Pergamon

Tetrahedron Letters, Vol. 37, No. 14, pp. 2361-2364, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00291-2

Oxidative Cyclization of Acyclic Ureas with *Bis*(trifluoroacetoxy)iodobenzene to Generate *N*-Substituted 2-Benzimidazolinones

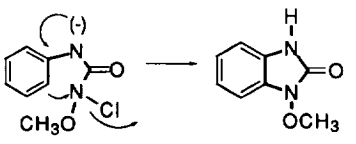
Arthur G. Romero*, William H. Darlington, E. Jon Jacobsen, John W. Mickelson[1]

Medicinal Chemistry Research, Pharmacia & Upjohn, Inc., Kalamazoo, MI 49001

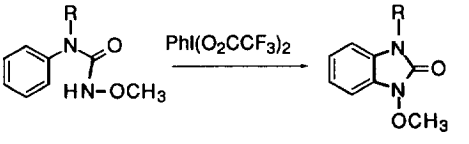
[1]Current address: 3M Pharmaceuticals, St. Paul, MN.

Abstract: A facile method to synthesize N-substituted 2-benzimidazolinones from secondary aromatic amines is presented. Sequential treatment of a secondary aromatic amine with phosgene and methoxylamine afforded an acyclic 3-substituted 3-aryl-1-methoxy urea. Brief exposure of this urea to *bis*(trifluoroacetoxy)iodobenzene induced an oxidative cyclization to the *ortho*-position of the benzene ring, resulting in the formation of a 3-substituted 1-methoxy-2-benzimidazloinone. Hydrogenation over Pd/C cleaves the methoxy group to afford the N-substituted 2-benzimidazolinone.

The synthesis of benzo-fused cyclic ureas (2-benzimidazolinones) typically involves treating a 1,2-diaminobenzene with a phosgene equivalent. While this procedure works well for simple systems, it lacks versatility and is not suitable for aryl substrates substituted with only one amine. Furthermore, while methods for the attachment of one amine onto an benzene ring are numerous,[1] obtaining an aryl ring substituted with two adjacent amines is not straight forward, creating a serious obstacle to routine synthesis of benzo-fused aromatic ureas. A far more versatile approach to synthesizing 2-benzimidazolinones is the annulation of acyclic N-aryl substituted ureas by activation of the remote urea nitrogen and its resulting electrophilic cyclization to the *ortho*-position. This type of oxidative cyclization has been developed to enable the synthesis of 3-H substituted 1-methoxy-2-benzimidazolinones from primary aromatic amines.[2] This method requires generating unstable acyclic 1-chloro-1-methoxy ureas, subsequently inducing cyclization through the intermediacy of the 3-N nitrogen anion which is generated by strong base (Equation 1). Yields are modest, and ring chlorination can be a problem for benzene rings without electron withdrawing groups. Furthermore, the need for a hydrogen on the benzene substituted urea nitrogen limits this approach to N-H substituted 2-benzimidazolinones, from primary aryl amines.[3]



Equation 1.

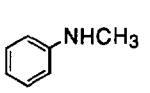
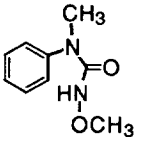
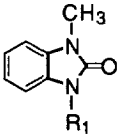
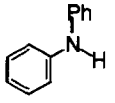
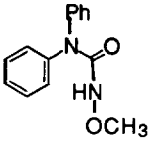
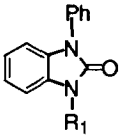
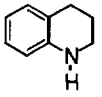
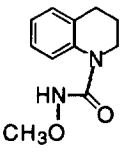
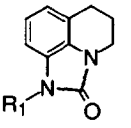
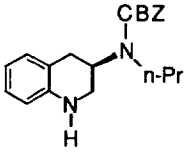
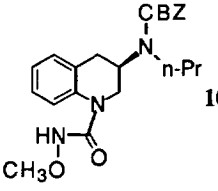
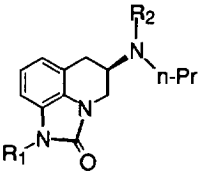
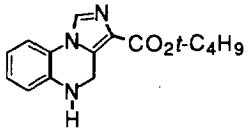
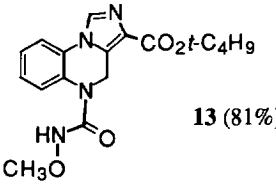
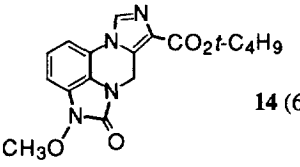
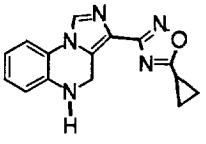
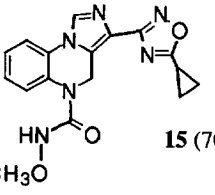
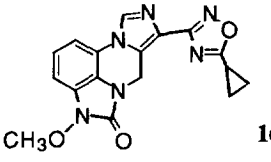


Equation 2.

R=alkyl, aryl

We describe herein a method for the synthesis of the more general N-alkyl (or aryl) substituted 2-benzimidazolinone ring system from secondary amines, allowing for the synthesis of more complex 2-benzimidazolinones. This is an important distinction since it allows for the incorporation of the benzo-fused urea

Table 1. Preparation and cyclization of N'-methoxy ureas to generate N-substituted 2-benzimidazolinones.[4]

Entry	Starting amine	Cyclization precursor (yield)	Product	(yield)
1		 **1** (74%)		**2** (79%)[a] **3** (84%)[b]
2		 **4** (68%)		**5** (76%)[a] **6** (81%)[b]
3		 **7** (69%)		**8** (73%)[a] **9** (76%)[b]
4		 **10** (100%)		**11** (71%)[a,c] **12** (66%)[b,d]
5		 **13** (81%)		**14** (60%)
6		 **15** (70%)		**16** (26%)

a) Yield of 1-methoxy-2-imidazolinone, $R_1 = OCH_3$. b) Yield of 2-imidazolinone after hydrogenation over Pd/C, $R_1 = H$.

c) R_2 = CBZ. d) $R_2 = H$. Values given are purified yields.

into other rings. (see Table 1). This oxidative cyclization (Equation 2) is effected by the use of the powerful oxidant *bis*(trifluoroacetoxy)iodobenzene,[5] obviating the need to generate the nitrogen anion to increase the reactivity of the aryl ring. This new procedure is complementary to the two-step method described above, since, in contrast, it *requires* that the oxidative cyclization precursor contain an alkyl (or aryl) substituent on the benzene substituted nitrogen atom (compare **1** and **17**), as depicted in Equation 2.

The cyclization occurs in minutes at temperatures between 0° and 25°C, affording 3-alkyl (or aryl) substituted 1-methoxy-2-benzimidazolinones in good yields. No side-products arising from other types of benzene ring oxidations were identified. Although yields are typically not as good, the less reactive oxidant *bis*(acetoxy)iodobenzene can be utilized, converting it *in situ* to the more reactive trifluoroacetoxy-substituted reagent by the addition of 10 equivalents of trifluoroacetic acid to the reaction.[6] If desired, the 1-methoxy group can be removed by catalytic hydrogenation over Pd/C to cleanly afford the desired cyclic urea (see Table 1 for examples).

A plausible mechanism for this annulation is shown below (Figure 1), where the relatively acidic N-H group undergoes exchange with trifluoroacetic acid as a ligand on the iodine (III) atom. Fragmentation of this species generates an excellent leaving group, with concomitant oxidation of the nitrogen, where the incipient positive charge is stabilized by the methoxy group; subsequent electrophilic cyclization affords the cyclic urea. Besides the required N-alkyl (or aryl) substituent, the 1-methoxy group is critical to the success of this cyclization, and in its absence no cyclization occurs.[7]

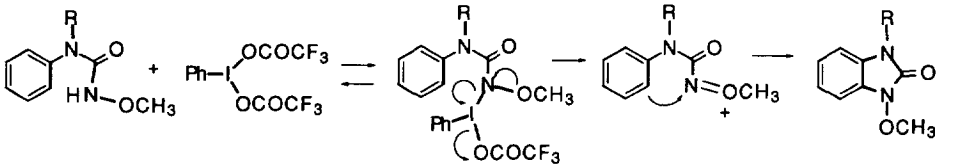
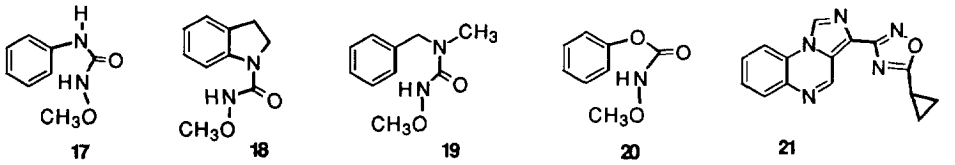


Figure 1.

Interestingly, substrates **17-20** failed to cyclize, giving unidentifiable product mixtures (Figure 2). Compounds **17-19** contain other potentially oxidizable groups in addition to the methoxy substituted nitrogen and can oxidize at these alternate activated N-H or C-H positions to give other products. In the case of **18**, the indoline ring is well known to undergo facile oxidation to the indole, which is itself susceptible to further oxidation. An attempt to extend the methodology to cyclic carbamates (i.e. **20**) failed, presumably due to the attenuated reactivity of the benzene ring. Interestingly, a major side product of the oxidative cyclization of **15** was **21**, where the urea group is missing and the fully aromatic heterocycle is generated.[8]



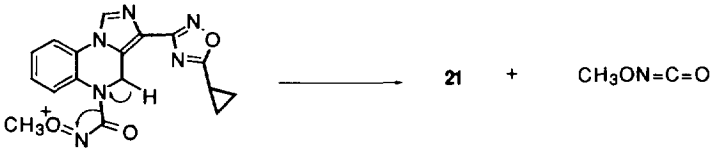
17 **18** **19** **20** **21**

Figure 2.

Typical procedure: The N-methoxy urea cyclization precursors were readily obtained by *Method A:* Sequential treatment of aromatic secondary amines in THF or CH_2Cl_2 with diisopropylethylamine (3.2 eq.), phosgene (1 equivalent), and then methoxylamine hydrochloride (1.1 equivalents) at 0°C; or *Method B*: Substituting carbonyldiimidazole for the phosgene and utilizing only 1.1 equivalents of diisopropylethylamine. These procedures generate the acyclic N-methoxy urea cyclization precursors in good yield. The cyclization is performed by the addition of 1.1 equivalents of *bis*(trifluoroacetoxy)iodobenzene, in portions, to a 0° to 25°C solution of the substrate in methylene chloride. Typically, within 30 minutes the reaction is complete and extraction followed by chromatography gives the pure 3-alkyl (or aryl) substituted 1-methoxy-2-benzimidazolinones. If desired, the N-methoxy group can be removed by hydrogenation over Pd/C in ethanol at 50 p.s.i.

References and Notes:

1. For example, nitration/reduction. For a superior one-pot method utilizing aryl carbanions (Li or Mg) and diphenylphosphoryl azide, see S. Mori, T. Aoyama, T. Shioiri, *Tetrahedron Lett.* **1984**, *25*, 429-432.
2. Perronner, J.; Demoute, J.-P. *Gazz. Chim. Ital.* **1982**, *112*, 507-511.
3. A related one-pot oxidative cyclization induced by lead tetraacetate has been reported. The cyclization substrates (similar to **17**) possess a hydrogen substituent on the 3-N aryl substituted urea nitrogen: J.H. Cooley and P.T. Jacobs, *J. Org. Chem.* **1975**, *40*, 552-557.
4. All products were fully characterized and gave acceptable C,H,N analyses.
5. *Bis*(trifluoroacetoxy)iodobenzene has been used in a similar fashion to obtain cyclic N-methoxy lactams. Y. Kikugawa and M. Kawase, *Chem. Lett.* **1990**, 581-582. For reviews of hypervalent iodine chemistry, see: R.M. Moriarty, O. Prakash, *Acc. Chem. Res.* **1986**, *19*, 244-250; A. Varvoglis, *Synthesis* **1984**, 709-726.
6. *Bis*(trifluoroacetoxy)iodobenzene is prepared by carboxylic acid exchange, i.e. dissolving *bis*(acetoxy)iodobenzene in trifluoroacetic acid.
7. Other alkyloxy groups such as benzyloxy can be substituted for methoxy.
8. It is interesting to speculate that this product is generated by the loss of CH_3ONCO from the aryl nitrogen by loss of the adjacent C-H proton; this type of side product was not seen with cyclization precursor **13**.



(*Received in USA* 12 *January* 1996; *accepted* 6 *February* 1996)