DIAZOO COUPLING REACTIONS OF AMINO AND OF MERCAPTOPYRIMIDINES

Derek T. Hurst*, Anthony D. Stacey and Deepthi K. Weerasinghe,
School of Chemical and Physical Sciences, Kingston Polytechnic,
Kingston upon Thames, KT1 2EE, England.

ABSTRACT Diazo coupling reactions of aminopyrimidines can result in the formation
of diazoamino compounds, arylhydrazones of pyrimidine-4-aldehydes by attack at a
methyl group or 5-substitution depending on the pyrimidine, the conditions and the
reagent. Unless precautions are taken to remove excess nitrous acid
deamination can also occur. In the case of mercaptopyrimidines arylation of the
mercapto group is the favoured reaction in many cases.

Diazo coupling reactions of pyrimidines have been used frequently in order to
introduce a 5-amino substituent into the ring. The 5-position is that which is most likely to
be attacked by electrophilic reagents although the presence of at least one electron-releasing
group such as NH₂ or OH, preferably in the 2-position, is required for the reaction to be
successful.¹,² The reaction is very useful since the introduction of the arylazo group and its
subsequent reduction to give the 5-aminopyrimidine can be carried out under very mild conditions.

4,5-Diaminopyrimidines are valuable as intermediates in the synthesis of purines and pteridines
many of which have useful biological activities. Some 5-arylazopyrimidines have interesting
pharmacological activity themselves (for example see refs. 3 and 4).

However, the reaction is not as widely applicable as might be supposed. It has been
found that some methylpyrimidines undergo reaction at the methyl substituent⁵ whilst 4-hydroxy-
2-mercaptopyrimidine and the 6-methyl analogue have been reported to undergo reaction at the
sulphur atom to give arylthiopyrimidines.⁶ However, these last two compounds have been
reported by another group of workers to undergo 5-position substitution.⁷

We have begun an extensive investigation of the diazo coupling reactions of
pyrimidines and this preliminary communication reports our initial findings.

The addition of diazotised 4-chloroaniline to aqueous acetic acid solutions of the
amino-methylpyrimidines la, b, c and 3a have given the corresponding diazoamino compounds
2a, b, c and 3b in good yield. When diazotised 4-nitroaniline was added to aqueous
hydrochloric acid solutions of 1a and 1b attack occurred at the 4-methyl group to give the 4-nitrophenylhydrazones 4a and 4b. However 4-amino-2,6-dimethylpyrimidine again gave a diazo-amino compound 3c.

2-Amino-4-hydroxy-6-methylpyrimidine coupled with diazotised 4-chloroaniline to give the 5-arylazo product 5 which we have also obtained from attempted coupling reactions of 2-amino-4-chloro-6-methylpyrimidine without isolating the corresponding 4-chloro-5-coupled product. We have noted the loss of a 4-halogen from pyrimidines under nitrosation conditions in another study (D.T. Hurst, unpublished work).

In our studies so far we have not been able to confirm the reaction of 2-amino-4-methyl-6-phenylpyrimidine with diazotised 4-chloroaniline to give the 5-arylazo product reported by Garg and Sharma. From reactions in which excess nitrous acid was not removed by the addition of urea we have obtained the deaminated product 6a (confirmed by a reaction starting from the corresponding 2-hydrazyl compound) in good yield. When excess nitrous acid was removed we have obtained low yields of the amino product 6b.

The structures of the products are clearly established by $^1$H nmr spectroscopy and are confirmed by microanalytical and by mass spectral data.

There have been conflicting reports concerning the diazo coupling reactions of mercapto pyrimidines. Polonovski and Pesson were unable to couple 4-hydroxy-2-mercapto-6-methylpyrimidine with phenyldiazonium chloride. Falco, Hitchings and Russell attempted to couple diazotised 4-chloroaniline with 4-hydroxy-2-mercapto and 4-hydroxy-2-mercapto-6-methylpyrimidine and were only able to isolate in high yield the respective 4'-chlorophenylthio ethers.
However Mahesh, Goyal and Gupta\(^7\) have reported the synthesis, in good yield, of a number of 5-arylazo derivatives of 4-hydroxy-2-mercapto-6-methylpyrimidine and of the 2-methylthio analogue by diazo coupling reactions.

We have investigated the reaction of diazotised 4-chloroaniline with several mercaptoypyrimidines (7a to e) and have in each case obtained the corresponding 4'-chlorophenylthioethers (8) as the principal product with very small quantities of other products resulting from further reactions of the arylthiopyrimidines. In the case of the hydroxy-mercapto-pyrimidines (7a,b) we have obtained the arylthio compounds as the major product with only very minor quantities of other compounds including the product of 5-diazo coupling.

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\begin{align*}
7 \quad & \text{(a) } R=\text{OH}, \quad R'=\text{H} \\
& \text{(b) } R=\text{OH}, \quad R'=\text{Me} \\
& \text{(c) } R=R'=\text{H} \\
& \text{(d) } R=\text{Me}, \quad R'=\text{H} \\
& \text{(e) } R=R'=\text{Me}
\end{align*}
\]

We have not yet characterised and quantitated all of the products, shown to be present by TLC, of the reactions of amino and of mercaptoypyrimidines.

By diazo coupling reactions of appropriate hydroxypyrimidines we have also obtained compounds 10 to 13 during these studies.

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\begin{align*}
10 \quad & \text{(a) } R=\text{H} \\
& \text{(b) } R=\text{Me}
\end{align*}
\]

Our studies show that the products of diazo coupling reactions of pyrimidines need to be investigated in each case since the product of the reaction will depend on the pyrimidine, the conditions and the diazo coupling reagent. In many cases mixtures of products are obtained although one may be isolated as the preponderant product. Care is therefore necessary in using such reactions as synthetic methods.
We hope to be able to provide rationale for the observed reactions and to report on the results of an extensive study at a later date.

REFERENCES

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