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A New Strategy for the Synthesis of Chromans and Chromenes

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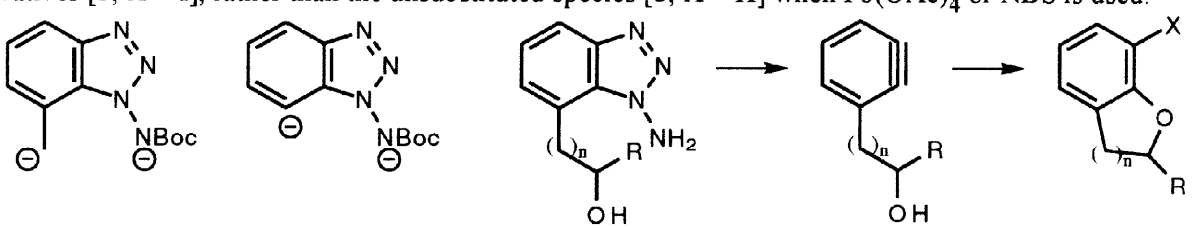
Abstract:- *Sonogashira coupling of 7-iodobenzotriazole derivative **9** with propargylic alcohols followed by alkyne reduction leads to alkanols **11** or alkenols **12** which cyclize upon benzyne generation to give the iodo-chromanes **14** and iodo-chromenes **16**.*

Keywords: arynes; trapping reactions; chromans; Sonogashira

1-Aminobenzotriazole is a useful benzyne precursor, especially as it can be converted into this highly reactive intermediate under essentially neutral conditions by treatment with either lead(IV) acetate or *N*-bromosuccinimide.[1] We have begun to address one limitation of this chemistry, that of a general lack of availability of substituted 1-aminobenzotriazoles, by the development of the dianionic species **1** and **2**.[2] The former has proven especially useful on an approach to the heterocycles **5**, following condensation of this dianion with carbonyls or epoxides to give the alcohols [**3**; n = 1,2], after deprotection. Subsequent benzyne **4** generation was followed by smooth intramolecular trapping by the hydroxyl function.[3] Especially useful was the discovery that when *N*-iodosuccinimide was used to generate the benzyne, the products were the iodo derivatives [**5**; X = I], rather than the unsubstituted species [**5**; X = H] when $Pb(OAc)_4$ or NBS is used.[1]



1 **2** **3** **4** **5**

We reasoned that an alternative strategy would be to use the dianion **2** as a precursor to the 7-substituted derivatives **8**, where "X" might be halogen, a stannyl group, a boronic acid residue *etc*. This should then enable us to introduce the aliphatic side chains [*cf.* **3**] under essentially neutral conditions, using one of the many transition metal-catalysed sp^2-sp^2 and -sp coupling methods which have made such enormous contributions to synthetic methodology in the recent past.[4] Another attraction of this strategy is the brevity of the approach to

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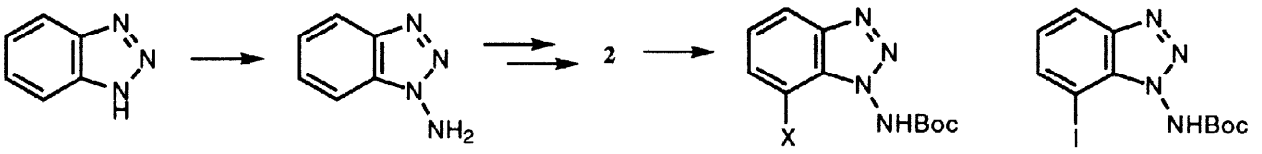
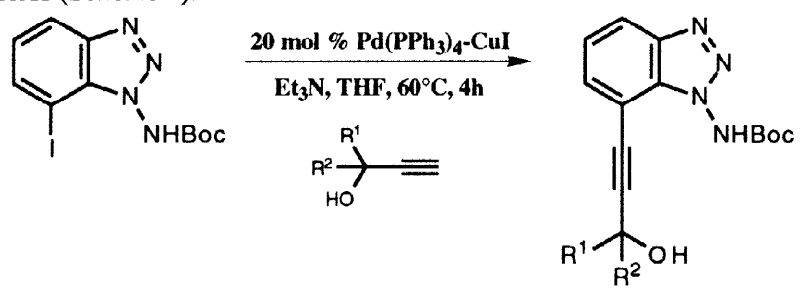
the dianion **2** by direct, optimized *N*-amination of benzotriazole **6**,[5] followed by *N*-protection and lateral deprotonation. Of a number of options so far examined, we have found that the iodo derivative **9** represents an attractive intermediate in such a strategy.



6 **7** **8** **9**

When the dianion **2** is generated using butyl lithium in tetrahydrofuran in the presence of tetraglyme, followed by lithium-cerium exchange with cerium(III) chloride,[2] subsequent iodination using 1,2-diiodoethane leads to the 7-iodo derivative **9** in >95% isolated yield, as a stable crystalline solid, m.p. 142-144°C. We were pleased to find that, despite the rather electron-rich nature of the aryl ring, this underwent smooth and direct coupling with a range of propargyl alcohols under Sonogashira conditions using $Pd(PPh_3)_4$-CuI as the catalyst in hot, degassed tetrahydrofuran containing triethylamine, to give the homologues **10** in generally excellent yields (Scheme 1).[6]

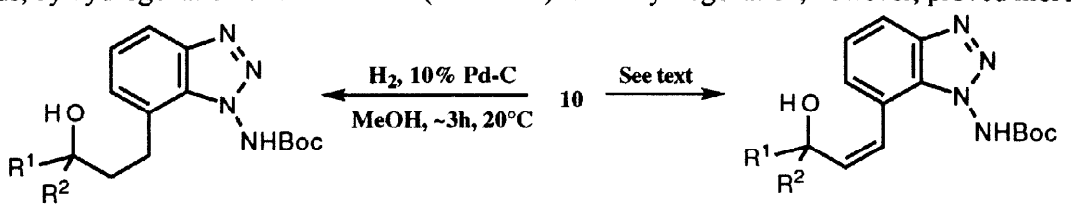


9 **10**

a) $R^1 = R^2 = H$ [92%]
b) $R^1 = Et$; $R^2 = H$ [91%]
c) $R^1 = R^2 = Me$ [87%]
d) $R^1 = CH_2OH$; $R^2 = Me$ (S) [72%]
e) $R^1 = p\text{-}MeOC_6H_4$; $R^2 = H$ [81%]

Scheme 1

The alkynes **10** were all smoothly reduced to the corresponding saturated derivatives **11** in excellent yields, by hydrogenation over 10%Pd-C (Scheme 2). Semi-hydrogenation, however, proved more difficult. The



11 a) $R^1 = R^2 = H$ [95%]
b) $R^1 = Et$; $R^2 = H$ [94%]
c) $R^1 = R^2 = Me$ [95%]
d) $R^1 = CH_2OH$; $R^2 = Me$ (S) [72%]
e) $R^1 = p\text{-}MeOC_6H_4$; $R^2 = H$ [0%]

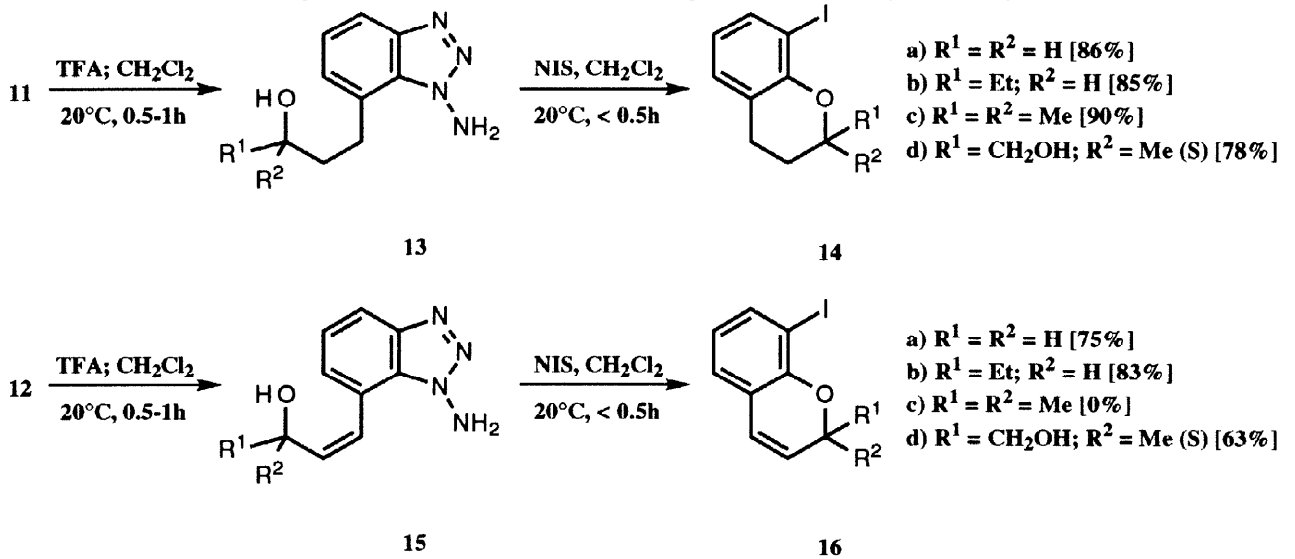
12 a) $R^1 = R^2 = H$ [90%] [L]
b) $R^1 = Et$; $R^2 = H$ [94%] [R]
c) $R^1 = R^2 = Me$ [80%] [R]
d) $R^1 = CH_2OH$; $R^2 = Me$ (S) [60%] [L]
e) $R^1 = p\text{-}MeOC_6H_4$; $R^2 = H$ [0%] [L; R]

Scheme 2

unsubstituted alkyne **10a** could be converted into the (Z)-alkene **12a** in excellent isolated yield using Lindlar

catalyst (L in Scheme 2), but this method proved extremely capricious with this and all the other alkynols **10**. For example, such a reduction of the alkyne-diol **10d**, while providing a 60% return of the (Z)-alkenol **12d** in one instance, was difficult to repeat. We therefore examined alternatives methods. A combination of *i*-butyl-magnesium chloride and Cp_2TiCl_2[7] proved only partially successful, but use of the Rieke zinc in aqueous methanol[8] (R in Scheme 2) provided a solution and delivered the (Z)-alkenols **12b** and **12c** in reproducible yields of ≥90%. One limitation of this methodology is that, to date, all attempts to reduce the aryl-substituted alkynol **10e** have met with failure, presumably due to the highly sensitive nature of the hydroxyl function.

With these substrates in hand, we were able to complete this new approach to chromanes and chromenes and assess some of its scope and limitations; the results are presented below (Scheme 3).



Scheme 3

Removal of the *N*-Boc function from the alkanols **11** occurred smoothly upon exposure to trifluoroacetic acid in dichloromethane in all cases, to give excellent yields of the free amines **13**. When treated with *N*-iodosuccinimide (NIS) in dichloromethane at ambient temperature,[3] benzyne generation proceeded cleanly and provided excellent returns of the 8-iodochromans **14** (Quoted in Scheme 3 are isolated yields over these two steps). Hence, this method is suitable for the elaboration of 2-unsubstituted, 2-alkyl and 2,2-dialkyl-chromans. Interestingly, the diol **13d** gave only the chroman **14d**, despite involving selective attack by a tertiary hydroxyl group in preference to a primary one. We could not detect the presence of the corresponding seven-membered benzoxepin in the cyclized product from amine **13d**. Six-ring formation does therefore seem to be highly favoured in these systems; trial experiments with simpler w-hydroxy homologues resulted in only very poor yields of ring sizes larger than six using this chemistry. Similarly, the corresponding (Z)-alkenols **12** could be converted into the iodo-chromenes **16** by the same procedures. One limitation in this series is that the *gem*-dimethyl amine **15c** was not formed, due to dehydration during the acidic deprotection step. This is not especially serious, as it should be possible to oxidise the corresponding chroman **14c** and similar 2,2-disubstituted species to the related chromenes [*eg* **16c**], especially as the potentially reactive 2-position α-to the ether oxygen is blocked.

In conclusion, we have demonstrated that, in many instances, this new strategy for the elaboration of both chromans and chromenes[9] is both brief and highly efficient, leading to the cyclized products **14** and **16** in only seven steps from benzotriazole. The disconnection which this route represents is also attractive, as it effectively separates the aliphatic from the aromatic portions of the target heterocycles. Finally, we have already shown that, despite being adjacent to an ether oxygen, the iodine atom in the initial products **14** and **16** can be replaced by a range of carbon-based substituents.[3] We are currently examining methods to extend this chemistry to more highly substituted systems, as well as attempting to find solutions to the foregoing limitations, particularly with respect to the incorporation of 2-aryl substituents.

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