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Intramolecular Diels-Alder Reaction of 1-Aminoisobenzofurans: Application to the Synthesis of Benzo[c]phenanthridines

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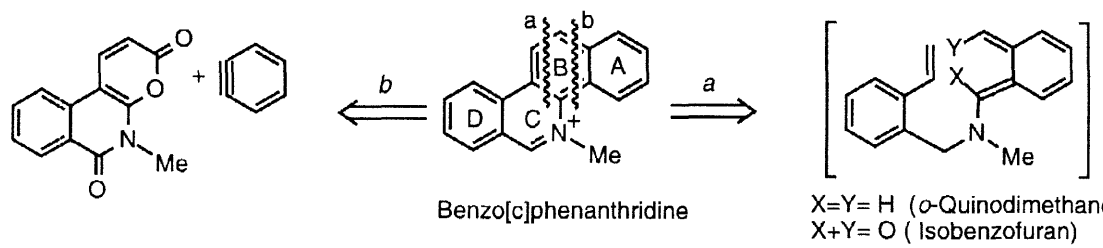
Abstract

Intramolecular Diels-Alder reactions of 1-aminoisobenzofurans give benzo[c]phenanthridines. The reactive intermediates are generated from o-(diazomethyl)benzamides.

Keywords: Alkaloids; Cycloadditions; Diels-Alder reactions; Isobenzofurans.

The interest of benzo[c]phenanthridinium salts as antitumour agents led us some years ago to explore their synthesis via intermolecular Diels-Alder additions to arynes [1,2]. In one of the approaches studied [2], ring B was constructed by cycloaddition of an α-pyrone to a benzyne (Scheme 1, route *b*). We have now considered the related route *a*, in which ring A is supplied by the diene instead of the dienophile. This approach involves an intramolecular Diels-Alder (IMDA) reaction in which the diene bears an amino group and involves simultaneous formation of rings B and C. In the first attempt to implement route *a*, Oppolzer *et al* used an *o*-quinodimethane as the cycloaddition diene [3]. In this work we used a 1-aminoisobenzofuran, isobenzofurans (IBFs) being more reactive and more easily generated [4].



Scheme 1

Most IBFs are transient species; only those with exocyclic conjugation are stable enough to be isolated and characterized. They are highly reactive as Diels-Alder dienes and are commonly generated in the presence of a dienophilic trap. IBFs bearing alkyl or aryl groups at positions 1 and 3 have been widely used for both inter- and intramolecular Diels-Alder reactions, but there are few references to IBFs with heteroatoms at these positions [5]. AM1

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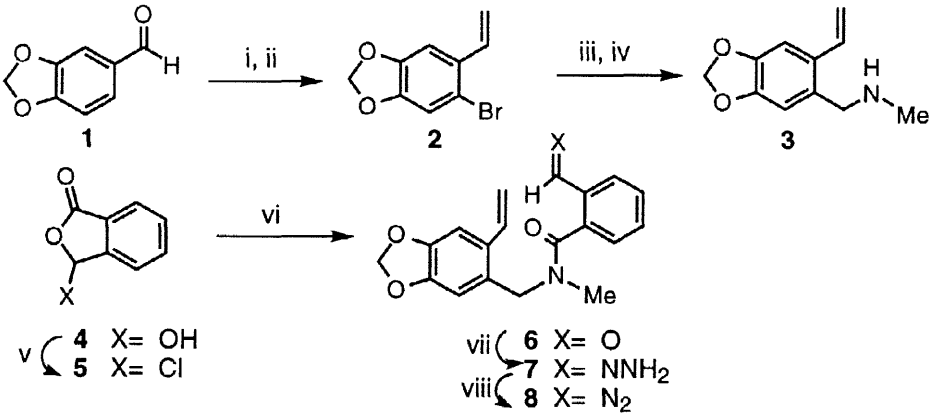
calculations confirm one's expectation that donor atoms at positions1 and/or 3 decrease the HOMO-LUMO energy gap, which must increase reactivity. Cycloaddition of 1-amino IBFs affords products with oxygen-bridges that open spontaneously to yield the corresponding hydroxy-derivatives [5d-h]. The IMDA cycloadditions of 1-amino IBFs have recently led to tricyclic systems [5f-h]; here we report our results on their application to the synthesis of benzophenanthridines.

Of the three reported methods for generation of 1-amino IBFs, we chose metal-induced decomposition of an *o*-(diazomethyl)benzamide [5e].[1] Diazomethyl-benzamide **8** was prepared in good overall yield as follows (Scheme 2).[2] Bromination of piperonal (**1**) followed by olefination with methyltriphenylphosphonium iodide in a biphasic system (20% aqueous NaOH /toluene) gave styrene **2** as a colourless oil after 40 h of vigorous stirring. Treatment with *n*-BuLi in THF at -78 °C and trapping of the resulting organolithium with DMF gave the corresponding benzaldehyde, which was converted into amine **3** in 65% yield by treatment with 40% aqueous methylamine in CH_2Cl_2 in the presence of 4Å molecular sieves followed by reduction with sodium borohydride. *N*-acylation of this amine with 3-chlorophthalide [6] (obtained quantitatively by heating commercially available 2-carboxybenzaldehyde in refluxing $SOCl_2$) afforded *o*-formylbenzamide **6** in 89% yield. Condensation of benzamide **6** with hydrazine gave a quantitative yield of hydrazone **7**, which was oxidised to *o*-(diazomethyl)benzamide **8** by treatment with mercuric oxide (HgO) [7] in benzene for 20 h in the presence of a dehydrating agent (Na_2SO_4) and a base (catalytic KOH/EtOH).[3]



i) Br_2, AcOH, rt, 48 h (60%). ii) Ph_3PMeI, NaOH (20 %), $PhCH_3$, rt, 40 h (88%). iii) a- *n*-BuLi, THF, -78 °C, 30 min. b- DMF (85%). iv) a- NH_2Me, CH_2Cl_2, mol. sieves (4Å), rt, 4 h. b- $NaBH_4$, CH_2Cl_2:MeOH (1:1), rt, 30 min (76%). v) $SOCl_2$, reflux, 30 min, vi) Compound **3**, Et_3N, THF, rt, 2 h, (89%). vii) NH_2-NH_2·H_2O, CH_2Cl_2, rt, 16 h. viii) HgO, C_6H_6, KOH/EtOH, Na_2SO_4, rt, 4 h.

Scheme 2

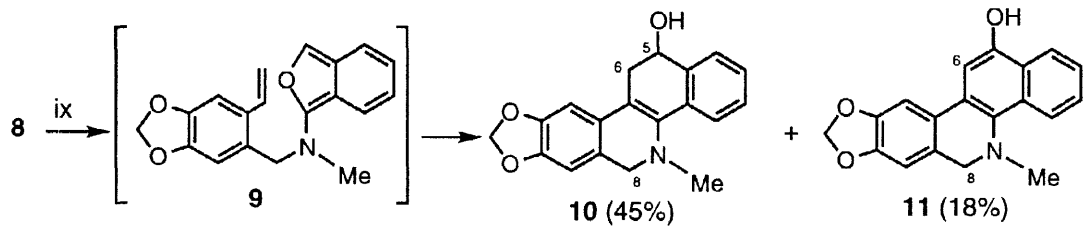
1 Initially, we attempted the other route described by Beak and Chen [5e], decomposition of the corresponding *o*-(bromomethyl)benzamide. However, the instability of the ionic intermediate gave rise to complex mixtures of compounds in which no cycloadducts were detected

2 All new compounds had satisfactory ^1H and ^{13}C NMR, IR and mass spectra and accurate mass and/or elemental analyses.

3 Diazocompounds **8** and **15** showed intense IR absorption at 2030 and 2095 cm^{-1} respectively.

The crude reaction mixture containing **8** was filtered and concentrated to dryness and the residue was dissolved in THF and refluxed under argon in the presence of $Rh_2(OAc)_4$ [8] to generate the isobenzofuran intermediate **9** (Scheme 3), which under these conditions was rapidly transformed into a mixture of benzo[c]phenanthridines **10** and **11** in 45 and 18% yield respectively from hydrazone **7**.[4] Benzophenanthridine **10** is the expected product of the IMDA of IBF **9**; while compound **11** is the result of subsequent oxidation. Compound **10** was stable during work-up and isolation, but on standing at room temperature was converted to a complex mixture of products that according to thin layer chromatography, did not include compound **11**.

Unfortunately, the oxidation of hydrazone **7** was found not to be easily reproducible (especially when the scale was raised to >100 mg of starting hydrazone). Our attempts to remedy this included changing the oxidant (NiO_2, $Pb(OAc)_4$, MnO_2, Ag_2O), the solvent



ix) $Rh_2(OAc)_4$, THF, reflux, 30 min.

Scheme 3

(CH_2Cl_2, $CHCl_3$, DME, Et_2O, THF) and the base or dehydrating agent (K_2CO_3, molecular sieves), raising the temperature to reflux and sonicatin to increase the reactivity of the solid materials; all these efforts failed. Eventually we decided to prepare a stabilized diazo-derivative, by transferring the diazo group from tosylazide (Scheme 4) [9]. Selective ethanolysis of anhydride **12** in refluxing ethanol followed by *in situ* activation of acid **13** with DCC and condensation with amine **3** gave ester **14**, which after deprotonation with LDA in THF at -78 °C was converted to α-diazoester **15** in 48% isolated yield by treatment with TsN_3. Treatment with $Rh_2(OAc)_4$ in refluxing THF, as previously described, then afforded benzophenanthridine **18** in 52% yield *via* isobenzofuran **16** and the cycloadduct **17**.[5] Compound **15** and benzophenanthridine **18** were more stable than **8** and **10** respectively, and results were easily reproducible up to 400 mg scale of **14**.

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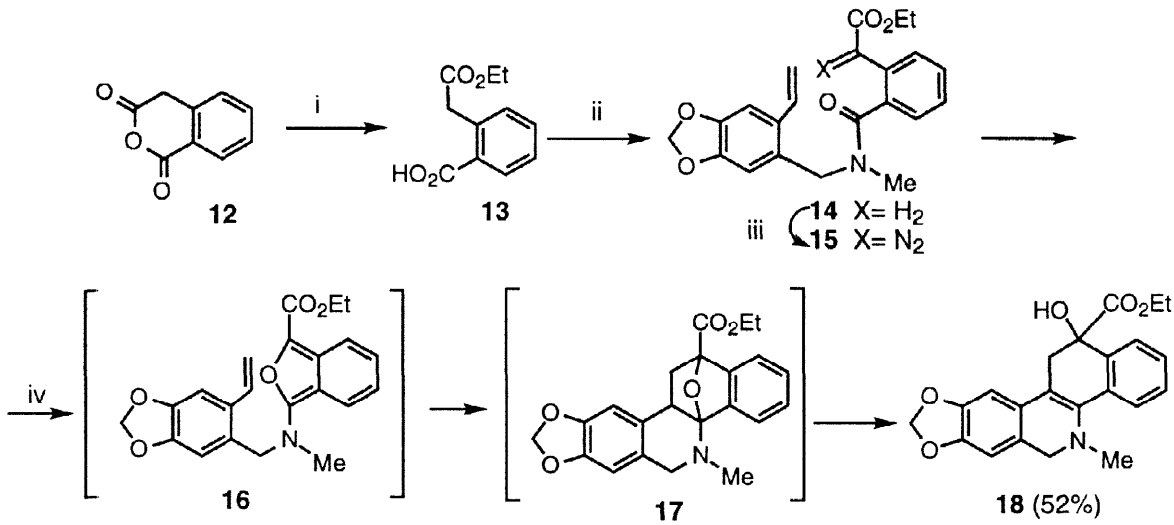
4 The ^1H NMR spectrum of **10** shows an AB system at 2.87 and 3.01 ppm (J=16.4 Hz) corresponding to the hydrogens attached to C6. These protons are coupled (J=5.0 Hz) to the hydrogen at C5, which appears as a multiplet centred at 4.86 ppm. The protons at C8 also appear as an AB system, at 4.09 and 4.01 ppm (J=16.2 Hz). In the ^1H NMR spectrum of **11**, the hydrogen at C6 appears as a singlet in the aromatic region and the protons at C8 as a singlet at 4.12 ppm.

5 A solution of benzamide **14** (348 mg, 0.91 mmol) in 5.0 mL of THF was added dropwise under argon to a solution of freshly prepared LDA (1.37 mmol) in 1.0 mL of THF at -78 °C. After 15 min stirring at low temperature, the dark orange solution was treated with 380 mg (1.92 mmol) of tosyl azide (TsN_3) in 1.0 mL of THF. The resulting colourless solution was warmed to room temperature, poured into EtOAc, washed twice with H_2O and once with brine, dried (Na_2SO_4) and concentrated to dryness, and the residue was chromatographed on silicagel (2:1, EtOAc:hexanes) to obtain 178 mg (0.44 mmol, 48%) of diazocompound **15** as a yellow oil. This compound was dissolved in 25 mL of dry deoxygenated THF and was refluxed for 30 min under argon in the presence of 6 mg (0.0014 mmol) of $Rh_2(OAc)_4$. The solvent was removed under reduced pressure and the residue was



i) EtOH, reflux, 3 h (93%). ii) **3**, DCC, THF, rt, 2 h (55%). iii) a- LDA, THF, -78 ^{o}C, 30 min. b- TsN_3 (48%). iv) THF, $Rh_2(OAc)_4$, reflux, 30 min.

Scheme 4

In conclusion, 1-aminoisobenzofurans can easily be generated from *o*-(diazomethyl)benzamides and used for intramolecular Diels-Alder reactions to produce the tetracyclic system of benzophenanthridine alkaloids. Heterogeneous phase oxidation of hydrazones to unstabilized diazo compounds proved to be non reproducible, but preparation of stabilized diazo compounds allowed decigram scale preparation.

Acknowledgements

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chromatographed on SiO_2 (1:2, EtOAc:hexanes) to give benzophenanthridine **18** as a foam. **1H-NMR** ($CDCl_3$, 250 MHz) δ 7.71 (d, 7.4 Hz, 1H, Ar*H*), 7.40-7.25 (m, 3H, Ar*H*), 6.84 (s, 1H, Ar*H*), 6.69 (s, 1H, Ar*H*), 5.95-5.94 (m, 2H, OCH_2O), 4.28-4.10 (m, 2H, OCH_2), 4.04 (s, 2H, $ArCH_2N$), 3.40 (wide s, 1H, O*H*), 3.19 (d, 16.5 Hz, 1H, H-6), 3.06 (d, 16.5 Hz, 1H, H-6), 2.42 (s, 3H, NCH_3), 1.13 (t, 7.1 Hz, CH_2CH_3). **13C-NMR** ($CDCl_3$, 75 MHz) δ 175.7 (C=O), 147.1, 146.6, 139.6 , 136.1, 132.2, 128.8 (d), 127.7 (d), 127.1, 125.0 (d), 124.9 (d), 123.9, 117.0, 107.2 (d), 102.7 (d), 101.0 (OCH_2O), 74.5, 62.38 (t, OCH_2), 54.9 (t, $ArCH_2N$), 38.1 (q, NCH_3), 34.2 (t, CH_2), 14.0 (q, CH_3). **IR** ($CHCl_3$) 3470, 1720, 1480 cm^{-1}. **MS** m/z (rel. int.) 379 (M^+, 88), 378 (100).