylimine derivative of cyclodienal



(1)



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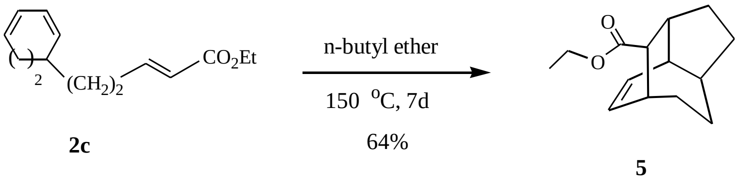
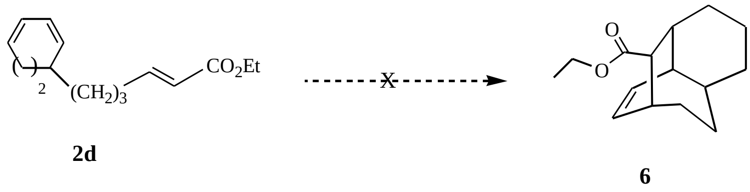
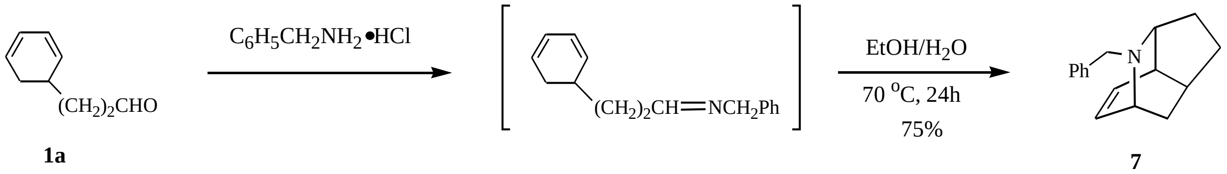


(3)



not formed

(4)



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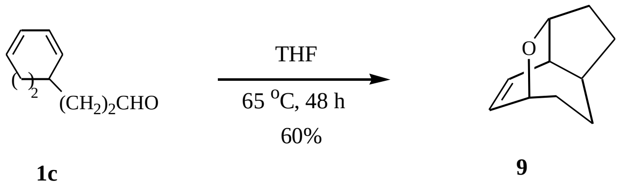
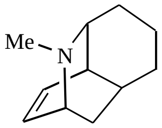


(6)

1a by slow addition of **1a** over 10 h to a 1.0 M solution of benzylamine hydrochloride (excess) in water/ethanol (1:1) at *ca*. 70 °C. The reaction was further stirred at 70 °C for 24 h to produce 2-benzyl-2-azatricyclo[4.3.1.$0^{3,7}$]dec-8-ene (**7**) in 75% yield. The formation of **7** was derived from IMDA reaction of the initially formed benzylimine with the cyclic 1,3-diene (eq 5). The spectral data for **7** are similar to those of **8** found in the literature.[5] Moreover, IMDA reaction of the seven-membered ring substrate, **1c**, also provided 2-oxatricyclo[4.3.2.$0^{3,7}$]undec-8-ene (**9**) in 60% yield after refluxing **1c** in THF at 65 °C for 48 h (eq 6).

IMDA reaction of cyclohexa- and cyclohepta-1,3-dienes with an α,β-unsaturated ester moiety proceeded in a stereo-controlled manner to give bridged tricyclic skeletons. This chemistry can be extended to bridged tricyclic amine and ether derivatives by IMDA reaction of cyclic 1,3-dienes with an imine and aldehyde functionality, respectively.



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EXPERIMENTAL

All reactions were run under an argon atmosphere in oven-dried glassware unless otherwise indicated. Complexes **2a-d** were synthesized following the literature procedures.[6] Anhydrous solvents or reaction mixtures were transferred via an oven-dried syringe or cannula. Tetrahydrofuran (THF) was predried by molecular sieves and then by passing through an Al_2O_3 column.[9] *n*-Butyl ether was distilled from CaH_2 prior to use. Flash column chromatography, following the method of Still, was carried out with E. Merck silica gel (Kieselgel 60, 230-400 mesh) using the indicated solvents.[10] ^1H nuclear magnetic resonance (NMR) spectra were obtained with Bruker-AC 400 (400 MHz) and Varian G-200 (200 MHz) spectrometers. The chemical shifts are reported in parts per million with either tetramethylsilane (0.00 ppm) or $CDCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR spectra were recorded with Bruker-AC 400 (100.4 MHz) spectrometer with $CDCl_3$ (77.0 ppm) as the internal standard. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer. Mass spectra were acquired on a JEOL JMS-D 100 spectrometer at an ionization potential of 70 eV and are reported as mass/charge *(m/e)* with percent relative abundance. High-resolution mass spectra were obtained with an AEI MS-9 double-focusing mass spectrometer and a JEOL JMS-HX 110 spectrometer at the Department of Chemistry, Central Instrument Center, Taichung, Taiwan.

General Procedure I: IMDA Reaction of Cyclic 1,3-Dienes Containing an α,β-Unsaturated Ester Moiety

A solution of **2a** (0.33 mg, 1.60 mmol) in 100 mL of dry *n*-butyl ether was refluxed under nitrogen. The reaction was terminated until substrate **2a** was no longer detected on ^1H NMR.

Tricyclo[4.3.1.0^{3,7}]dec-8-ene-2-carboxylic acid ethyl ester (3)

The crude mixture from IMDA reaction of **2a** (0.33 mg, 1.60 mmol) was purified via flash column chromatography (silica gel, hexanes/ethyl acetate = 40/1) to give **3** (0.20 g, 0.96 mmol, 60%). ^1H-NMR ($CDCl_3$, 400 MHz): δ 6.20 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.86 (m, 1H), 2.45 (m, 1H), 2.36 (m, 1H), 2.17 (dd, *J* = 5.3, 2.7 Hz, 1H), 1.88 (m, 2H), 1.46 (m, 3H), 1.24 (t, 7.2 Hz, 3H), 0.98 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 174.73, 132.54, 131.43, 60.20, 54.19, 41.93, 39.27, 37.46, 34.17, 32.05, 31.85, 31.36, 14.29; IR (CH_2Cl_2): 3055, 2985, 2685, 2305, 1733, 1423, 1674, 1258 cm^{-1}; MS (20 ev) *m/e*: 206 (M^+), 160, 133, 104, 91, 79, 77; HRMS (EI) *m/e* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1304.

Tricyclo[5.3.1.0^{3,8}]undec-9-ene-2-carboxylic acid ethyl ester (4)

The crude mixture from IMDA reaction of **2b** (0.37 mg, 1.68 mmol) was purified via flash column chromatography (silica gel, hexanes/ethyl acetate = 40/1) to give **4** (0.17 g, 0.79 mmol, 47%). ^1H-NMR ($CDCl_3$, 400 MHz): δ 6.37 (t, *J* = 7.1 Hz, 1H), 6.18 (t, *J* = 6.9 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.89 (d, *J* = 3.1 Hz, 1H), 2.32 (dd, *J* = 4.6, 2.5 Hz, 1H), 2.12 (dt, *J* = 6.4, 2.7 Hz, 1H), 2.05 (m, 1H), 1.68 (m, 2H), 1.56 (m, 2H), 1.43 (m, 5H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.50, 136.59, 131.99, 60.13, 47.68, 38.49, 34.60, 32.33, 30.32, 29.53, 29.04, 14.86, 14.24; IR (CH_2Cl_2): 3049, 2986, 2929, 2685, 2410, 2305, 1422, 1264 cm^{-1}; MS (20 ev) *m/e*: 220 (M^+), 174, 130, 91, 79, 77; HRMS (EI) *m/e* calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1459.

Tricyclo[4.3.2.0^{3,7}]undec-8-ene-2-carboxylic acid ethyl ester (5)

The crude mixture from IMDA reaction of **2c** (0.23 mg, 1.05 mmol) was purified via flash column chromatography (silica gel, hexanes/ethyl acetate = 40/1) to give **5** (0.14 g, 0.79 mmol, 64%). ^1H-NMR ($CDCl_3$, 400 MHz): δ 6.03 (dd, *J* = 11, 8.5 Hz, 1H), 5.89 (t, *J* = 9.0 Hz, 1H), 4.03 (q, *J* = 5.9 Hz, 2H), 2.77 (t, *J* = 9.3 Hz, 1H), 2.46 (m, 2H), 2.16 (m, 1H), 2.08 (m, 1H), 1.80 (m, 2H), 1.53 (m, 3H), 1.40 (m, 3H), 1.15 (t, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.20, 130.67, 128.40, 60.25, 55.50, 43.75, 42.23, 36.26, 35.53, 33.73, 27.60, 27.29, 25.41, 14.25; IR (CH_2Cl_2): 3055, 2975, 2928, 2358, 1717, 1605, 1558, 1317 cm^{-1}; MS (20 ev) *m/e*: 220 (M^+), 201.2, 191.2, 174.2, 149, 117.1, 114.1, 105.1, 91.1, 79.1, 77.1; HRMS (EI) *m/e* calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1459.

2-Benzyl-2-azatricyclo[4.3.1.0^{3,7}]dec-8-ene (7)

Benzylaminehydrochloride (0.95 g, 7.25 mmol) was added to a 25-mL round-bottom flask containing 3.3 mL of 50% $EtOH/H_2O$. Dienal **1a** (0.2 g, 1.50 mmol) in 3.3 mL of 50% $EtOH/H_2O$ was added slowly to the reaction mixture. The reaction was stirred for 40 h at 70 °C. The reaction was quenched with saturated $NaHCO_3$ solution and was extracted with ethyl acetate (*ca.* 30 mL). The resultant solution was washed with water, brine and dried with anhydrous $MgSO_4$. The solution was filtered and concentrated on a rotary evaporator to give the crude mixture. The crude mixture was purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 40/1) to give **7** (0.25 g, 1.11 mmol, 75%). ^1H-NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.37 (m, 2H), 3.68 (d, *J* = 13.6 Hz, 1H), 3.36 (d, *J* = 13.4 Hz, 1H), 3.30 (m, 1H), 2.47 (m, 1H), 2.41 (m, 1H), 1.74 (m, 4H), 1.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.54, 133.95, 129.76, 128.90, 128.03, 126.55, 63.17, 60.83, 50.62, 42.13, 38.59, 32.97, 32.68, 31.44; IR (CH_2Cl_2): 3055, 2985, 2685, 2305, 1733, 1423, 1674, 1258 cm^{-1}; MS (20 ev) *m/e*: 226 (M+1), 201.2, 174.2, 149.0, 117.1, 114.1, 105.1, 91.1, 79.1, 77.1; HRMS (EI) *m/e* calcd for $C_{16}H_{19}N$ 225.1517, found 225.1523.

2-Oxatricyclo[4.3.2.0^{3,7}]undec-8-ene (9)

The crude mixture from IMDA reaction of **1c** (0.20 mg, 1.33 mmol) was purified via flash column chromatography (silica gel, hexanes/ethyl acetate = 40/1) to give **9** (0.12 g, 0.80 mmol, 60%). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.21 (m, 2H), 4.38 (t, J = 5.1 Hz, 1H), 3.93 (t, J = 4.3 Hz, 1H), 2.54 (q, J = 5.0 Hz, 1H), 2.36 (q, J = 5.3 Hz, 1H), 1.89 (m, 2H), 1.68 (m, 2H), 1.56 (m, 2H), 1.40 (m, 1H), 1.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 130.21, 129.06, 77.93, 71.87, 43.86, 37.12, 34.72, 27.54, 26.76, 25.58; IR (CH_2Cl_2): 3056, 2925, 2361, 1734, 1653, 1559, 1419, 1387 cm^{-1}; MS (20 ev) *m/e*: 149 (M-1), 121.1, 113.2, 97.1, 83.1, 71.1, 57.1. Compound **9** was unstable and decomposed after it was stored at 0 °C for 2 days.

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REFERENCES

1. (a) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2002**, *67*, 7361. (b) Liao, C. C.; Peddiniti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (c) Shea, K. J.; Lease, J. G.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 8627.
2. Takusu, K.; Mizutani, S.; Ihara, M. *J. Org. Chem*. **2002**, *67*, 2881.
3. Shea, K. J.; Wise, S. *J. Am. Chem. Soc.* **1978**, *100*, 6519.
4. Ng, S. M.; Beaudry, C. M.; Trauner, D. *Org. Lett.* **2003**, *5*, 1701.
5. Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553.
6. (a) Yeh, M. C. P.; Sheu, B. A.; Fu, H. W.; Tau, S. I.; Chuang, L. W. *J. Am. Chem. Soc.* **1993**, *115*, 5941. (b) Yeh, M. C. P.; Sun, M. L.; Lin, S. K. *Tetrahedron Lett*. **1991**, *32*, 113. (c) Yeh, M. C. P.; Liang, J. H.; Jiang, Y. L.; Tsai, M. S. *Tetrahedron* **2003**, *59*, 3409. (d) Yeh, M. C. P.; Chuang, S. C.; Lai, M. L.; Chou, C. C. *Organometallics* **1997**, *16*, 4435. (e) Blankenfeldt, W.; Liao, J. W.; Lo, L. C.; Yeh, M. C. P. *Tetrahedron Lett.* **1996**, *37*, 7361.
7. Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223.
8. Taber, D. F. *Intramolecular Diels-Alder and AlderEne Reactions*; Springer-Verlag: Berlin, 1984. Roush, W. R. *Adv. Cycloaddit.* **1990**, *2*, 91.
9. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
10. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.