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WORKABLE SYNTHETIC ROUTES TO FUNCTIONALIZED 1,6-BENZODIAZOCINES‡

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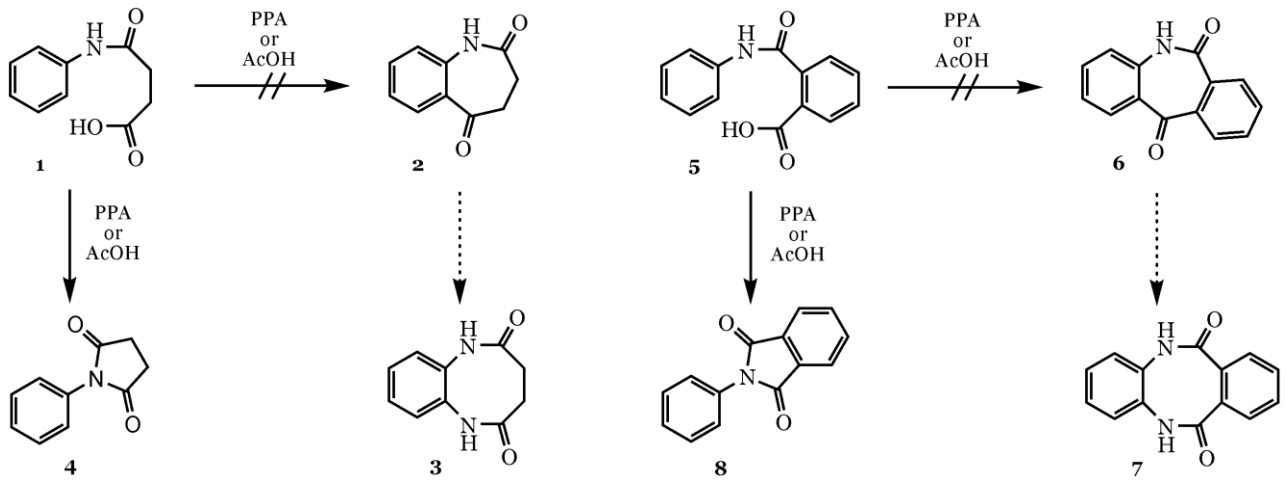
Abstract - Two strategies for fusing a medium-sized building block to a benzene ring in the form of a functionalized 1,6-diazocine unit via one-pot procedures are presented.

Although interest in the pharmacological activity of benzodiazepines has persisted for many decades,[1] a comparable level of scrutiny has, only in select instances, been accorded to eight-membered homologs, likely because of more limited synthetic accessibility.[2] Notable in this connection are members of the uncommon 1,6-benzodiazocine class, as exemplified by the alleged preparation of **3**.[3] Contrary to the claims of the Bhusare group, the acid-catalyzed cyclization of **1** does not lead to **2** and is not a source of **3**,[4] but produces instead the known[5] succinimide derivative **4** (Scheme 1). A comparable error in structural assignment has been reported for the dibenzo derivative as **5** → **8**[4] and not **5** → **6**.[6]

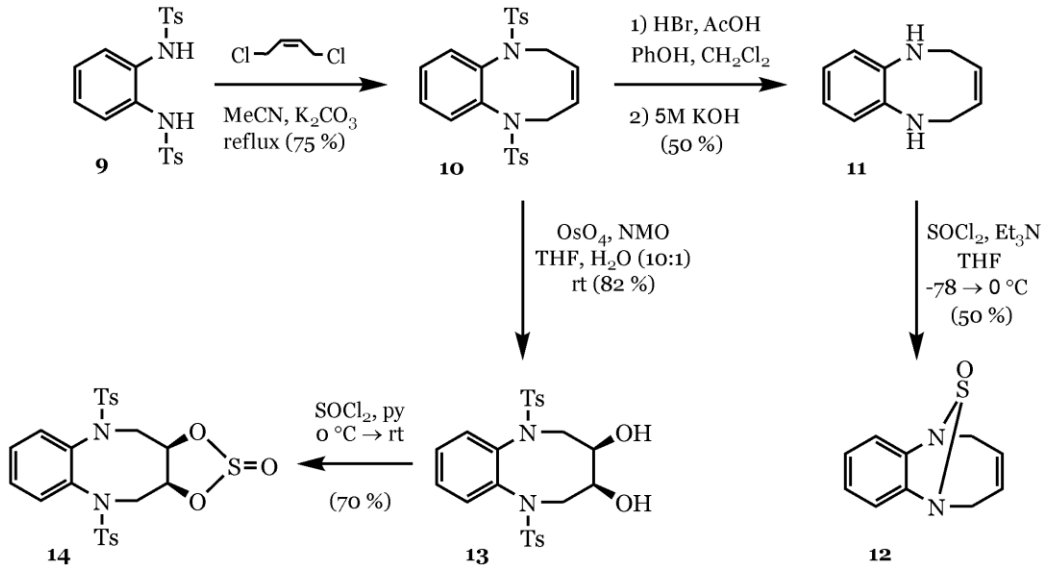


Scheme 1

‡Dedicated with best wishes to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

Our quest of functionalized 1,6-benzodiazocines has led us to investigate the feasibility of eight-membered ring annulation reactions involving the bis-sulfonamide **9**[7] as the principal reagent. The proven ability of *cis*-1,4-dichloro-2-butene to undergo efficient conversion to macrocyclic products[8] foreshadowed its capability for delivering **10**[2] smoothly in the presence of potassium carbonate (Scheme 2).

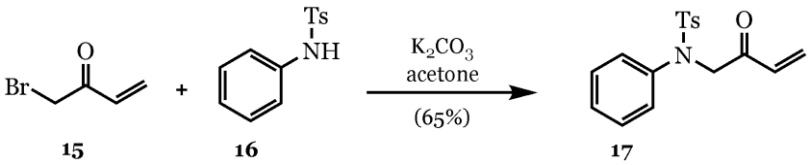
The importance of gaining viable access to **10** was heightened when the possibility for effectively removing the *p*-toluenesulfonyl protecting groups with phenol and HBr/AcOH in CH_2Cl_2 at room temperature[10,11] was demonstrated. Incorporation of a sulfinyl group into **11** delivered the bridged diamide **12** as a single configurational isomer at sulfur.[12] Presumably the double bond residing in **12** can be exploited as an implementation site for further functionalization.



Scheme 2

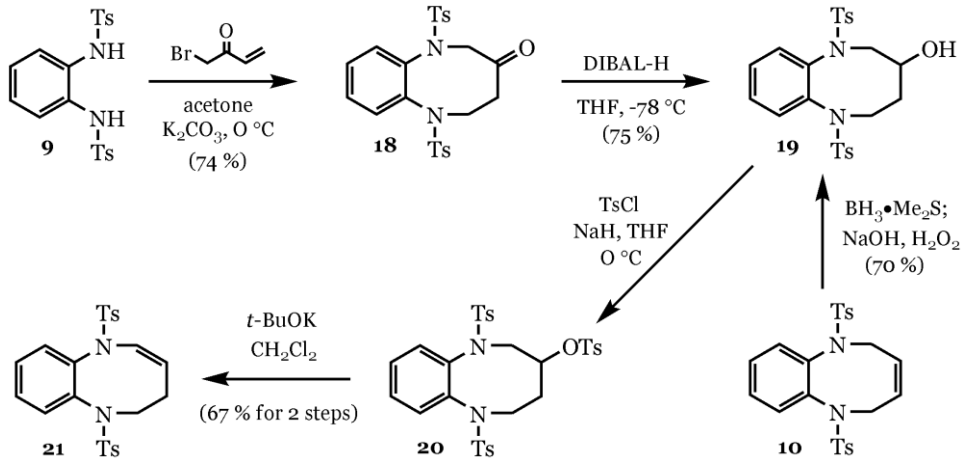
With a view toward the development of an eventual route to conjugated diene intermediates, other investigations into the chemistry of **10** were carried out. To illustrate, this entity lent itself to *cis*-dihydroxylation, and subsequently to formation of the cyclic sulfite **14**.[13]

At this point, the possibility of a complementary annulation process was explored. Bromomethyl vinyl ketone (**15**)[14] was selected as the test case. Although this reagent is an electrophilic species capable of reaction at three sites, mechanistic studies have suggested, but not proven, that primary amines are thought to enter into the initial S_N2 displacement of bromide ion.[15] To the contrary, enamines are prone to attack $XCH_2COCH=CH_2$ (X=Cl, I) via Michael addition.[16]



Scheme 3

We have removed this ambiguity in the present circumstances by first adding **15** to the somewhat less functionalized sulfonamide **16** (Scheme 3). Under conventional conditions, only **17** proved to be generated. As a direct consequence of symmetry, the projected variation involving **9** would lead to **18** by either mechanistic pathway. In practice, the experiment furnished **18** in 74 % yield (Scheme 4). Reduction of **18** with diisobutylaluminum hydride at -78 ºC proceeded uneventfully with the formation of carbinol **19**, which was expectedly identical with the product of hydroboration of **10**. Treatment of **19** with *p*-toluenesulfonyl chloride in the presence of sodium hydride gave rise to tosylate **20**, which was subjected to elimination in the presence of potassium *tert*-butoxide to afford **21** as a single regioisomer.[17] Independent high-pressure hydrogenation of **10** and **21** converged as anticipated to the same saturated diazocine.[18]



Scheme 4

In summary, the two routes described above are serviceable in that the one-step construction of a pair of 1,6-benzodiazocines is achieved. No unwanted transannular side reactions proved to be competitive with eight-membered ring formation. Further deployment of these observations awaits advances made in the context of more complex settings.

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