Tetrahedron Letters, Vol. 34, No. 12, pp. 2019-2020, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Pyridinium-N-(2-pyridyl)aminides: A Selective Approach to Substituted 2-Aminopyridines

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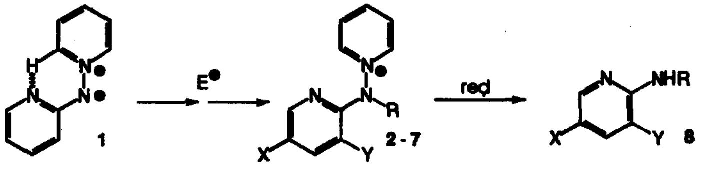
Abstract: *Differently substituted 2-aminopyridines have been prepared in two steps from pyridinium-N-(2-pyridyl)aminide, by reaction with the corresponding electrophiles and reduction of the N-N bond.*

As the body of knowledge about the reactivity of azinium *N*-ylides expands, the interest in such compounds as building blocks for the synthesis of heterocyclic derivatives continuously increases.[1] Some of our work in the field has been concerned with the synthesis of heteroaryl-stabilized cycloiminium ylides as a way of producing highly stable dipoles, with heterocyclic moieties of unusual reactivity.[2]

In this paper we wish to report our first results with the pyridinium-N-(2-pyridyl)aminide **1** in which there is a negatively charged 2-aminopyridine fragment. The precursor pyridinium bromide was prepared by using the method of Beyer,[3] and converted into the stable aminide **1** by treatment with K_2CO_3/acetone. The structure of **1** in solution showed an intramolecular hydrogen bond as indicated, which has been described for related compounds.[4]

Fig. 1



Because of its structure in solution, reaction of **1** with alkyl halides produced regioselective alkylation on the exocyclic nitrogen (compounds **2**, Fig. 2), with no signs of alkylation on the N1 of the 2-pyridyl ring.

Reaction of **1** with electrophiles producing C-substitution was obtained under very mild conditions. Thus, iodination with equimolar amounts of iodine at room temp., yielded the monoiodo salt **3** (61%), while when iodination was made in the presence of base (K_2CO_3), the initially formed **3** was deprotonated and attacked again, being the diiodo betaine **4** isolated (22%). On treatment with bromine, the process was out of control, being obtained then a mixture of 5-bromo and 3,5-dibromo salts (1:4), even when working at $0^{o}C$. Again, in the presence of base, only the 3,5-dibromo betaine **5** was obtained (75%).

Other electrophiles were tested against **1**. Thus, phenyldiazonium chloride produced the diazo compound **6** as a red solid (50%). Reactions with Michael substrates were not successful, due to the good leaving character of the aminide, but with quinones the initial adduct eliminated pyridine as described in a related process by Kakehi,[5] when silica gel was used as catalyst. Thus quinone adducts **7a** (64%) and **7b** (65%) were obtained. Finally, cleavage of the N-N bond was carried out using a Zn/acetic acid reduction system,[6] and in this way the corresponding 2-aminopyridines **8** were obtained with yields .

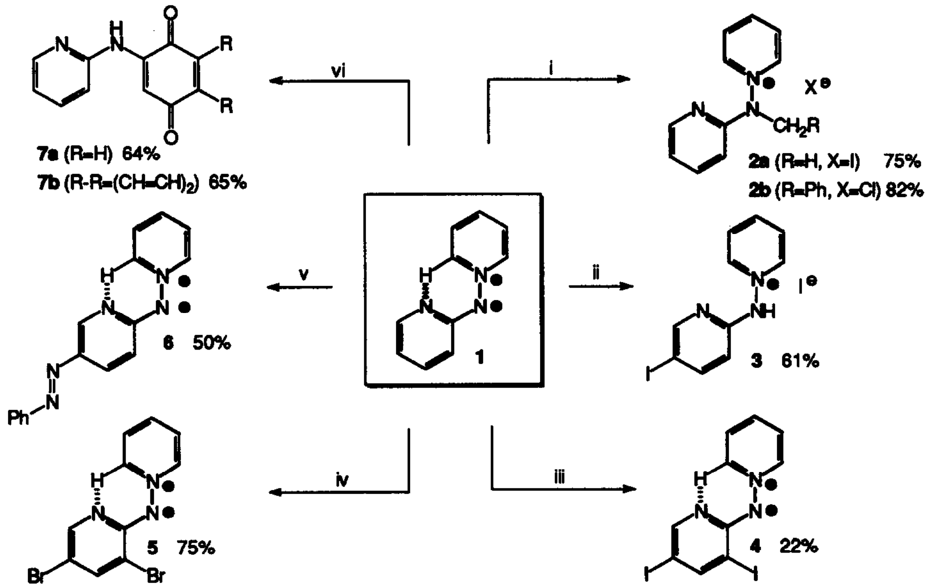


Fig. 2 Reagents and Conditions: i) MeI/acetone, r.t. or BzCl/toluene, reflux; ii) I_2/CH_2Cl_2; iii) $3I_2/K_2CO_3/CH_2Cl_2$, r.t.; iv) $2Br_2/K_2CO_3/CH_2Cl_2$, r.t.; v) PhN_2^+ Cl^-/water, r.t.; vi) Quinone/silica/CH_2Cl_2, r.t.

In summary, the use of heteroaryl-stabilized azinium aminides provides an easy, mild and selective approach to diferently substituted 2-aminopyridines. Further experiments are in progress to extend the process as a general methodology to other azines.

Acknowledgements. Authors wish to thank the Comisión Interministerial de Ciencia y Tecnología (C.I.C.Y.T.) for financial support (Proj. PB 90-0284), Ministerio de Educación y Ciencia (M.E.C.) for a grant to one of us (R.C.M.) and ALTER S.A. for a generous gift of chemicals.

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(Received in UK 22 January 1993)