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Optimisation, scope and limitations of the synthesis of 5-aminoindolizines from oxazolo[3,2-*a*]pyridinium salts

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Abstract—In this letter, we report on our efforts to optimise the reaction conditions and to explore the scope and limitations of the preparation of 5-aminoindolizines starting from oxazolo[3,2-*a*]pyridinium salts and different amines to evaluate the utility for combinatorial library construction. Thus, we were able to reduce the amount of amine to 1.1 equiv by applying microwave heating, acetonitrile as solvent and DMAP as additional base. Further, we observed that only aliphatic secondary amines with limited steric demand could deliver the desired compounds.

1. Introduction

Chemists in academia and pharmaceutical industry have recently become attracted to indolizines due to their interesting and promising biological properties. Although aromatic indolizine systems have not been discovered in nature until now,[1] they have found widespread application in biological and pharmaceutical research. Thus, several reports have appeared showing the potential of indolizine derivatives as histamine H_3 receptor antagonists,[2] antimycobacterial agents,[3] calcium entry blockers[4] and inhibitors of 15-lipoxygenase.[5] In addition, various studies have shown that indolizines offer antioxidant properties,[6] delayed replicative senescence of human diploid fibroblasts[7] and possess antiviral and antileishmanial activity.[8]

Over the years, several approaches have been developed to synthesise indolizine systems, which can be subdivided into four main categories: (1) Condensation reactions of 2-alkyl-pyridines with carboxylic acid anhydrides or α-halo ketones known as Scholtz[9] or Tschitschibabin[10] reaction, respectively. (2) Reactions of α-unsubstituted pyridines with acyl- or aryl-substituted allyl halides or esters[11] and methyl propiolate.[13] (3) 1,3-Dipolar cycloadditions of pyridinium *N*-methylides with acetylenes[11] and ethylenes.[11d,12] (4) Copper-assisted cycloisomerisations of alkynylpyridines.[13] The last method has been developed only recently, while the other procedures have already been known for decades. Apart from these four approaches to obtain indolizine system, methods have been developed to functionalise existing indolizine nuclei and thereby expanding the scope of available indolizine derivatives.[14]

Recently, a method has been reported by Babaev et al. to create 5-aminoindolizine systems that does not fit into the above mentioned classification. This approach applies a 5-methyl substituted oxazolo[3,2-*a*]pyridinium moiety as stable intermediate, which can be easily prepared in two steps from 2-methoxy-6-picoline and phenacylbromides. This cationic heterocyclic system reacts with secondary amines to form the desired indolizines in a rearrangement-like fashion (Scheme 1).[15]

Although we believe that this approach offers an unique entry into a broad spectrum of indolizines, the reaction has been exploited for only one oxazolo[3,2-*a*]pyridinium salt and three different cyclic secondary amines, which have been applied in large excess either neat (piperidine, morpholine) or in acetonitrile (hexamethylene imine). This restriction might be due to the observation that only 4-nitrophenyl 5-aminoindolizine derivatives could be isolated (Scheme 1, $R^1 = NO_2$).[15a]

Nevertheless, we saw a considerable potential of this chemistry for generating diversity in the synthesis of combinatorial libraries.[16] For that reason, we decided

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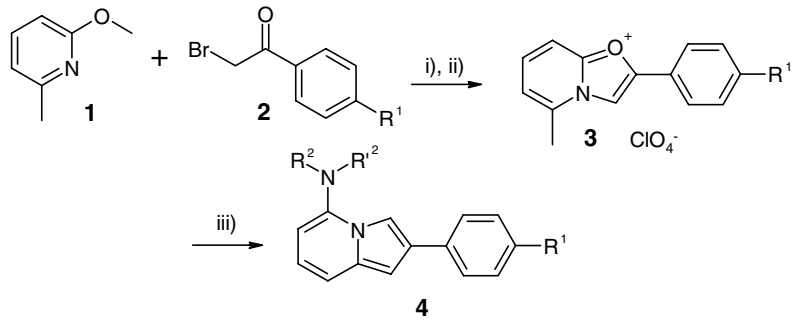


Scheme 1. Reagents, yield: (i) acetone, 48 h, reflux, 40–60%; (ii) concd sulfuric acid, then 70% perchloric acid, ~70%; (iii) neat amine, reflux, 65–80%.

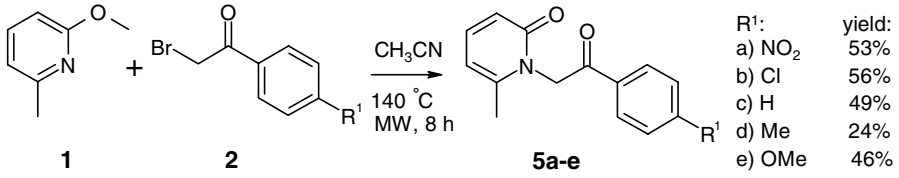
to optimise all synthetic procedures at first. In particular, the improvement of the indolizine formation step was of primary interest for us by optimising amine equivalents, solvent, use of an additional base and microwave heating. Further, we were interested in broadening the scope of applicable phenacylbromides and amines in particular, that is, by varying the steric and nucleophilic character using different primary and secondary amines.

2. Results and discussion

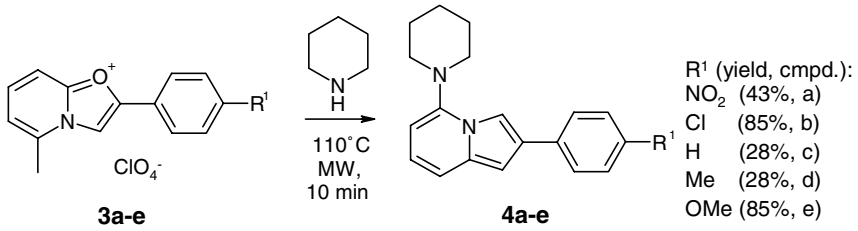
To examine the scope and limitations of this method for synthesising 5-aminoindolizines and to optimise the synthetic procedures, we first tried to improve the synthesis of the intermediate oxazolo[3,2-*a*]pyridinium salts. Starting with the reaction of phenacylbromides **2** with methoxy-picoline **1**, we investigated the possibility of reducing the reaction time by microwave heating. A solvent screening to identify the best solvent for this reaction was performed using acetonitrile, ethanol, DMF, DMSO, 1,4-dioxane, acetone, THF and toluene. Although acetonitrile was identified as the best solvent, the reaction was still slow; the mixture had in fact to be heated for 8 h in a microwave oven at 140 °C. Nevertheless, different *para*-phenyl-substituted 6-methyl 1-phenacylpyridin-2-ones **5** (Scheme 2) were obtained in moderate yields. The products either precipitated from the reaction mixture or had to be purified by flash chromatography.

The next step, dehydration/cyclisation by applying concentrated sulfuric acid and subsequent precipitation with perchloric acid by slightly modifying the published procedure[15,17] gave the desired methyl oxazolo[3,2-*a*]-pyridinium perchlorate salts **3** in moderate to good yields (Scheme 1, isolated yields (R^1): **3a**: 78% (NO_2), **3b**: 81% (Cl), **3c**: 40% (H), **3d**: 58% (Me), **3e**: 83% (OMe)). In case of pyridone **5e** carrying a methoxy substituent, 64% sulfuric acid had to be applied for cyclisation to avoid additional sulfonation of the phenyl ring.[18]

Next, we wanted to investigate the influence of the *para*-substituent on the formation of 5-aminoindolizines, which were derived from different oxazolopyridinium salts **3a**–**e**. By applying the faster and usually cleaner methodology of microwave heating we were confident to isolate pure products in contrast to earlier work (Scheme 3).[15a] We were pleased to find that using excess piperidine without solvent under microwave heating allowed us to isolate all desired products in approximately 95% purity for every substituent.



Scheme 2. Synthesis of 6-methyl 1-phenacylpyridin-2-ones **5** by microwave heating.



Scheme 3. Reaction of piperidine with different oxazolo[3,2-*a*]pyridinium salts **3** carrying various *para*-substituents.

The differences in isolated yields (Scheme 3) were not due to a differing reactivity but caused by the work up procedure. Typically, the reaction mixture was poured into water followed by filtration or centrifugation to isolate the precipitated product. In some cases, this proved to be very difficult due to the finely dispersed precipitate.

The fact that the desired 5-aminoindolizines were obtained in almost pure form in all cases might not only be due to the heating by microwave irradiation, but also to the simplified work up. Since in earlier work the crude products were always purified by column chromatography, we believe that the acidic nature of silica gel might be responsible for the described instability.

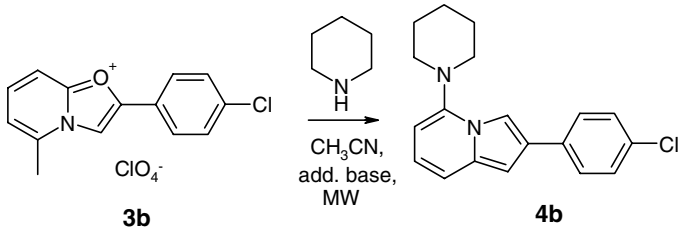
As we were interested in the construction of a combinatorial library of 5-aminoindolizines by applying this reaction sequence, we found it highly desirable to use the amine just in stoichiometric quantities and to perform the reaction in a common organic solvent. For that reason, we tried to optimise the synthetic procedure with regard to amine equivalents, additional base and reaction conditions by using piperidine and 5-methyl-2-(*p*-chlorophenyl)-oxazolo[3,2-*a*]pyridinium salt **3b** as substrate (Scheme 4). Selected results of this screening process are presented in Table 1.

We were able to reduce the amount of amine to 1.1 equiv by using an additional base. Results by employing DMAP were slightly superior compared to triethylamine (entries 9–11 and 5–8). This is of importance for library construction so that a large and diverse set of amines could be applied in stoichiometric amounts. In contrast, the reaction time had only a small effect (entries 2/3, 6/7 and 10/11), while no conclusion can be drawn for the temperature (entries 10/11). Even without an additional base, the reaction could be run to completion by using three amine equivalents. Thus, the best result was obtained by employing 1.1 equiv of piperidine and 2 equiv of DMAP at 100 °C for 1 h.[20,21]

After optimising the synthetic procedure, we finally performed a small amine screen to explore the scope and limitations of the formation of 5-aminoindolizines addressing the impact on reactivity of some primary and secondary amines with different steric and electronic character (Scheme 5).

Sterically less demanding aliphatic secondary amines **6**–**8** deliver the desired indolizine system, in two out of three cases even in quantitative yield as determined by LC/MS.[22] The low yield for diethylamine (**8**) is most likely due to its high volatility. Further, 4-amino-piperidine (**7**) carrying both a primary and a secondary amine reacts only with the more nucleophilic secondary nitrogen delivering the product in 100% regioselectivity. Sterically hindered aliphatic (i.e., **9**) and the less nucleophilic aromatic amines (i.e., **10** and **11**) do not react.

With all primary amines **12**–**16**, no 5-aminoindolizine derivatives could be detected. Aromatic amines **12**–**14** remained unchanged. However, with aliphatic amines like **15** and **16**, a different product was detected in quantitative yield. After isolation and analytical investigation of these compounds, they were identified to be imidazo[3,2-*a*]pyridinium salts (Scheme 6a). In these cases cyclisation does not occur via the methyl, but via the amino group. To the best of our knowledge, this type

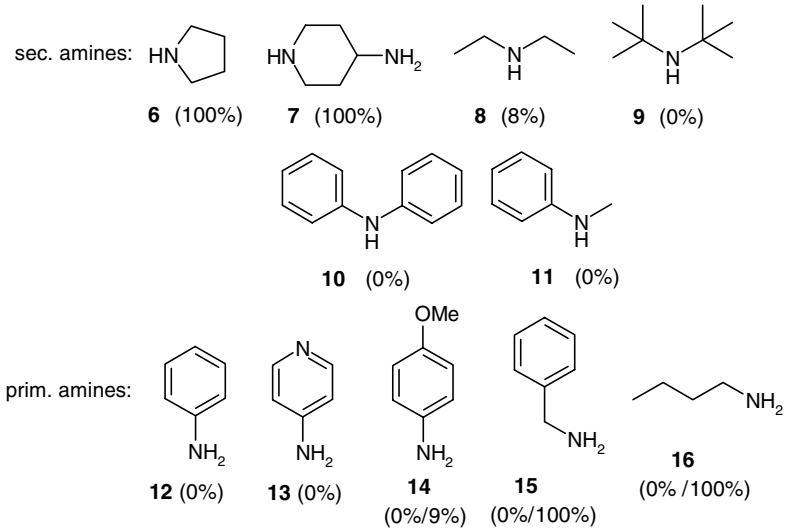


Scheme 4. Test reaction to screen for best reaction conditions and amine equivalents.

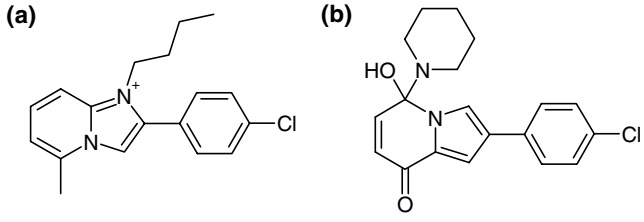
Table 1. Selected results of the optimisation process towards the synthesis of 5-aminoindolizines

Entry	Amine equivalents	Additional base	Temperature (°C)	Reaction time (h)	Yield[a] (%)
1	4	—	100	0.5	100
2	3	—	100	0.5	89
3	3	—	100	1	97
4	1.1	—	100	3	70
5	3	2 equiv triethylamine	100	0.5	100
6	2	2 equiv triethylamine	100	0.5	91
7	2	2 equiv triethylamine	100	1	100
8	1.1	2 equiv triethylamine	100	0.5	76
9	2	2 equiv DMAP	100	1	100
10	1.1	2 equiv DMAP	100	1	94
11	1.1	2 equiv DMAP	140	3	97

[a] Yields were determined by LC/MS (DAD purity), reaction conditions: solvent: acetonitrile, microwave heating (max 300 W).



Scheme 5. Set of amines applied in the synthesis of 5-aminoindolizines to explore the scope and limitations. The yields of 5-aminoindolizines as determined by LC/MS are given in parentheses. For primary amines the yield of side product (see text below) is also given (substrates **14**–**16**, second percentage value in parentheses).



Scheme 6. Proposed structures of (a) imidazo[3,2-*a*]pyridinium salts and (b) chinoid oxidation products.

of compound has so far not been prepared starting from oxazolo[3,2-*a*]pyridinium salts.

Finally, we performed stability measurements to ensure the utility of 5-aminoindolizines for library construction. For that reason, we stored some 5-aminoindolizine derivatives in DMSO at rt in the presence of air. Unfortunately, the products slowly oxidised to form chinoid structures as evidenced by high resolution mass spectrometry (Scheme 6b). This instability towards oxidation has already been shown for 8-aminoindolizine derivatives.[19]

In conclusion, we have demonstrated the utility of oxazolo[3,2-*a*]pyridinium salts to create a set of diverse 5-aminoindolizines. Microwave heating in conjunction with the use of an auxiliary base and a common organic solvent made it possible to reduce the necessary amount of amines to 1.1 equiv, which makes the procedure suitable for the production of highly diverse combinatorial libraries. Further, we were able to extend the reported procedure[15] to a wider range of applicable bromoketones. More critical is the observation that these indolizines are slowly oxidised in solution and may therefore cause storage problems. The procedure is however limited to sterically less demanding secondary amines, while with primary aliphatic amines imidazopyridinium salts are formed.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.033.

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20. Since the effect of applying higher temperature and longer reaction times on the yield was marginal, we decided to choose the milder and faster conditions as 'best' result.
21. Typical procedure: 100 mg (291 μmol) of **3b** were dissolved in 2 ml acetonitrile, whereafter 71 mg (581 μmol) DMAP and 31.6 μl (320 μmol) of piperidine were added. The reaction mixture was heated for 1 h to 100°C in a microwave oven (CEM Discover™, max 300 W, for details see Supplementary material) and poured into 10 ml of water. Most of the yellow product precipitated after standing at rt overnight so that the supernatant could be decanted. The residue was carefully washed with water and dissolved in ethyl acetate. The supernatant was centrifuged for 1 h at 3000 rpm, whereafter some more product could be obtained after decantation and washing with water. This second crop was also dissolved in ethyl acetate and the combined organic layer was dried with sodium sulfate. After removal of the solvent the product was isolated in approx. 95% purity. Yield: 58 mg (61%).
22. For analytical data of all isolated 5-aminoindolizines see Supplementary material.