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A Novel Approach To Polycyclic Indolic Systems

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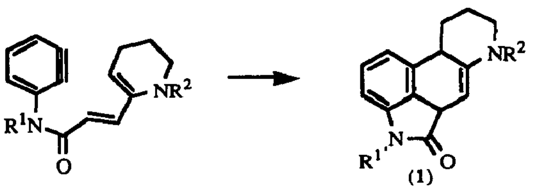
Abstract:- An intramolecular Diels-Alder strategy has been developed for the synthesis of polycyclic oxindole-containing systems.

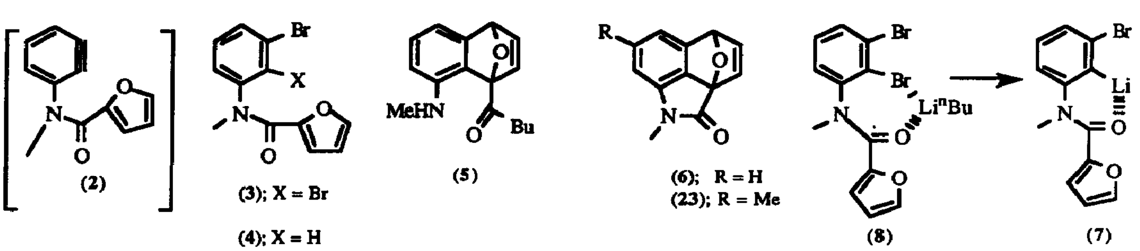
The development of new synthetic routes to indolic systems continues to be an active area of interest.[1] Whereas there are numerous[2] examples of IMDA reaction of alkenes with suitably functionalised dienes, there exist few reports[3] of the analogous IMDA reactions of arynes. Our efforts in this area have centred upon the development of a mild method for the generation of highly reactive intermediates, which upon reaction with a suitably functionalised diene would afford the functionalised ergot skeleton (1) in a single step, **Scheme 1.** The results of our initial efforts in this area are documented in this *Letter*.



Scheme 1

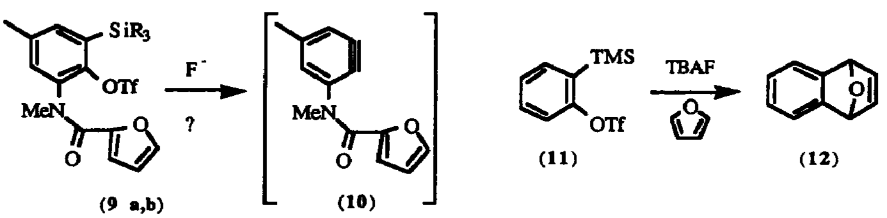
Initial attempts to prepare the functionalised aryne (2) using transmetallation-fragmentation procedures were largely unsuccessful. Treatment of the readily available[4,5] furanamide (3) with ^{n}BuLi (2.2eq) in THF: ether (1:1; -78 °C to ambient) merely afforded the mono-bromide (4) in moderate isolated yield[6] (42%). Repeating the reaction at lower temperatures (-78 °C) using a limited quantity of ^{n}BuLi (1.1eq) again afforded the mono-bromide (4) as the major product (52%), with concomitant formation of the ketone (5) in low yield (7%). Formation of the ketone (5) presumably arose *via* the initial formation of the adduct (6), followed by nucleophilic attack at the activated amide carbonyl group. Attempts to optimize the generation of the ketone (5) or the adduct (6) met with failure. The regioselectivity observed of the halogen-metal exchange and unusual stability of the intermediate (7) towards fragmentation may be ascribed to the initial formation of an amide -

^{n}butyl lithium complex[7] (**8**) which gave rise to the formation of the stable, chelated intermediate[8] (**7**) upon halogen-metal exchange (**Scheme 2**).



Scheme 2

In an effort to effect the desired fragmentation step under milder reaction conditions, we considered that the silyl triflates (**9a,b**) would serve as ideal precursors to the required aryne intermediate (**10**). Kobayashi[9] has reported that the silyl triflate (**11**) undergoes a fluoride induced fragmentation, at or near ambient temperature, and under essentially neutral reaction conditions, to afford benzyne, which can be trapped with furan to afford the adduct (**12**) in high yields, **Scheme 3**. We[10] and others[11] have subsequently shown this to be a mild method for the generation of benzynes, although few synthetic applications of this process have been reported to date.

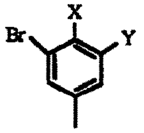


Scheme 3

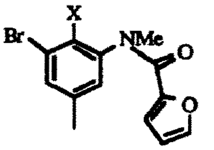
Conversion[12] of the readily available phenol (**13**) to the mono-nitro compound (**14**) ($NaNO_2$/AcOH; 86%) and protection ($PhCH_2Br$/NaOH/MeOH/reflux; 60%) afforded the ether (**15**), which was cleanly reduced[13] to the aniline (**16**) using "NaSH" (Na_2S (1.7eq) $NaHCO_3$/MeOH/H_2O; 40 min; 82%) on a multigram scale. Acylation of the aniline (**16**) with 2-furoyl chloride (1.1eq; Et_3N (1.1eq), 0 °C to ambient) afforded the amide (**17**) (72%), which upon *N*-methylation (NaH (1.3eq), THF; MeI (25eq); (**18**) 87%) and subsequent deprotection ((i)BCl_3(2.5eq); CH_2Cl_2;-10 °C; (ii) MeOH; 92%) afforded the phenol (**19**) as a white crystalline solid (m.p. 189-90 °C).

Conversion of the phenol (**19**) to the crystalline silyl ether (**20a**) (NaH; THF; TBDMSCl, 0 °C; 87%) and metallation (^{t}BuLi (2.2eq); THF; -78 °C; 3 hours) afforded the rearranged silane[14] (**21a**) in excellent yield (93%). Unfortunately, all attempts to convert (**21a**) to the triflate (**22a**) met with failure, presumably due to adverse steric interactions. Silylation of the phenol (**19**) (NaH; TMSCl (5eq); THF; yield of (**20b**) ~100%), metallation (^{t}BuLi (2.2eq); -78 °C; 30 min) and subsequent 1,3-silatropic rearrangement[14] afforded the phenol (**21b**) as a white crystalline solid (m.p. 159 °C; 90%). After some experimentation, conversion of the phenol

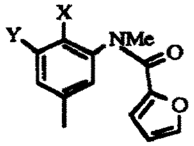
(21b) to the pivotal intermediate **(22b)** was achieved under carefully controlled conditions (($(CF_3SO_2)_2O$ (3eq); pyridine (12eq); DMAP (2eq) in CH_2Cl_2 at -20 °C;) in 63% yield after "flash" chromatography.



(13) X = OH; Y = Br
(14) X = OH; Y = NO_2
(15) X = OBn; Y = NO_2;
(16) X = OBn; Y = NH_2;
(17) X = OBn; Y = NHCO(2-furyl)
(18) X = OBn; Y = NMeCO(2-furyl)
(19) X = OH; Y = NMeCO(2-furyl)

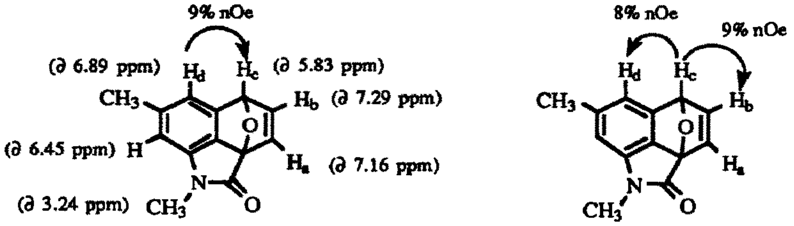


(20a) X = OTBDMS
(20b) X = OTMS



(21a) X = OH; Y = TBDMS
(21b) X = OH; Y = TMS
(22a) X = OTf; Y = TBDMS
(22b) X = OTf; Y = TMS

Having developed a route to the key intermediate **(22b)**, the crucial aryne generation step was attempted. Remarkably, addition of TBAF (1.25eq in THF) to a solution of **(22b)** in redistilled acetonitrile (2.4 x 10^{-2} M. soln.) at room temperature (2 hours) afforded the highly unstable adduct **(23)** in essentially quantitative yield. Confirmation of the identity of the product was secured on the basis of ^{1}H nmr, ir and mass spectroscopy. Irradiation of H_b (δ 7.29 ppm; dd; J = 6.25; 2.5 Hz) caused Hc (δ 5.83 ppm; d; J = 2.5Hz) and Ha (δ 7.16 ppm ; d; J = 6.25Hz) to collapse to singlets. In addition, irradiation of the singlet at δ 6.89 ppm (H_d) caused a 9.0% enhancement of the doublet at δ 5.83 ppm (H_c), whereas irradiation of H_c produced an 8% enhancement of H_d and a 9% enhancement of H_b (Figure 1). Finally, the adduct **(23)** exhibited a high carbonyl stretching frequency (γ_{max} 1720 cm^{-1}) in the infra-red spectrum, characteristic of a strained amide carbonyl, and produced a molecular ion in the mass spectrometer ($C_{13}H_{11}NO_2$ requires 213.0790; found 213.0793).



(23)

Figure 1

From a mechanistic stand-point, molecular models would indicate that cycloaddition of the highly reactive intermediate **(10)** to the strained system **(23)** proceeds*via* an asynchronous transition state[2b,15] or a di-radical intermediate[16] **(Figure 2)**, rather than by a truly concerted process.

Figure 2

This sequence clearly illustrates the potential advantage of the Kobayashi fragmentation over alternate methods of aryne generation. The synthetic utility of this rather uncommon cycloaddition sequence will be the subject of further reports.

Acknowledgements

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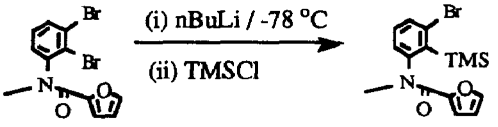
4. Prepared in two steps from 2,3-dibromoaniline^a ((a) Liedholm, B. *Acta. Chem. Scand.*, **1984**, *B38*, 877):- (i) 2,3-dibromoaniline, 2-furanoyl chloride (1 eq.), HCl (excess), NaOAc; 88%; (ii) NaH, THF, MeI; 88%.
5. All new compounds were fully characterised by ^{1}H nmr, ir, high resolution mass spectroscopy and/or combustion microanalysis.
6. Identical to an authentic sample prepared from 3-bromoaniline.
7. For a recent example see Beak, P.; Musick, T. J.; Liu, C.; Cooper, T.; Gallagher, D. J. *J. Org. Chem.*, **1993**, *58*, 7330.
8. For the preparation of stable *o*-lithiohaloarenes see Iwao, M. *J. Org. Chem.*, **1990**, *55*, 3622. The anion (7) may be intercepted with a variety of electrophiles, e.g. TMSCl, affording the silane (24) in 63% yield:-



(3) (24)

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