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A New Synthesis of Indoles

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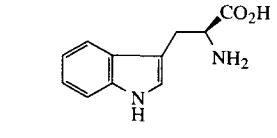
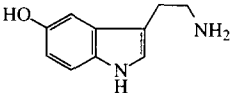
Abstract. Aryl radical cyclisation onto appropriate vinyl bromides leads to a new route to indoles.

Indoles display a wide range of biological activities; this is exemplified by the amino-acid tryptophan (**1**), the hormones serotonin (**2**) and melatonin (**3**), the anti-arthritic indomethacin (**4**), the psychotropic LSD (**5**) and the anti-tumour agent vinblastine (**6**). Accordingly, the synthesis of indoles has long been a topic of fundamental interest to organic and medicinal chemists, and many of the 'named' syntheses of indoles are long established and associated with famous chemists of classical heterocyclic chemistry[1].



(**1**)



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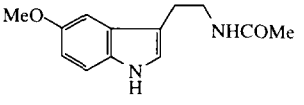

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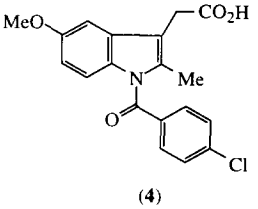

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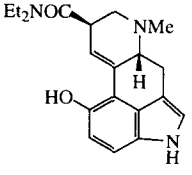

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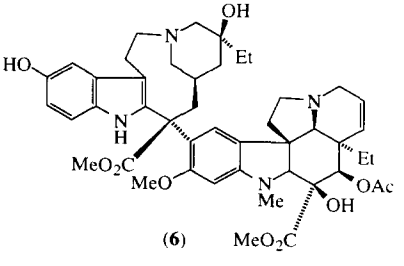

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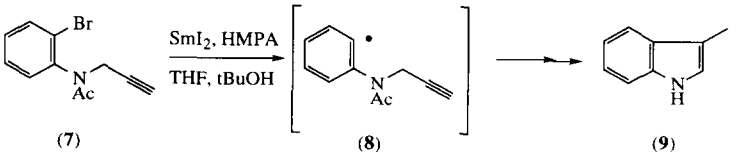
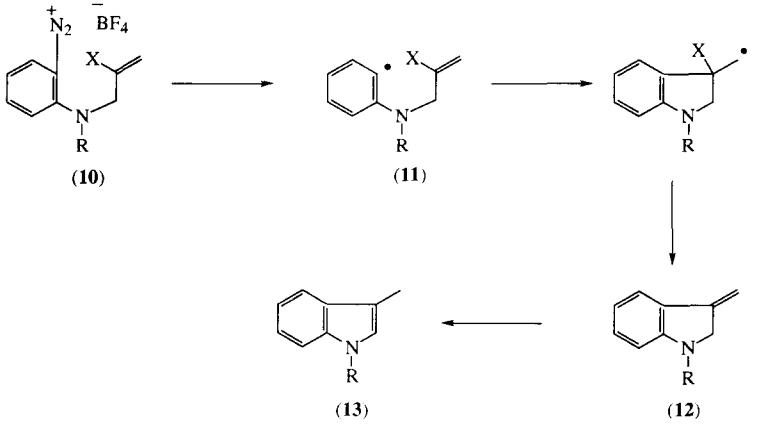


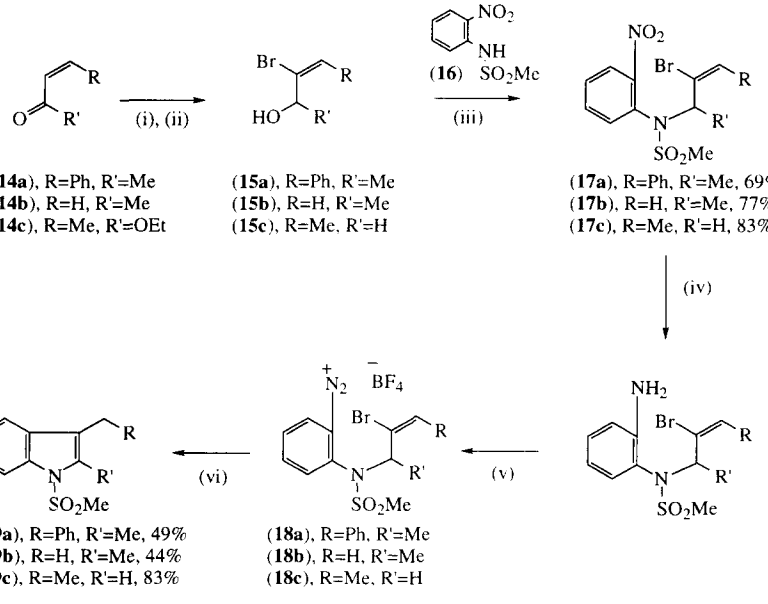
(**7**) (**8**) (**9**)

More recently, routes based on modern synthetic methods have been developed. Free radical chemistry has featured in the recent revival. Besides the considerable interest[2-10] in indolines and indolones, direct approaches to indoles include the samarium iodide-induced transformation[11] of haloalkynes (**7**) to indoles (**9**) *via* aryl radical (**8**).



(10) (11) (12) (13)

As discussed below, our interest in indoles extends to compounds where the precursor cannot include an alkyne. Moreover, our efforts to make radical chemistry more environmentally acceptable would preclude the use of HMPA. Accordingly we have investigated an addition-elimination route to indoles in which cyclisation occurs by attack of an aryl radical (**11**) onto a suitably substituted alkene . Elimination of X• would afford the *exo*-alkene (**12**) which by tautomerism should then afford the indole product (**13**). Generation of the aryl radical from diazonium salt (**10**) avoids the need to use trialkyltin reagents.



(**14a**), R=Ph, R'=Me
(**14b**), R=H, R'=Me
(**14c**), R=Me, R'=OEt

(i), (ii)

(**15a**), R=Ph, R'=Me
(**15b**), R=H, R'=Me
(**15c**), R=Me, R'=H

(**16**) (iii)

(**17a**), R=Ph, R'=Me, 69%
(**17b**), R=H, R'=Me, 77%
(**17c**), R=Me, R'=H, 83%

(iv)

(**18a**), R=Ph, R'=Me
(**18b**), R=H, R'=Me
(**18c**), R=Me, R'=H

(v)

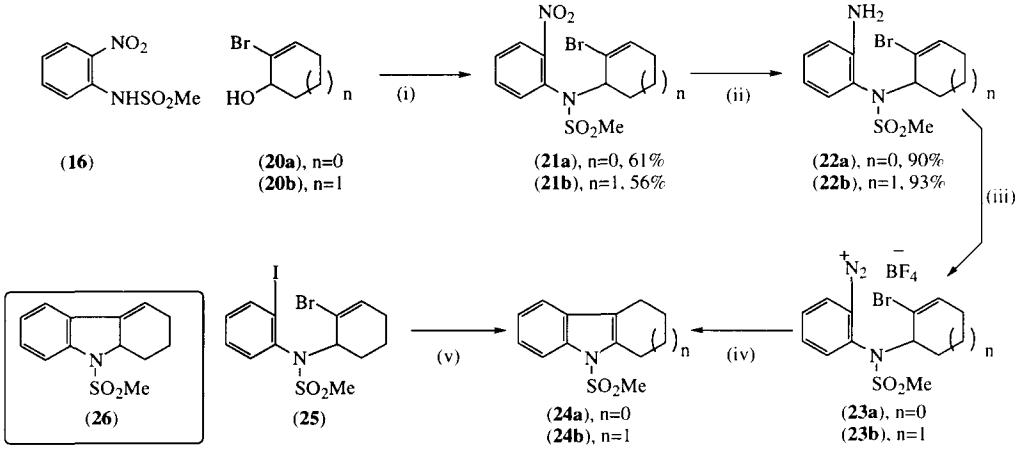
(vi)

(**19a**), R=Ph, R'=Me, 49%
(**19b**), R=H, R'=Me, 44%
(**19c**), R=Me, R'=H, 83%

Reagents and Conditions : (i) Br_2, DCM, 0°C, then Et_3N, r.t. (ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH r.t. (iii) Ph_3P, DEAD, THF, 0°C (iv) $Cu(acac)_2$, $NaBH_4$, EtOH, r.t. (v) $NOBF_4$, DCM, 0°C; (vi) NaI, Acetone.

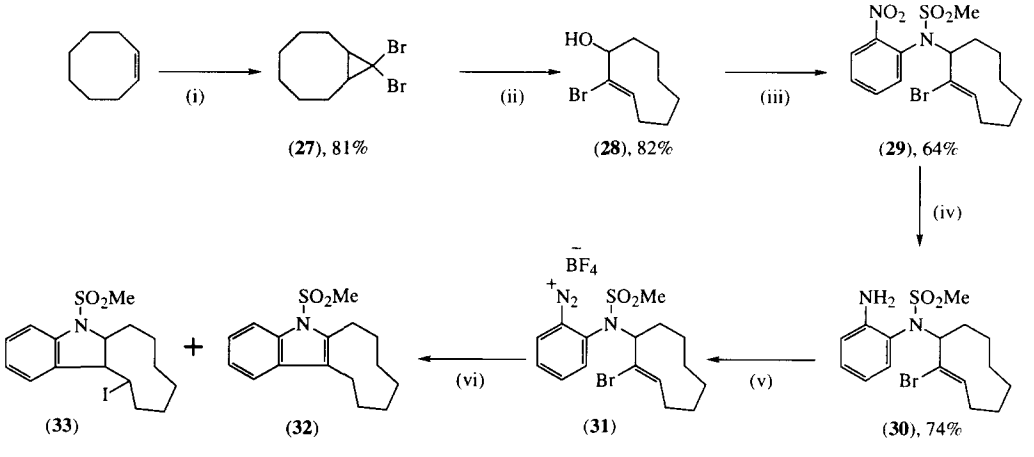
Initially three substrates (**18a-c**) were prepared as shown. The precursors (**14a-c**) were brominated and then subjected to dehydrobromination affording the α-bromo-α,β-unsaturated derivatives, the carbonyl groups of which were then reduced to afford allylic alcohols (**15a-c**). Mitsunobu coupling with the sulfonamide (**16**) afforded coupled nitro products (**17a-c**); reduction to the aromatic amines and then diazotisation afforded the required diazonium salts (**18a-c**). Treatment of the diazonium salts with sodium iodide afforded the expected

indoles (**19**) in moderate to excellent yields as the sole isolated reaction products. (The quoted yields of indoles are from the appropriate amines, since the diazonium salts were not isolated).



Reagents and Conditions : (i) Ph_3P, DEAD, THF, 0°C, 72h; (ii) $Cu(acac)_2$, $NaBH_4$, EtOH, r.t., 1h, (iii) $NOBF_4$, DCM, 0°C, 1h, (iv) NaI, Acetone, 24h, (v) Bu_3SnH, AIBN, PhH, Δ.

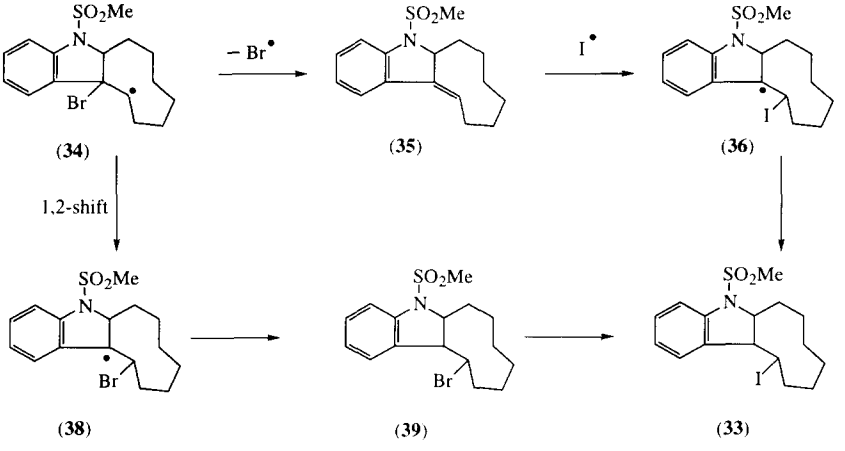
The indoles described above could equally easily have been formed by cyclisation onto an alkyne. However, indoles could not be made in that way where the radical terminus is part of a 5- or 6-membered ring. Accordingly, the substrates (**23a-b**) were prepared as indicated. Cyclisation to the indoles (**24a-b**) was effected in 65% and 54% respectively (quoted yields are from the respective amines, since the diazonium salts were not isolated). For comparison with radical methodology using organotin compounds, the iodide (**25**) was prepared starting from the *o*-iodoarenesulfonamide analogous to (**16**), and reacted with tributyltin hydride and AIBN. This gave rise to the indoline (**26**) (26%) and the indole (**24b**) (49%) as products. Treatment of the indoline by-product (**26**) with *p*-toluenesulfonic acid transformed it to the indole.



Reagents and Conditions : (i) KOtBu, $CHBr_3$, hexane; (ii) $AgClO_4$, acetone, H_2O; (iii) N-methanesulfonyl-2-nitroaniline (**16**), Ph_2MeP, DEAD, THF; (iv) $Cu(acac)_2$, $NaBH_4$, EtOH; (v) $NOBF_4$, DCM, 0°C then (vi) NaI, acetone.

In a more complex example, we investigated the preparation of an indole fused to a 9-membered ring, such as is found in vinblastine (**6**). The requisite allylic alcohol (**28**) was prepared by subjecting the dibromocyclopropane (**27**) to silver perchlorate[12] in aqueous acetone. The nine-membered ring compound displayed complex NMR spectra resulting from not only the *E/Z* isomerism of the alkene but also the

conformational isomerism of the 9-membered ring, which is also seen in derivatives of vinblastine (**6**)[13]. Treatment of the diazonium salt (**31**) prepared *in situ*, afforded the indole (**32**) in 20% yield from amine (**29**). A second compound was also isolated. Intriguingly, this proved to be the indoline (**33**) (13%).



(**34**) (**35**) (**36**)

(**38**) (**39**) (**33**)

Considering how this molecule may be formed, the intermediate radical (**34**) was expected to eliminate Br• very rapidly, as in all the other examples we have investigated. If so, I• must re-add to the resulting alkene (**35**) to afford the benzylic radical (**36**). The final hydrogen atom abstraction presumably occurs from solvent. Alternatively, the conversion of (**34**) to (**33**) may feature an initial 1,2–migration of bromine to afford (**38**). Such reactions are reported to have very high rate constants[14], although the examples of which we are aware all occur on very simple substrates. Hydrogen atom abstraction giving (**39**), followed by S_N2 displacement by iodide ion would then lead to (**33**).

In conclusion, a simple approach to indoles has been developed, utilising the free radical chemistry of diazonium salts.

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