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# ACID-CATALYZED CYCLIZATIONS OF AROMATIC DIAZOACETAMIDES: SYNTHESIS OF SPIRODIENONE LACTAMS, ISOQUINOLINONES, AND BENZAZEPINONES

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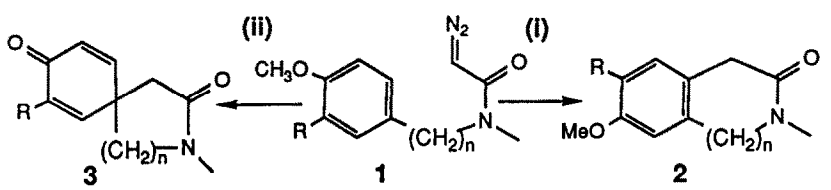
**Abstract:** Acid-catalyzed cyclizations of aromatic diazoacetamides produce good yields of simple isoquinolinones and benzazepinones. The intermediacy of a spirodienone oxonium species has been demonstrated by trapping and isolation of synthetically useful spirodienone lactams, also in good yield.

During the course of some of our efforts in isoquinoline alkaloid synthesis[1], we were interested in developing a synthetic approach to the 1,4-dihydro-3(2H)-isoquinolinone system that might be more general and efficient than currently existing methods[1,2]. A potentially simple route to this system would be by acid-catalyzed cyclization of suitably substituted N-benzyldiazoacetamides such as **1**. Analogous acid-catalyzed cyclizations of aromatic diazoketones have been thoroughly explored by Mander and coworkers[3] and by others[4], as have copper- and rhodium-catalyzed intramolecular carbenoid insertions and additions of aromatic diazoketones[4,5]. The only such studies on diazoacetamides, however, have been those of Doyle and coworkers[6] who have used rhodium(II)-catalyzed diazoacetamide cyclizations to provide efficient syntheses of 2(3H)-indolinones[6a] and azabicyclo-[5.3.0]-decatrienones[6b,c]. We wish to report application of the acid-catalyzed reaction to generate 1,4-dihydro-3(2H)-isoquinolinones, as well as 1,4,5-trihydro-3-benzazepin-2(3H)-ones and novel spirodienone lactams.

Diazoacetamides such as **1** are conveniently prepared by the acetoacetylation of the corresponding secondary amines (diketene, $CH_2Cl_2$), followed by diazo transfer (tosyl azide and DBU, $CH_2Cl_2$) and deacylation (KOH and $H_2O$, $CH_3CN$) according to reported methods[7]. The reaction course in the acid-catalyzed cyclizations depends on the conditions employed. Two procedures are described here:

(i) A methylene chloride solution of the diazoacetamide is added to a mixture of anhydrous trifluoroacetic acid and methylene chloride (4:1) at 25°C and the reaction is allowed to proceed for at least 20 minutes. At this time the reaction mixture is diluted with methylene chloride and poured into cold saturated sodium carbonate. The organic phase is collected and the products are purified by chromatography on silica.

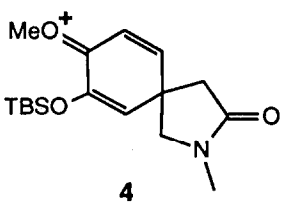
(ii) A methylene chloride solution of the diazoacetamide is added to a mixture of anhydrous trifluoroacetic acid and methylene chloride (4:1) at -20°C and the reaction is quenched by immediate addition of water. Work-up and purification are identical to (i).



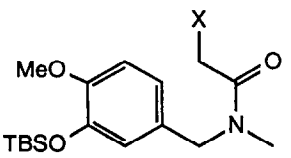

**3** **1** **2**

| | R | n | %2 | %3 |
|---|---|---|---|---|
| **a** | TBSO | 1 | 85 | 75 |
| **b** | MeO | 1 | 77 | 80 |
| **c** | H | 1 | --- | 62 |
| **d** | MeO | 2 | 70 | 49 |
| **e** | H | 2 | --- | 52 |

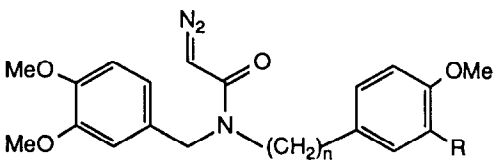
Exposure of the diazoacetamide **1a** to the reaction conditions described in (i) results in formation of the isoquinolinone **2a**[8] in 85% isolated yield. In contrast, exposure of **1a** to the rapid-quench conditions described in (ii) affords a comparable yield of the spirodienone lactam **3a**, demonstrating the intermediacy of the spirodienone oxonium species **4**[9]. Under either set of conditions the solvolysis product **5a** is the minor product, formed in 10-20% yield based on the isolation of the α-hydroxy amide **5b**, which results from the hydrolysis of the trifluoroacetate during work-up. Analogous results are obtained in the cyclization of the diazoacetamide **1b**. Interestingly, the N-phenethyldiazoacetamide **1d** smoothly provides the benzazepinone **2d**; the relatively low yield of dienone **3d** is due to the formation of some **2d** even under the rapid quench conditions. Note that in the cases of diazoacetamides **1c** and **1e**, where R = H, the corresponding spirodienone lactams **3c** and **3e** are obtained as the only cyclic products, even under the conditions described in (i); the in-situ rearrangement does not occur presumably due to the lack of a cation-stabilizing substituent.




**4**



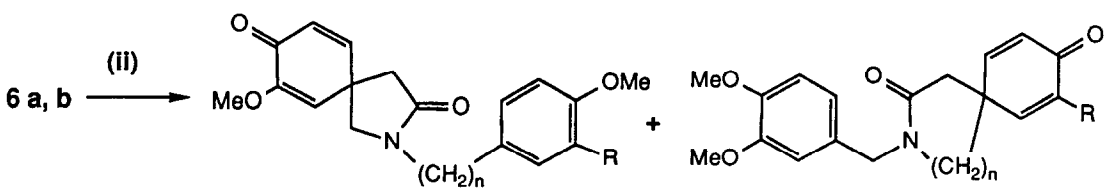

**5 a** X = $OCOCF_3$
**5 b** X = OH




**6 a** n = 1, R = H
**6 b** n = 2, R = OMe

The formation of the spirodienone oxonium intermediate in these systems indicates that the diazonium ion formed initially upon protonation of the diazoacetamide exhibits a kinetic preference for spirocyclization even in the presence of a second activated aryl site, substitution at which would lead to the formation of fused products[10]. The exclusive formation of the isoquinolinone **2a** from the diazoacetamide **1a** requires a regiospecific in-situ rearrangement of the intermediate spirocycle, with the methylene adjacent to nitrogen preferentially migrating.

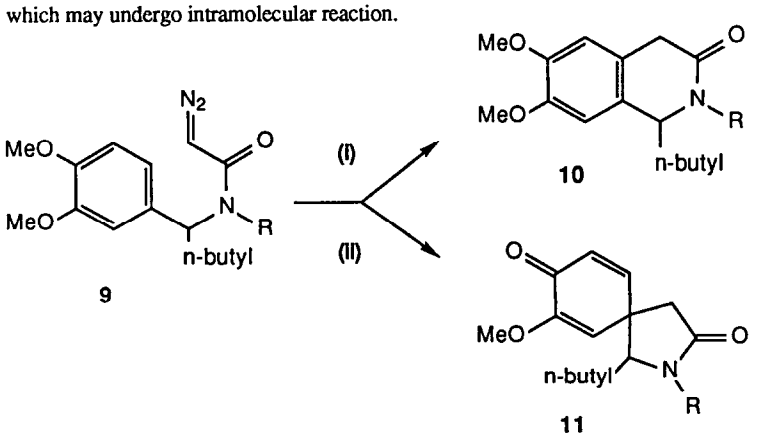
Further insight into the selectivity and generality of these cyclizations is provided by intramolecular competition experiments. Under the rapid quench conditions, diazoacetamide **6a** gives a 55:45 mixture of the dienones **7a** and **8a**, respectively, in a combined yield of 55%; hence, there is no kinetic preference for a doubly activated aromatic terminator in the spirocyclization. Cyclization of diazoacetamide **6b** is remarkable in that the formation of the spirodienone lactams **7b** and **8b** in a ratio of 55:45, and a combined yield of 68%, seems to rule out ring size as the basis for the observed kinetic preference for spirocyclization. In light of these results, the kinetic formation of spirocyclic products over fused cyclic products may be summarized as kinetic preference for 5-*exo*- or 6-*exo*-ring closure over 6-*endo*- or 7-*endo*-ring closure[11].




**7 a** n = 1, R = H
**7 b** n = 2, R = OMe

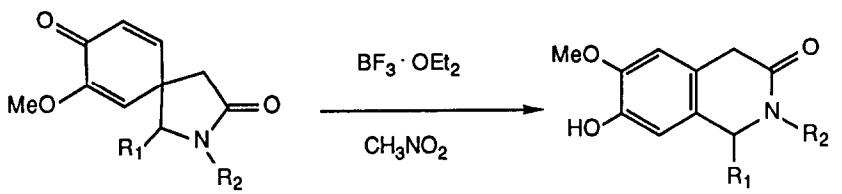
**8 a** n = 1, R = H
**8 b** n = 2, R = OMe

Extension of this cyclization method to the preparation of 1-substituted isoquinolinones is crucial if it is to be employed as a method for the synthesis of isoquinoline alkaloids. Attempts to cyclize the α-substituted-benzyl-N-methyl diazoacetamide **9a** were disappointing; regardless of conditions, the acyclic solvolysis product was predominant. However, significantly improved yields of cyclic products are obtained using the N-tert-butyldiazoacetamide **9b**, as indicated below. Apparently, the increased steric bulk of the α-substituted benzyl group is sufficient to slow rotation about the amide C-N bond relative to the rate of reaction of the diazonium cation, and the products are therefore determined by rotamer population. The bulky tert-butyl substituent on nitrogen is counteractive in this sense, influencing the rotamer population in favor of those which may undergo intramolecular reaction.




| | | R | % 10 | % 11 |
|---|---|---|---|---|
| 9 | a | Me | 19 | 0 |
| | b | t-butyl | 57 | 48 |

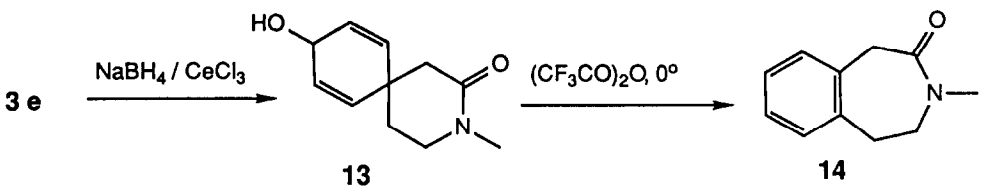
The ability to isolate spirodienone lactams lends versatility to this method of cyclization as an approach to oxygenated isoquinolinones and benzazepinones. These remarkably stable dienones[12] have proven suitable for further synthetic manipulation. For example, the spirodienone lactam **3b** undergoes dienone-phenol rearrangement upon brief (5 min.) treatment with boron trifluoride etherate in refluxing nitromethane to give the phenolic isoquinolinone **12a** (86%). The spirodienone lactam **11b** undergoes analogous rearrangement to the phenolic isoquinolone **12b** (89%), but with concomitant loss of the tert-butyl substituent.




**3 b, 11 b**

**12 a** $R_1 = H, R_2 = Me$
**12 b** $R_1 = n\text{-butyl}, R_2 = H$

Spirodienone lactams such as **3e** which lack the cation-stabilizing methoxy substituent resist dienone-phenol rearrangement under these conditions. However, reduction of **3e** to spirodienol lactam **13** proceeds cleanly (96%)[13] and subsequent dienol-benzene rearrangement provides the benzazepinone **14** (88%).




13 14

The described acid-catalyzed cyclizations of aromatic diazoacetamides thus provide convenient access to simple isoquinolinones and benzazepinones as well as to synthetically useful spirodienone lactams. The application of these transformations to alkaloid synthesis is currently under investigation.

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