Au(I)-Catalyzed Synthesis of Trisubstituted Indolizines from 2-Propargyloxypyridines and Methyl Ketones

Matthew D. Rossler,[†] Colin T. Hartgerink,[†] Emily E. Zerull,[†] Benjamin L. Boss, Abigail K. Frndak, Miles M. Mason, Leslie A. Nickerson,[‡] Evan O. Romero, Jaimie E. Van de Burg, Richard J. Staples,[§][®] and Carolyn E. Anderson^{*®}

Department of Chemistry and Biochemistry, Calvin College, Grand Rapids, Michigan 49546, United States

S Supporting Information



ABSTRACT: A new Au(I)-catalyzed method for the preparation of trisubstituted indolizines from easily accessible 2-propargyloxy-pyridines is reported. The reaction tolerates a wide range of functionality, allowing for diversity to be introduced in four distinct regions of the product (R, R^1 , R^2 , and Ar). The proposed mechanism proceeds via enol addition to an allenamide intermediate and explains the observed increase in yields when electron poor methyl ketones are utilized.

I ndolizines are versatile heterocyclic cores that are commonly found within pharmaceutical targets for a broad array of therapeutic indications (Figure 1).¹ The medicinal value of indolizines has resulted in the development of a number of methods for the synthesis of this privileged motif.² Beyond the classical strategies of Scholtz³ and Tschichibabin,⁴ methods for the synthesis of the indolizine



core largely fall into one of three categories: 1,3-dipolar cycloaddition to pyridinium ions,⁵ cyclocondensations,⁶ or transition metal catalyzed cycloisomerization reactions.⁷

As these are the common approaches to indolizine formation, we were surprised to observe trisubstituted indolizine 4 as a significant byproduct during the synthesis of pyridonyl enol ether 2 from 2-propargyloxypyridine 1 (Scheme 1).⁸ To the best of our knowledge, this is the first synthesis of trisubstituted indolizines from a 2-alkoxypyridine, and it represents a unique approach to the indolizine core. Formation of compound 4 was confirmed by NMR and X-ray analysis. Given the medicinal importance of indolizines and the simplicity of the starting materials, efforts were undertaken to explore this reaction further.

Optimization

Initial investigations focused on the 1-phenylethanol solvent. While indolizine 4 was originally observed under conditions where only 1-phenylethanol, MgSO₄, and catalyst **5a** were thought to be present, closer inspection of product 4 suggested that an oxidized form of the alcohol, specifically acetophenone, was being incorporated. This was confirmed by ¹H NMR analysis of the original lot of 1-phenylethanol, which was found to contain ~10% acetophenone. When the reaction was performed with 1-phenylethanol that lacked this contamination, no indolizine was observed (Table 1, entry 1). By intentionally adding acetophenone to the reaction, it was possible to recreate the original conditions (entries 2 and 3).

Figure 1. Pharmaceutical targets containing indolizine cores.

Scheme 1. First Observation of Trisubstituted Indolizines



^aThe 1-phenylethanol solvent was later found to contain $\sim 10\%$ acetophenone, as determined by ¹H NMR (*vide infra*).

Table 1. Solvent Studies

entry	1-phenylethanol	acetophenone	yield 4 (%) ^{<i>a</i>}
1	0.5 M	-	0
2	0.5 M	1 equiv	23
3	0.5 M	3 equiv	34
4	0.5 M ^b	3 equiv	32
5	5 equiv	0.5 M	42
6	2.5 equiv	0.5 M	39
7		0.5 M	20
^a Condition	a catalizat 5a (5 mal	%) 100 °C 18 b b	Mago (1 again)

"Conditions: catalyst Sa (5 mol %), 100 °C, 18 h. "MgSO₄ (1 equiv) added.

Further improvement could be realized if acetophenone was used as the solvent; however, the reaction still benefitted from a small amount of alcohol (entries 5–7). These studies also revealed that MgSO₄ was unnecessary (entry 4 versus entry 3) and that the product could be obtained reproducibly when heated conventionally at 100 °C for 18 h. Increasing the duration of the reaction further had no impact on the yield of compound 4, as the remainder of the mass was converted into ketone 3 under the reaction conditions.

Using this combination of solvents, additional Au(I) and Pt(II) catalysts were screened in the reaction (Scheme 2). Electron-rich biaryl triflimide Au(I) catalysts **5c** and **5e** and PtCl₂ were found to work best, providing compound **4** in 54, 52, and 50%, respectively. Biaryl Au(I) catalysts in which gold was ligated to chlorine, as well as NHC catalysts, were found to be inefficient in the reaction. Improved yields could be achieved with these catalysts upon addition of Ag salts (e.g., **5b** plus AgSbF₆, **6a** or **6d** plus AgOTf, Scheme 2); however, catalysts that were precomplexed with weakly coordinating groups (e.g., CH₃CN, NTf₂) still provided the highest yields. NaAuCl₄·2H₂O was also screened in the indolizine formation, as it has been shown previously to activate 2-propargyloxy-

Scheme 2. Catalyst Screen



pyridine 1 toward nucleophilic addition;^{8,9} however, in this case, it was found to be ineffective. For simplicity, catalyst **5c** was utilized for all further studies.

Attempts to improve the reaction yield by adding water scavengers (e.g., Na_2SO_4 , $CaSO_4$, or molecular sieves) resulted in no enhancement in yield over reactions run in the absence of any such additives (see Supporting Information for full details). Further, augmenting the reaction with either acidic (e.g., TsOH) or basic additives (e.g., pyridine, morpholine, K_2CO_3) gave either similar or decreased yields of indolizine 4. **Reaction Scope**

The reaction scope was then evaluated, focusing initially on different methyl ketones (Table 2). In these cases, yields were found to be higher when the reactions were performed at a lower concentration (0.25 M versus 0.5 M). Utilizing a series of substituted acetophenone derivatives, it was observed that electron-poor methyl ketones provided yields of indolizine 7 that were higher than those of either acetophenone or electron-rich variants (entries 9-13 versus entries 1-5). This suggests that a more electrophilic carbonyl correlates to higher reaction yields. Interestingly, fluorinated acetophenone derivatives do not seem to follow this electronic trend, as only 3-fluoroacetophenone gives yields in the expected range for an electron deficient methyl ketone (entries 6-8). This may be due to the ability of ortho- and para-fluorine substituents to serve as π -electron donors rather than as strictly σ -withdrawing groups.¹⁰ Similarly, pyridinyl ketones, which would also be expected to be electron-poor, give only slightly improved yields of the corresponding indolizines 7m and 7n (entries 14 and 15). Attempts to utilize alkyl methyl ketones failed to yield an isolable amount of the corresponding indolizine 70 due to its rapid decomposition (entry 16).

Extension of the indolizine formation to differently substituted 2-propargyloxypyridines 8 was also accomplished (Table 3). In general, substitution at the terminal position was well tolerated with even large cyclohexyl substituents proceeding in moderate to good yields, depending on the coupling partner (entries 5–7). As was observed previously in other gold-catalyzed reactions of 2-propargyloxypyridines,⁸

Table 2. Viability of Diverse Methyl Ketones

	catalyst 5c (5 mol%) 1-phenylethanol (5 equ	iv) M	e O Ar
^N C C ₅ H ₁₁ 1	O Me Ar 100 °C, 18 h	← C ₅ H ₁₁ ← 7	N
entry	Ar		yield (%) ^a
1	Ph	4	54
2	4-Me-C ₆ H ₄	7a	40
3	4-OMe-C ₆ H ₄	7b	40
4	3-OMe-C ₆ H ₄	7c	38
5	2,3-OCH ₂ O-C ₆ H ₃	7d	38
6	2-F-C ₆ H ₄	7e	41
7	$3-F-C_6H_4$	7f	66
8	$4-F-C_6H_4$	7g	51
9	$4-NO_2-C_6H_4$	7h	73
10	$3-NO_2-C_6H_4$	7i	76
11	$3,5-(CF_3)_2C_6H_3$	7j	80
12	2-naphthyl	7k	62
13	furyl	71	71
14	3-pyridonyl	7 m	51
15	2-pyridonyl	7 n	59
16	CH ₂ CH ₂ CH ₃	7 o	-
'Isolated yields.	Mean values from multipl	e experimen	its ($\pm 2\%$).

silylated substrate **8d**, bearing a two carbon linker, is more reactive than the analogous substrate **8e** with only a methylene linker (entries 8–10). The methyl ketone coupling partner continued to be the largest predictor of reaction yield with more electron-poor methyl ketones providing higher yields of indolizine **9**, regardless of the substitution pattern (entries 2, 4, 6, 7, 9, and 12 versus entries 1, 3, 5, 8, 10, 11, and 13). Substituents at the propargylic position were also tolerated, providing indolizines **9f**, **9ff**, and **9g**, bearing extended chains at the C-2 position, in reasonable yields (entries 11–13).

Substitution on the pyridine ring was also evaluated (Table 4). Unlike substitution on the propargyl chain of the substrate,

Tab	ole	3.	Eva	luation	of	Side	Chain	Su	bstitution

Table 4. Substitution on the Pyridine Ring

R ¹	¥ ∭	catalys 1-phenyl	st 5c (5 ethanol	mol%) (5 equiv)	Me	—Ar		
$C_{5}H_{11} = 10 O C_{5}H_{11} N = 1 C_{5}H_{11} N = 1$								
entry	SM	\mathbb{R}^1	Х	Ar	product	yield (%) ^a		
1	10a	СООН	CH	Ph	11a	-		
2	10b	CO ₂ Me	CH	Ph	11b	-		
3	10c	NHPiv	CH	Ph	11c	65		
4	10c	NHPiv	CH	$3-F-C_6H_4$	11cc	56		
5	10d	NHPiv	CH	$3-NO_2-C_6H_4$	11ccc	65		
6	10d	CH ₂ OTIPS	CH	Ph	11d	62		
7	10d	CH ₂ OTIPS	CH	$3,5-(CF_3)_2C_6H_3$	11dd	86 ^b		
8	10e	Н	Ν	$4-F-C_6H_4$	11e	8		
9	10e	Н	Ν	$3,5-(CF_3)_2C_6H_3$	11ee	27		
^a Isolated yields. Mean values from multiple experiments ($\pm 2\%$). ^b Mean values from multiple experiments ($\pm 3\%$).								

the electronics of the substituent at C-3 of the pyridine directly impacted the observed yield. When electron withdrawing groups were present, formation of the indolizine was not observed (entries 1 and 2). Conversely, when electron donating substituents were added, good to excellent yields of substituted indolizines **11c**, **11cc**, **11cc**, **11d**, and **11dd** were observed (entries 3–7). Pyrimidine **10e** was also susceptible to the reaction; however, only low yields of dinitrogen analogues **11e** and **11ee** were observed due to their instability. Substitution could also be tolerated at the C-6 position, although in this case, the sterics of the reaction seem to dominate, as no change in yield was observed with a more electron deficient methyl ketone (Scheme 3).

		R^1 R^2	catalyst 5c (5 mol% 1-phenylethanol (5 eq 0 Me Ar 100 °C, 18 h	$ \xrightarrow{\text{o)}}_{\text{o)}} \xrightarrow{\text{R}^2}_{\text{R}^1} \xrightarrow{\text{O}}_{\text{Ar}} $		
entry	SM	\mathbb{R}^1	\mathbb{R}^2	Ar	product	yield (%) ^a
1	8a	$(CH_2)_3Ph$	Н	Ph	9a	49
2	8a	$(CH_2)_3Ph$	Н	$4-NO_2-C_6H_4$	9aa	72
3	8b	$(CH_2)_2Ph$	Н	Ph	9b	49
4	8b	$(CH_2)_2Ph$	Н	$3,5-(CF_3)_2C_6H_3$	9bb	64
5	8c	Су	Н	Ph	9c	40
6	8c	Су	Н	$3-F-C_6H_4$	9cc	57
7	8c	Су	Н	$3,5-(CF_3)_2C_6H_3$	9ccc	71
8	8d	$(CH_2)_2 OTIPS$	Н	Ph	9d	45
9	8d	$(CH_2)_2OTIPS$	Н	$3-F-C_6H_4$	9dd	59
10	8e	CH ₂ OTIPS	Н	Ph	9e	5
11	8f	Et	Me	Ph	9f	37
12	8f	Et	Me	$3,5-(CF_3)_2C_6H_3$	9ff	69
13	8g	C_4H_9	Et	Ph	9g	41

^aIsolated yields. Mean values from multiple experiments ($\pm 2\%$).

Scheme 3. Substitution at the C-6 Position



Solvent Recycling

While utilizing substituted acetophenones as the reaction solvent is unusual, it has been shown that the solvent mixture can be recovered after Kugelrohr distillation of the crude reaction mixture (containing both methyl ketone and 1-phenylethanol). This mixture can then be reused in subsequent reactions without any loss in efficiency (Scheme 4).





Mechanism

Formation of indolizine 4 and its analogues was originally thought to proceed via ketone 3. However, subjecting ketone 3 to the reaction conditions provided no evidence of indolizine formation (Scheme 5). Adding a small amount of 2-propargyloxypyridine 1 provided indolizine 4 but only in proportion to the amount of starting material 1 that was added. Given these results, ketone 3 was eliminated as a possible intermediate, and allenamide 14 was pursued, as it had

Scheme 5. Formation of Pyridonyl Ketones 3⁹ and Indolizine 4



been previously implicated in the synthesis of pyridonyl ketone 3.⁹ Attempts to synthesize intermediate 14 independently were unsuccessful due, we believe, to its high reactivity. It was, however, possible to prepare saturated allenamide analogue 15. Upon subjecting compound 15 to the reaction conditions, a small but isolable amount of analogue 16 was obtained (Scheme 6). The low yields of compound 16 can be attributed





to its instability, as it was observed to decompose both during purification and on the benchtop. Despite this, the formation of heterocycle **16** suggests that allenamide **14** and its analogues are indeed likely intermediates in the formation of indolizine **4**.

Conversion of allenamide 14 into indolizine 4 is proposed to occur as shown in Scheme 7. Beginning with the addition of





enol 17 to the central carbon of allenamide 14, subsequent protodeauration, either from the alcohol or methyl ketone, would then lead to the formation of β , γ -unsaturated ketone 19. The proposed enol 17 is expected to form more rapidly when the aryl group is electron-poor, leading to higher yields with electron-poor methyl ketones as reported (see Table 2). Enolization of compound 19 followed by aldol reaction and loss of water would then provide indolizine 4.

The protodeauration of compound 18 is expected to occur through a combination of pathways involving either deprotonation of the alcohol or the methyl ketone. In order to determine the relative rates of these processes, the reaction was performed in d_3 -acetophenone in the presence of proteo alcohol (Scheme 8). In this case, 23% deuterium incorporation was observed at the exocyclic methyl group, suggesting that protodeauration is ~3× faster from the alcohol than the methyl ketone (see Supporting Information).





Summary

A new method for the synthesis of trisubstituted indolizines from 2-propargyloxypyridines and aryl methyl ketones has been discovered. The reaction proceeds in the highest yields in the presence of electron-poor ketones, presumably due to the ease of forming enol 17 under the reaction conditions. The wide scope of this reaction and the simplicity of the starting materials make this transformation significant within the array of methods available for the synthesis of indolizine-containing medicinal targets.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01929.

Representative experimental procedures, further optimization studies, solid-state packing diagrams for 4, spectroscopic support for the formation of partially deuterated indolizine 4/4', and ¹H and ¹³C NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1920795 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: Carolyn.Anderson@calvin.edu. ORCID [©]

Richard J. Staples: 0000-0003-2760-769X Carolyn E. Anderson: 0000-0001-8797-4120

Present Addresses

[‡]L.A.N.: Department of Chemistry, University of California-Davis, Davis, CA 95616

⁸R.J.S.: Department of Chemistry, Michigan State University, East Lansing, MI 48824

Author Contributions

^TM.D.R., C.T.H., and E.E.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Gundersen, L.-L.; Charnock, C.; Negussie, A. H.; Rise, F.; Teklu, S. Eur. J. Pharm. Sci. 2007, 30, 26-35. (b) Hsieh, H.-P.; Chao, Y.-S.; Liou, J.-P.; Chang, J.-Y.; Tung, Y.-S. Preparation of bicyclic heterocyclo phenyl ketones as antitumor agents. U.S. Pat. Appl. US 20060148801 A1, 2006. (c) Nekkar, P.; Rao, P.; Kabir, S. N. Preparation of indolizine derivatives as inhibitors of lipoprotein associated phospholipase A2 and 15-lipoxygenase. PCT Int. Appl. WO 2013116948 A1, 2013. (d) Hynd, G.; Ray, N. C.; Finch, H.; Montana, H. G.; Cramp, M. C.; Harrison, T. K.; Arienzo, R.; Blaney, P.; Griffon, Y.; Middlemiss, D. Indolizine derivatives as CRTH2 receptor modulators, their preparation, pharmaceutical compositions, and use in therapy. PCT Int. Appl. WO 2007031747 A1, 2007. (e) Oku, T.; Sawada, K.; Kuroda, A.; One, K. Preparation of indolizines as cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors. Jpn. Kokai Tokkyo Koho JP 10120680 A, 1998. (f) Stearns, B. A.; Roppe, J. R.; Parr, T. A.; Stock, N. S.; Volkots, D.; Hutchinson, J. H. Preparation of indolizine inhibitors of 5lipoxygenase for treating respiratory, cardiovascular, and other leukotriene-mediated conditions. PCT Int. Appl. WO 2011038086 A2, 2011.

(2) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Curr. Opin. Chem. Biol. 2010, 14, 347-361.

(3) Scholtz, M. Ber. Dtsch. Chem. Ges. 1912, 45, 734-746.

(4) Tschitschibabin, A. E. Ber. Dtsch. Chem. Ges. B 1927, 60, 1607–1617.

(5) (a) Brioche, J.; Meyer, C.; Cossy, J. Org. Lett. **2015**, *17*, 2800–2803. (b) Li, F.; Chen, J.; Hou, Y.; Li, Y.; Wu, X.-Y.; Tong, X. Org. Lett. **2015**, *17*, 5376–5379. (c) Xu, J.; Hu, H.; Liu, Y.; Wang, X.; Kan, Y.; Wang, C. Eur. J. Org. Chem. **2017**, *2017*, 257–261. (d) Wang, W.; Han, J.; Sun, J.; Liu, Y. J. Org. Chem. **2017**, *82*, 2835–2842.

(6) (a) Kucukdisli, M.; Opatz, T. Eur. J. Org. Chem. 2014, 2014, 5836–5844.
(b) Tverdokhleb, N. M.; Khoroshilov, G. E.; Dotsenko, V. V. Tetrahedron Lett. 2014, 55, 6593–6595.
(c) Mohan, D. C.; Ravi, C.; Pappula, V.; Adimurthy, S. J. Org. Chem. 2015, 80, 6846–6855.
(7) Review: Wang, L.-X.; Tang, Y.-L. Eur. J. Org. Chem. 2017, 2017,

2207–2213.

(8) Romero, E. O.; Reidy, C. P.; Bootsma, A. B.; PreFontaine, N. M.; Vryhof, N. W.; Wierenga, D. C.; Anderson, C. E. J. Org. Chem. **2016**, *81*, 9895–9902.

(9) Romero, N. A.; Klepser, B. M.; Anderson, C. E. Org. Lett. 2012, 14, 874–877.

(10) Carroll, T. X.; Thomas, T. D.; Bergersen, H.; Borve, K. J.; Saethre, L. J. Org. Chem. 2006, 71, 1961–1968.