Pergamon

Tetrahedron Letters 41 (2000) 5837–5840

TETRAHEDRON LETTERS

N-Azinylpyridinium *N*-aminides: tandem reactions with α-halocarbonyl derivatives and analogs

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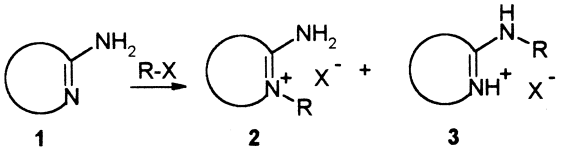
Received 4 February 2000; accepted 23 May 2000

Abstract

Pyridinium-*N*-(2′-pyridyl)aminide was reacted with different α-halocarbonyl derivatives and related compounds. The method allows an easy preparation of several heterocyclic building blocks, all including the 2-aminopyridine moiety. © 2000 Published by Elsevier Science Ltd.

Keywords: alkylation; amidines; pyridinium salts; ylides.

Primary heterocyclic amidines **1** are 1,3-dinucleophiles bearing two differentially reactive centers: The endocyclic sp^2 nitrogen and the exocyclic amine. Usually, alkylation of **1** occurs regioselectively on the endocyclic nitrogen, or leads to a mixture of both *endo* **2** and *exo* **3** substituted derivatives (Scheme 1).[1] The alkylation, however, can be preferentially directed to the exocyclic nitrogen using different methods, including deprotonation of the exocyclic amino group. We recently described the use of pyridinium *N*-(azinyl)aminides **4** (Scheme 2), where the exocyclic nitrogen anion is stabilized by the presence of a pyridinium moiety. Moreover, the endocyclic nitrogen is partially blocked by an intramolecular hydrogen bond, making the alkylation highly regioselective, with no signs of *N*-ring alkylations. Final fission of N–N bond could allow the synthesis of 2-alkylamino derivatives.[2–4]



Scheme 1.

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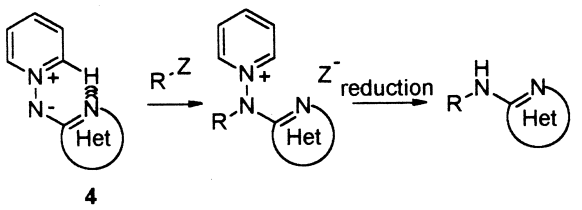
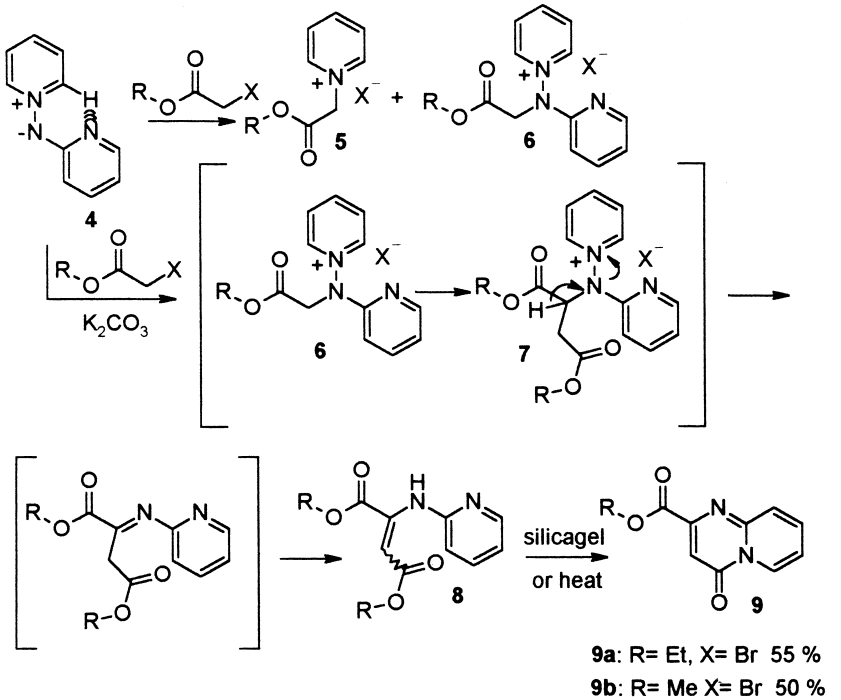
PII: S0040-4039(00)00839-X



Scheme 2.

This communication discusses the nucleophilic properties of **4** in the presence of α-halocarbonyl compounds and related esters and nitriles, and the use of **4** as precursors of different heterocyclic building blocks.

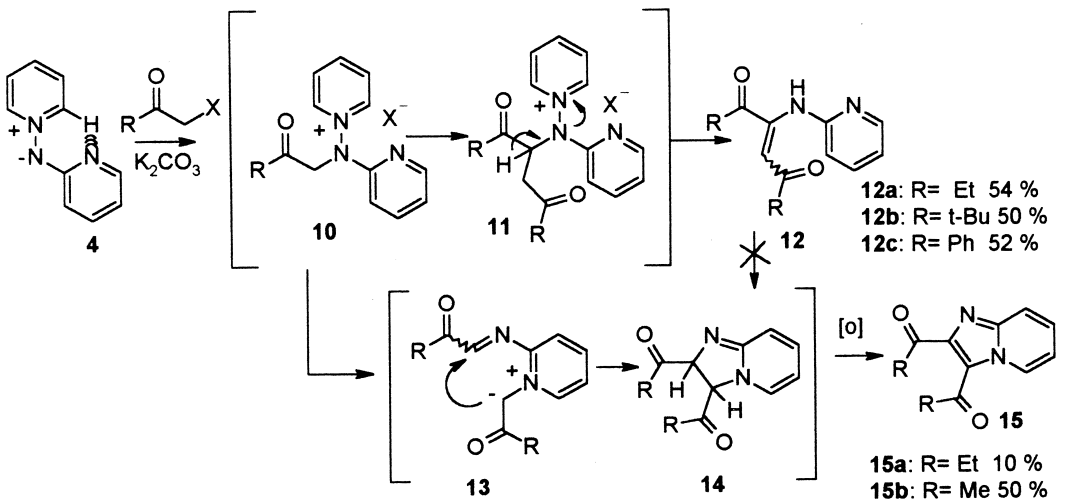
In the initial experiments, alkylation with α-haloesters was investigated. Reaction of **4** (Het = 2-pyridyl, Scheme 3) with alkyl bromoacetates under mild conditions (acetone, rt), produced a mixture of pyridinium salts **5** and **6**. Pyridinium salt **5** was formed along the expected reaction pathway, and the formation of compound **6** could be explained through a process involving elimination of pyridine, on the initially formed **5**, followed by alkylation. When the process was carried out in the presence of a base (potassium carbonate, acetone, rt, 24 h), the only compounds isolated were **8** and **9**. In addition, **8** was converted into **9** when attempted to separate them by chromatography. To rationalise the process, it appears that the initially formed salt **6** was deprotonated and reacted again with an additional molecule of electrophile, yielding the salt **7**. In



Scheme 3.

the presence of base, **7** may undergo elimination of the pyridine ring, yielding the enamine **8**, which cyclized to the pyrido[1,2-*a*]pyrimidin-4-one **9**, either spontaneously or by the action of silica gel. Varying the halide considerably altered the final yield (for **9a**, when Z = Cl, 25%, when Z = I, 30%). The preparation of pyrido[1,2-*a*]pyrimidin-4-ones has been extensively studied by Hermecz and Stanovnik.[5–7]

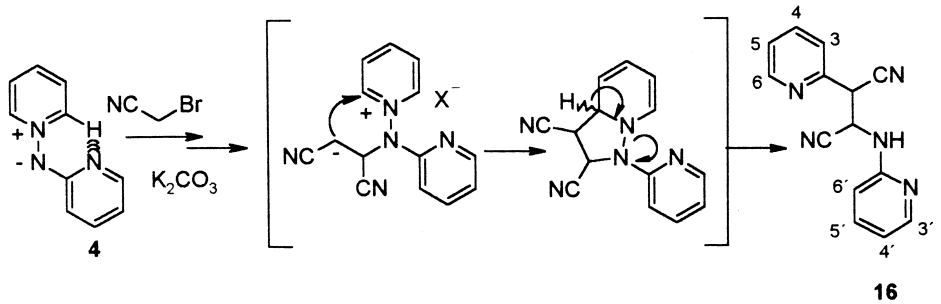
When alkylations were performed with α-haloketone derivatives under the same initial conditions (potassium carbonate, acetone, rt, 24 h), either enamines **12** (X = Br, R = *t*-Bu, Ph) or imidazo[1,2-*a*]pyridine **15b** (X = Cl, R = Me) were isolated as the main products (Scheme 4). Initially, the results suggested a reaction pathway similar to that shown in Scheme 3, where enamine **12**, by the intramolecular Michael addition and easy thermal dehydrogenation, may yield the imidazopyridine **15** and where the final product would be either **12** or **15** depending of the steric hindrance of the *R*-substituent. When X = Br and R = Et, however, both **12a** and **15a** were isolated, and attempts to convert **12a** to **15a** in acid or basic conditions failed. Consequently, a competing alternative[8] could be suggested, via the intermediate pyridinium ylide **13**, explaining the lack of conversion from **12** to **15**. The dehydrogenation step from **14** to **15** has been previously reported.[9,10] This would mean that both mechanisms would compete, for all the subtrates, and differences observed are related to the stability of the final compounds, specifically in terms of the steric hindrance of the R groups.



Scheme 4.

In recent years, biological properties of imidazo[1,2-*a*]pyridine derivatives, in particular of the 3-acyl derivatives have attracted much attention. Despite numerous applications of the most common approach for this system, condensation of 2-aminopyridines with α-halocarbonyl compounds, alternative methods are still required.[9–12]

Other electrophiles were reacted with **4**. Thus, reaction with α-halomethylsulphones was not successful, but with α-halocarbonitriles under the same conditions (potassium carbonate, acetone, rt, 24 h), the substituted pyridine **16** was isolated, from a complex mixture, as the main product of the process.[13] The reaction course and results are summarized in Scheme 5.



Scheme 5.

In conclusion, the use of heteroaryl-stabilized azinium aminides provides a simple approach for producing different heterocyclic fragments bearing the 2-aminopyridine moiety. Further experiments are in progress to extend the process as a general methodology to other azine derivatives.

Acknowledgements

Author wish to thank C.I.C.Y.T. for financial support (Project PM97-0074) and the Universidad de Alcalá for a grant to one of us (R.R.).

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13. The assignment of protons and estimation of coupling constants for the compound **16** were carried out by means decoupling spectra. δ_H (300 MHz, CD_3CO) 9.61 (1H, m, NH), 8.50 (1H, ddd, $J=6.8$, 2, 0.8 Hz, H6), 8.45 (1H, ddd, $J=7.2$, 1.2, 1.1 Hz, H6′), 8.00 (1H, ddd, $J=8.4$, 7.4, 2 Hz, H4), 7.55 (1H, bd, $J=8.4$ Hz (w $1/2=0.8$ Hz, H3), 7.51 (1H, ddd, $J=9.2$, 1.2, 1.1 Hz, H3′), 7.41 (1H, ddd, $J=9.2$, 6.9, 1.2 Hz, H4′), 7.30 (1H, ddd, $J=7.4$, 6.8, 0.8 Hz, H5), 7.08 (1H, ddd, $J=7.2$, 6.9, 1.2 Hz, H5′), 4.45 (2H, m, CH-CN).