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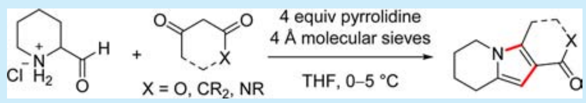
Single-Step Synthesis of 5,6,7,8-Tetrahydroindolizines via Annulation of 2-Formylpiperidine and 1,3-Dicarbonyl Compounds

Simona S. Capomolla, Ngiap-Kie Lim, and Haiming Zhang*

Small Molecule Process Chemistry, Genentech Inc., 1 DNA Way, South San Francisco, California 94080, United States

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]

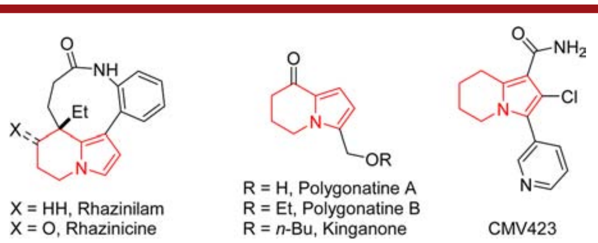
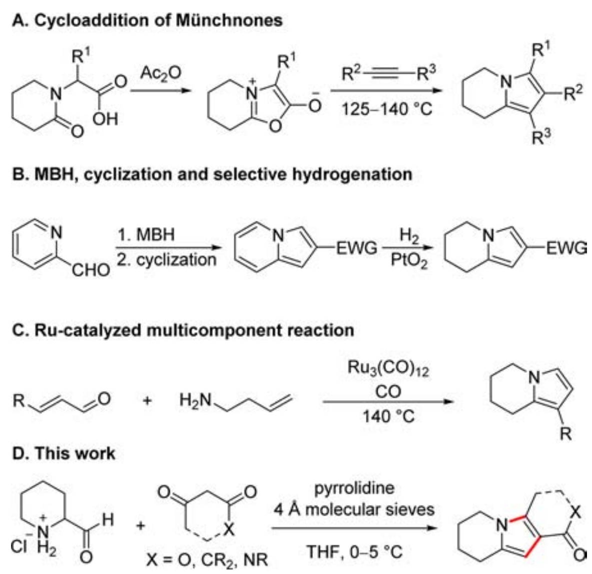


Figure 1. Biologically active 5,6,7,8-tetrahydroindolizines.

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 münchnones[9] with acetylenic dipolarophiles followed by elimination of CO_2 (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 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.

Scheme 1. Synthetic Strategies to Tetrahydroindolizines



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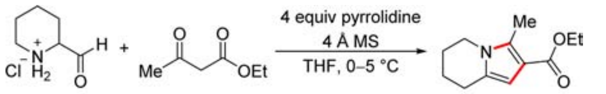
tetrahydroindolizines by annulating **2a** with *β*-ketoesters, ketones, or amides (Scheme 1D).

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 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 K_2CO_3 or organic base Et_3N 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).

Table 1. Effect of Reaction Parameters on Annulation of 2a and 3a to Generate Tetrahydroindolizine 1a[a]



2a, 1.4 equiv **3a** MS = molecular sieves **1a**

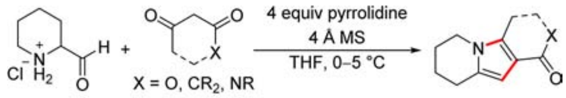
"standard conditions"

entry	variation from the "standard" conditions	conv[b] (%)	yield[c] (%)
1	none	94	80(73)[d]
2	23 °C instead of 0−5 °C	90	61
3	no 4 Å molecular sieves	92	74
4	K_2CO_3 as base	0	0
5	Et_3N as base	85	<5
6	piperidine as base	100	55
7	azepane as base	100	69
8	CH_2Cl_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

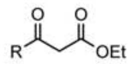
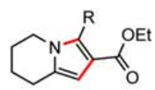
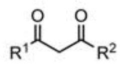
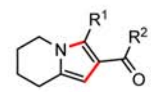
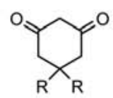
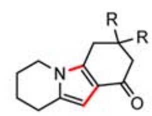
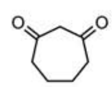
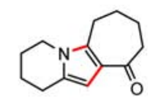
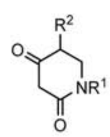
[a]Reactions were performed using **3a** (2.0 mmol, 260 mg) in solvent (3.9 mL, 15 mL/g) in 15 mL vials under N_2 for 2 h. [b]Determined by HPLC analysis. [c]Assay yields were obtained by quantitative HPLC analysis. [d]Isolated yield.

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 1,3-dicarbonyl 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 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

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



2a, 1.4 equiv **3** **1**

entry	1,3-dicarbonyls	product	yield[b] (%)
	 R =		
1	Me, **3a**	**1a**	73
2	*c*-Pr, **3b**	**1b**	50
3	*t*-Bu, **3c**	**1c**	12
4	Ph, **3d**	**1d**	45
5	4-$MeOC_6H_4$, **3e**	**1e**	42
6	4-$CF_3C_6H_4$, **3f**	**1f**	43
7	4-pyridyl, **3g**	**1g**	41
	 R^1, R^2 =		
8	Me, Me, **3h**	**1h**	60
9	Me, Ph, **3i**	**1i**	76
	 R =		
10	H, **3j**	**1j**	58
11	Me, **3k**	**1k**	71
			
12	**3l**	**1l**	39
	 R^1, R^2 =		
13	Boc, H, **3m**	**1m** (R^1 =H)	62[c]
14	PMB, H, **3n**	**1n**	68
15	Boc, Et, **3o**	**1o**	61

[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 N_2 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.

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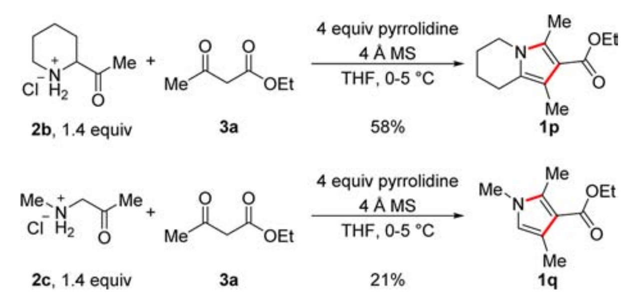
reactions could be attributed to possible competitive decomposition of the free 2-formylpiperidine under the reaction conditions as the electrophilicity and corresponding reactivity of the carbonyl group decreased. In fact, the reactions did not proceed further after 2 h with starting materials **3d−g** 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 1,3-diketones 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 **3o** generated products **1n** and **1o** 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, 1,2,3,4-tetrasubstituted pyrrole **1q** could also be prepared using *N*-methylaminoacetone (**2c**) and ethyl acetoacetate (**3a**), albeit in a low yield of 21% (Scheme 2).[13]

Scheme 2. Synthesis of Highly Substituted Pyrroles



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

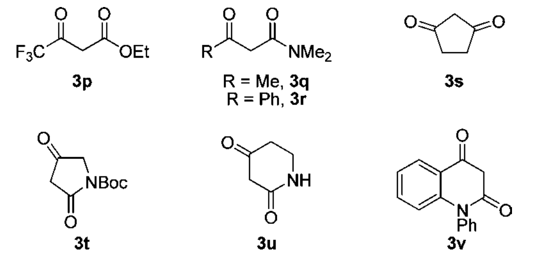
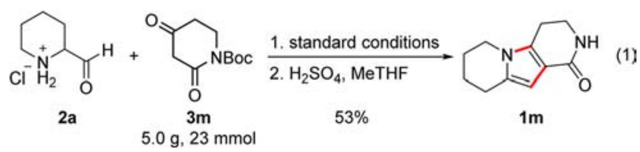


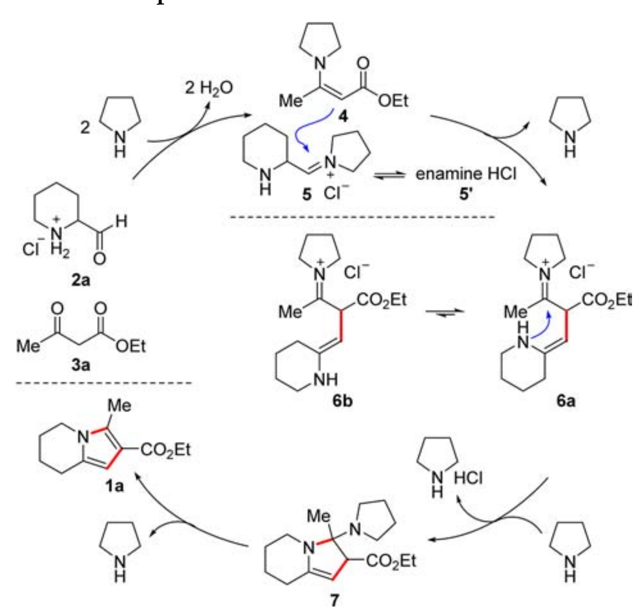
Figure 2. Unproductive 1,3-dicarbonyl compounds.

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 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 ^{1}H 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

Scheme 3. Proposed Mechanism



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sieves in THF-d_8 also showed the disappearance of the characteristic aldehyde peak. However, the mixture was too complex on ^{1}H NMR to conclusively identify iminium species **5**. We reasoned that the complex ^{1}H 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 1,2,3,4-tetrasubstituted pyrrole was also demonstrated using 2-piperidinylethanone 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 ^{1}H NMR and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01671.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhang.haiming@gene.com.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Baudoin, O.; Guénard, D.; Guéritte, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 333−341. (b) Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48*, 1822−1842. (c) Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *13*, 909−912. (d) Gerasimenko, I.; Sheludko, Y.; Stöckigt, J. *J. Nat. Prod.* **2001**, *64*, 114−116. (e) Kam, T.-S.; Subramaniam, G.; Chen, W. *Phytochemistry* **1999**, *51*, 159−169. (f) David, B.; Sévenet, T.; Morgat, M.; Guénard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317−326. (g) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7168−7171.

(2) (a) Schröder, F.; Franke, S.; Francke, W.; Baumann, H.; Kaib, M.; Pasteels, J. M.; Daloze, D. *Tetrahedron* **1996**, *52*, 13539−13546. (b) Movassaghi, M.; Ondrus, A. E. *Org. Lett.* **2005**, *7*, 4423−4426.

(3) (a) Sun, L.-R.; Li, X.; Wang, S.-X. *J. Asian Nat. Prod. Res.* **2005**, *7*, 127−130. (b) Dinsmore, A.; Mandy, K.; Michael, J. P. *Org. Biomol. Chem.* **2006**, *4*, 1032−1037.

(4) Snoeck, R.; Andrei, G.; Bodaghi, B.; Lagneaux, L.; Daelemans, D.; de Clercq, E.; Neyts, J.; Schols, D.; Naesens, L.; Michelson, S.; Bron, D.; Otto, M. J.; Bousseau, A.; Nemecek, C.; Roy, C. *Antiviral Res.* **2002**, *55*, 413−424.

(5) (a) Harju, K.; Manevski, N.; Yli-Kauhaluoma, J. *Tetrahedron* **2009**, *65*, 9702−9706. (b) Dalla Croce, P.; La Rosa, C. *Heterocycles* **2001**, *55*, 1843−1858. (c) Nayyar, N. K.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1997**, *62*, 982−991.

(6) Teodoro, B. V. M; Correia, J. T. M.; Coelho, F. *J. Org. Chem.* **2015**, *80*, 2529−2538.

(7) Biletzki, T.; Imhof, W. *Eur. J. Org. Chem.* **2012**, 6513−6516.

(8) (a) Bowie, A. L., Jr.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581−1586. (b) Ghosh, S. K.; Buchanan, G. S.; Long, Q. A.; Wei, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008**, *64*, 883−893. (c) Rocchiccioli, S.; Settambolo, R.; Lazzaroni, R. *J. Organomet. Chem.* **2005**, *690*, 1866−1870. (d) Marchalin, S.; Cvopova, K.; Pham-Huu, D.-P.; Chudik, M.; Kozisek, J.; Svoboda, I.; Daich, A. *Tetrahedron Lett.* **2001**, *42*, 5663−5667. (e) Lehmann, T.; Gmeiner, P. *Heterocycles* **2000**, *53*, 1371−1378. (f) Wang, M. D.; Alper, H. *Tetrahedron Lett.* **1995**, *36*, 6855−6858. (g) Gmeiner, P.; Lerche, H. *Heterocycles* **1990**, *31*, 9−12. (h) Tanis, S. P.; Raggon, J. W. *J. Org. Chem.* **1987**, *52*, 819−827.

(9) (a) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 135−136. (b) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C. *Chem. Ber.* **1970**, *103*, 2611−2624. (c) Santiago, B.; Dalton, C. R.; Huber, E. W.; Kane, J. M. *J. Org. Chem.* **1995**, *60*, 4947−4950. (d) Gribble, G. W. In *Oxazoles: Synthesis, Reactions, and Spectroscopy, A*; Palmer, D. C., Ed.; Wiley: New York, 2003; Vol. *60*, pp 473−576.

(10) Tetrahydroindolizine **1a** was previously synthesized in 12% yield by the condensation of pyridine-2-carboxaldehyde and ethyl acetoacetate (**3a**), followed by hydrogenation; see: Sprake, J. M.; Watson, K. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 5−8.

(11) Compound **1j** was previously prepared by three different methods with each involving a multiple-step synthesis; see: refs 5c and 6, and Zheng, Z.; Tu, H.; Zhang, L. *Chem. - Eur. J.* **2014**, *20*, 2445−2448.

(12) For a previous multistep synthesis, see: Crawford, J. J.; Ortwine, D. F.; Wei, B.; Young, W. B. PCT Int. Appl. 2013067274, 10 May 2013.

(13) For a previous synthesis, see: Grob, C. A.; Camenisch, K. *Helv. Chim. Acta* **1953**, *36*, 49−58.

(14) (a) McMurry, J. E. *Org. Synth.* **1973**, *53*, 59−62. (b) Gravel, D.; Labelle, M. *Can. J. Chem.* **1985**, *63*, 1874−1883.

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