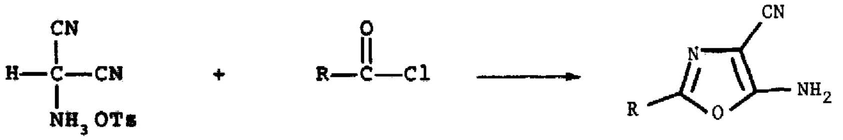
Tetrahedron Letters,Vol.30,No.20,pp 2631-2632,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

PREPARATION OF 2-ALKYL- AND 2-ARYL-5-AMINO-4-CYANO-1,3-OXAZOLES

Fillmore Freeman* and Darrick S.H.L. Kim
Department of Chemistry
University of California, Irvine
Irvine, California 92717

Summary: Aminopropanedinitrile p-toluenesulfonate (aminomalononitrile tosylate, AMNT) reacts with acid chlorides to give 2-alkyl- and 2-aryl-5-amino-4-cyano-1,3-oxazoles in good to excellent yields.

The chemistry of 1,3-oxazoles is of considerable interest owing to their use as synthetic substrates for a wide variety of heterocycles and to the presence of the oxazole ring in natural products and biologically active compounds.[1-13] Although oxazole derivatives can be prepared by various cyclization procedures and rather lengthy and complex reaction sequences, effective methods for the direct introduction of functional groups on the oxazole ring are rare.[6,7] During a search for facile preparations of functionalized oxazoles to be used in the synthesis of C-nucleosides,[14] we observed that alkanoyl and aroyl chlorides [(RC(O)Cl; R = methyl (63%); ethyl (76%); isopropyl (80%); phenyl (93%); 4-methoxyphenyl (51%); 4-nitrophenyl (95%); 2-furyl (53%)] react with readily available aminopropanedinitrile p-toluenesulfonate (aminomalononitrile tosylate, AMNT, 1)[15-19] in 1-methyl-2-pyrrolidinone to give 2-alkyl- and 2-aryl-5-amino-4-cyano-1,3-oxazoles (2).[19-23]



1 2

Experimental Procedure: To a stirred solution (23-25 °C) of 1.17 g (4.6 mmol) of aminomalononitrile tosylate (AMNT, 1) and 12 mL (11.6 g; 117 mmol) of 1-methyl-2-pyrrolidinone in a 50-mL round bottomed flask were added 1.1 equivs of acid chloride in one portion. The reaction mixture was stirred at 23-25 °C overnight (12 to 18 h)[24,25] and then diluted with 100 mL of a 1:1 solution of ethyl ethanoate:ethyl ether. This solution was washed with water (2 x 100 mL), with 10% sodium hydrogen carbonate solution (50 mL), and with water (2 x 100 mL). The organic layer was dried ($MgSO_4$), the solvent was evaporated in vacuo, and the 1,3-oxazole (2) was recrystallized from ethyl ethanoate/ethyl ether.

Acknowledgment is made to the National Science Foundation (CHE 86-19651) for partial support of this research.

References

1. Dondoni, A.; Fantin, G.; Fogagnolo, M; Mastellari, A.; Medici, A.; Pedrini, P. J. Org. Chem. 1984, 49, 3478.

2a. Vedejs, E.; Grissom, J.W. J. Am. Chem. Soc. 1988, 110, 3238.

2b. Vedejs, E.; Grissom, J.W. J. Org. Chem. 1988, 53, 1876.

2c. Vedejs, E.; Grissom, J.W. J. Org. Chem. 1988, 53, 1882.

3. Liesch, J.M.; Rinehardt, K.L., Jr. J. Am. Chem. Soc. 1976, 99, 1645.

4. Nagao, Y.; Yamada, S.; Fujita E. Tetrahedron Lett. 1983, 24, 2287; 2291.

5. Meyers, A.I.; Amos, R.A. J. Am. Chem. Soc. 1980, 102, 870.

6a. Turchi, I.J.; Dewar, M.J.S. Chem. Rev. 1975, 75, 389.

6b. Turchi, I.J. Chemistry of Heterocyclic Compounds; Turchi, I.J., Ed.; Wiley: New York, 1986, Vol. 45.

6c. Turchi, I.J. Ind. Eng. Chem. Prod. Res. Dev. 1981, 20, 32.

7. Lakhan, R.; Ternai, B. in "Advances in Heterocyclic Chemistry", Vol. 17, Katritzky, A.R.; Boulton, A.J., Eds., Academic Press, New York, 1974.

8. Lakhan, R.; Singh, R.L. J. Heterocycl. Chem. 1988, 25, 1413.

9. Wasserman, H.H.; Lu, T.-J. Tetrahedron Lett. 1982, 23, 3831.

10. Takeuchi, H.; Yanagida, S.; Ozaki, T.; Hagiwara, S.; Eguchi, S. J. Org. Chem. 1989, 54, 431.

11. Boyd, G.V. Comprehensive Heterocyclic Chemistry; Katritzky, A.R.; Rees, C.W.; Eds.; Pergamon Press: Oxford, 1984, Vol. 6, Part 4B, Chapter 18.

12. Sainsbury, M. Rodd's Chemistry of Carbon Compounds, Vol. IVC; Ansell, M.F.; Ed.; Elsevier: Amsterdam, 1986, Chapter 17.3.

13. Dominguez, X.A.; de la Fuente, G.; Gonzalez, A.G., Reina, M.; Timon, I. Heterocycles 1988, 27, 35, and references cited therein.

14. Freeman, F.; Scheuerman, R.A., unpublished data.

15. Niels Clauson-Kaas Laboratory, Farnum, Denmark.

16. Taylor, E.C.; Sun, J.-H Synthesis 1980, 801.

17. Junek, H.; Mittelbach, M. Z. Naturforsch. [B] 1979, 34, 280.

18. Ferris, J.P.; Sanchez, R.A.; Mancusco, R.W. Org. Synth. Coll. Vol. V. 1973, 32.

19. Ferris, J.P.; Orgel, L.E. J. Am. Chem. Soc. 1966, 88, 3829.

20. Ferris, J.P.; Orgel, L.E. J. Am. Chem. Soc. 1965, 87, 4976.

21. Freeman, F. Synthesis, 1978, 925.

22. Fatiadi, A.J. Synthesis, 1978, 165, 241.

23. The melt points of the 2-alkyl- and 2-aryl-5-amino-4-cyano-1,3-oxazoles (2) agreed with literature values and/or gave satisfactory high resolution mass spectra (HRMS). In addition, 2-phenyl-5-amino-4-cyano-1,3-oxazole was converted with formamidine to its known adenine analogue.[19-21]

24. Although thin layer chromatography (TLC, developed in 1:2 ethyl ethanoate:hexanes and treated in a diiodine chamber) showed the disappearance of substrates within 30 min, the yields were lower [(R = methyl (30%); R = ethyl (35%).

25. This procedure has several advantages over a previously reported method[19,20] that used acid anhydrides. In this procedure the experimental details are simpler, the reaction times are shorter, the yields are higher, and all of the carbonyl substrate is utilized.

(Received in USA 14 February 1989)