The First High-yielding Benzyne Cyclisation Using a Phenolic Nucleophile: A New Route to Xanthenes

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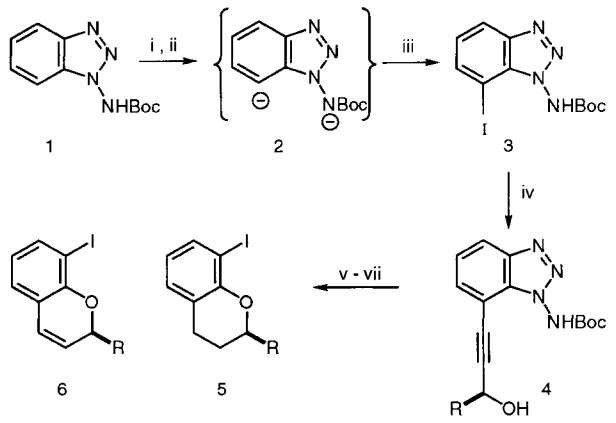
Abstract: Condensation of dianion **2** derived from aminobenzotriazole **1** with *O*-benzyl-salicylaldehydes **11** gives intermediate alcohols **12** in good yields. Double hydrogenolysis gives phenols **13** which, upon deprotection and benzyne generation using *N*-iodosuccinimide, undergo smooth cyclisation to give the iodo-xanthenes **14** in excellent overall yields.

Although the construction of annulated benzenes by intramolecular nucleophilic trapping of benzynes has been exploited for many years,[1] to the best of our knowledge, phenolic nucleophiles have not yet been successfully employed. We reasoned that this was due to a lack of viable synthetic routes to the required precursors, explaining, perhaps, why the only example we found was that reported by Castedo *et al.*[2] who employed a phenoxide-benzyne cyclisation in a synthesis of oxocularine, which delivered only a 20% yield, a competing reaction pathway accounted for the low yield. There is much precedent for phenolic nucleophiles trapping benzynes in an *inter*-molecular fashion,[1] many of which deliver excellent yields. This, combined with our recent interest in the elaboration of substituted benzyne precursors[3] led us to examine this area.



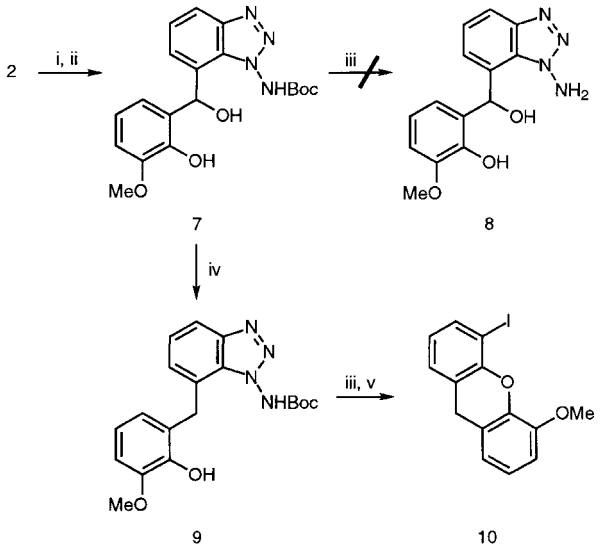
Reagents: i) 2.2 eq BuLi, 5 eq tetraglyme, THF, -78°C; ii) 1 eq $CeCl_3$, -78°C, 3h; iii) 1.1 eq 1,2-diiodoethane, 20°C, 16h; iv) 20 mol % $Pd(PPh_3)_4$, 20 mol % CuI, THF, Et_3N, 1.1 eq acetylene, reflux, 16h; v) H_2, 10% Pd-C, MeOH, 4h; vi) CF_3CO_2H, CH_2Cl_2, 0.5h; vii) N-iodosuccinimide, CH_2Cl_2, 20°C, 0.5h

Scheme 1

We have shown that iodination of the dianion **2** gives excellent yields of the 7-iodo derivative **3**, under appropriate conditions; subsequent coupling with a propargylic alcohol under Sonogashira conditions leads to the homologues **4**. Partial or complete reduction of the alkyne function and benzyne generation from the derived 1-amino-benzotriazole using *N*-iodosuccinimide (NIS), results in efficient trapping of the benzyne by tethered oxygen nucleophiles with concomitant iodine incorporation (Scheme 1). This methodology has been used to form benzofurans, chromans **5** and chromenes **6**.[3] Herein, we describe how this route has been extended to incorporate phenol motifs as tethered traps, leading to a new synthesis of xanthenes.

Xanthenes are incorporated in some of the oldest known dyes;[4] their rigid flat core also makes them useful linkers for unnatural amino acids[5] and peptide synthesis.[6] Previous syntheses of xanthenes have featured either cyclodehydrations,[7] alkylations γ to the heteroatom[8] and reduction of the corresponding xanthones.[9] Xanthenes can also be oxidised to the corresponding xanthones by a number of reagents.[10,11]

As we had in hand a method of forming the dianion **1**, a potent nucleophile towards both aldehydes and ketones,[3] it seemed natural to base our approach around this methodology. Initially, the TBS ether of 3-methoxysalicylaldehyde was employed as the electrophile (Scheme 2); reaction with dianion **1** gave the expected homologue **7**,[12] following desilylation, in excellent overall yield. However, all attempts to remove the Boc protecting group using trifluoroacetic acid, to give the free aminobenzotriazole **8**, gave only unrecognizable products. Alternative reagents[13] for the removal of Boc groups were tried but all led to similar failure. Having had difficulties in the past removing *N*-Boc functions in the presence of benzylic hydroxyl groups, we reasoned that a solution could be to remove this latter functionality.



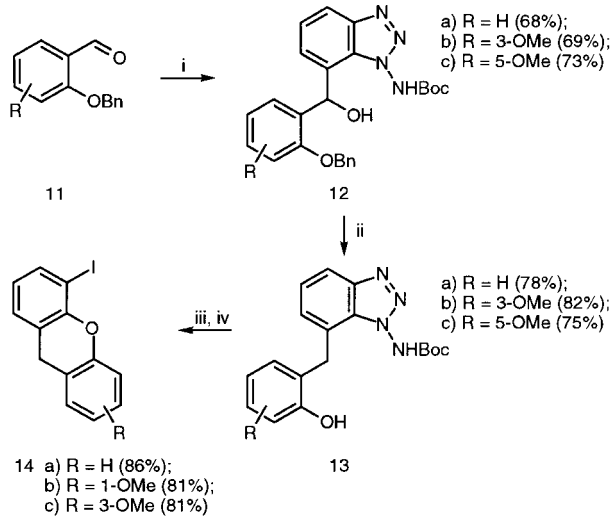
Reagents: i) 1.1 eq *O*-TBS-3-methoxysalicylaldehyde, 78%; ii) HF-py, CH_2Cl_2, 20°C, 83%; iii) CF_3CO_2H, CH_2Cl_2, 20°C, 0.5h; iv) H_2, 5% Pd-C, MeOH, 20°C, 4h, 78%; v) N-iodosuccinimide, CH_2Cl_2, 20°C, 0.5h, 81% based on **9**

Scheme 2

We were delighted to find that an atmospheric pressure hydrogenation of alcohol **7** in methanol with 5% Pd-C as catalyst rapidly gave the desired dehydroxylated product **9**.[12] The reduction was clean enough that the product **9** could be used without purification. Significantly, we found that after 1h, reaction with a 20% solution of trifluoroacetic acid in dichloromethane led directly to the corresponding amino-benzotriazole without any noticeable byproducts being formed. This

then underwent a smooth cyclisation upon reaction with *N*-iodosuccinimide to give the iodo-methoxyxanthene **10**[12] in an excellent 81% isolated yield, from the protected aminobenzotriazole **9**. We had thus achieved our first goal, namely to demonstrate that a tethered phenol will cleanly trap a benzyne; incorporation of the additional iodine atom clearly opens opportunities for additional homologation.

By changing the protecting group on the salicylaldehyde electrophile from silyl to benzyl, we wondered if deprotection and dehydroxylation could be effected concurrently. This turned out to be the case, with the benzyl group being cleaved before the dehydroxylation was complete.

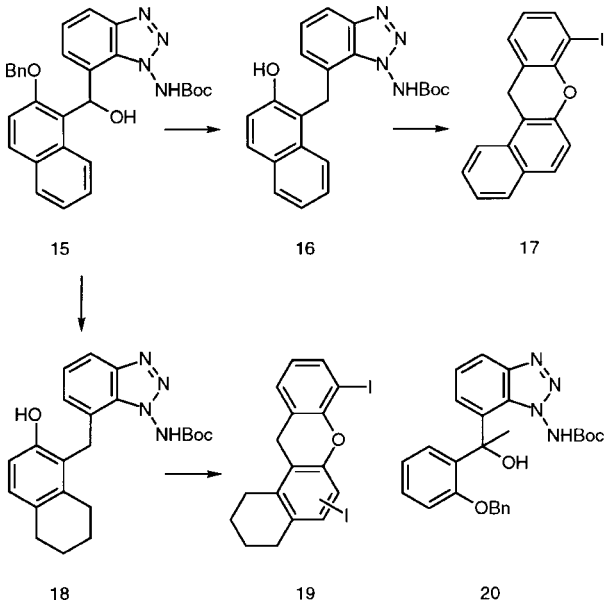


Reagents: i) 0.9 eq dianion **2**; ii) H_2, 5% Pd-C, MeOH, 20°C, 4h; iii) CF_3CO_2H, CH_2Cl_2, 20°C, 1h; iv) NIS, CH_2Cl_2, 20°C, 0.5h

Scheme 3

We synthesized the benzyl protected alcohols **12** (Scheme 3) in good yield by condensations between dianion **2** and aldehydes **11**. These were smoothly reduced and deprotected in one operation to give the corresponding phenols **13** which were then deprotected at nitrogen and cyclized to give the xanthenes **14** in good overall yields.[12,14] We extended this approach to include a naphthol moiety (Scheme 4). Thus, 2-benzyloxy-1-naphthaldehyde was condensed with dianion **2** under the usual conditions to give the expected homologue **15**. Hydrogenation then gave the free naphthol **16** in 82%, which underwent the deprotection/cyclisation procedure to give the benzoxanthene **17** in 75% yield.[12] When the initial alcohol **15** was hydrogenated for 48h, the tetralin **18** was formed in 79% yield. Unexpectedly, after hydrolysis of the *N*-Boc group and benzyne generation using NIS, the diiodides **19** were isolated; presumably, a second electrophilic iodination occurs after benzyne trapping. When 2-benzyloxy-acetophenone was condensed with dianion **2**, the tertiary alcohol **20** was produced (72%).[12] Although the benzyl protecting group was easily removed as before, the alcohol was stable to all hydrogenolytic conditions. Dehydration with tosic acid also failed; however, reaction with trifluoroacetic acid gave no identifiable products.

This relatively brief approach is complementary to the established Friedel-Crafts and other methods for xanthene[7-9] and hence xanthone[10] synthesis. An additional feature is the incorporation of the iodine atom which will no doubt permit further homologation using the many transition metal-catalysed coupling reactions currently available.



Scheme 4

Acknowledgements

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(14) *Representative procedures:- General procedure for generation of dianion* **2**:- Butyl lithium (2.2 equiv. of a 1.6M solution in hexanes) was added to a stirred solution of tetraglyme (5 equiv.) in tetrahydrofuran (10 ml $mmol^{-1}$ of *N*-Boc-aminobenzotriazole **1**) maintained at -78° C. After 0.5 h, a solution of the benzotriazole **1** (1 equiv.) in tetrahydrofuran (10 ml $mmol^{-1}$) was added dropwise *via* syringe. The resulting deep purple solution was stirred at -78° C for 0.5 h. During this period, anhydrous cerium(III) chloride (1.1 equiv.) was stirred in tetrahydrofuran (30 ml $mmol^{-1}$), the suspension cooled to -78° C and treated with butyl lithium (1.6M solution in hexanes) until a faint orange colouration persisted (typically 1 ml $mmol^{-1}$). The purple dianion solution was then rapidly transferred *via* syringe into this suspension which was then stirred at -78° C for 3 h before the addition of the benzaldehyde (1.1 equiv.) in tetrahydrofuran (1 ml $mmol^{-1}$). The resulting mixture was stirred for 16 h without the addition of further coolant then quenched with saturated aqueous ammonium chloride, made acidic with 2M hydrochloric acid and the organic products extracted into ether (3 x 30 ml $mmol^{-1}$). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (10 ml $mmol^{-1}$), water (10 ml $mmol^{-1}$) and brine (10 ml $mmol^{-1}$), dried ($MgSO_4$) and evaporated. Column chromatography in 40-60 petrol/diethyl ether (7:3) was used to separate the pure products.

Condensation of benzotriazole **1** with aldehyde **11a** under these conditions give the *alcohol* **12a** (1.145 g, 68%) as a beige solid, m.p. 67-68 °C, ν_{max}/cm^{-1} (CH_2Cl_2) 3263 and 1744; δ_H ($CDCl_3$; 323K) 1.41-1.48 (9H, br s, ^tBuO), 3.23 (1H, br d, *J* 4.4, OH), 4.98 (1H, d, *J* 11.1, C*H*$_a$H$_b$Ph), 5.05 (1H, d, *J* 11.1, CH$_a$*H*$_b$Ph), 6.62 (1H, d, *J* 4.4, C*H*OH), 7.02-7.06 (2H, m), 7.10 (1H, d, *J* 7.1, 6-H), 7.25-7.38 (8H, m), 7.80-7.85 (1H, br s, NH) and 7.99 (1H, dd, *J* 7.1 and 2.1, 4-H); δ_C ($CDCl_3$) 28.4 (C(*C*H$_3$)$_3$), 70.7 (CH_2), 84.0 (*C*(CH$_3$)$_3$), 112.1, 120.4, 121.8, 124.8 (all CH), 126.8 (C), 127.9, 128.0, 129.0, 129.3, 129.7 (all CH), 130.3, 136.4, 145.5, 154.2 (all C) and 156.1 (CO); m/z (APCI) 447 (M^+ + 1, 100%), 391 (9) and 347 (12) [Found: C, 67.04; H, 5.63; N, 12.29. $C_{25}H_{26}N_4O_4$ requires C, 67.25; H, 5.87; N, 12.55%].

A solution of the foregoing alcohol **12a** (0.160 g) in methanol (11 ml) containing 5% palladium on charcoal (0.05 g) was vigorously stirred under an atmosphere of hydrogen for 4 h at 20° C then filtered through celite. The solid was washed with dichloromethane and the combined filtrates evaporated to leave the *phenol* **13a** (0.078 g, 78%) as a colourless solid, m.p. 97-98° C, ν_{max}/cm^{-1} (CH_2Cl_2) 3268 and 1723; δ_H ($CDCl_3$; 323° K) 1.22-1.50 (9H, br s, ^tBuO), 4.30-4.39 (2H, br s, CH_2Ar), 6.80-6.89 (2H, m), 6.99 (1H, d, *J* 7.5, Ar-H), 7.12 (1H, dd, *J* 7.5 and 7.5, 5-H), 7.19 (1H, d, *J* 7.5, 6-H), 7.25 (1H, dd, *J* 7.8 and 7.8, Ar-H), 7.81 (1H, br d, *J* 7.5, 4-H) and 8.75-8.82 (1H, br s, NH); δ_C ($CDCl_3$) 28.4 (C(*C*H$_3$)$_3$), 30.3 (CH_2), 84.3 (*C*(CH$_3$)$_3$), 116.3, 118.3, 121.0 (all CH), 124.3 (C), 125.4 (CH), 125.7 (C), 128.6, 129.9, 131.2 (all CH), 131.4, 136.2, 144.8 (all C) and 154.4 (CO); m/z (APCI) 341 (M^+ + 1, 100%).

The foregoing phenol **13a** (0.088 g) was dissolved in dichloromethane (2 ml) containing trifluoroacetic acid (0.2 ml) and the resulting solution stirred at ambient temperature for 1.5 h. The solution was then basified by the addition of aqueous 2M sodium hydroxide (2 ml) and then the pH adjusted to ~5 by the careful addition of 2M hydrochloric acid. The aqueous layer was separated, saturated with sodium chloride and extracted with dichloromethane (3 x 10 ml). The combined organic solutions were washed with saturated brine, dried ($MgSO_4$) and filtered. To the stirred filtrate was added *N*-iodosuccinimide (0.090 g) in one portion. When gas evolution had ceased, the solution was stirred at 20° C for 0.5 h then washed with saturated aqueous sodium thiosulfate (5 ml), water (5 ml) and brine (10 ml) then dried and evaporated. Column chromatography of the residue using 40-60 petrol separated the *xanthene* **14a** (0.066 g, 86%) as a colourless solid, m.p. 56-59 °C, ν_{max}/cm^{-1} (CH_2Cl_2) 3062, 2962, 1926, 1622, 1597, 1445, 1426, 1246, 1099, 891 and 754; δ_H ($CDCl_3$) 3.95 (2H, s, CH_2), 6.69 (1H, dd, *J* 7.7 and 7.7, 4-H), 6.99 (1H, dd, *J* 7.6 and 7.6, Ar-H), 7.03-7.26 (4H, m) and 7.58 (1H, d, *J* 7.6, 5-H); δ_C ($CDCl_3$) 27.4 (CH_2), 83.7 (CI), 115.8 (CH), 119.6, 120.8 (both C), 122.5, 123.4, 126.7, 127.5, 128.0, 136.5 (all CH), 150.1 and 150.9 (both C); m/z (EI) 308 (M^+, 10%), 181 (32), 152 (41), 139 (20), 127 (73) and 74 (100) [Found: M^+, 307.9693. $C_{13}H_9IO$ requires *M*, 307.9700].