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Pyridinium *N*-2′-pyridylaminide: radical cyclization in the synthesis of annulated 2-aminopyridines

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Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday

Abstract—The synthesis of annulated 2-aminopyridines by intramolecular radical pyridylation of the appropriate substrates, obtained from pyridinium *N*-2′-pyridylaminide, can be performed using TTMSS and AIBN.

Substituted 2-aminopyridines and their annulated derivatives constitute an important class of organic compounds, widely represented in the molecules of pharmacological interest, in both therapeutic[1] and recognition agent fields.[2]

In recent years, particular attention has been devoted to the development of synthetic methods that provide an entry into this class of compounds. Thus, 7-azaindoline **I** and 1,2,3,4-tetrahydro[1,8]naphthyridine **II** (Fig. 1) derivatives which have been described as therapeutically important compounds,[3] remain a somewhat inaccessible class of derivatives. Simple 7-azaindoline structures have been prepared by the sluggish hydrogenations of azaindoles.[4] More recently, a free radical-mediated aryl-amination has been reported, whereby an aryl radical adds to the nitrogen of an azomethine bond to supply the required compound.[5] Alternatively, Wijtmans et al.[6] have described a new sequence based on Van der Plas's reaction. 1,2,3,4-Tetrahydro[1,8]naphthyridines are usually prepared by the selective catalytic hydrogenations of the corresponding precursors, either prepared by Skraup,[7] Friedländer[1d,e,8] or Friedel–Crafts[6] approaches. Moreover, Palukcki and co-workers.[9] reported the preparation of 1,2,3,4-tetrahydro[1,8]naphthyridine fragments, using two different methods, one of which relied, again, on variations of Friedländer reaction,[9a] the other being based in a double Suzuki–Miyaura reaction and Chichibabin cyclization.[9b,c] Therefore, in addition to more specific methodologies, a universal synthetic method, which allows entry into these annulated systems would be highly desirable. Accordingly, Davies et al.[10] recently described how the ortho alkylation of Boc-protected 2-aminopyridines with α,ω-dihaloalkanes, followed by in situ cyclization, results in the corresponding annulated pyridine derivatives in good yields.

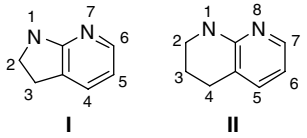

Figure 1. Compounds containing a pyridine nucleus fused to a saturated nitrogen-containing ring. **I**: 7-azaindoline; **II**: 1,2,3,4-tetrahydro[1,8]naphthyridine.

On the other hand, Zard and coworkers[11] reported the preparation of a series of compounds containing a 2-aminopyridine nucleus fused to a saturated ring (7-azaoxindole, 7-azaindoline, tetrahydro[1,8]naphthyridine and tetrahydro-5*H*-pyrido[2,3-*b*]azepin-8-one), starting from various 2,6-dichloropyridines, through a radical xanthate-mediated cyclization. Although this approach is more general and flexible than previous traditional routes, initial studies starting from the suitable 2-aminopyridines produced unwanted reactions on the cyclic nitrogen, as a result of its higher nucleophilicity. In this context, during the past few years our research group has been interested in the chemistry of pyridinium

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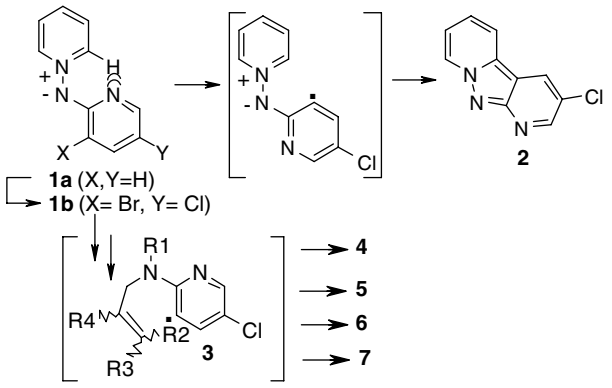
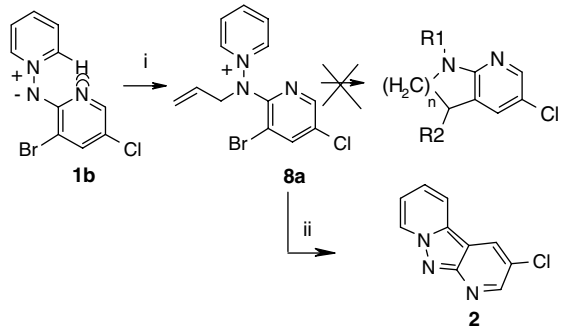


Scheme 1. Radical sequence plan.

N-2′-pyridylaminide **1a** (Scheme 1). Compound **1a** is a stable heterocyclic betaine in which the exocyclic nitrogen anion is stabilized by the presence of a pyridinium moiety.[12] Moreover, the cyclic nitrogen is partially blocked by an intramolecular hydrogen bond, making N-alkylation highly regioselective. This compound has proven to be a versatile scaffold in a wide range of transformations, such as halogenations (for example, to supply **1b**, Scheme 1) or sulfonylations, and the final fission of the N–N bond allows the synthesis of the corresponding substituted 2-aminopyridine derivatives.[12e]

As part of our work on free radical heteroarylations[12e,13] using tris(trimethylsilyl)silane and azobisisobutyronitrile (TTMSS/AIBN) under reductive conditions, we described an efficient approach to pyrazolopyridines **2** (Scheme 1) through an intramolecular radical process. In this approach, a pyridyl radical was added to the pyridinium nucleus, and the system was subsequently rearomatized.[13c] Herein, we wish to report an extension of the method to provide an improved access to annulated aminopyridine derivatives (Scheme 1, compounds **4**–**7**). In this method, a pyridyl radical **3** is intramolecularly added onto an alkenyl fragment obtained from aminide **1b**. This strategy could yield the target compounds through a careful choice of alkene intermediate.

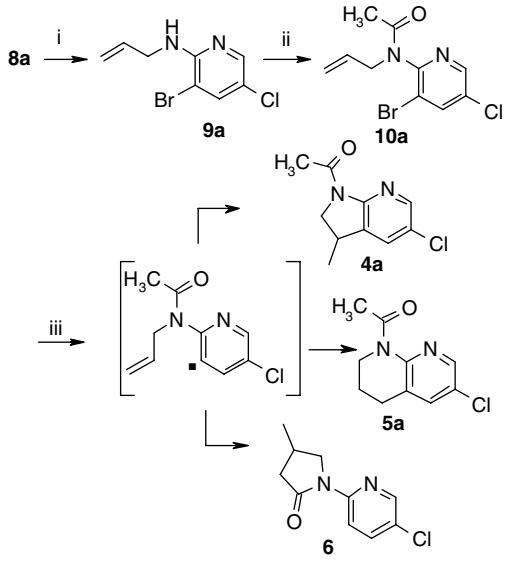
Our initial studies started from salts **8**, obtained from *N*-aminide **1b** by reaction with different allyl bromides (**8a** from **1b** and allyl bromide, **8c** from **1b** and 3,3-dimethylallyl bromide and **8d** from **1b** and 2-methylallyl bromide). Initial experiments on pyridyl radical cyclization were then undertaken on **8a** (Scheme 2) bearing in mind our previous experience on the intramolecular process.[13c] However, in agreement with previous results,[12e] the slow dropwise addition (via syringe pump) of a solution of TTMSS (2 equiv) and AIBN (2 equiv) to a solution of **8a** in *m*-xylene/acetonitrile did not generate detectable yields of annulated derivatives, and only poor yields of tricyclic compound **2** were obtained.



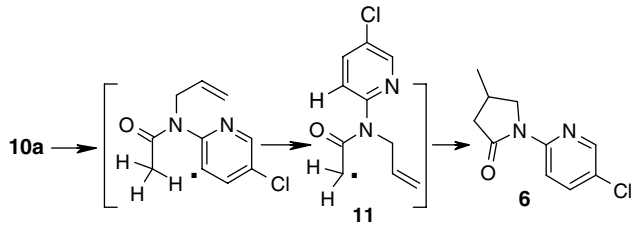
Scheme 2. Initial radical studies from salt **8a**. (i) Allyl bromide/acetone, 68%; (ii) TTMSS/AIBN/*m*-xylene/acetonitrile.

Cyclization of compound **8a** did not seem to be an efficient process, so N,N-reduction and acetylation in the presence of the base were performed. The treatment of **10a** under standard radical conditions,[14] gave a mixture of 7-azaindoline **4a**, 1,2,3,4-tetrahydro[1,8]naphthyridine **5a** and pyrrolidin-2-one **6** (3:1:3). Careful examination of the reaction mixture by NMR spectroscopy showed only half of the product arising from the direct cyclization of the heteroaryl radical onto the allyl double bond to give **4a** and **5a** (28% and 10% yield, respectively) (Scheme 3).

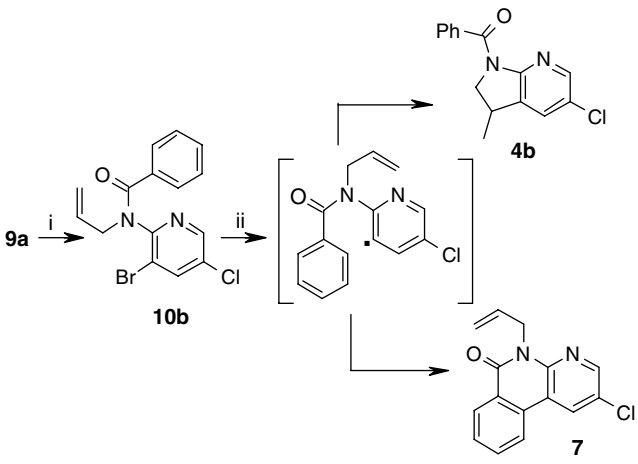
The main product **6**, however, resulted from [1,5]-hydrogen transfer followed by a 5-*exo trig* cyclization, in preference to direct cyclization, despite the fact that this route proceeds via a methyl radical intermediate **11** (Scheme 4). This kind of radical translocation has previously been studied by different authors for alternative substrates.[15] In order to avoid the unwanted [1,5]-hydrogen atom transfer process, **10b** (Scheme 5) was prepared and, under similar cyclization conditions, gave a mixture (2:1, 49%) of *N*-allyl-2-chloro-5*H*-benzo[*c*][1,8]naphthyridin-6-one **7** and *N*-acetyl-5-chloro-3-methyl-7-azaindoline **4b**. These results show the preference of the pyridyl radical, in this case, to take part in homolytic aromatic substitution.



Scheme 3. Preliminary results in the obtention of compounds **4** and **5**. (i) Et_3B/EtOH, 64%; (ii) AcCl/Et_3N, 51–80%; (iii) TTMSS/AIBN/*m*-xylene, 70% (3:1:3).



Scheme 4. [1,5]-Hydrogen transfer and 5-*exo trig* cyclization.

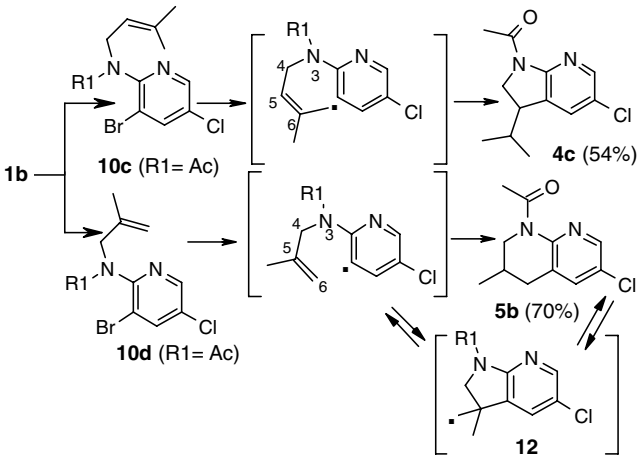


Scheme 5. Radical cyclization from **10b**. (i) $BzCl/CH_2Cl_2/Et_3N$ 56%; (ii) TTMSS/AIBN/*m*-xylene, 49% (1:2).

Finally, on the assumption that:[16]

(a) alkenylaryl radicals are systems in which the lack of chain flexibility greatly increases the difference in strain energy between the transition states for *exo* and *endo* ring closures,
(b) when the 3-position is occupied by a heteroatom (N in the present case), both lengths and angles in the transition state are modified, leading to a variation of the rate of cyclization and regioselectivity (*exo*/*endo*),
(c) in the well-studied case of the hexenyl radical, the presence of a substituent such as Me has a different effect on the rate and the regioselectivity depending on its position in the chain, additional experiments were carried out using alkenylheteroarylderivatives **10c** and **10d**. These products have been obtained from salts **8c** and **8d**, by N,N-reduction (to supply compounds **9c** and **9d**) and acetylation, respectively. The results of these experiments are summarized in Scheme 6. Both azaindoline **4c** and tetrahydro[1,8]naphthyridine **5b** were obtained with satisfactory yields (54% and 70%, respectively) with only traces of other isomeric compounds. It is, however, to be emphasized that although the control of regioselectivity in compound **5b** should be due to a 6-*endo* cyclization, a rapid rearrangement of radical **12**, via a reversible 5-*exo trig* cyclization, as occurs in related systems,[17] cannot be excluded.

In conclusion, the synthesis of annulated 2-aminopyridines by intramolecular radical pyridylation of appropriate substrates, obtained from pyridinium *N*-2′-pyridylaminide, can be performed using an easy, mild and selective approach. The methodology seems to be generally more flexible than conventional routes, and should be complementary to other approaches in the preparation of all the fused pyridines described.



Scheme 6. Obtention of compounds **4** and **5**.

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Supplementary data

Available selected experimental procedures and selected spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.092.

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14. General procedure: A solution of TTMSS (0.248 g, 1 mmol) and AIBN (0.164 g, 1 mmol) in *m*-xylene (10 mL) was added dropwise by a syringe pump during 13 h to a stirred solution of the corresponding allyl derivative **10** (0.5 mmol) in *m*-xylene (2 mL), at 80 °C (bath temperature). Stirring was maintained at the same temperature for further 12 h. The solution was concentrated and the crude mixture was separated by flash chromatography, yielding the pure compounds (49–70%).
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