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A convenient access to benzo-substituted phthalazines as potential precursors to DNA intercalators

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Abstract—2-Nitro-5-methoxybenzaldehyde is converted to amines **2** and **7** via two alternative routes. Upon diazotisation and Sandmeyer reaction, halides **4** and **9** are formed, which, through lithiation and formylation lead to the *o*-phthalaldehyde. Further cyclisation with hydrazine gives the 5-methoxy-substituted phthalazine.

Antitumour antibiotics that bind to DNA by intercalation form a large family of potent agents that have potential in the clinic.[1] These include bis-intercalators such as echinomycin, sandramycin, triostin A, the luzopeptins[2] and quinaldopeptin,[2] as well as monointercalating alkylators such as the azinomycins A and B.[3] Studies of structure–activity relationships for these compounds have been fairly limited because of their structural complexity and, without doubt, this has contributed to their lack of progression into useful therapeutic entities. Combinatorial methods and solid-phase reagents and synthesis offer us an alternative route into these structurally complex molecules and, as part of an ongoing research programme to investigate the effects of structure on the biological activity of both natural[4] and synthetic intercalators,[5] we required easy synthetic access to a library of potential chromophore structures.

The 1,2-disubstitution of aromatic nuclei is an important target in synthesis, as it provides an entry to either functionalisation or ring annelation.[6,7] Phthalazines, like the other members of the isomeric benzodiazine series, have found wide application as therapeutic agents.[8] Despite their significance, there are only a limited number of routes for their synthesis, especially when diverse substitution is required on the benzene ring to allow their conjugation to more complex structures.[7,8] The most commonly employed approach is through *o*-disubstituted benzenes. Thus, condensation of 1,2-diacylbenzenes or their aldehyde counterparts with hydrazine gives 1,4-disubstituted- or the parent, unsubstituted-phthalazines, respectively.[7] Most of the reported methods for the synthesis of *o*-phthalaldehydes involve the oxidation of a suitably 1,2-disubstituted benzene.[9] Reductive[10] or oxidative[11] ring-opening of heterocycles has also been reported. There has also been a report on the lithiation and formylation of a simple benzene ring.[12] Despite the ingenuity of most of these methods, there are limitations with regard to: (a) the nature and pattern of substitution on the benzene unit that could tolerate the reaction conditions and (b) the accessibility of suitably substituted benzene precursors.

A convenient route to 1,4-substituted phthalazines that could comfortably tolerate substituents on the benzene ring involves the rearrangement of hydrazones of *o*-hydroxyaryl ketones.[13] The present report, complementary to the latter, describes a convenient access to phthalazines that allows a diverse substitution pattern on the benzene ring for benzo- and *peri*-annelation (Scheme 1). A 5-methoxy-substituent, through its directing effects for lithiation, serves as an entry for later stage derivatisation of the benzene ring, ultimately leading to further functionalisation and/or 'linear' or 'angular' benzo- and *peri*-annelation.

Aldehyde **1** (obtained by methylation of the corresponding commercially available hydroxy compound[14]) is reduced by either of the two routes A or B (Scheme 1). Catalytic hydrogenation (route A) gives **2** in 74% yield. Diazotation of the amine, in the presence of trimethylsilyl halide (either chloride or bromide—both

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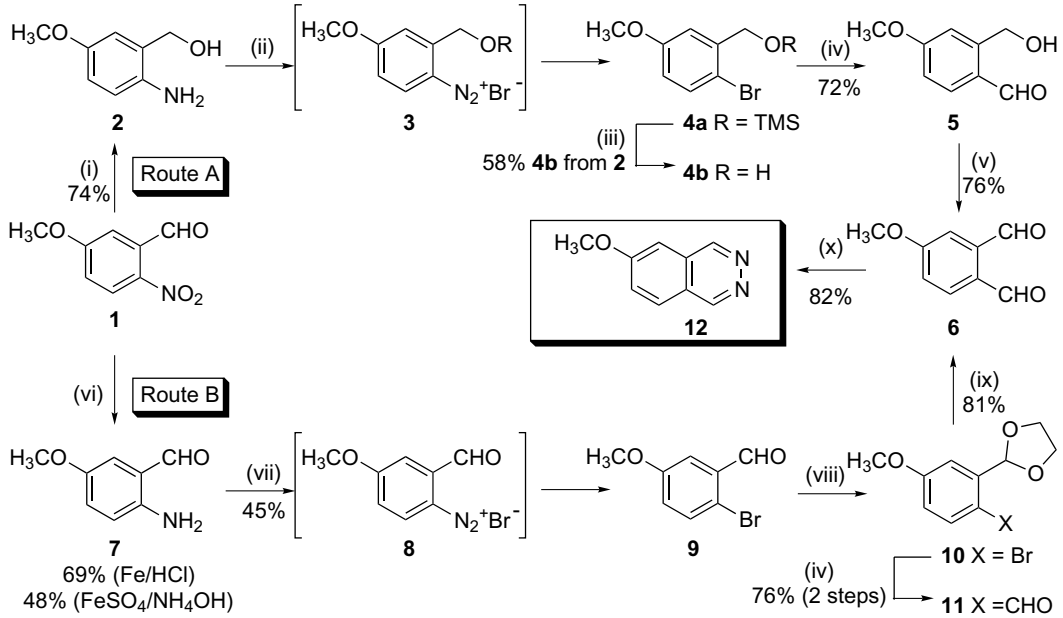
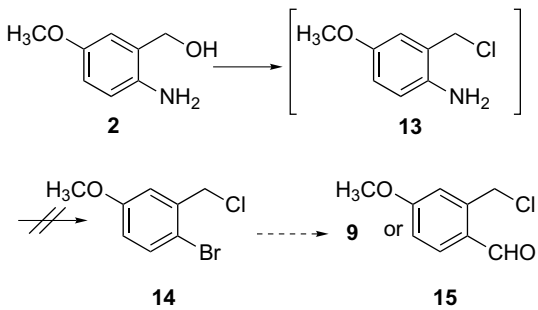


Scheme 1. (i) H_2, Pd/C (10%), rt, 48 h; (ii) $NaNO_2$, TMSBr(Cl); (iii) TBAF, CH_2Cl_2, rt; (iv) *n*-BuLi, −78°C, THF, DMF; (v) PCC, CH_2Cl_2, rt, 6 h; (vi) Fe, HCl or $FeSO_4$, NH_4OH; (vii) ^{t}BuONO, CuBr, HBr; (viii) $(CH_2OH)_2$, TSA, C_6H_6, Δ, 24 h; (ix) 3N HCl, 12 h; (x) N_2H_4/EtOH/0°C–rt.

were equally effective)[15] gave a mixture of both the *O*-silyl-derivative and the free alcohol **4a** and **4b,** respectively.[16] The former is easily converted into the free alcohol, giving a final yield for the conversion of **2** to **4** of 58%. Halogen lithium exchange followed by formylation leads to **5**, which is mildly oxidised to the *o*-phthalaldehyde **6**.

Alternatively, the amine **7** is obtained by the selective reduction of **1** by either of the two well-known reagents Fe/HCl[17] or $FeSO_4/NH_4OH$[18] in 69 and 48% yields, respectively. Diazotation followed by Sandmeyer reaction furnishes the bromide **9**.[19] 1,3-Dioxolane protection of the aldehyde, followed by lithiation/formylation gives **11**[20] in 76% yield. Deprotection of **11** readily leads to **6**. The *ortho*-phthalaldehyde **6** is converted to the target phthalazine **12** in excellent (82%) yield.[21]

An attempt to prepare the mixed halide **14**[15,22] and subsequently convert it to either **15** or **9** (and ultimately to **6**) was unsuccessful (Scheme 2). Thus, **2** was treated with DMSO/TMSCl to obtain the amine **13** in situ



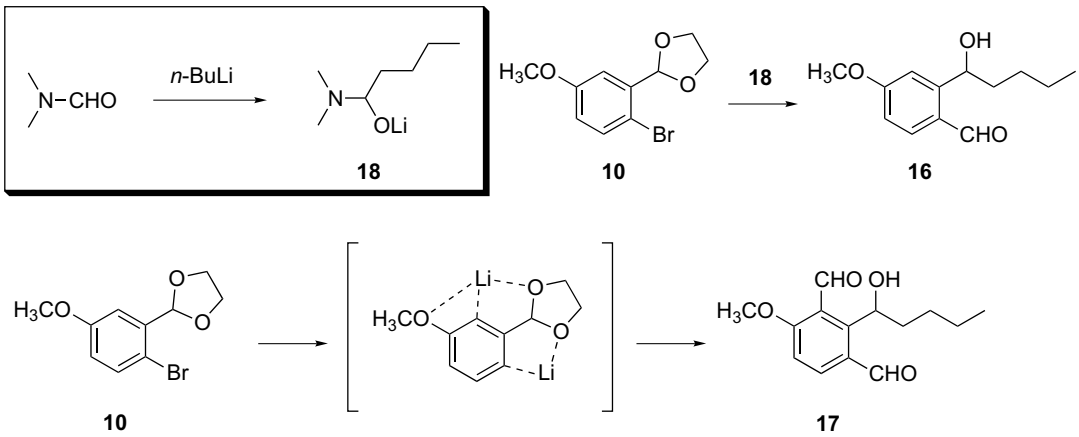
Scheme 2.

along with the *N*-silyl derivative. Diazotation/Sandmeyer reaction conditions, similar to those for the conversion of **2** to **4**, gave ill-defined products.

An alternative approach to **4** and **5** through bromination of the commercially available *m*-anisaldehyde, although seemingly attractive, suffers from two serious limitations: (a) a mixture of all *o*-/*p*-bromo-isomers is obtained, thus necessitating chromatographic separation of the desired isomer on a preparative scale and (b) as a consequence of (a), the substitution pattern diversity in the benzene ring is limited.
Attempts to protect the aldehyde **1** as the acetal or dioxolane prior to reduction were unsuccessful, probably due to steric impedance known in acetal formation.[14]

The aldehydes **16** and **17** were isolated in minor yields (<5%) from the conversion of **10** to **11**. Aldehyde **16** can be derived from a nucleophilic displacement of either 1,3-dioxolane or the bromide by the *O*-lithiated **18** (Scheme 3) followed by hydrolysis.[23] Aldehyde **17** on the other hand, appears to be the result of a directed *ortho*-lithiation by 1,3-dioxolane **10**,[24] the effect enhanced by the *m*-methoxy-group.[25] A recent literature report is in agreement with this rationale.[23] Carrying out the lithiation at −100°C and using *n*-BuLi and DMF in the minimum possible excess (e.g. 1.2 and 2.0 mol equiv., respectively) suppresses the formation of both **16** and **17**.

Bromination of **12** (Br_2/AcOH 0°C to rt, 6 h) appears to favour substitution at the 5- rather than the alternative 7-position. This is in line with the analogous case in 6-hydroxy-substituted quinolines.[26]



Scheme 3.

The aldehyde **1** has also recently been used as the starting material in a synthesis of cinnolines[27] and quinazolines[28] and can be considered a common starting point for the synthesis of these benzodiazines, a feature of synthetic significance.

In conclusion, a simple and convergent access to phthalazines is described, which allows a diverse substitution pattern on the benzene ring. Coupled with the arylhydrazone rearrangement reaction,[13] this may serve as an efficient and recommended general route for the synthesis of phthalazines.

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