Organic LETTERS

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# Deformylative Intramolecular Hydroarylation: Synthesis of Benzo[*e*]pyrido[1,2-*a*]indoles

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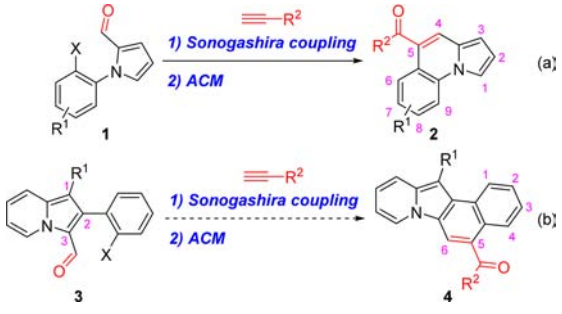
Supporting Information

**ABSTRACT:** Attempted cyclization of indolizines bearing both formyl and alkyne groups under acid catalysis provided benzo[*e*]pyrido[1,2-*a*]indoles with an aryl substituent at the C6 position as major products, along with the expected C5-acylated benzo[*e*]pyrido[1,2-*a*]indoles as minor ones, which resulted from preferential deformylative intramolecular hydroarylation instead of intended alkyne-carbonyl metathesis.


As part of our interest in the design and synthesis of indolizine-embedded skeletons,[1] we recently communicated the construction of pyrrolo[1,2-*a*]quinolines with an acyl group at the C5 position by way of successive Sonogashira cross-coupling/intramolecular alkyne-carbonyl metathesis (ACM) (Scheme 1a).[2] Along these lines, we surmised that 2-(2-haloaryl)indolizine-3-carbaldehydes such as **3** would be converted to the corresponding C5-acyl benzo[*e*]pyrido[1,2-*a*]indoles by similar procedures (Scheme 1b).

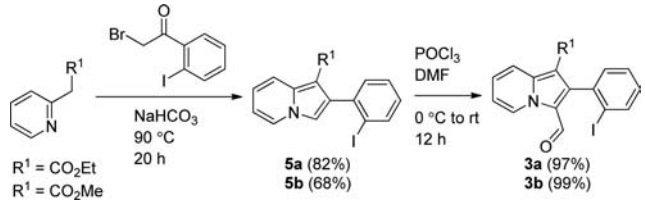
Despite its presence in many biologically active natural products, pharmaceuticals, and imaging agents,[3] not many synthetic approaches to this chemical core structure have appeared in the literature.[4] Although this tetracyclic compound was accessed by employing Larock's cascade carbopalladation–annulation protocol,[4a] regioselective incorporation of unsymmetrical internal alkynes was not realized.[5] As our strategy allows for not only the regioselective introduction of a substituent but also a unique substitution pattern around this polycyclic structure, we decided to investigate an intramolecular ACM route to benzo[*e*]pyrido[1,2-*a*]indoles decorated with an acyl moiety at the C5 site. During our study, we discovered that an unprecedented deformylative intramolecular hydroarylation[6] was a major pathway leading to formation of benzo[*e*]pyrido[1,2-*a*]indoles with an aryl or alkyl group at the C6 position, which we wish to report here.

**Scheme 1. Synthetic Strategies to Indolizine-Containing Structures via Sonogashira Coupling/Intramolecular ACM**



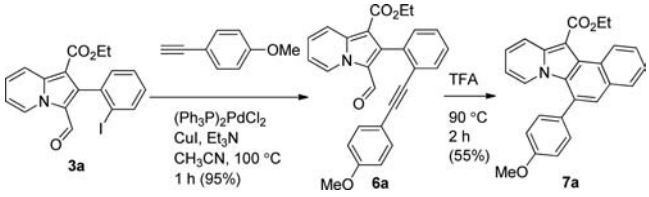

This study began with preparation of the requisite 2-(2-iodophenyl)indolizine-3-carbaldehydes **3** (Scheme 2). Base-mediated condensation of 2-pyridylacetates with 2-bromo-2′-iodoacetophenone provided indolizines **5** in good yields.

**Scheme 2. Synthesis of 3**[a]




[a]A mixture of 2-bromo-2′-iodoacetophenone (3.45 mmol), ethyl or methyl 2-pyridylacetates (5.18 mmol, 1.5 equiv) and $NaHCO_3$ (2.0 equiv) in acetone (10 mL) was heated at 90 °C. A mixture of **5** (2.04 mmol) and $POCl_3$ (3 equiv) in DMF (1 mL) was stirred at 0 °C to rt.

**Scheme 3. Unexpected Formation of 7a**[a]




[a]A mixture of **3a** (1.19 mmol), 4-ethynylanisole (2 equiv), $(Ph_3P)_2PdCl_2$ (0.1 equiv), CuI (0.1 equiv), and $Et_3N$ (4 equiv) in $CH_3CN$ (25 mL) was heated at 100 °C. A mixture of **6a** (0.07 mmol) in TFA (0.6 mL) was stirred at 90 °C.

**Received:** August 11, 2015
**Published:** September 8, 2015





DOI: 10.1021/acs.orglett.5b02331
*Org. Lett.* 2015, 17, 4600–4603

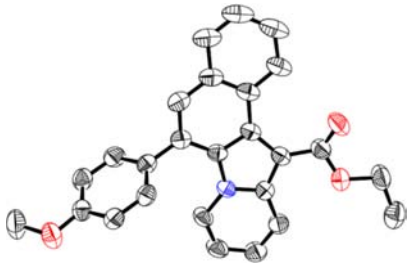


**Figure 1.** Crystal structure of **7a**.

**Scheme 4. Proposed Mechanism for Formation of 7a**

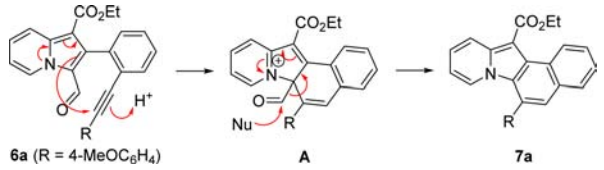
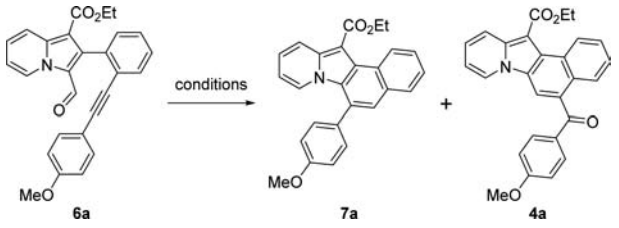



**Table 1. Reaction of 6a under Various Conditions**[a]




| | | | | | yield (%)[b] | |
|---|---|---|---|---|---|---|
| entry | catalyst (equiv) | temp (°C) | time (h) | solvent | **7a** | **4a** |
| 1 | TFA | rt | 1 | – | 80 | 13 |
| 2 | TFA | rt | 1 | DCE | 72 | 18 |
| 3 | $InCl_3$ (0.3) | rt to 60 | 72 | DCE | 72 | 6 |
| 4 | $In(OTf)_3$ (0.3) | rt | 48 | DCE | 56 | 33 |
| 5 | $In(OTf)_3$ (0.05) | 60 | 22 | DCE | 60 | 21 |
| 6 | $In(OTf)_3$ (0.05) | 60 | 28 | DCM | 60 | 33 |

[a]A mixture of **6a** (0.07 mmol) and catalyst in solvent (1 mL) was stirred at the indicated temperature and time unless otherwise noted. [b]Isolated yield (%).

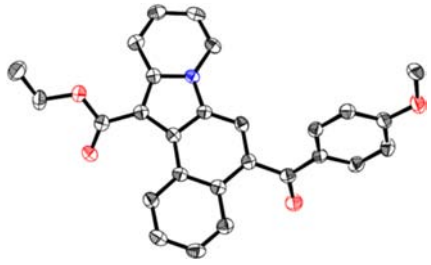
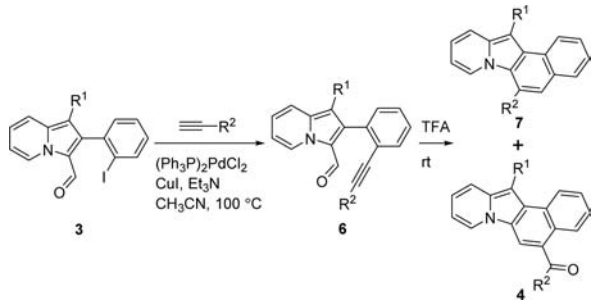


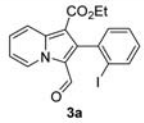
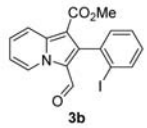
**Figure 2.** Crystal structure of **4a**.

Subsequent Vilsmeier–Haack formylation took place uneventfully to afford the corresponding aldehydes **3**.

At this point, we used **3a** to optimize the following reaction conditions. Sonogashira cross-coupling of **3a** with 4-ethynylanisole furnished **6a** in excellent yield (Scheme 3). Based on our previous results, **6a** was exposed to TFA at 90 °C to induce intramolecular ACM. Surprisingly, however, the major product was not the expected **4a**; instead, **7a** was isolated in 55% yield. The structure of **7a** was unambiguously established by X-ray crystallographic analysis (Figure 1).[7] Although deformylation of

**Table 2. Syntheses of 7 and 4 from 3**[a]




| entry | **3** | **6** (%)[b] | **7** (%)[b] | **4** (%)[b] |
|---|---|---|---|---|
| 1 |  | **6b** ($R^2$ = Ph) (92) | **7b** (47) | trace |
| 2 | **3a** | **6c** ($R^2$ = 4-$MeC_6H_4$) (90) | **7c** (76) | **4c** (13) |
| 3 | **3a** | **6d** ($R^2$ = 4-MeO-2-$MeC_6H_3$) (89) | **7d** (86) | trace |
| 4 | **3a** | **6e** ($R^2$ = 4-$NCCH_2C_6H_4$) (76) | **7e** (48) | trace |
| 5 | **3a** | **6f** ($R^2$ = 6-MeO-2-naphthalene) (78) | **7f** (79) | **4f** (15) |
| 6 | **3a** | **6g** ($R^2$ = 1-naphthalene) (92) | **7g** (63) | **4g** (7) |
| 7 | **3a** | **6h** ($R^2$ = cyclopentyl) (90) | c | |
| 8 | **3a** | **6i** ($R^2$ = n-Bu) (36) | c | |
| 9 |  | **6j** ($R^2$ = Ph) (94) | **7j** (56) | trace |
| 10 | **3b** | **6k** ($R^2$ = 3-$MeOC_6H_4$) (95) | **7k** (72) | trace |
| 11 | **3b** | **6l** ($R^2$ = 4-$PhC_6H_4$) (88) | **7l** (60) | **4l** (14) |
| 12 | **3b** | **6m** ($R^2$ = 3,5-$(MeO)_2C_6H_3$) (98) | **7m** (47) | trace |
| 13 | **3b** | **6n** ($R^2$ = 3-thiophene) (99) | **7n** (50) | **4n** (22) |

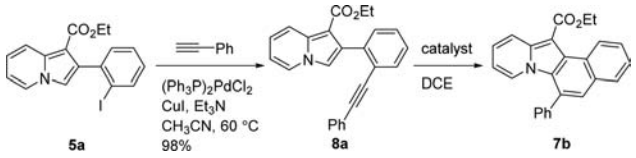
[a]A mixture of **3** (0.24 mmol), alkyne (2 equiv), $(Ph_3P)_2PdCl_2$ (0.1 equiv), CuI (0.1 equiv), and $Et_3N$ (4 equiv) in $CH_3CN$ (2 mL) was heated at 100 °C. A mixture of **6** (0.07 mmol) in TFA (0.6 mL) was stirred at rt. [b]Isolated yield (%) [c]Complex mixture.

compounds possessing pyrrole-2-carboxaldehyde under acidic conditions was known in the literature,[8] to the best of our knowledge, no examples where intramolecular cyclization occurs at the site bearing a formyl group with concomitant deformylation have been disclosed. This is surprising because the compound derived from **1** was transformed into **2** in good yield without loss of a formyl group under similar conditions. As shown in Scheme 4, formation of **7a** can be understood by



DOI: 10.1021/acs.orglett.5b02331
*Org. Lett.* 2015, 17, 4600–4603

**Table 3. Synthesis of 7 from 8a**[a]




| entry | catalyst (equiv) | temp (°C) | time (h) | 7b (%)[b] |
|---|---|---|---|---|
| 1 | TFA[c] | rt to 60 | 24 | 50 |
| 2 | $In(OTf)_3$ (0.1 equiv) | rt to 40 | 24 | 42 |
| 3 | $Bi(OTf)_3$ (0.1 equiv) | rt to 40 | 24 | 36 |
| 4 | AgOTf (0.2 equiv) | rt | 5 | 64 |
| 5 | TfOH (0.2 equiv) | 0 to rt | 24 | 40 (53)[d] |

[a]A mixture of **5a** (0.767 mmol), alkyne (2 equiv), $(Ph_3P)_2PdCl_2$ (0.1 equiv), CuI (0.1 equiv), and $Et_3N$ (4 equiv) in $CH_3CN$ (6 mL) was heated at 60 °C. A mixture of **8a** (0.03 mmol) and catalyst (0.2 equiv) in DCE (0.5 mL) was stirred at the indicated temperature unless otherwise stated. [b]Isolated yield (%) [c]TFA was used as solvent. [d]Yield in parentheses is based on recovered starting material.

initial attack of the C3 site of indolizine **6a** to the neighboring alkyne unit to form the indolizinium salt **A**, which is followed by deformylation to restore aromaticity.[9]

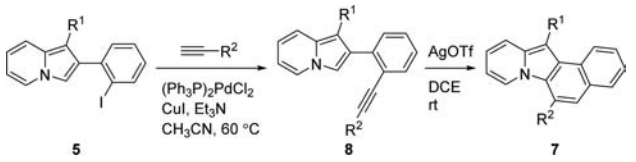
Lowering the reaction temperature to rt produced **7a** as well as **4a** (Table 1, entry 1). The structure of **4a** was again confirmed by X-ray crystal analysis as shown in Figure 2.[10] Reaction in TFA/DCE mixture gave a similar result (entry 2). $In(OTf)_3$ exhibited superior reactivity to $InCl_3$ (entries 3 and 4). Exposure of **6a** to $In(OTf)_3$ (0.05 equiv) at 60 °C led to a mixture of products in a ratio of 3:1 or 2:1 (entries 5 and 6). It seemed that deformylative intramolecular hydroarylation was a preferred pathway rather than the ACM we initially anticipated.

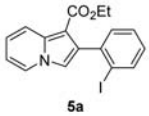
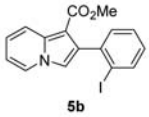
When several indolizines **6** having other alkynes were prepared and treated with TFA at rt, similar results were observed (Table 2). However, when $R^2$ is cyclopentyl or *n*-butyl, a complex mixture of products was observed (entries 7 and 8).

As compound **7** could be directly obtained via the intramolecular hydroarylation of **8**, we synthesized **8** to investigate the reactivity of these compounds toward 6-endo-dig cyclization (Table 3). To this end, Sonogashira coupling of **5a** was first conducted at 60 °C to give the corresponding adduct **8a** in good yields. When **8a** was treated under the same conditions applied for **6**, surprisingly, no reaction took place. The cyclized product was obtained in 50% yield by increasing the temperature to 60 °C (entry 1). Although the isolated product yields are about the same, the cyclization reactivity of **6a** seemed higher than that of **8a**, supporting the idea that transformation of **6** to **7** does not occur via **8**. Use of $In(OTf)_3$ or $Bi(OTf)_3$ as catalysts at 40 °C for 24 h produced the desired **7b** in 42% and 36% yield, respectively (entries 2 and 3). Reaction of **8a** under the influence of AgOTf provided **7b** in 64% yield (entry 4). Incomplete conversion was observed with triflic acid even after 24 h (entry 5).

To examine the generality of this intramolecular hydroarylation, **5** was reacted with more alkynes to afford the various adducts in good to excellent yields (Table 4). Overall, the subsequent Ag(I)-catalyzed hydroarylation[11] went smoothly with arylalkyne-substituted indolizines. Modest yields of the products were obtained with substrates having an alkylalkyne (entries 7 and 8). Thiophene-containing benzo[*e*]pyrido[1,2-*a*]indole **7n** was isolated in 74% yield (entry 14).

**Table 4. Syntheses of 7 via Ag(I)-Catalyzed Hydroarylation**[a]




| entry | 5 | 8 (%)[b] | 7 (%)[b] |
|---|---|---|---|
| 1 |  5a | **8a** ($R^2$ = Ph) (98) | **7b** (64) |
| 2 | **5a** | **8b** ($R^2$ = 4-$MeOC_6H_4$) (91) | **7a** (87) |
| 3 | **5a** | **8c** ($R^2$ = 4-$MeC_6H_4$) (96) | **7c** (70) |
| 4 | **5a** | **8d** ($R^2$ = 4-MeO-2-$MeC_6H_3$) (88) | **7d** (94) |
| 5 | **5a** | **8e** ($R^2$ = 4-$NCCH_2C_6H_4$) (98) | **7e** (68) |
| 6 | **5a** | **8f** ($R^2$ = 6-MeO-2-naphthalene) (80) | **7f** (79) |
| 7 | **5a** | **8g** ($R^2$ = 1-naphthalene) (92) | **7g** (74) |
| 8 | **5a** | **8h** ($R^2$ = cyclopentyl) (92) | **7h** (29)[c] |
| 9 | **5a** | **8i** ($R^2$ = n-Bu) (88) | **7i** (40)[c] |
| 10 |  5b | **8j** ($R^2$ = Ph) (96) | **7j** (67) |
| 11 | **5b** | **8k** ($R^2$ = 3-$MeOC_6H_4$) (74) | **7k** (87) |
| 12 | **5b** | **8l** ($R^2$ = 4-$PhC_6H_4$) (96) | **7l** (79) |
| 13 | **5b** | **8m** ($R^2$ = 3,5-$(MeO)_2C_6H_3$) (85) | **7m** (78) |
| 14 | **5b** | **8n** ($R^2$ = 3-thiophene) (97) | **7n** (74) |
| 15 | **5b** | **8o** ($R^2$ = 6-MeO-2-naphthalene) (79) | **7o** (86) |

[a]A mixture of **5** (0.767 mmol), alkyne (2.0 equiv), $(Ph_3P)_2PdCl_2$ (0.1 equiv), CuI (0.1 equiv), and $Et_3N$ (4.0 equiv) in $CH_3CN$ (6 mL) was heated at 60 °C. A mixture of **8** (0.08 mmol) and AgOTf (0.2 equiv) in DCE (1 mL) was stirred at rt. [b]Isolated yield (%) [c]Reaction temperature: rt to 60 °C

In summary, during our endeavor to construct benzo[*e*]-pyrido[1,2-*a*]indoles with an acyl moiety at the C5 site via intramolecular alkyne-carbonyl metathesis, an unprecedented intramolecular hydroarylation with concomitant extrusion of a formyl group was discovered to give rise to the same skeleton with an aryl substituent at the C6 position as the major product under acidic media. Alternatively, facile formation of the latter from the indolizines without a formyl group at the C3 position was demonstrated in the presence of a Ag(I) catalyst. Comparison of the reactivity of both substrates revealed that the presence of a formyl group at the C3 position of indolizines



DOI: 10.1021/acs.orglett.5b02331
*Org. Lett.* 2015, 17, 4600−4603

seems to facilitate intramolecular hydroarylation. A plausible mechanism is proposed. These findings will enable benzo[*e*]-pyrido[1,2-*a*]indoles to be synthesized with suitable substituents. More efforts to decorate this skeleton in a regioselective manner as well as evaluation of these new compounds in various settings are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02331.

File for **7a** (CIF)
File for **4a** (CIF)
Full experimental details, $^{1}H$ and $^{13}C$ NMR spectra of **3**–**8** (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (2014R1A2A1A11050491).

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(5) Similarly, for Rh-catalyzed annulations of *N*-phenylpyrazoles, 2-arylimidazo[1,2-*a*]pyridines, or 7-azaindoles with internal alkynes, examples of successful regioselective incorporation of unsymmetrical internal alkynes are limited. See: (a) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13. (b) Qi, Z.; Yu, S.; Li, X. *J. Org. Chem.* **2015**, *80*, 3471. (c) Peng, H.; Yu, J.-T.; Jiang, Y.; Wang, L.; Cheng, J. *Org. Biomol. Chem.* **2015**, *13*, 5354. (d) Li, S.-S.; Wang, C.-Q.; Lin, H.; Zhang, X.-M.; Dong, L. *Org. Lett.* **2015**, *17*, 3018. (e) Kotla, S. K. R.; Choudhary, D.; Tiwari, R. K.; Verma, A. K. *Tetrahedron Lett.* **2015**, *56*, 4706.

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(7) CCDC 1410649 contains the supplementary crystallographic data for compound **7a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) Furuta, H.; Maeda, H.; Furuta, T.; Osuka, A. *Org. Lett.* **2000**, *2*, 187.

(9) Deformylated compounds such as **8** were not detected during TLC monitoring of the reaction. One reviewer commented that the aldehyde group could be protonated so that it may stabilize the resonance form pertaining negative charge on C3 carbon and positive charge on the indolizine nitrogen.

(10) CCDC 1410653 contains the supplementary crystallographic data for compound **4a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) For a recent review on Ag-catalyzed reactions of alkynes, see: Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, DOI: 10.1039/C5CS00027K.




DOI: 10.1021/acs.orglett.5b02331
*Org. Lett.* 2015, 17, 4600–4603