Pergamon

Tetrahedron Letters, Vol. 35, No. 49, pp. 9189-9190, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02069-8

A Direct Preparation of 1,4-Benzodiazepines. The Synthesis of Medazepam and Related Compounds via a Common Intermediate

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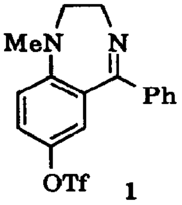
Key Words: benzodiazepine; triflate; palladium; photochemistry

Abstract: *The benzodiazepine skeleton was prepared from benzoquinone in three steps. Medazepam was prepared from 9.*

. The 1,4-benzodiazepine skeleton has been the object of a variety of synthetic strategies. Interest in this unit stems from the commercially significant antianxiety activity of Diazepam (Valium).[1] Most syntheses use a Friedel-Crafts reaction to assemble the benzophenone subunit and then form the diazepine ring by condensation with a derivative of glycine. One exception is the Sumitomo synthesis which makes the benzophenone unit by oxidation of an indole with chromium trioxide.[2] As part of a program designed to develop environmentally benign syntheses of industrial products,[3] we have developed a general synthesis of benzodiazepines from triflate **1**. Medazepam (**2**), which can be converted into Diazepam (**3**) in one step,[4] has also been synthesized.



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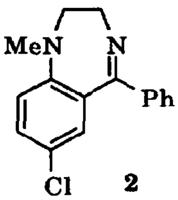

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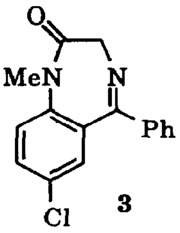

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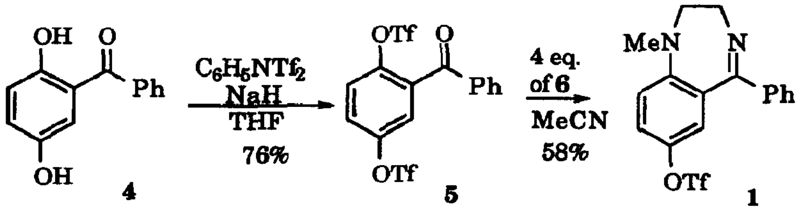
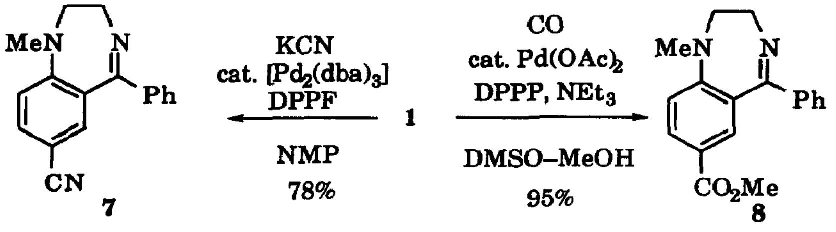
The benzophenone **4** was constructed by the photochemically-mediated reaction of benzoquinone with benzaldehyde.[5] This reaction proceeds in 60% yield with few byproducts. In this case it is a convenient alternative to a Friedel-Crafts reaction. Surprisingly, a literature search revealed that this compound had never been converted into a benzodiazepine. To the best of our knowledge, the conversion of an ortho-hydroxybenzophenone directly into a benzodiazepine has no precedent.[6]

Initial attempts to convert **4** directly into a benzodiazepine by reaction of **4** or its corresponding dimethyl ether with ethylenediamine resulted in the recovery of **4**. The bis-triflate **5** could be readily prepared from **4** using NaH and N-phenyltriflimide. Although the reaction of ethylenediamine with **5** afforded a mixture of products, the reaction of N-methylethylenediamine (**6**) provided benzodiazepine **1** in 58% yield.

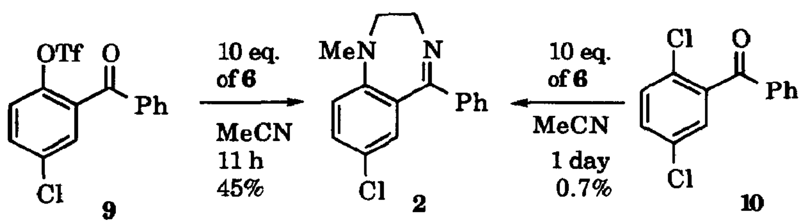
We view **1** as a key intermediate for the synthesis of substituted benzodiazepines. Aryl triflates are known



to be excellent substrates for palladium-mediated transformations.[7] Using this technology, we prepared nitrile 7[8] and ester 8 in 78% and 95% yields, respectively.



In order to investigate the generality of the reaction involving N-methylethylenediamine, we synthesized triflate 9 and chloride 10[9]. The reaction of diamine 6 with 9 provided Medazepam (2) in 45% yield. The NMR and IR spectra and melting point of our compound 2 was identical to those reported for Medazepam. The



reaction of 6 with 9 was slower than the reaction of 5 with 6. Interestingly, the reaction of chloride 10 with 6 under the same conditions yielded 90% recovered starting material and only a 0.7% yield of 2.

Acknowledgements - We thank the EPA Office of Pollution Prevention and Toxics, Design for the Environment Program and the National Science Foundation Environmentally Benign Synthesis Program for support.

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(*Received in USA* 9 *August* 1994; *revised* 7 *October* 1994; *accepted* 14 *October* 1994)