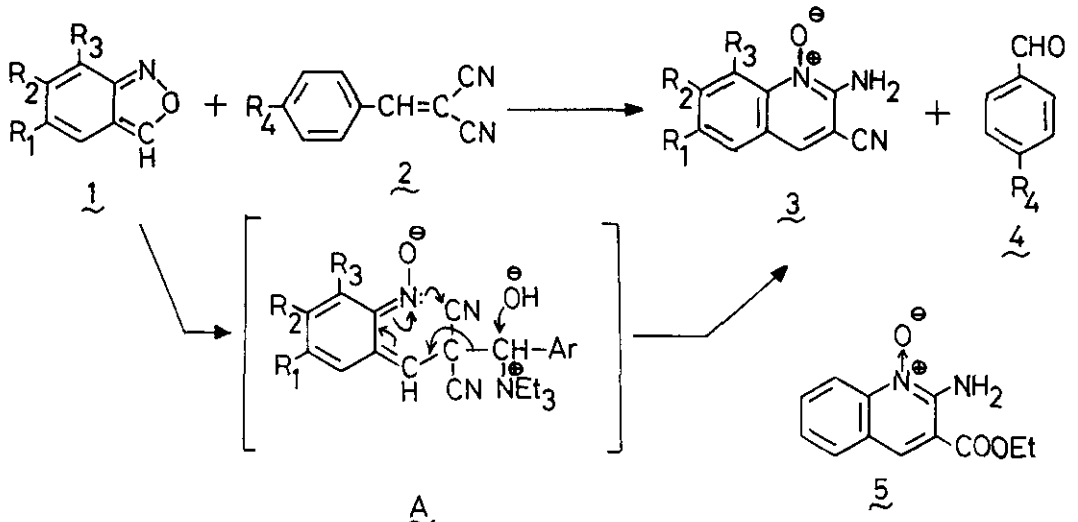
A BASE-CATALYSED REACTION OF ARYLIDENEMALONONITRILE WITH 2,1-BENZISOXAZOLES

Dilip Konwar, Romesh Chandra Boruah, and Jagir Singh Sandhu*
Division of Drugs and Pharmaceuticals
Regional Research Laboratory, Jorhat 785 006, India

Abstract - Quinoline-N-oxide derivatives were prepared in good yields by a triethylamine-catalysed reaction of arylidenemalononitrile with 2,1-benzisoxazoles.

2,1-Benzisoxazoles readily undergo hetero ring cleavage with carbon nucleophiles[1], bases[2], hydrazines[2] and primary aromatic amines[2]. The heterocyclic ring system has a considerable diene character[3,4], although a substituent at the C-3 position inhibits (4+2) cycloaddition[4]. The olefinic character at the carbocyclic ring of 1 is also well investigated[5]. Ylidenemalononitrile is a versatile reagent having diverse utilities in organic synthesis[6]. Recently we have reported the synthesis of quinoxaline-N'N-dioxide from the reaction of benzofuroxanes and arylidenemalononitrile[7]. In continuation we wish to report here the facile synthesis of a biologically important class of quinoline-N-oxides[8] by the reaction of electron-deficient arylidenemalononitriles with C-3 unsubstituted 2,1-benzisoxazoles.

2,1-Benzisoxazole (1a) reacted with an equimolar quantity of benzylidenemalononitrile (2, R_4=H) in refluxing methanol in the presence of a catalytic amount of triethylamine to give 2-aminoquinoline-3-carbonitrile-1-oxide (3a) (80%). The structures were confirmed through elemental and spectral analyses, m/z 185 (M^+), 170 (M^+-O), IR ν_{max} (KBr) 2220(CN), 3225 and 3310(-NH_2); ^{1}H NMR (d_6 - DMSO) : δ 8.32-9.00 (m, 5H). When substituted arylidenemalononitriles (2, R_4=NO_2, Cl etc.) were employed, the same product 3a was obtained. Isolation of the corresponding arylaldehydes (4, R_4=H, Cl, CH_3 etc.) as a byproduct offered further evidence for the insertion of malononitrile moiety into 1. When the carbocyclic ring of 1 was substituted by a chloro or a nitro group (1b-e), the corresponding 2-aminoquinoline-3-carbonitrile-1-oxides (3b-e) were obtained in good yields (Table).



	a	b	c	d	e
R_1	H	NO_2	H	H	Cl
R_2	H	H	NO_2	NO_2	H
R_3	H	H	H	CH_3	H.

Table

Characteristic data of quinoline-N-oxides 3

Compd.	Yield (%)	mp °C (Solvent)	IR (KBr) cm^{-1}	^1H NMR (DMSO - d_6)	MS m/e M^+ (rel. int. %).
3a	80	215-17 (DMSO)	3310, 3225, 2220.	8.32-9.00(m, 5H).	185(100), 170(25).
3b	70	265-67 (DMSO)	3315, 3220, 2215, 1540, 1350.	8.20-9.05(m, 4H).	230(100), 214(15), 184(40).
3c	73	274-77 (DMSO)	3320, 3230, 2210, 1525, 1350.	8.15-8.99(m, 4H).	230(100), 214(10), 184(36).
3d	62	260-62 (DMF)	3300, 3205, 2225, 1530, 1345.	8.25-8.85(m, 3H), 3.15(s, 3H).	244(100), 228(12), 198(25).
3e	60	237-39 (DMSO)	3310, 3220, 2220.	8.15-8.95(m, 4H).	219(100), 203(10).
5	68	195-97 (Ethanol)	3410, 3300, 1710, 1525, 1350.	8.25-9.10(m, 4H), 4.45(q, 2H), 1.40(t, 3H).	277(100), 261(12), 231(30).

All compounds gave satisfactory microanalyses, C, $\pm$ 0.25 ; H, $\pm$ 0.30 ; N, $\pm$ 0.35.

Regarding the mechanism of this reaction it is proposed that probably the arylidenemalononitrile (2, R_4=H) is initiated by triethylamine to behave as a nucleophile onto C-3 position of 2,1-benzisoxazole (1) thereby rupturing the C–O bond in 1 which is followed by rearrangement and elimination of the aryl-aldehyde. The reaction did not proceed in absence of triethylamine.
When (1a) was allowed to react with α-cyanoethylcinnamate under the identical conditions, the product 2-amino-3-ethoxycarbonyl-quinoline-1-oxide (5) was isolated. Substitution of the C-3 position of 1 with an aryl or carboalkoxy group gave negative result and in all the cases the starting materials were recovered unchanged.

General Procedure - A mixture of 2,1-benzisoxazole (1a, 10 mmol), benzylidene-malononitrile (2, R_4 = H, 10 mmol) and dry triethylamine (few drops) in dry methanol (30 ml) was gently refluxed for 2 h and concentrated to dryness in vacuo. The resulting solid was chromatographed over silica gel using ethyl acetate as eluent. Recrystalisation from dimethylsulfoxide gave the product 3a in 80% yield. mp 215-217°C (Decomp.).

ACKNOWLEDGEMENT

The authors wish to express their thank to Prof. W. Pfleiderer, Universitat Konstanz, West Germany and Analytical Division of this laboratory for providing spectral and elemental analyses of our research samples.

REFERENCES

1. E. C. Taylor and J. Bartulin, Tetrahedron Lett., 1967, 25, 2337.
2. (a) K. W. Wunsch and A. J. Boulton, 'Advance in Heterocyclic Chemistry', Edited by A. R. Katritzky and A. J. Boulton, Academic Press, Inc. New York, 1967, 8, 277.
   (b) R. K. Smalley, Ibid., 1981, 29, 1.
3. R. C. Boruah, J. S. Sandhu and G. Thyagarajan, J. Heterocyclic Chem., 1981, 18, 1081.
4. (a) E. C. Taylor, D. R. Ekroth and J. Bartulin, J. Org. Chem., 1967, 32, 1899.
   (b) V. P. Arya and S. J. Shenoy, Ind. J. Chem., 1976, 14B, 780.

5. (a) R. C. Boruah and J. S. Sandhu, Synthesis, 1982, 677.
(b) R. C. Boruah, P. Devi and J. S. Sandhu, J. Heterocyclic Chem., 1979, 16, 1555.
(c) S. A. Lang Jr. and Y-i-Lin, 'Comprehensive Heterocyclic Chemistry', Edited by A. R. Katritzky and C. W. Rees, Pargamon Press, London, 1984, 6, 35.
(d) A. Schonberg and A. Mostafa, J. Chem. Soc., 1943, 654.
6. (a) F. Freeman, Chem. Revs., 1980, 80, 329.
(b) F. Freeman, Synthesis, 1981, 925.
7. H. N. Borah, R. C. Boruah and J. S. Sandhu, Heterocycles, 1984, 22, 2323.
8. A. R. Katritzky and J. M. Lagowski, 'Chemistry of Heterocyclic N-oxides', Organic Chemistry, A series of monograph, Academic Press, 1971, Vol. 19, p. 20.

Received, 22nd April, 1985