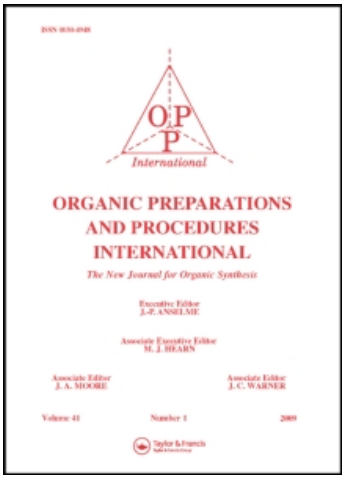

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5,6-DIHYDRO-4H-1,3-OXAZINES BY A MODIFICATION OF THE TILLMANNS-RITTER PROCEDURE

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5,6-DIHYDRO-4H-1,3-OXAZINES BY A MODIFICATION OF THE TILLMANNS-RITTER PROCEDURE[1]

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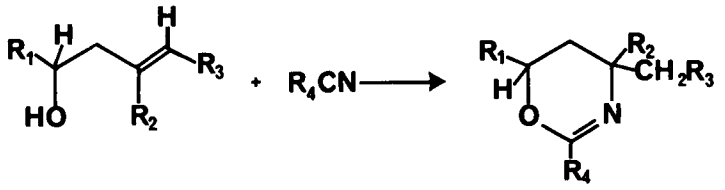
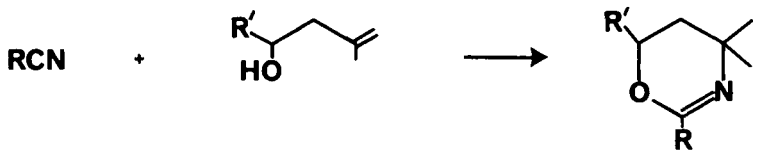


In 1957 Tillmanns and Ritter described the synthesis of some 1,3-oxazine derivatives by the reaction of 2,2,4-trimethyl-2,4-pentanediol with nitriles in 92% sulfuric acid.[3,4] The usefulness of the reaction as a general method has been limited by the lack of readily available diols with the appropriate substituents. Meyers[5] introduced an innovation where the 1,3-oxazine or dihydropyridine derivative could be isolated depending on the acid concentration used. In his study, Meyers substituted α-(1-cyclopentenyl)-t-butyl alcohol for the diol and obtained the product through initial carbonium ion formation and nitrile attack at the alcohol carbon. Presumably, for steric and electronic reasons, the tertiary carbonium ion forms faster from the alcohol than it does from the olefin. One a priori would predict that 1,3-oxazine derivatives could also be formed through protonation of the double bond in an appropriately substituted allylic carbinol.

When some oxazine derivatives were required for spectral comparisons, the latter procedure was investigated since, for the desired derivatives that route was the only one available where all starting materials could be purchased. A typical procedure is described below and our results for several simple allylic carbinols

TABLE



R	R'	% Yield	b.p.	n_D^{20}	Picrate m.p.	Picrate Anal. Calcd. C	H	Found[a] C	H
CH_3	H	48	58.5-59°/37mm[b]	1.4440	166-167°	43.82	4.53	44.06	4.54
CH_3	CH_3	51	59-60°/28mm[c]	1.4348	152-153°				
CH_3	n-C_3H_7	56	d	1.4567	140-141°	48.24	5.57	48.38	5.61
C_6H_5	CH_3	50	99-102°/2.8mm[e]						
$C_6H_5CH_2$	CH_3	44[f]	76°/0.5mm[g]	1.5130	125-126°				

[a] Microanalyses were performed by Gailbraith Laboratories, Inc., Knoxville, Tenn. [b] i.r., 1670 cm^{-1} (C=N), n.m.r. (in CCl_4 solution; TMS internal ref.; Varian A-60 instrument; we are grateful to the Rohm and Haas Company for obtaining these spectra.) 8.27τ (C-2 Me), 8.92τ (C-4 Me), 5.94τ (multiplet, C-6 H); [c] lit.[3] b.p. 56°/24mm, n_D^{25} 1.4370, picrate m.p. 153-154°; [d] purified by column chromatography on acid-washed alumina, eluted with 50:50 benzene-ether; i.r. 1666 cm^{-1} (C=N), n.m.r., 8.22τ (C-2 Me), 8.91τ (C-4 Me), 6.17τ (multiplet, C-6 H); [e] extracted a cold, slightly acidic solution with two portions of $CHCl_3$ prior to making basic; m.p. 33-34°, lit.[3] m.p. 34-35°, b.p. 103-106°/3mm; [f] yields reported by Tillmanns and Ritter[3] for the 2-CH_3, 2-C_6H_5, and 2-$C_6H_5CH_2$ derivatives are 44%, 47%, and 26% respectively; [g] lit.[3] b.p. 116-119°/5mm, n_D^{20} 1.5125, picrate m.p. 125-126°.

are summarized in the Table. Included, for comparison, are the three oxazines reported by Tillmanns and Ritter in their original work.[3]

On the basis of our studies, we believe that the reaction shown in the equation above represents the most versatile of the three possible modifications of the Tillmanns-Ritter procedure. For example, since methallyl chloride and 2-phenylallyl chloride are both readily available, many unknown oxazine derivatives can be reached through the appropriate Grignard reaction.[6] In addition to the 4,4-dimethyl or 4-methyl-4-phenyl-2,6-disubstituted derivatives obtained by the method above, other derivatives such as the unknown 2,4-dimethyl-4-ethyl-5,6-dihydro-4H-1,3-oxazine could be prepared by use of the commercially available 3-methyl-3-penten-1-ol.

We have modified the work-up procedure from that generally used.[3] Our method gives improved yields in most cases. For example, the lowest yield reported by Tillmanns and Ritter[3] was the case using phenylacetonitrile (yield 26%). We reproduced their yield with their procedure, but improved it to 40-46% using our modified work-up. In our procedure, the product is allowed to dwell in the dilute acid range for only a very short period of time; and it is extracted upon liberation.[7,8] Our modification does not totally circumvent the general disadvantage of all Ritter procedures——that is, the use of a large volume of solvents with respect to the amount of product obtained. However, the working time is reduced by virtue of the reduction in the number of extractions.

Experimental

2,4,4-Trimethyl-5,6-dihydro-4H-1,3-oxazine Over a period of 0.5 hr., 10.55g (0.256 mole) of acetonitrile was added dropwise with stirring to 116g of 92% sulfuric acid at 3-8°C. While the temperature was maintained at 8-10°, 3-methyl-3-buten-1-ol (20g., 0.232 mole) was slowly added to the sulfuric acid solution. A yellow color formed immediately and became more pronounced throughout the addition. After the addition was complete, the reddish brown solution was stirred for 0.4 hr. as the flask was allowed to gradually warm to room temperature. To a 3 liter, three-necked flask[9] fitted with a mechanical stirrer, was added 900 ml. of a 10% solution of sodium hydroxide previously cooled in ice. To

the flask submerged in an ice bath, was added 200 ml. diethyl ether. The contents were rapidly stirred as the acid solution containing the salt of the product was carefully added. After rapid stirring for an additional 5-10 minutes, the layers were separated, the organic layer was dried (Na_2SO_4), and the solvent was distilled. The liquid residue was distilled through a Vigreux column and 14.2g (48%) of product was collected at 58.5-59°/37mm. The product should be stored in a clean bottle under nitrogen.[7]

References

1. (a) Acid-catalyzed Cyclization Reactions. VII. For paper VI, see C. U. Pittman and S. P. McManus, J. Am. Chem. Soc., 91, 5915 (1969); (b) Supported in part by grants from the Petroleum Research Fund, administered by the American Chemical Society, and the National Aeronautics and Space Administration.

2. American Chemical Society Petroleum Research Fund Undergraduate Scholar, 1969.

3. E. J. Tillmanns and J. J. Ritter, J. Org. Chem., 22, 839 (1957).

4. For a recent review, see L. I. Krimen and D. J. Cota, Org. Reactions, 17, 213 (1969).

5. A. I. Meyers, J. Schneller, and N. K. Ralhan, J. Org. Chem., 28, 2944 (1963).

6. M. Tamele, C. J. Ott, K. E. Marple, and G. Hearne, Ind. Eng. Chem., 33, 115 (1941).

7. Cyclic imino ethers are very susceptible to ring opening and/or polymerization; c.f. W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Their, and H. Hellman, Angew. Chemie, Internat. Edit., 5, 875 (1966).

8. In some cases, it is still desirable to extract a cold, dilute acidic solution to remove non-basic starting materials that may boil in the vicinity of the product. An alternative is column chromatography since the oxazines generally can be separated from excess nitrile or alcohol.

9. The operation can be simplified by substituting a separatory funnel-type flask and using ice in the base solution.

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