A New Route to the Isoindole Nucleus *via* Furan–Pyrrole Ring-Exchange

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Isoindole is readily synthesized *via* intramolecular cycloaddition and successive ring opening of Boc-protected furfuryl propargylamine in the presence of base.

In contrast to indoles, isoindoles appeared late in the history of chemistry, probably because of their instability. A few synthetic methods have been reported since their initial synthesis by Bonnett and Brown in 1972.[1] The isoindole formed was a white solid that rapidly darkened and resinified at room temperature especially in the presence of acid. Reaction of the transient isoindole with *N*-phenyl maleimide gave a mixture of the *endo* and *exo* adducts (2 : 3).[1] Previously, we have developed the furan-ring transfer reaction: a facile method for the construction of fused furans and synthetically useful isobenzofurans.[2] Linde *et al.* reported a sulfur counterpart of the reaction.[3] Extension of this reaction to nitrogen-containing systems has potential difficulty owing to the trivalent nature of nitrogen relative to divalent oxygen or sulfur. However, nitrogen containing systems lead to the potential of controlling the reaction with the additional substituent at nitrogen. We chose the *tert*-butyloxycarbonyl group (Boc) which should survive reaction conditions as the protective substituent of the nitrogen atom. The requisite species **2** was easily prepared from readily available furfuryl aldehyde *via* three steps.† Due to the limited reactivity of furan as a diene, propargylamine was isomerized to allenylamine with potassium *tert*-butoxide in 1,1-dimethylethanol. Spontaneous intramolecular Diels–Alder reaction and successive base-induced ring opening of the resulting adduct gave compound **5** under mild conditions.‡ Nonprotected **1** or methyl substituted propargylamine did not afford corresponding products and led to decomposition. The observations can be rationalized in two ways. The electron withdrawing property of Boc suppresses the electron donating effect of the lone pair of nitrogen and prevents the prototropic isomerization of the propargyl group at the allene stage by preventing further isomerization to propyn-1-ylamine. The bulky Boc group is also throught to have an entropic effect which enables the allene to adopt the correct conformation to react with furan.[5] Attempts to dehydrate compound **5** directly into isoindole failed.§ By reaction with reactive dienophiles, the transient isoindole was trapped successfully. Reaction of compound **5** with dimethyl acetylene dicarboxylate (DMAD, 2 equiv.) in the presence of pyridinium toluene-*p*-sulfonate (PPTS) led to the formation of an adduct in high yield. Addition of methyl orthoformate as the water binding agent facilitated the reaction. Similarly easy adduct formation with *N*-phenylmaleimide and *p*-benzoquinone was confirmed. Interestingly, reaction with *N*-phenylmaleimide and *p*-benzoquinone afforded corresponding *endo* adducts as the sole products.

We anticipate this reaction to be useful for the construction of polysubstituted isoindole compounds because the positions of substituents on furfuryl propargylamine, which are easy to control, can determine the positions of substituents on isoindole.

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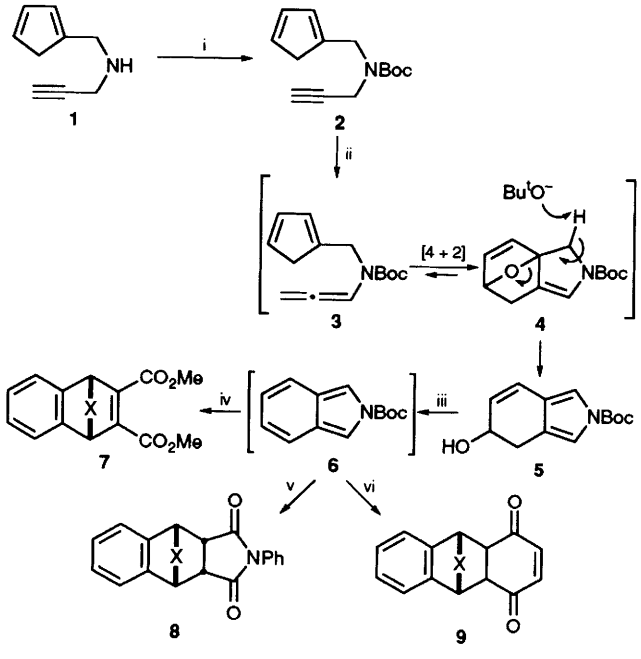

Scheme 1 *Reagents and conditions*: i, di-*tert*-butyldicarbonate, DMAP (cat.), TEA, CH_2Cl_2, room temp., 92%; ii, Bu^{t}OK (5 equiv.), Bu^{t}OH, 30 min, 63%; iii, PPTS, methyl orthoformate; iv, DMAD, THF, reflux, 80%; v, *N*-phenylmaleimide, CH_2Cl_2, reflux, 70%; vi, *p*-benzoquinone, CH_2Cl_2, reflux, 52%

Footnotes

† Condensation of furfuryl aldehyde with propargylamine in the presence of a catalytic amount of PPTS followed by reduction with $NaBH_4$ gave compound **1**. Protection with Boc gave compound **2**.

‡ Procedure of furan–pyrrole ring exchange reaction: a solution of propargylamine **2** (478 mg, 2.035 mmol) and Bu^{t}OK (1.22 g, 10 mmol) in Bu^{t}OH (20 ml) was heated at 40 °C. After **2** was rapidly consumed (30 min), 1 ml of water and NH_4Cl powder was added and stirred at room temp. until the evolution of ammonia gas ceased. The solution was filtered and extracted with ether. The extract was washed with brine and dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel with hexane–ethyl acetate (2 : 1) as eluent.

§ Dehydration in acidic (PPTS) or alkaline conditions (thionyl chloride, TEA) and/or methyl orthoformate was attempted with a variety of solvents and different temperatures.

¶ As determined by ^{1}H NMR of the bridgehead hydrogen: **8** δ 3.92–3.91 (m, 2H), **9** 3.58–3.56 (m, 2H), ref. 1. *Selected data*: **5**: ^{1}H NMR ($CDCl_3$): δ 7.07 (br d, *J* 1.7, 1H), 7.01 (br s, 1H), 6.49 (dd, *J* 9.3, 1.0, 1H), 5.93 (dd, *J* 9.3, 4.1, 1H), 4.48 (br s, 1H), 2.92–2.73 (ddm, *J* 6.1, 1.3, 2H), 1.72 (br s D_2O exchange, 1H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 148.96 (s), 129.09 (d), 121.97 (d), 121.75 (s), 119.52 (s), 116.69 (d), 114.89 (d), 83.44 (s), 65.71 (d), 29.73 (t), 28.02 (q); FDMS *m/z* 235 M$^+$. **8**: ^{1}H NMR ($CDCl_3$): δ 7.38–7.23 (m, 7H), 6.41–6.38 (m, 2H), 5.58–5.56 (m, 2H), 1.45 (s, 9H); FABMS *m/z* 391 M + H$^+$. **9**: ^{1}H NMR ($CDCl_3$): δ 7.14 (br, s 4H), 6.04 (s, 2H), 5.54–5.52 (m, 2H), 3.58–3.56 (m, 2H), 1.45 (s, 9H); FABMS *m/z* 326 M + H$^+$

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