Preparation of Tricyclic and Tetracyclic Benzoxepin Derivatives by One-Pot Enyne Metathesis/Diels-Alder Reaction

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Received 14 June 2001

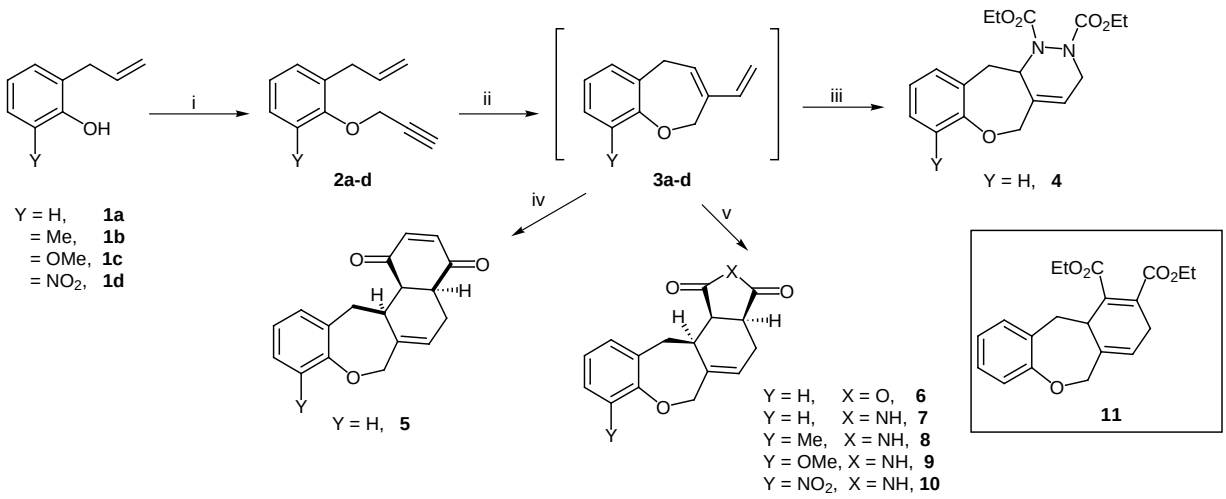
Abstract: Tricyclic and tetracyclic benzoxepin derivatives were prepared by one-pot enyne metathesis/Diels–Alder reactions starting from differently substituted 2-allyl-1-propargyloxybenzenes (*endo* stereoselectivity).

Key words: ruthenium, catalysis, enyne metathesis, Diels-Alder reactions, tandem reactions

The ring-closing metathesis[1] (RCM) reaction of olefins promoted by metal carbenes has become in the last years an efficient and selective method for C=C bond cleavage and formation leading to carbo and heterocyclic compounds of different size, from five-membered rings to macrocyclic structures. Ring closing enyne metathesis has also been explored in recent years,[2–4] providing 1-vinylcycloalkene derivatives[5,6] from acyclic enynes in an atom economical process. These diene derivatives can be useful substrates for subsequent Diels–Alder reaction. Several yne-ene cross-metathesis/cycloaddition sequences have been recently reported in the literature in a stepwise manner.[7] Sequential ring-closing metathesis/[4+2] cycloaddition have also been used in the last years for the preparation of several carbocyclic and heterocyclic systems.[8] Spontaneous dimerization by Diels–Alder reaction of 2-vinylbutenolide prepared by enyne metathesis gives the perhydroisobenzofuranone *rac*-differolide.[9] One-pot ring-closing enyne metathesis/Diels–Alder reaction without isolation of diene intermediate has been reported in the preparation[10] of tetrahydropyran and dihydrofuran derivatives, for the construction of heterocyclic boronic ester derivatives,[11] and in the synthesis[12] of perhydroindenes and perhydroisoindoles. In the last case the cycloaddition was carried out under Lewis acidic conditions. Prompted by these very recent reports we want to present here our work concerning the preparation of tricyclic and tetracyclic benzoxepin derivatives by one-pot enyne metathesis and Diels–Alder reaction from 2-allyl-1-propargyloxybenzenes.

There are no general syntheses of benzoxepin derivatives. Snieckus *et al* had reported[13] the preparation of benzannulated oxygen heterocycles of different ring size by connecting directed *ortho* metalation and olefin metathesis strategies. In this way they obtained the natural products radulanin A and racemic helianane containing 2,5-dihydrobenzoxepin and benzoxepane moieties.

Our work is summarized in the Scheme. Treatment of phenolic derivatives **1a–d** with propargyl bromide and potassium carbonate in refluxing acetone gave 2-allyl-1-propargyloxybenzenes **2a–d** (72–98%). Compound **1d**



Scheme i: Propargyl bromide, K_2CO_3, acetone, reflux; ii: $RuCl_2(PCy_3)_2$=CHPh (2–6% molar), CH_2Cl_2, r.t., 5 h; iii: EtO_2C-N=N-CO_2Et, CH_2Cl_2, reflux, 4 days; iv: benzoquinone, CH_2Cl_2, reflux, 4 days; v: maleimide or maleic anhydride, CH_2Cl_2, reflux, 4 days.

Synlett 2001, No. 11, 26 10 2001. Article Identifier:
1437-2096,E;2001,0,11,1784,1786,ftx,en;D14701ST.pdf.

ISSN 0936-5214

was prepared[14] from *o*-nitrophenol by standard allylation and subsequent Claisen rearrangement.

Enyne metathesis on **2a**–**d** with Grubbs' catalyst[15] (2-6% molar) in dichloromethane (0.024-0.048 M) at room temperature for 5 h afforded 3-vinyl-2,5-dihydrobenzo[*b*]oxepins **3a**–**d**. Only diene **3a** was isolated once.[16] In all cases the corresponding dienophile was added to the dichloromethane solution containing the enyne and the mixture was refluxed for 4 days to give cycloadducts **4**–**10**. Overall yields and representative analytical data of the compounds are collected in the Table.

Table Results from One-Pot Enyne Metathesis and Diels–Alder Reactions.

Comp.	Overall Yield (%)	Mp (°C) (solvent)	EA or HRMS (Calcd.) (Found)
4	82	oil	346.1528 346.1543
5	50	129–130 (cyclohexane)	280.1099 280.1106
6	53	184–186 (isopropanol)	270.0892 270.0892
7	51	177–179 (CH_2Cl_2 /Et_2O)	71.36%C, 5.61%H, 5.20%N 71.10%C, 5.59%H, 5.19%N
8	50	87–90 (Et_2O)	283.1208 283.1214
9	61	224–225 (CH_2Cl_2 /Et_2O)	299.1157 299.1158
10	62	209–211 (CH_2Cl_2)	314.0903 314.0909
11	8	oil	314.1154 314.1158

Cycloaddition of **3a** with 1,2-diphenyldiazene failed in refluxing dichloromethane and in toluene at 100 °C. Diethyl acetylenedicarboxylate reacted also sluggishly and the corresponding cycloadduct **11** could be isolated in only 8% overall yield (chromatography on SiO_2, hexane–diethyl ether 9:1) after treatment of **2a** with Grubbs' catalyst in toluene at room temperature for 5 h and then five days with the dienophile in refluxing toluene. Compounds **4** and **7**[17] were isolated by flash chromatography of the crude mixture on silica gel. In the case of compound **7** only one diastereoisomer was eluted, corresponding to the *endo* stereochemistry, the *exo* diastereoisomer being not detected. In the other cases the cycloadducts crystallized from the dark oily crude mixtures by addition of diethyl ether. Once again, only the *endo* diastereoisomer was isolated.[18]

In summary, tricyclic and tetracyclic compounds **4**–**10** have been stereoselectively obtained by one-pot ring-closing enyne metathesis and Diels–Alder cycloaddition from **2a**–**d** in good overall yields, without removal of the ruthenium catalyst or isolation of the intermediate dienes **3a**–**d**. No Lewis acidic conditions are required for the [4+2] cycloaddition and most of the cycloadducts can be isolated and purified without chromatography of the crude mixtures.

Acknowledgement

Financial support from DGESIC (project PB98-0902 and predoctoral scholarship to A.S.) and CIRIT-Generalitat de Catalunya (projects SGR98-0056 and SGR2000-0062) is gratefully acknowledged.

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(14) *o*-Nitrophenol (2.1 g, 15.1 mmol) was added to a suspension of K_2CO_3 (3.14 g, 23.1 mmol) in acetone (40 mL) and the mixture was refluxed for 30 min. Then, allyl bromide (1.7 mL, 2.4 g, 19.6 mmol) was added and the mixture was maintained under reflux for 16 h. After addition of H_2O (30 mL), the solution was extracted with CH_2Cl_2. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated to give 1-allyloxy-2-nitrobenzene (2.36 g, 87% yield) as an oil. This compound (1.00 g, 5.6 mmol) was heated at 170 °C for 45 h (GC monitoring). A 5 M aqueous solution of NaOH was added to the crude mixture and the resulting solution extracted with hexane. The aqueous phase was acidified with 6 M HCl and extracted with CH_2Cl_2. The organic layer was washed with water, it was dried with anhydrous Na_2SO_4 and the solvent was evaporated to give **1d** (664 mg, 66% yield) as an oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 8.02 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.50 (dd, *J* = 7.3, 1.6 Hz, 1 H), 6.94 (dd, *J* = 8.5, 7.3 Hz, 1 H), 6.09–5.93 (m, 1 H), 5.18–5.09 (m, 2 H), 3.50 (d, *J* = 6.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ = 153.0, 137.2, 134.8, 133.4, 131.1, 122.8, 119.2, 116.5, 33.3; IR (film) 3215, 1610, 1540, 1451, 1334, 1249 cm^{-1}; MS (EI) *m/z* (%) = 179 (M^+, 53), 162 (100), 132 (88), 131 (68), 104 (22), 103 (58), 77 (64).

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(16) After evaporation of CH_2Cl_2 and flash chromatography on SiO_2 (cyclohexane–CH_2Cl_2, 5:1) diene **3a** was obtained in 41% yield as an oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 7.28–7.02 (m, 4 H), 6.24 (dd, *J* = 17.7, 11.2 Hz, 1 H), 5.97 (td, *J* = 5.6, 0.6 Hz, 1 H), 4.93 (d, *J* = 11.3 Hz, 1 H), 4.91 (d, *J* = 17.7 Hz, 1 H), 4.81 (d, *J* = 1.8 Hz, 2 H), 3.59 (d, *J* = 5.6 Hz, 1 H); MS (EI) *m/z* (%) = 173 (13), 172 (M^+, 100), 171 (32), 157 (48), 145 (28), 144 (28).

(17) Preparation of 2,3,3a,4,6,12,12a,12b-octahydro-1*H*-benzo[6,7]-oxepino[4,3-*e*]isoindole-1,3-dione, **7**: A solution of **2a** (0.510 g, 2.9 mmol) and Grubbs' catalyst (85 mg, 0.11 mmol) in degassed CH_2Cl_2 (60 mL) was stirred under nitrogen at r.t. for 5 h. Then, a solution of maleimide (0.320 g, 3.3 mmol) in CH_2Cl_2 (10 mL) was added and the mixture refluxed for 4 days. The solvent was evaporated and the crude oily residue was flash chromatographed on SiO_2. Elution with hexane–EtOAc 9:1 afforded **7** as a white solid (0.410 g, 51%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (br s, 1 H), 7.09 (br t, *J* = 8.2 Hz, 2 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 6.81 (br t, *J* = 7.3 Hz, 1 H), 6.77 (d, *J* = 7.9 Hz, 1 H), 6.06–6.04 (m, 1 H), 5.09 (d, *J* = 13.2 Hz, 1 H), 4.31 (d, *J* = 12.6 Hz, 1 H), 4.16 (apparent t, *J ca* 13.7 Hz, 1 H), 3.29–3.20 (m, 2 H), 2.91 (br d, *J ca* 13 Hz, 1 H), 2.81 (dd, *J* = 15.8, 2.9 Hz, 1 H), 2.76 (dd, *J* = 15.5, 7.1 Hz, 1 H), 2.23 (br d, *J ca* 15.5 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 180.1, 178.4, 156.8, 140.7, 132.7, 128.5, 126.7, 125.4, 121.4, 119.4, 70.3, 46.0, 41.9, 38.9, 34.5, 24.6; IR (KBr) 3244, 1781, 1720, 1694 cm^{-1}; MS (EI) *m/z* (%) = 270 (8), 269 (M^+, 45), 172 (23), 171 (68), 107 (100), 91 (50), 77 (21).

(18) The structural assignments were based on the data obtained from ^{1}H and ^{13}C NMR on compound **7**: COSY, DEPT and HMBC experiments were used to assign the proton and carbon signals of the spectra. NOE experiments showed a relative *cis* configuration between all three methinic protons (H_{12a}, H_{12b}, and H_{3a}). Coupling constants are in agreement with this assignment. The methinic proton H_{12a} (2.91 ppm, br d, *J ca* 13.7 Hz) shows a large *J* value with one of the protons at C-12 (at 4.16 ppm), and two other small *J* values due to the coupling with the other proton at C-12 (at 2.81 ppm) and with the H_{12b} (in a relative *cis* position).