LETTERS

Single-Step Synthesis of 5,6,7,8-Tetrahydroindolizines via Annulation of 2-Formylpiperidine and 1,3-Dicarbonyl Compounds

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(5) Supporting Information

ABSTRACT: An expedient single-step synthesis of 5,6,7,8-tetrahydroindolizines has been achieved via the annulation of commercially available 2-formylpiperidine hydrochloride and 1,3-dicarbonyl compounds in THF in the presence of pyrrolidine and 4 Å



molecular sieves. A variety of β -ketoesters, ketones, and amides participated in this annulation chemistry, affording the desired 5,6,7,8-tetrahydroindolizines in moderate to good yields.

5,6,7,8-Tetrahydroindolizine is a structural motif found in many biologically active compounds, and as such, is of general interest to the synthetic and medicinal chemistry community.¹⁻⁴ For example, 5,6,7,8-tetrahydroindolizine cores are found in the anticancer natural alkaloids rhazinilam and rhazinicine,¹ and the antimicrobial agents polygonatine A, polygonatine B, and kinganone.³ CMV423, a 5,6,7,8-tetrahydroindolizine derivative, shows promise for the treatment of human cytomegalovirus (HCMV) infections (Figure 1).⁴





There are several reported approaches to the synthesis of 5.6.7.8-tetrahydroindolizines in the literature, each of which centered on certain substitution pattern of the tetrahydroindolizine core.⁵⁻⁸ For example, 5,6,7,8-tetrahydroindolizines are synthesized via a 1,3-dipolar cycloaddition of münchnones⁹ with acetylenic dipolarophiles followed by elimination of CO₂ (Scheme 1A).⁵ However, this process not only requires multistep synthesis and high reaction temperature (125-140 °C) but also affords low overall yields and poor regioselectivity when unsymmetrical acetylenes are employed. Recently, Coelho reported that 5,6,7,8-tetrahydroindolizines were prepared from selective hydrogenation of indolizines that were derived from the intramolecular cyclization of Morita-Baylis-Hillman (MBH) adducts prepared from acrylates or α_{β} -unsaturated ketones and substituted 2-pyridinecarboxaldehydes (Scheme 1B).⁶ Similarly, this chemistry also suffers from multistep operations and low overall yields. A single step synthesis of 5,6,7,8-tetrahydroindolizines has been previously achieved by a ruthenium-catalyzed multicomponent reaction (Scheme 1C).7 Unfortunately, this

Scheme 1. Synthetic Strategies to Tetrahydroindolizines

A. Cycloaddition of Münchnones



B. MBH, cyclization and selective hydrogenation



C. Ru-catalyzed multicomponent reaction



strategy employs high loading of an expensive ruthenium catalyst (3 mol % $Ru_3(CO)_{12}$), high CO pressure (20 bar), and high temperature (140 °C). Therefore, the synthetic utility of these aforementioned methods is limited, and we believe that a more efficient and economic synthesis of 5,6,7,8-tetrahydroindolizines is highly desirable.

In order to support an internal drug research and development program, we were required to develop an efficient synthesis of a wide variety of 5,6,7,8-tetrahydroindolizines for structure– activity relationship (SAR) studies and further process development. We decided to focus on a synthetic strategy involving an annulation reaction of commercially available 2-formylpiperidine hydrochloride (**2a**) and 1,3-dicarbonyl compounds. Herein, we wish to report a facile one-step synthesis of 5,6,7,8-

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tetrahydroindolizines by annulating 2a with β -ketoesters, ketones, or amides (Scheme 1D).

We initiated our studies by examining the annulation reaction of 2-formylpiperidine hydrochloride (2a) and ethyl acetoacetate (3a) to form 2,3-disubstituted 5,6,7,8-tetrahydroindolizine 1a (Table 1).¹⁰ Under the best conditions described in Table 1, the

| Table 1. Effect of Reaction Parameters on Annulation of 2a |
|--|
| and 3a to Generate Tetrahydroindolizine 1a ^a |

| $ \begin{array}{c} $ | + Me OEt Hereit 4 equiv pyrrolidine 4 Å MS THF, 0–5 °C | | Ae OEt ∕∕ | |
|--|---|------------------------------|------------------|--|
| 2a , 1.4 equiv | 3a MS = molecular siev | es 1a | i | |
| "standard conditions" | | | | |
| entry variatio | on from the "standard" conditions c | $\operatorname{onv}^{b}(\%)$ | yield c (%) | |
| 1 | none | 94 | $80(73)^d$ | |
| 2 | 23 $^{\circ}\mathrm{C}$ instead of 0–5 $^{\circ}\mathrm{C}$ | 90 | 61 | |
| 3 | no 4 Å molecular sieves | 92 | 74 | |
| 4 | K ₂ CO ₃ as base | 0 | 0 | |
| 5 | Et ₃ N as base | 85 | <5 | |
| 6 | piperidine as base | 100 | 55 | |
| 7 | azepane as base | 100 | 69 | |
| 8 | CH ₂ Cl ₂ as solvent | 100 | 59 | |
| 9 | 2-MeTHF as solvent | 93 | 79 | |
| 10 | EtOH as solvent | 75 | 29 | |
| 11 | PhMe as solvent | 90 | 28 | |
| 12 | 2 equiv of pyrrolidine | 85 | 46 | |
| 13 | 1 equiv of 2a | 87 | 50 | |

^aReactions were performed using **3a** (2.0 mmol, 260 mg) in solvent (3.9 mL, 15 mL/g) in 15 mL vials under N₂ for 2 h. ^bDetermined by HPLC analysis. ^cAssay yields were obtained by quantitative HPLC analysis. ^dIsolated yield.

reaction afforded 94% conversion in 80% HPLC assay yield and 73% isolated yield by employing 1.4 equiv of 2a, 2 mmol of 3a, 4 equiv of pyrrolidine as the base, and 150 wt % of 4 Å molecular sieves as the dehydrating agent in THF at 0-5 °C for 2 h (Table 1, entry 1). Performing the reaction at 23 °C or in the absence of molecular sieves generated slightly lower assay yields (Table 1, entries 2-3). The reactions carried out using inorganic base K₂CO₂ or organic base Et₂N resulted in much inferior conversion or assay yield (Table 1, entries 4-5). The use of cyclic secondary amine bases such as piperidine and azepane gave quantitative conversion, albeit in lower assay yields (Table 1, entries 6-7). A screening of solvents such as dichloromethane, 2-methyltetrahydrofuran, ethanol, and toluene did not afford any advantage over the solvent of choice THF (Table 1, entries 8-11). Finally, reduction of the stoichiometry of pyrrolidine base from 4 equiv to 2 equiv or that of compound 2a from 1.4 equiv to 1 equiv both resulted in decreased conversion and assay yields (Table 1, entries 12-13).

With a set of optimized conditions in hand, we next examined the scope and limitations of this annulation reaction by reacting 2-formylpiperidine hydrochloride (2a) with various 1,3dicarbonyl compounds (Table 2). A cyclopropyl group can be readily incorporated in the 3-position of tetrahydroindolizine 1b in 50% yield when ethyl 3-cyclopropyl-3-oxopropanoate (3b) was employed (Table 2, entry 2). Disappointingly, a sterically bulky *tert*-butyl substituted β -ketoester 3c only generated 12% yield of product 1c, indicating that this annulation reaction is sensitive to the steric property of the 1,3-dicarbonyl compounds (Table 2, entry 3). Interestingly, β -ketoesters substituted with an

Table 2. Scope of 1,3-Dicarbonyl Compounds 3^a





^{*a*}Reactions were performed using 2.0 mmol of 3, 1.4 equiv of 2a, 4 equiv of pyrrolidine, 150 wt % of 4 Å MS in THF (15 mL/g) in 15 mL vials under N₂ at 0–5 °C for 2 h. ^{*b*}Isolated yield. ^{*c*}Reaction was performed using 4.0 mmol of 3m. The annulation product was contaminated with an unknown impurity after silica gel column chromatography. Therefore, the reaction mixture was directly carried to *N*-Boc deprotection and 1m was isolated.

aryl group, whether electron-neutral (3d), rich (3e), or deficient (3f), all produced the desired tetrahydroindolizines 1d-f in about 40% yield (Table 2, entries 4–6). Pyridine-substituted β -ketoester 3g also gave the intended product 1g in a moderate 41% yield (Table 2, entry 7). The relatively low yields of these

Organic Letters

reactions could be attributed to possible competitive decomposition of the free 2-formylpiperidine under the reaction conditions as the electrophilicity and corresponding reactivity of the carbonyl group decreased. In fact, the reactions did not proceed further after 2 h with starting materials 3d-g remaining.

Gratifyingly, besides β -ketoesters, 1,3-diketones can also participate in the annulation chemistry and produce tetrahydroindolizine derivatives in good yields. For example, acyclic 1,3diketones pentane-2,4-dione (3h) and 1-phenylbutane-1,3-dione (3i) reacted with 2-formylpiperidine hydrochloride (2a), forming tetrahydroindolizines 1h and 1i in 60% and 76% yields, respectively (Table 2, entries 8-9). It is worth noting that in the latter reaction mixture, only trace amount of the minor isomer was observed by LCMS analysis. Cyclic 1,3-diketones, such as cyclohexane-1,3-dione (3j), 5,5-dimethylcyclohexane-1,3-dione (3k), and cycloheptane-1,3-dione (3l), also produced the desired products 1j-l in 58%, 71%, and 39% yields (Table 2, entries 10-12).¹¹ In addition, N-Boc protected piperidine-2,4-dione 3m underwent the annulation reaction with 2-formylpiperidine hydrochloride (2a) and afforded the heterotricyclic product 1m in 62% yield after direct N-Boc deprotection (Table 2, entry 13).¹² Similarly, *p*-methoxybenzyl (PMB) protected piperidine-2,4-dione 3n and N-Boc protected 5-ethylpiperidine-2,4-dione 30 generated products 1n and 10 in 68% and 61% yields, respectively (Table 2, entries 14-15).

It is noteworthy that, besides 2,3-disubstituted tetrahydroindolizines, 1,2,3-trisubstituted tetrahydroindolizine could also be attained by this annulation chemistry when a 2-piperidinyl ketone was employed. For example, 2-piperidinylethanone (**2b**) reacted with ethyl acetoacetate (**3a**) under our standard conditions, affording 58% yield of the desired 1,2,3-trisubstituted tetrahydroindolizine **1p** (Scheme 2). Thus, one can readily





envision that a wide spectrum of 1,2,3-trisubstituted tetrahydroindolizines can be achieved in a single step from 2-piperidinyl ketones and 1,3-dicarbonyl compounds. Furthermore, 1,2,3,4tetrasubstituted pyrrole **1q** could also be prepared using *N*methylaminoacetone (**2c**) and ethyl acetoacetate (**3a**), albeit in a low yield of 21% (Scheme 2).¹³

A few observed limitations to this annulation reaction included the use of certain 1,3-dicarbonyl compounds shown in Figure 2. Examples included ethyl trifluoroacetoacetate (**3p**), β -ketoamides **3q** and **3r**, 5-membered cyclic 1,3-dicarbonyl compounds **3s** and **3t**, as well as unprotected piperidine-2,4-dione (**3u**) and 1-phenylquinoline-2,4-dione (**3v**), which all gave <10% product by HPLC and LCMS analysis, even after prolonged reaction time and/or elevated reaction temperature. We attributed the lack of success for these reactions to decomposition/polymerization of the reactant under the standard reaction conditions (for **3p** and **3u**), decreased electrophilicity of the 1,3-dicarbonyl (for **3q**, **3r**



3n

3t

and 3v), or higher activation energy arising from five-five ring strain in the transition states of the reaction (for 3s and 3t).

30

Finally, the scalability of this annulation chemistry was successfully demonstrated using 2-formylpiperidine hydrochloride (2a) and N-Boc piperidine-2,4-dione (3m) at 5.0 g scale. The reaction went smoothly and provided the desired tricyclic compound 1m in a slightly lower 53% yield than the small scale (4.0 mmol) reaction after direct Boc deprotection (eq 1).



We propose a mechanism for this annulation process exemplified by the reaction of 2-formylpiperidine hydrochloride (2a) and ethyl acetylacetate (3a) (Scheme 3). It is believed that

Scheme 3. Proposed Mechanism



compounds 3a and 2a, upon treatment with pyrrolidine and the dehydrating reagent molecular sieves, gave rise to enamine 4^{14} and iminium species 5, respectively. In fact, enamine 4 was observed by HPLC and LCMS in the reaction mixture. The formation of enamine 4 was further confirmed by ¹H NMR spectroscopy when the reaction was performed in THF- d_8 solvent under the standard reaction conditions absent of compound 2a. Similarly, treatment of 2-formylpiperidine hydrochloride (2a) with pyrrolidine (4 equiv) and molecular

3v

Organic Letters

sieves in THF- d_8 also showed the disappearance of the characteristic aldehyde peak. However, the mixture was too complex on ¹H NMR to conclusively identify iminium species **5**. We reasoned that the complex ¹H NMR of the mixture could be a result of equilibration of iminium species **5** and enamine **5**′, and/ or potential decomposition of **5** and **5**′. Intermediates **4** and **5** then react to generate isomeric iminium species **6a** and **6b**. Under the reaction condition, species **6b** converts to **6a**, which cyclizes to afford the bicyclic intermediate 7. Intermediate 7 then extrudes pyrrolidine to produce the desired 5,6,7,8-tetrahydroindolizine **1a**.

In conclusion, we have developed an expedient single-step synthesis of 5,6,7,8-tetrahydroindolizines via the annulation of commercially available 2-formylpiperidine hydrochloride and 1,3-dicarbonyl compounds under very mild conditions. A variety of β -ketoesters, ketones, and amides participated in this annulation chemistry, affording the desired 5,6,7,8-tetrahydroindolizines in moderate to good yields. In addition, the formation of 1,2,3-trisubstituted 5,6,7,8-tetrahydroindolizine and 1,2,3,4tetrasubstituted pyrrole was also demonstrated using 2piperidinylethanone and N-methylaminoacetone. We anticipate that this practical method will provide rapid access to useful quantities of versatile 5,6,7,8-tetrahydroindolizines.

ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization of new compounds, and copies of ¹H NMR and ¹³C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01671.

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Notes

The authors declare no competing financial interest.

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