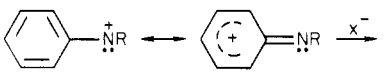
Intramolecular Cyclization of Arylnitrenium Ions. Formation of Carbon–Carbon Bonds and of Lactones

Summary: Arylnitrenium ions bearing a meta side chain having a suitable nucleophilic center are generated by the acid-catalyzed decomposition of the appropriate azide; they undergo intramolecular cyclization leading to new carbon–carbon bonds or to lactones in preparatively useful yields.

Sir: Nitrenium ions have received considerable attention in recent years.[1] Arylnitrenium ions have reportedly been generated mainly by treatment of arylhydroxylamines[2] or azides[3] with strong acids or by the solvolysis of *N*-chloroanilines.[4] The delocalized intermediates (1) have been trapped at carbon *intermolecularly* by nucleophiles, which have included methanol,[1a] water,[2] halide ions,[3b] benzene, and toluene,[5] to give **2**. There have been reports



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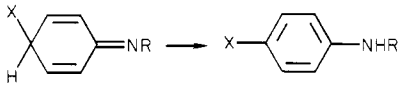

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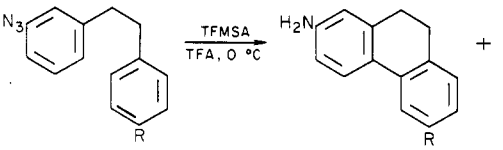
of *intramolecular* trapping at carbon of intermediates formed by reduction of 1-(nitrobenzyl)tetrahydroisoquinolines with zinc and trifluoromethanesulfonic acid[6a] or by acid-catalyzed heterolysis of preformed acylhydroxylamines[6b]—both of which may involve at least a partial dissociation to the arylnitrenium ion. We now describe the first examples of what could potentially be an extremely useful and general new method of effecting intramolecular cyclizations at aromatic carbon by the acid-catalyzed decomposition of aryl azides.

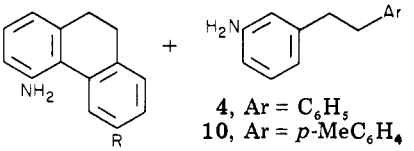
3-Azidobibenzyl (**3**)[7] (from 3-aminobibenzyl (**4**)[8]) in trifluoroacetic acid was decomposed at 0 °C by the addition of trifluoromethanesulfonic acid (TFMSA) to give 2- (**5**)[9] (72.5%) and 4-amino-9,10-dihydrophenanthrene (**6**;[11] 15.2%), together with hydrogen abstraction product **4** (2%). Similarly, **7** [bp 100–105 °C (0.025 mm)] (from **10**: mp 53–54 °C) gave **8** (65.5%), **9** (23.9%), and **10** (2.7%).[7]

cis- (**11**) and *trans*-α-phenyl-*m*-nitrocinnamic acid (**12**)[12]



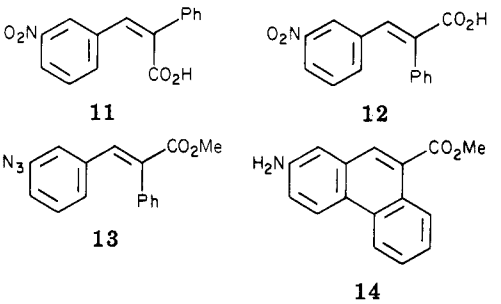
3, R = H
7, R = Me

5, R = H
8, R = Me



4, Ar = C_6H_5
10, Ar = *p*-MeC_6H_4

6, R = H
9, R = Me



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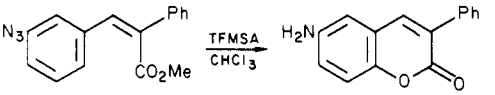
were esterified, reduced to the primary amine (Zn dust/$CaCl_2$), and converted to the azides. *trans*-*m*-Azidocinnamate (**13**; mp 76 °C (hexane)) in chloroform was treated with 2 equiv of TFMSA (0 °C → room temperature, 24 h) to give methyl 2-aminophenanthrene-9-carboxylate (**14**; 82%):[7] mp 175 °C (CH_2Cl_2–hexane). This procedure affords an interesting alternative to the Pschorr cyclization.

cis-*m*-Azidocinnamate (**15**; yellow oil) in chloroform was decomposed with 1 equiv of TFMSA to give 6-amino-3-phenyl-2*H*-1-benzopyran-2-one (**16**;[7] 65%): mp 158 °C,



15 **16**

identical with an authentic sample prepared from 5-nitrosalicylaldehyde and sodium phenylacetate followed by reduction of the nitro group. In a similar sequence, methyl 3-nitrobiphenyl-2′-carboxylate was converted to the amine hydrochloride (mp 150 °C) and then to the azide (**17**; bp 115–120 °C (0.05 mm)). Cyclization was effected by treating a solution of **17** in CCl_4 with 2 equiv of TFMSA at 40 °C for 30 h. The expected aminobenzocoumarin **18** (mp 187 °C) was obtained (52%). Small amounts of the ortho isomer (mp 158 °C) were also formed (comparison with authentic sample).[7]

Finally, the decomposition of *m*-azidophenylacetic acid was examined (TFMSA (1 drop) to a solution in TFA) and yielded 3-aminocoumaranone (**21**;[7] (36%): mp 117–119 °C; $\nu_{C=O}$ 1790 cm^{-1}; *m/e* 149 ($M^{+\cdot}$, 100%). Similarly, **20** also gave **21** (66%). Consequently, it is the carbonyl oxygen in **20** that acts as the nucleophile to trap the nitrenium ion. This novel lactone ring formation should prove to have valuable applications.

A number of other intramolecular cyclizations involving nitrenium ions leading to the formation of both homocyclic

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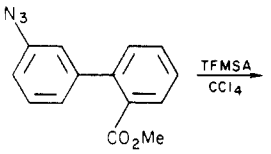

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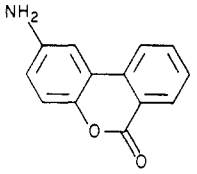

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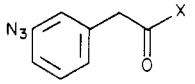
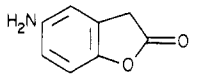


19, X = OH
20, X = NH_2



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and heterocyclic rings are currently under investigation and will be reported soon.

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Registry No. 3, 83542-55-6; 4, 5369-22-2; 5, 76302-58-4; 6, 83527-88-2; 7, 83527-87-1; 8, 83527-89-3; 9, 83527-90-6; 10, 83527-91-7; 11, 83527-92-8; 12, 22161-41-7; 13, 83527-93-9; 14, 83527-95-1; 15, 83527-94-0; 16, 21408-]6-2; 17, 83527-98-4; 18 (isomer 1), 83527-99-5; 18 (isomer 2), 83527-00-1; 19, 83527-01-2; 20, 83527-02-3; 21, 83527-03-4; methyl 3-nitrobiphenyl-2′-carboxylate, 83527-96-2; methyl 3-aminobiphenyl-2′-carboxylate hydrochloride, 83527-97-3.

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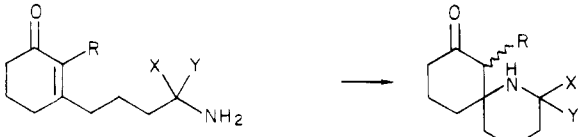
Trimethylsilyl Iodide Catalyzed Spirocyclization of Amines. Synthesis of Perhydrohistrionicotoxin

Summary: A trimethylsilyl iodide catalyzed Michael reaction of an enone amine and a trimethylsilyl iodide catalyzed S_N2' spirocyclization of an allylic alcohol amine are the crucial reactions in two new syntheses of perhydrohistrionicotoxin.

Sir: The histrionicotoxins, a class of spirocyclic alkaloids isolated from the skin of the frog, *Dendrobates histrionicus*,[1] have received considerable attention from synthetic chemists because of their distinctive structural features and their unique properties as inhibitors of the ion transport mechanism of the cholinergic receptor.[2] An intensification of interest in these alkaloids has recently occurred based on reports that a variety of structurally simplified analogues maintain high levels of neurological activity.[3,4] Perhydrohistrionicotoxin (1; PHTx), a non naturally occurring congener of histrionicotoxin that possesses comparable bioactivity, has served as the focus of this interest with several total syntheses[5-8] and synthetic approaches[9-11] having been reported, including our own[12] synthesis of 1, in which the key spirocyclization is achieved with use of organopalladium chemistry.

A number of investigators have explored entry into the [5,5]-1-azaspirocyclic ring structure of 1 via a Michael reaction with only mixed success. Corey[5a] has studied reactions of the tetrasubstituted enone **2a** but could not effect its cyclization. Michael reactions of the trisubstituted enone **2b** did proceed, but only to give a 1:1 mixture of isomers at the carbon bearing the *n*-pentyl group.[5a] Magnus[11] has reported the acid-catalyzed Michael reaction of the enone amine **2c**, but no results on the more pertinent tetrasubstituted enone were included in this work. The enone lactam **2d** has been successfully cyclized by Kishi[6] achieving a 1:2 ratio of desired to undesired ketones (**3a**/**3b**), which could be epimerized to only a 4:1 ratio (**3a**/**3b**).



2a, R = *n*-Bu; X = *n*-pentyl; Y = H
2b, R = H; X = *n*-pentyl; Y = H
2c, R = X = Y = H
2d, R = *n*-Bu; X, Y = O

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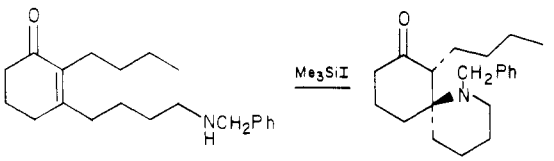
We herein report the development of two trimethylsilyl iodide (Me_3SiI)[13] catalyzed amine spirocyclization reactions. The first readily effects the Michael reaction of the tetrasubstituted enone amine **4** under mild conditions, providing **5** with the desired disposition of the *n*-butyl group predominating (5:1). In addition, this ratio can be enhanced to 13:1 by epimerization. The second Me_3SiI reaction catalyzes an intramolecular S_N2' reaction of the allylic alcohol amine **6**, producing the spiro olefin **7**. Conversions of both **5** and **6** to desamyl-PHTx (**8**) have been achieved.



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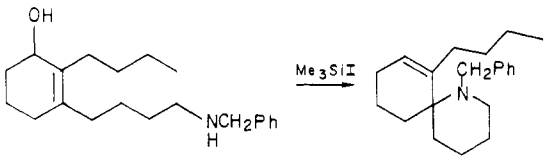

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