ZINC-MEDIATED METATHESIS IN THE BERNTHSEN CONDENSATION

Michael D. Mosher*, Troy D. Morris, Sarah Westerbuhr, and Cory Foster
Department of Chemistry
University of Nebraska at Kearney
Kearney, NE 68849-1150

Abstract

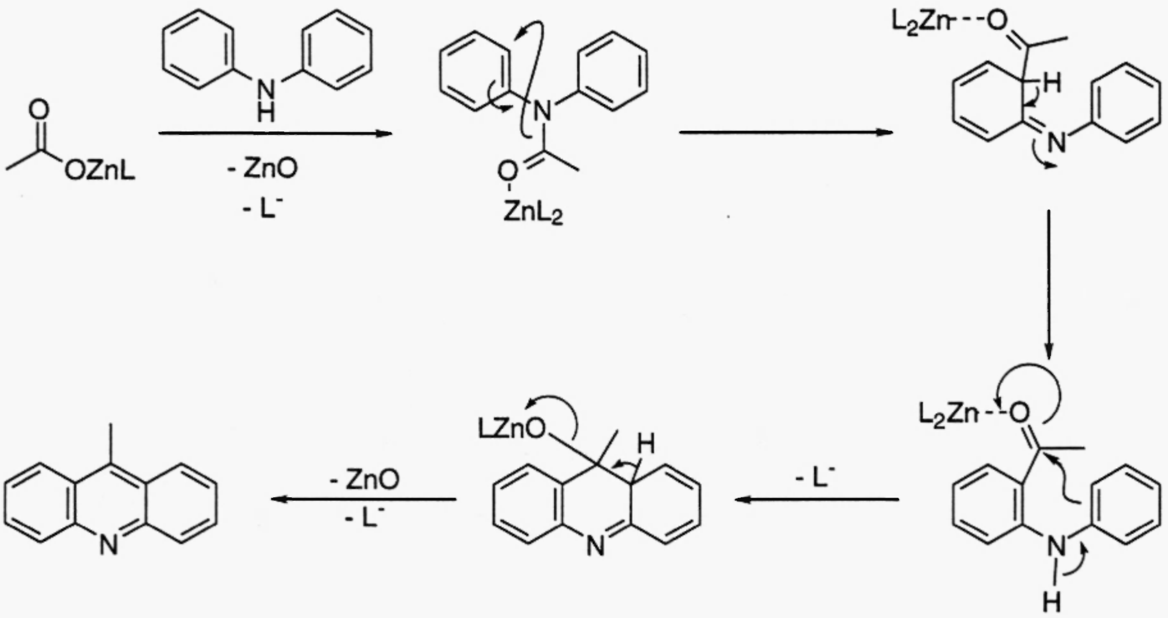
The Bernthsen Condensation is a convenient method for the preparation of 9-alkylacridines from the reaction of a carboxylic acid with diphenylamine. Attempts to prepare 9-substituted acridines using α,β-unsaturated carboxylic acids gave 9-methylacridine as the only isolable product. This compound most likely arises via the zinc-mediated metathesis of the carboxylic acid.

Introduction

The Bernthsen condensation involves the reaction of diphenylamine with an alkyl or aryl carboxylic acid in the presence of anhydrous zinc dichloride to provide a 9-alkyl- or 9-arylacridine (1). This reaction provides a one-step route to multigram scale quantities of product from commercially available starting materials. Other methods to prepare 9-alkyl substituted acridines include the reaction of an alkyl magnesium with 9-chloroacridine (2), or N-SEM-9-acridone (3). In the case of the organomagesium addition to 9-chloroacridine, the preparation and purification of 9-chloroacridine is required immediately before use (4) and produces a mixture of products resulting from over alkylation.

The Bernthsen Condensation to prepare 9-methylacridine proceeds at 250°C without solvent. The product (>98% pure as determined by NMR (5)) is isolated by treatment of the reaction mixture with warm 10% sulfuric acid (6). While the best yields for the reaction are observed with acetic acid (78%), products otherwise difficult to make are isolable in moderate yield (15-60%) (7).

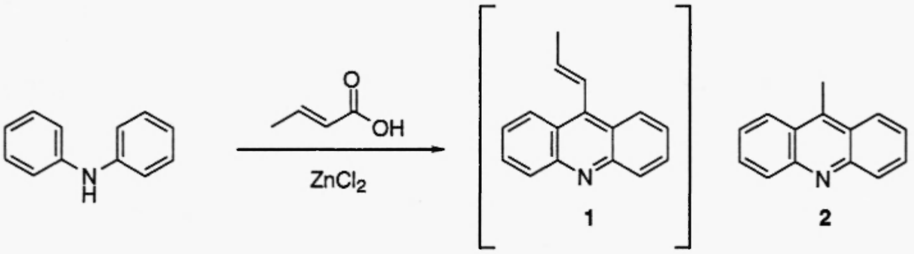
The mechanism (8), illustrated in Scheme 1, involves the condensation of the carboxylic acid and diphenylamine which provides the initial intermediate, an N,N-diphenylamide (9). The amide then undergoes a zinc-mediated 1,3-acyl transfer. The intermediate aryl ketone then provides the product via an intramolecular Friedel Crafts-type mechanism.



SCHEME 1: Mechanism of the Bernthsen Condensation

Results and Discussion

In our search for a facile route to 9-allylacridine 1, we proposed the synthesis of 1 via the Bernthsen Condensation. We predicted that the product would arise from the zinc-mediated condensation of crotonic acid and diphenylamine. However, all attempts to isolate the desired product failed. Instead, the only product isolated from the reaction mixture was 9-methylacridine 2 (10).

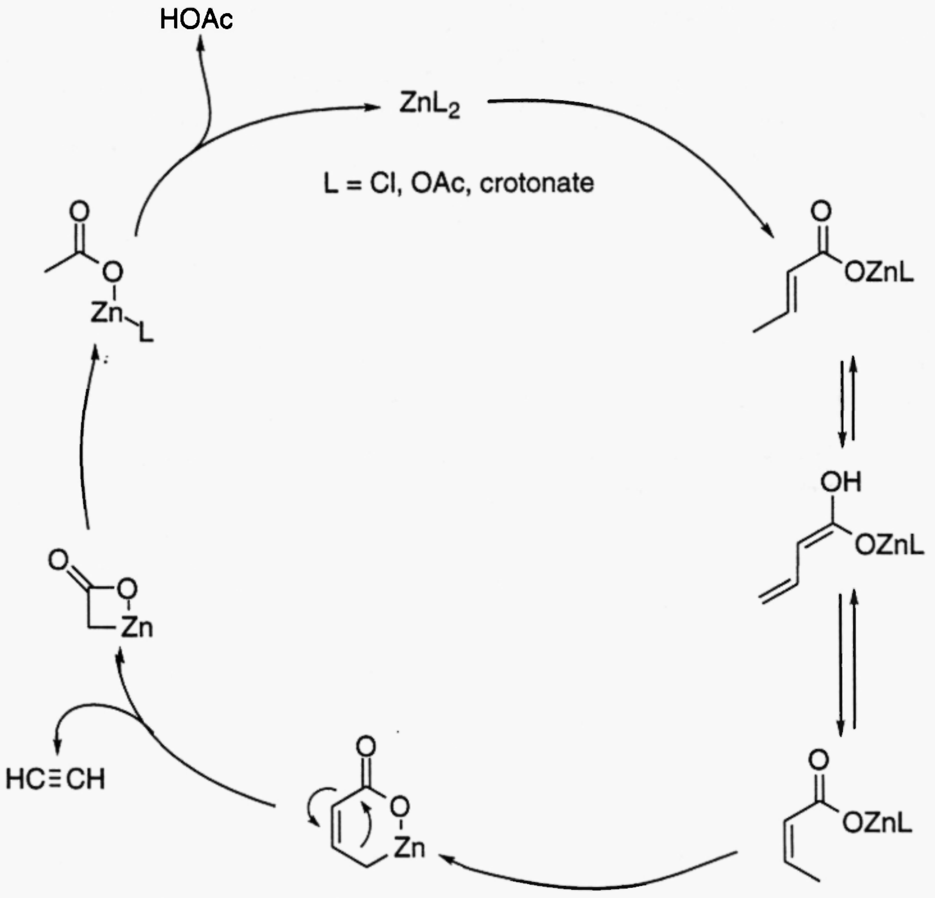


SCHEME 2: Unexpected outcome in the Bernthsen Condensation.

Similarly, our attempts to prepare 9-(3',5'-dimethyl-4'-isoxazolyl)-acridine directly from diphenylamine, anhydrous zinc dichloride, and 3,5-dimethyl-4-isoxazole carboxylic acid (11) resulted exclusively in the isolation of 2.

We postulate that the product of this reaction arises from the following zinc-mediated metathesis (see SCHEME 3). Reaction of zinc dichloride with the unsaturated carboxylic acid gives rise to the zincate salt (12). Acid catalyzed enol formation gives rise to scrambling of the geometry about the C=C. Once in the cis conformation, intramolecular cyclization brings about formation of the metallocycle. Then, metathesis provides a molecule of acetylene and a zinc acetate. The zinc acetate thus formed goes on to react with diphenylamine to provide 9-methylacridine 2.

Attempts to identify acetylene in the reaction mixture by bubbling the reaction gasses through a solution of bromine (both aqueous and organic) and isolating 1,1,2,2-tetrabromoethane were unsuccessful. Attempts to isolate the Diels-Alder adduct of methylisoxazolyne and anthracene in the reaction mixture were also unsuccessful. While these products of the proposed mechanism have not been isolated, the mechanism still appears to be the most plausible explanation of the reaction outcome.



SCHEME 3: Zinc Metathesis of Crotonic Acid.

Conclusions

The reaction of anhydrous zinc chloride, crotonic acid, and diphenylamine at the melt gives rise to 9-methylacridine. We have proposed a mechanism that involves a zinc mediated metathesis of the crotonic acid to acetic acid. Further evidence for this mechanism is seen in the reaction of zinc chloride, diphenylamine and 3,5-dimethyl-4-isoxazole carboxylic acid which provides 9-methylacridine. Work is currently underway to isolate intermediates in the proposed mechanism.

Acknowledgements

The authors would like to acknowledge financial support for this project by the Research Services Council and the Department of Chemistry at the University of Nebraska at Kearney.

References and Notes

1. A. Bernthsen, Liebigs Ann., 192, 1 (1878); F.D. Popp, J. Org. Chem., 27, 2658 (1962)

2. W.L. Semon, D. Craig, J. Amer. Chem. Soc., 58, 1278 (1936)

3. Z. Zeng, S.C. Zimmerman, Tet. Lett., 29, 5123 (1988)

4. 9-Chloroacridine undergoes autocatalyzed decomposition to HCl and 9-acridanone. S. Skonieczny, Heterocycles, 14, 985 (1980); J.M.F. Gagan, 9-Acridanones, in R.M. Acheson (Ed.), Acridines, vol.9; A. Weissberger, E.C. Taylor (Eds.), The Chemistry of Heterocyclic Compounds, Wiley, New York 1973

5. All data were collected on a Brüker WM-360 (360MHz for ^1H) spectrophotometer.

6. O. Tsuge, M. Nishinohara, M. Tashiro, Bull. Chem. Soc. Jpn., 36, 1477 (1963); R.E. Lehr, P.N. Kaul, J. Pharm. Sci., 64, 950 (1975)

7. See for example: F. Albert, J. Chem. Soc., 1225 (1948)

8. A. Albert, The Acridines: Their Preparation, Physical, Chemical, and Biological Properties and Uses, 2nd Ed., St. Martin's Press, New York, 1966

9. We have been able to extractively isolate this intermediate from the reaction of diphenylamine and 5-methyl-3-phenyl-4-isoxazole carboxylic acid with greatly reduced temperatures in good yield.

10. All compounds isolated possessed physical data (IR, UV-Vis, H-NMR, and mp) in agreement with that found in the literature.

11. Prepared by the nitrile oxide cycloaddition with the pyrrolidine enamine of ethyl acetoacetate: K.D. Bowles, D. Quincy, B. Mallet, J.L. McKenna, N.R. Natale, J. Chem. Ed., 62, 118 (1985)

12. Crystal structures of zincate salts have been obtained. For example, see: A.V. Capilla, R.A. Aranda, Cryst. Struct. Comm., 8, 795 (1979); W. Clegg, I.R. Little, B.P. Straughan, Acta Cryst., C42, 919 (1986); W. Clegg, I.R. Little, B.P. Straughan, B.P. Inorg. Chem., 27, 1916 (1988)

Received September 27, 1996