Tetrahedron Letters,Vol.23,No.33,pp 3357-3360,1982 0040-4039/82/333357-04$03.00/0
Printed in Great Britain

HETEROCYCLIC SYNTHESIS USING ETHYL CARBOETHOXYFORMIMIDATE

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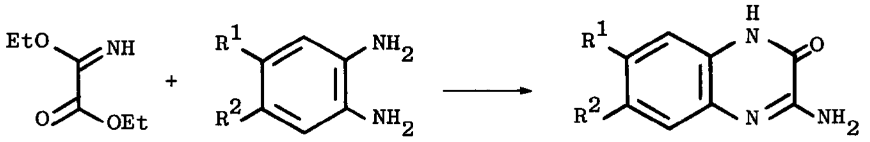
Abstract Ethyl carboethoxyformimidate is shown to be a versatile reagent for the synthesis of a variety of mono- and bicyclic heterocyclic systems.

The preparation and utilisation of small polyfunctional molecules for the synthesis of heterocycles is an aspect of heterocyclic chemistry which continues to attract considerable attention. Within this general context we wish to describe some applications of ethyl carboethoxyformimidate 1 to the synthesis of a variety of mono- and bicyclic heterocyclic systems. In contrast to many structurally simpler imidates, 1, which is readily available in bulk from ethyl cyanoacetate and is easily handled either as such or as the hydrochloride salt,[1,2] has been little used in synthesis. The few studies which have been reported have mainly been concerned with the preparation of 1,3,5-triazine derivatives.[2,3]

Condensation of the imidate 1 with o-phenylenediamine 2a proceeds smoothly in refluxing ethanol to give 3-amino-2(1H)-quinoxalinone 3a in essentially quantitative yield (equation (1)), and substituted o-phenylenediamines react similarly.[4] With 4-methyl-o-phenylenediamine 2b, ^{13}C nmr spectroscopy clearly reveals that as expected a mixture of the two possible isomeric products is obtained. By contrast, 4-nitro-o-phenylenediamine 2d reacts with 1 to give a single, pure product in excellent yield; this is

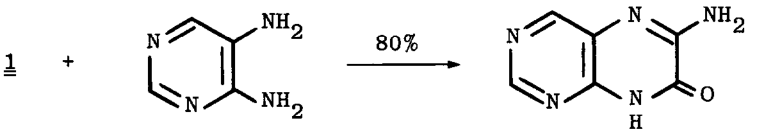


(1)

1 **2** **3**

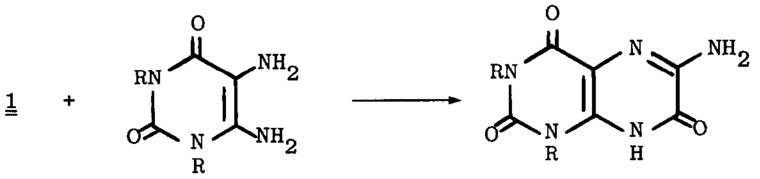
(a) $R^1 = R^2 = H$, 99%
(b) $R^1 = H$, $R^2 = Me$, 89%
(c) $R^1 = R^2 = Me$, 80%
(d) $R^1 = H$, $R^2 = NO_2$, 92%
(e) $R^1 = R^2 = Cl$, 58%

almost certainly **3d** as shown in equation (1), formed by initial nucleophilic attack of the more basic of the two nitrogen atoms in **2d** at the imidate carbon atom. Our studies thus far show that the preferred centre for nucleophilic attack in **1** is the imidate carbon in almost all cases. 4,5-Diaminopyrimidine **4** reacts smoothly with **1** to give 6-amino-7-(8*H*)-pteridinone **5** in 80% yield (equation (2)), the product being identical to a sample prepared independently from 6,7-dichloropteridine.[5] Similar results were obtained with 5,6-diaminouracil and 1,3-dimethyl-5,6-diaminouracil (equation (3)), but a mixture of isomeric products (^{13}C nmr) was obtained with 2,3-diamino-5-bromopyridine.



(2)

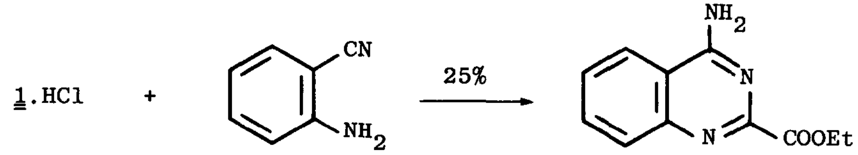
4 **5**



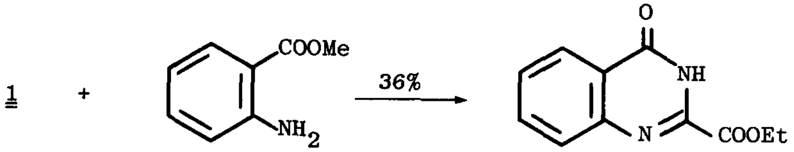
(3)

R = H, 60%
R = Me, 94%

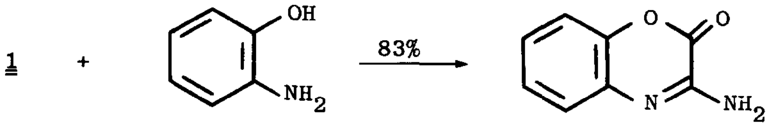
Other ortho-disubstituted aromatic compounds condense either with the imidate **1** or with the hydrochloride salt, and representative examples are shown in equations (4)-(6). By contrast, reaction of *o*-aminothiophenol **6** with **1** gave only 8% of the benzothiazinone **7**, together with 87% of the



(4)

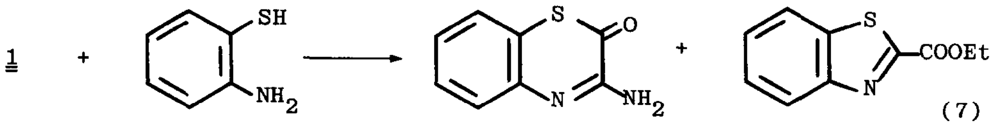


(5)



(6)

benzothiazole 8 (equation (7)). Five membered ring formation was also observed in the reaction of 1 with 2-imino-N-aminopyridine 9, which gave the triazolopyridine 10 in 82% yield (equation (8)), apparently, and in contrast to the above results, as a consequence of preferential nucleophilic attack at the ester carbonyl group followed by transesterification of the imidate by the solvent.

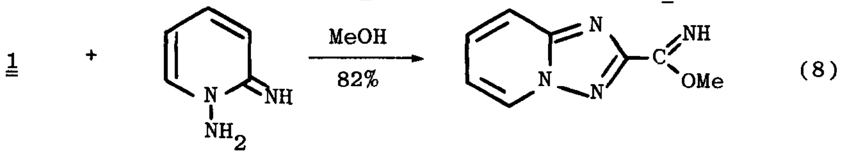


(7)

6

7 8%

8 87%

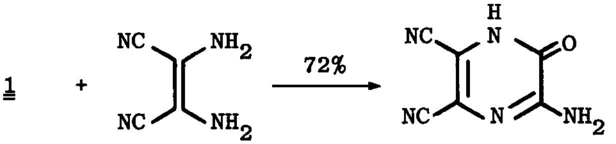


(8)

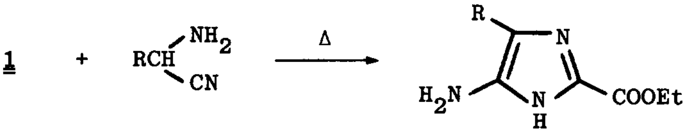
9

10

The imidate 1 can also be used for the preparation of a variety of monocyclic heterocycles, and representative examples are shown in equations (9)-(11). With α-aminonitriles $RCH(NH_2)CN$, where R is H, COOEt or $CONH_2$, the reactions proceed as shown in equation (10);[6] when R is alkyl or aryl, however, the initially formed aminoimidazole reacts further with 1. Nucleophilic attack of the amino group of the imidazole at the imidate carbon gives the



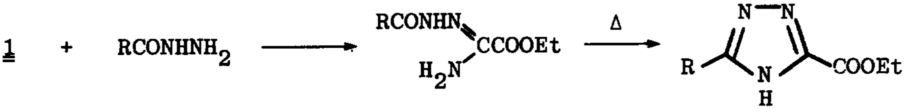
(9)



R = H, 91%

R = COOEt or $CONH_2$, 92%

(10)



(11)

R = Me, 70% R = Me, 52%

R = Ph, 80% R = Ph, 44%

corresponding amidine derivative, but yields are moderate. Moderate yields of 4H-isoimidazoles are also obtained by reaction of 1 with α-aminonitriles of the type $RR'C(NH_2)CN$. Reactions of 1 with acethydrazide and benzoylhydrazine gave the corresponding ethyl N'-acyloxamidrazonates which were readily cyclodehydrated to 1,2,4-triazoles (equation (11)).

The above results thus demonstrate that ethyl carbethoxyformimidate is a versatile reagent for heterocyclic synthesis. Further studies are in progress to extend the range of nucleophiles which react with 1.

Acknowledgements: A.H. acknowledges receipt of a CASE studentship and P.S.R. receipt of an SRC research studentship.

References:

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2. G.I. Braz, G.B. Myasnikova, A. Ya. Yakubovich and V.P. Bazov, Zh. Obsch. Khim., 34, 2980 (1964), Chem. Abstr., 62, 562 (1965).
3. F.C. Schaefer, J. Org. Chem., 27, 3608 (1962).
4. Satisfactory analytical and spectroscopic data were obtained for all new compounds.
5. A. Albert and J. Clark, J. Chem. Soc., 27 (1965).
6. The intermediate amidines can readily be isolated and characterised. Reaction of 1 with H_2NCH_2CN, for example, gives $EtOCOC(=NH)NHCH_2CN$ in 91% yield.

(Received in France 26 May 1982)