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SYNTHESIS OF NOVEL AMINOISOTHIAZOLOPYRIDINES

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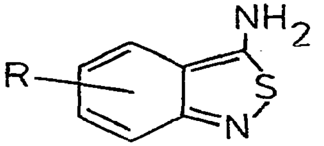
SUMMARY

The development of one strategic approach to the preparation of novel 3-aminoisothiazolopyridines is discussed. This new methodology involves, firstly, a reinvestigation of particular acid and base catalysed 6-EXO-DIG *ring closure processes which lead to highly functionalised pyridines. Secondly, the investigation of the selective addition of hydrogen sulphide to a cyano substituent and its ultimate utility to prepare 3-aminoisothiazolo*[3,4-b]*pyridines and a 3-aminoisothiazolo*[4,3-c]*pyridine bearing cyano substituents are highlighted. Furthermore, the utility of these systems to give blue and greenish-blue shades when incorporated in azo dyestuffs is exemplified.*

1. INTRODUCTION

It is well known that substituted 3-amino[2,1]benzisothiazoles (**1**), which possess an *o*-quinonoid structure, can give very bathochromic shades on polyester when

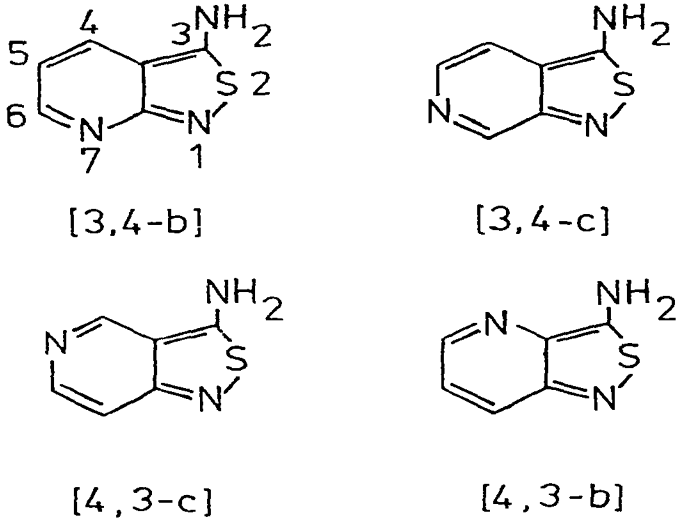


(**1**)

incorporated as diazo components in azo disperse dyestuffs.[1,2] This fact prompted the search for derivatives of related ring systems which could exhibit the same property. Isothiazolopyridines incorporating a 3-amino substituent (Scheme 1), are a relatively new class of heteroaromatic compounds. Four of the possible eight

Dyes and Pigments 0143-7208/82/0003-0123/$02·75

SCHEME 1

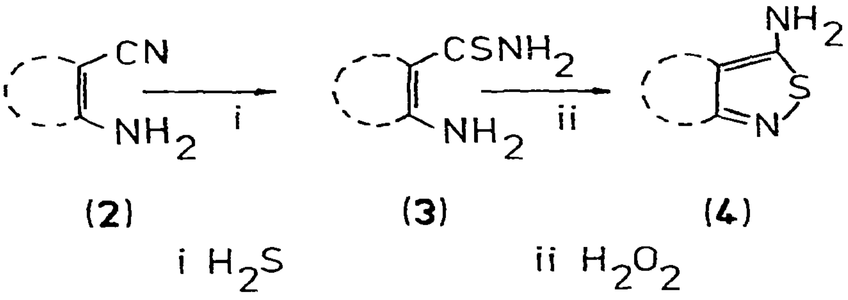


permutations of ring fusion possess *o*-quinonoid structures: only the [3,4-*b*] and [4,3-*b*] fused systems have been prepared and no substituted derivatives are known.[3]

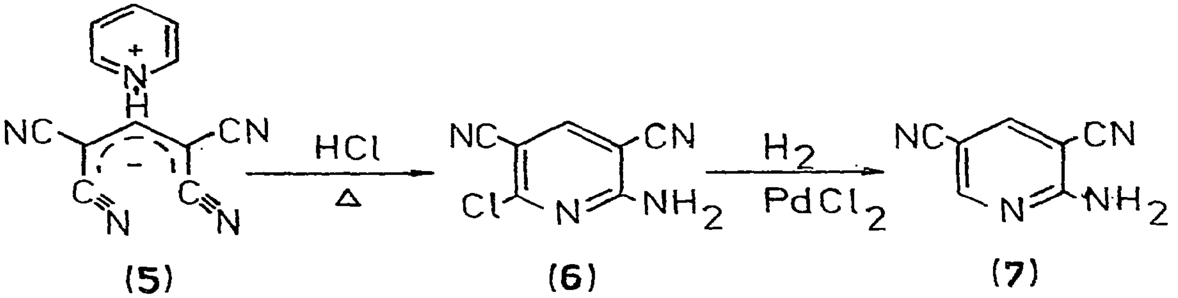
In this paper, the syntheses of 3-aminoisothiazolo[3,4-*b*]pyridines incorporating a 5-cyano substituent are described and the first reported synthesis of the 3-aminoisothiazolo[4,3-*c*]pyridine ring system highlighted.

2. DISCUSSION

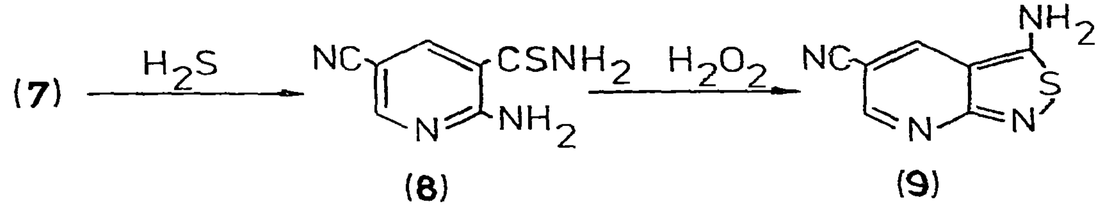
The strategy of synthesis of fused 3-aminoisothiazoles involves, firstly, preparation of the *o*-aminonitrile (2)[4] and its conversion to the corresponding *o*-aminothiocarbamoyl derivative (3) with hydrogen sulphide. The oxidation of (3) leads directly



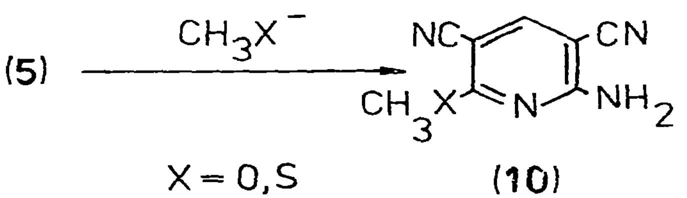
with concomitant loss of water to the required ring system (4).[1,5] These final stages of the synthesis normally proceed smoothly and in good yield. For the synthesis of 3-amino-5-cyanoisothiazolo[3,4-*b*]pyridine, this strategy requires the precursor 2-amino-3,5-dicyanopyridine (7). Compound (7) was synthesised by hydrogenation of



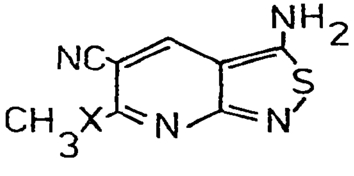
2-amino-3,5-dicyano-6-chloropyridine (6),[6] which was obtained by the 6-*EXO-DIG* cyclisation of the pyridinium salt of 1,1,3,3-tetracyanopropene (5) in the presence of hydrochloric acid.[7,8] The addition of hydrogen sulphide to (7) resulted in the specific formation of thiocarbamoyl derivative (8), this selectivity being caused by anchimeric assistance of the adjacent amino group. Oxidation of (8) resulted in an overall high-yield conversion to 3-amino-5-cyanoisothiazolo[3,4-*b*]pyridine (9).



The 6-*EXO-DIG* cyclisation of (5) with methoxide ion or methyl mercaptan, instead of a mineral acid, results in formation of 2-amino-3,5-dicyanopyridines of structure (10).[9]



Thus, 3-amino-5-cyanoisothiazolo[3,4-*b*]pyridines with a 6-methoxy or 6-thiomethyl substituent [(11) or (12) respectively] could be obtained in high yield by an analogous reaction sequence to that shown for the synthesis of (9).

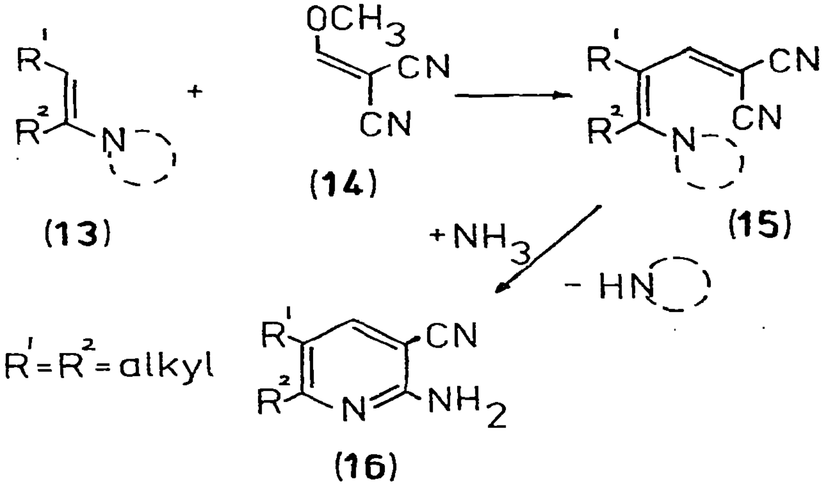


(11) X=O

(12) X=S

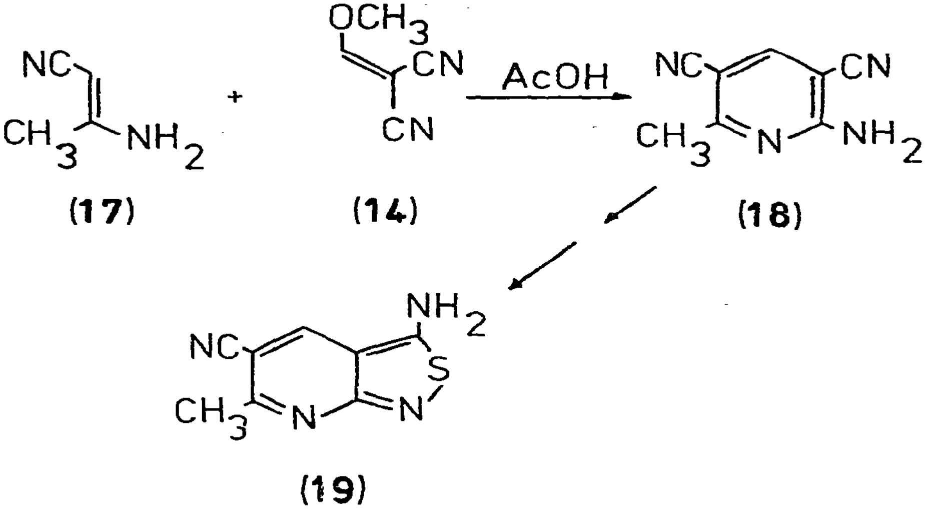
A limitation of the above methodology is apparent if 2-amino-3,5-dicyano-6-alkylpyridines are required for the preparation of 3-amino-5-cyanoisothiazolo[3,4-*b*]pyridines containing a 6-alkyl substituent. It has been reported that 5- and/or 6-alkyl substituted derivatives of 2-amino-3-cyanopyridine (**16**) can be synthesised via dienamine intermediates (**15**). These in turn are produced by the addition–elimination reaction of enamines (**13**) to methoxymethylenemalononitrile (**14**), prepared from trimethylorthoformate and malononitrile; see Scheme 2.[10]

SCHEME 2



However, there is little literature precedent relating to the reaction of acyclic enaminonitriles such as 3-aminocrotononitrile (**17**) with strong Michael acceptors, which could lead to a facile synthesis of 5-cyanopyridine derivatives ($R_1 = CN$).[11] We found that (**17**) reacted with (**14**) to give 2-amino-3,5-dicyano-6-methylpyridine (**18**) directly in high yield, in the presence of acetic acid as catalyst. Moreover, (**18**) could be converted to 3-amino-5-cyano-6-methylisothiazolo[3,4-*b*]pyridine (**19**) in overall high yield; see Scheme 3.

SCHEME 3



Furthermore, the reaction of (17) with trimethylorthoformate and malononitrile under conditions identical to those used to prepare (18) resulted in the formation of the novel isomeric pyridine product (21). A mechanism for this new synthesis is depicted in Scheme 4.

SCHEME 4

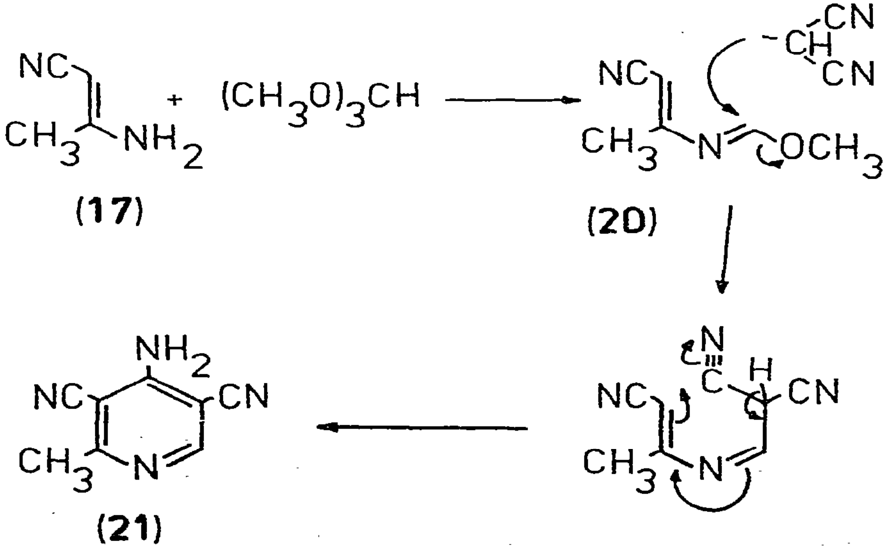
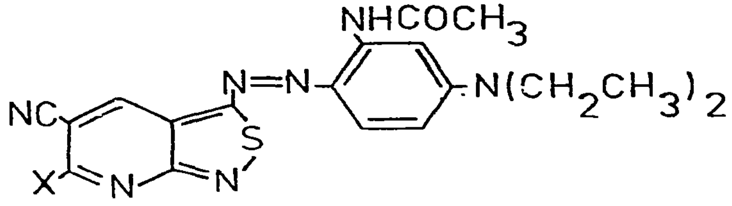


TABLE 1

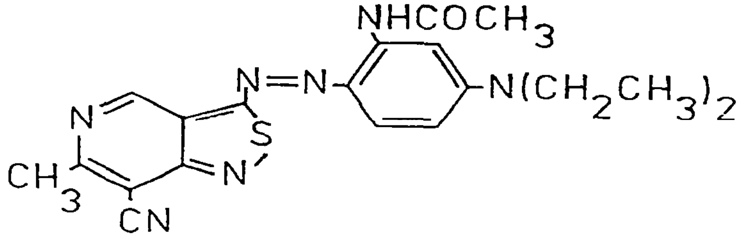
VISIBLE SPECTRA OF AZO DYESTUFFS DERIVED FROM 3-AMINO-5-CYANOISOTHIAZOLO[3,4-*b*]PYRIDINES WITH *N*,*N*′-DIETHYL-*m*-AMINOACETANILIDE AS COUPLING COMPONENT



Substituent *X*	λ_{max} *(CHCl$_3$)* *(nm)*	ε_{max} *(CHCl$_3$)*	λ_{max} *(Melinex film)* *(nm)*
CH_3O	614	56500	618
CH_3	625	51500	625
H	629	56000	635
CH_3S	624	50000	624

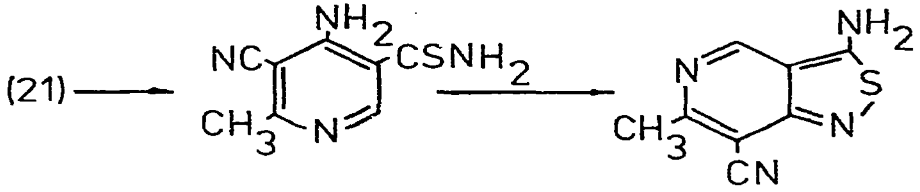
TABLE 2

VISIBLE SPECTRA OF AZO DYESTUFF DERIVED FROM 3-AMINO-6-METHYL-7-CYANO-ISOTHIAZOLO[4,3-*c*]PYRIDINE WITH *N*,*N*′-DIETHYL-*m*-AMINOACETANILIDE AS COUPLING COMPONENT



λ_{max} *(CHCl$_3$)* *(nm)*	ε_{max} *(CHCl$_3$)*	λ_{max} *(Melinex film)* *(nm)*
630	47000	631

It is postulated that trimethylorthoformate reacts with (**17**) to give the formimidate (**20**), rather than with malononitrile to give (**14**). The compound (**20**) then reacts with malononitrile and cyclises to give (**21**). With this novel pyridine (**21**) in hand, the synthesis of 3-amino-6-methyl-7-cyanoisothiazolo[4,3-*c*]pyridine (**23**) could be achieved easily by methods already discussed.



(22) (23)

To our knowledge this is the first report of the synthesis of the [4,3-*c*] ring fusion system.

These novel amines were diazotised in the conventional manner employed for 3-amino[2,1]benzisothiazoles[2] and coupled with *N*,*N*′-diethyl-*m*-aminoacetanilide to give very bathochromic shades in the greenish-blue region in both solution and on polyester fibre (see Tables 1 and 2).[12,13]

3. EXPERIMENTAL

All spectral and analytical data are consistent with the proposed structures.

3.1. *2-Amino-3-thiocarbamoyl-5-cyanopyridine* (8)

2-Amino-3,5-dicyanopyridine (15·0 g), dry pyridine (150 g) and triethylamine (20 g) were stirred at 0 °C and a steady stream of hydrogen sulphide gas was passed into the solution for 45 min. The homogeneous solution was then poured into 500 g of ice–water and the product, which precipitated completely, was removed by filtration, washed with water and dried, giving 15·4 g of 2-amino-3-thiocarbamoyl-5-cyanopyridine. Yield 83 %.

3.2. *3-Amino-5-cyanoisothiazolo*[3,4-b]*pyridine* (9)

2-Amino-3-thiocarbamoyl-5-cyanopyridine (14·0 g) was suspended in 800 g of methanol and heated to boiling with stirring. To this hot solution was added 250 g of 30 % aqueous hydrogen peroxide, rapidly. The suspension turned yellow and complete solution was obtained in 2 min. The product then precipitated from the hot methanol. After 2 min, the solution was cooled, diluted with 500 g of water and the product isolated by filtration. The pure product was obtained as a yellow crystalline powder (13·1 g). Yield 92 %.

The preparation of compounds (11) and (12) were carried out by analogous methods, via their respective thiocarbamoyl derivatives, in 86 % and 82 % overall yields respectively.

3.3. *2-Amino-3,5-dicyano-6-methylpyridine* (18)

A mixture of 8·2 g of 3-aminocrotononitrile and 12·2 g of methoxymethylenemalononitrile was stirred and warmed to 45 °C in 45 g of dry toluene. The solution was cooled to 20 °C and to it was added 4·7 g of glacial acetic acid all at once. The reaction mixture was stirred for 12 h at 20 °C and the precipitate was removed by filtration and washed with 2 × 10 ml of dry toluene. The compound was air dried giving 14·1 g of 2-amino-3,5-dicyano-6-methylpyridine. Yield 65 %.

Infrared spectrum (nujol mull): ν_{max} 3380, 3350 (NH_2), 3160–2750 (NH_2), 2240 (CN), 2230 (CN) cm^{-1}; n.m.r. δ 2·40 (s, 3. CH_3), 7·65 (s, 2. NH_2), 8·17 (s, 1. aromatic H); mass spectrum $M^{+\cdot}$ 158.

3.4. *2-Amino-3-thiocarbamoyl-5-cyano-6-methylpyridine*

This compound was prepared in an analogous fashion to that described for 2-amino-3-thiocarbamoyl-5-cyanopyridine, in 89 % yield.

3.5. *3-Amino-5-cyano-6-methylisothiazolo*[3,4-b]*pyridine* (**19**)

This compound was prepared in an analogous fashion to that described for 3-amino-5-cyanoisothiazolo[3,4-*b*]pyridine, in 98 % yield.

3.6. *4-Amino-3,5-dicyano-6-methylpyridine* (**21**)

3-Aminocrotononitrile (49·2 g) was added to methanol (150 g) and was stirred and warmed to 30 °C to achieve complete solution. To this solution at 20 °C was added a solution of malononitrile (39·6 g) in trimethylorthoformate (88·8 g) with stirring. The whole reaction mixture was stirred overnight at room temperature, after which the suspended solid was removed by filtration, washed with ethanol and dried to give 23·0 g 4-amino-3,5-dicyano-6-methylpyridine. Yield 24 %.

Infrared spectrum (nujol mull): ν_{max} 3360, 3320 (NH_2), 3200–2700 (NH_2), 2220 (CN), 1660 (C=N) cm^{-1}; n.m.r. δ 2·40 (s, 3. CH_3), 7·70 (s, 2. NH_2), 8·65 (s, 1. aromatic H); mass spectrum $M^{+\cdot}$ 158.

3.7. *4-Amino-5-cyano-6-methyl-3-thiocarbamoylpyridine* (**22**)

A solution of 4-amino-3,5-dicyano-6-methylpyridine (35 g) in pyridine (400 g) and triethylamine (28 g) was prepared at room temperature. To this solution was added 16 % ammonium sulphide aqueous liquor (110 g) and the reaction mixture was maintained at 45 °C for 10 h. The solution was then poured into 2 litres of water and the precipitate was filtered off, washed with water and dried to give 22·6 g of product. Yield 53 %.

3.8. *3-Amino-6-methyl-7-cyanoisothiazolo*[4,3-c]*pyridine* (**23**)

To a solution of 4-amino-5-cyano-6-methyl-3-thiocarbamoylpyridine (20 g) in 1 litre of methanol at 35 °C was added 30 % aqueous hydrogen peroxide (10 g). A precipitate slowly formed and was filtered off after 10 min, to give 13·3 g of product. Yield 70 %.

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