Tetrahedron Letters,Vol.25,No.35,pp 3837-3840,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A NEW "ONE POT" PREPARATION OF 2-N,N-DIALKYLAMINO-1,3-BENZOXAZINES AND NAPHTH[1,2-e][1,3]OXAZINES FROM CORRESPONDING *ORTHO* HYDROXYNITRILES AND PHOSGENIMINIUM SALTS

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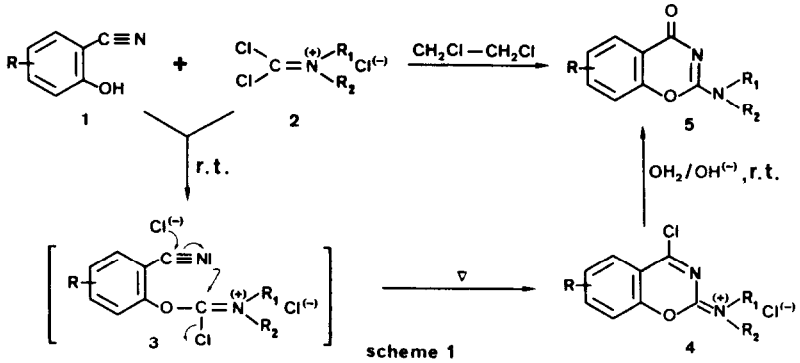
Abstract : Phosgeniminium salts 2 react easily with *ortho* hydroxybenzonitriles 1 and 2-hydroxy-1-naphthonitriles 6 to give 1,3-benzoxazine and naphth[1,2-e][1,3]oxazine derivatives respectively with a very good yield.

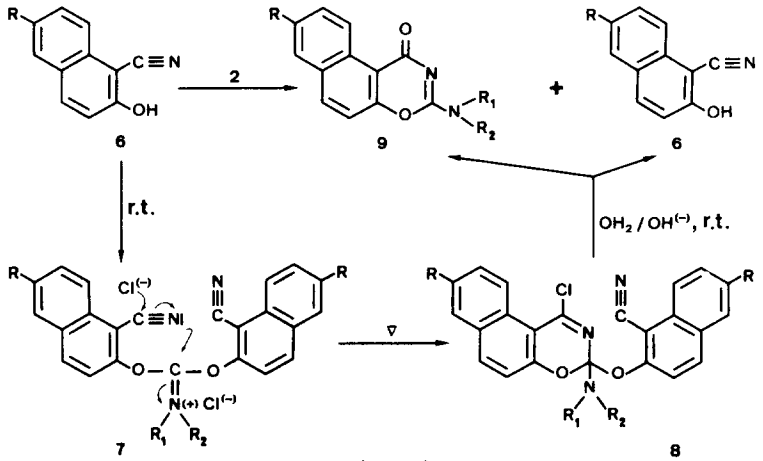
One step heterocyclisation reactions by insertion of one carbon atom bearing a dialkylamino group via Phosgeniminium salt condensations, have been proved to be very useful in organic synthesis (1-3). In our attempt to develop new simple procedures for the preparation of heterocyclic compounds of biological interest, we showed recently (4) that phosgeniminium salts react easily with *ortho* aminobenzonitriles leading, selectively, to corresponding 2-dialkylamino-4-chloroquinazolines. We wish to report now that phosgeniminium chlorides 2 react as well with *ortho* hydroxybenzonitriles 1 to give, under very mild "one pot" reaction conditions, and with a very good yield, the corresponding 1,3-benzoxazine derivatives 4 and 5 (R = H, 6-OCH_3, 7-OCH_3, 8-OCH_3, 6-Br, 6-Cl, 6-NO_2) :



scheme 1

Since 2 do not react with insufficiently activated nitriles (1), (2), (4), we assume that, that reaction proceeds very likely through formation of salts 3 and 4. The latter, which lead, after an *in situ* alkaline hydrolysis to the corresponding 2-N,N-dialkylamino-1,3-benzoxazin-4-ones 5 are very stable under dry conditions. They have actually been isolated for characterization purposes and further investigations of their synthetic utility.

Ortho hydroxynaphthonitriles of type 6 (R = H, OCH_3, Br) are converted into their corresponding oxazinones 9 as well (scheme 2). However, phosgeniminium salts 2 do not behave with these nitriles 6 as they do with nitriles 1. In fact, while 2 react with hydroxybenzonitriles 1 in an equimolecular ratio forming benzoxazinones 4 via phenoxychloromethyleniminium chlorides 9 (scheme 1), it was found that two equivalents of 2 are necessary to give naphthoxazinones 9 through naphthoxymethyleniminium salts 7 as shown in scheme 2.



scheme 2

Salts 7 cyclise under slight heating to form thermally stable ethers 8 which are converted, by base treatment, to naphthoxazinones 9. As expected the starting *ortho* hydroxynaphthonitriles 6 were also recovered. Based upon consumption of the starting material, this reaction proceeds in nearly quantitative yield.

The 1,3-benzoxazine and naphth[1,3]oxazine ring systems are usually formed from various ortho-substituted phenols, including *ortho* hydroxybenzonitriles (5-11), by condensation with compounds such as aldehydes, ketones, phosgene, isocyanates and acid chlorides. Although many routes are available, very few (12-14), can lead directly to the 2-N,N-dialkylamino substituted derivatives of type 5. These are usually prepared by more tedious methods starting with compounds such as 3-hydroxyisoxazoles (15) and salicyloylethylhydantoïn (16).

To our knowledge, 2-N,N-dialkylamino-naphth[1,2-e][1,3]oxazin-4-ones of type 9 were unknown so far.

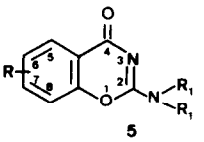
Typical procedures

1) 2-N,N-dimethylamino-1,3-benzoxazin-4-ones 5 ($R_1 = R_2 = CH_3$)

Ortho hydroxybenzonitriles 1 : R = H, 3-OCH_3, 4-OCH_3, 5-OCH_3, 5-Br, 5-Cl, 5-NO_2, (0.01 mole) was added to 2a : $R_1 = R_2 = CH_3$ (0.012 mole) and dry 1,2-dichloroethane (100 ml). The mixture, kept under stirring and dry atmosphere, was allowed to stand at room temperature for 2 hours, heated at 50-60°C for 2-3 hours, then refluxed for 5-6 hours and cooled at room temperature. The solvent was removed under vacuum and 20 ml of water added to the residue.

The resulting solution was alkalinized with an excess of potassium carbonate and extracted 4-5 times with chloroform to give 1,3-benzoxazin-4-ones 5 (yield 80 to 85 %).

NMR (17)



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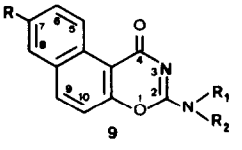
- 5a *(R = H, $CDCl_3$) : 8.15 (dd, 5H, J_{5-6} = 8.0 Hz, J_{5-7} = 2.0 Hz) ; 7.80 - 7.10 (5br, 6, 7 and 8-H) ; 3.25 (s, $N(CH_3)_2$).*
- 5b *(R = 6-OCH_3, $CDCl_3$) : 7.55 (br, 5-H) ; 7.15 (br, 7 and 8-H) ; 3.85 (s, OCH_3) ; 3.25 (s, $N(CH_3)_2$).*
- 5c *(R = 7-OCH_3, $CDCl_3$) : 8.05 (d, 5-H, J_{5-6} = 9.0 Hz) ; 6.85 (dd, 6H, J_{5-6} = 9.0 Hz, J_{6-8} = 3.0 Hz) ; 6.6 (d, 8-H, J_{6-8} = 3.0 Hz) ; 3.80 (s, OCH_3) ; 3.20 (s, $N(CH_3)_2$).*
- 5d *(R = 8-OCH_3, $CDCl_3$) : 7.70 (dd, 5-H, J_{5-6} = 7.0 Hz, J_{5-7} = 3.0 Hz) ; 7.45 - 7.15 (br, 6 and 7-H) ; 4.0 (s, OCH_3) ; 3.30 (s, $N(CH_3)_2$).*
- 5e *(R = 6-Br, $CDCl_3$) : 8.25 (d, 5-H, J_{5-7} = 2.0 Hz) ; 7.75 (dd, 7-H, J_{5-7} = 2.0 Hz, J_{7-8} = 9.0 Hz) ; 7.20 (d, 8-H, J_{7-8} = 9.0 Hz) ; 3.30 (s, $N(CH_3)_2$).*
- 5f *(R = 6-Cl, $CDCl_3$) : 8.10 (d, 5-H, J_{5-7} = 2.0 Hz) ; 7.60 (dd, 7-H, J_{5-7} = 2.0 Hz, J_{7-8} = 9.0 Hz) ; 7.15 (d, 8-H, J_{7-8} = 9.0 Hz) ; 3.25 (s, $N(CH_3)_2$).*
- 5g *(R = 6-NO_2, $CDCl_3$) : 9.00 (d, 5-H, J_{5-7} = 3.0 Hz) ; 8.50 (dd, 7-H, J_{5-7} = 3.0 Hz, J_{7-8} = 9.0 Hz) ; 7.40 (d, 8-H, J_{7-8} = 9.0 Hz) ; 3.35 (s, $N(CH_3)_2$).*

2) 2-N,N-dimethylamino-naphth[1,2-*e*][1,3]oxazin-4-ones **9** (R_1 = R_2 = CH_3).

Ortho hydroxynaphthonitriles 6 : R = H, OCH_3, Br, (0.01 mole), was added to 2a: R_1 = R_2 = CH_3 (0.006 mole), and dry 1,2-dichloroethane (50 ml). The mixture was stirred under dry atmosphere and kept at room temperature for 2 hours, heated at 50-60°C for 5-6 hours then refluxed for 3-4 hours. The solvent was removed under vacuum and the residue dissolved with 20 ml of water. The resulting solution was alkalinized with an excess of potassium carbonate and extracted 4-5 times with chloroform to give naphthoxazinones 9. The water layer, acidified with acetic acid, was extracted 4-5 times with chloroform to give *ortho* hydroxynaphthonitriles 6.

NMR (17)

- 9a *(R = H, $CDCl_3$) : 9.95 (dd/br, 5-H, J_{5-6} = 9.0 Hz) ; 8.0 (d, 9-H, J_{9-10} = 9.0 Hz) ; 7.8 - 7.4 (br, 6, 7 and 8-H) ; 7.25 (d, 10-H, J_{9-10} = 9.0 Hz) ; 3,2 (s, $N(CH_3)_2$).*
- 9b *(R = OCH_3 ; $CDCl_3$) : 9.80 (dd/br, 5-H, J_{5-6} = 9.0 Hz) ; 7.90 (d, 9-H, J_{9-10} = 9.0 Hz) ; 7.50 - 7.10 (br, 6, 8 and 10-H) ; 3.85 (s, OCH_3) ; 3.20 (s, $N(CH_3)_2$).*
- 9c *(R = Br ; TFA) : 9.30 (d, 5-H, J_{5-6} = 9.0 Hz) ; 8.45 (d, 9-H, J_{9-10} = 9.0 Hz) ; 8.25 (d, 8-H, J_{6-8} = 2.0 Hz) ; 8.05 (dd, 6-H, J_{5-6} = 9.0 Hz, J_{6-8} = 2.0 Hz) ; 7.65 (d, 10-H, J_{9-10} = 9.0 Hz) ; 3.65 and 3.60 (2s, $N(CH_3)_2$).*



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Acknowledgments

Financial support from the "Institut National de la Santé et de la Recherche Médicale" (I.N.S.E.R.M.) and the "Institut Curie", is gratefully acknowledged.

We wish to thank Mrs S. Risse and Dr. J. Einhorn for providing us with samples of some non-commercially available *ortho* hydroxybenzo (and naphtho)nitriles 1 and 6, and Dr. G. Bastian for valuable discussions.

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(17) H^1-NMR : (ppm)/TMS (Internal reference) : s = singlet, d = doublet, dd = doublet of doublet, br = broad, TFA = trifluoroacetic acid-d.

(Received in France 27 May 1984)