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Synthesis of Quinolinone Alkaloids via Aryne Insertions into Unsymmetric Imides in Flow

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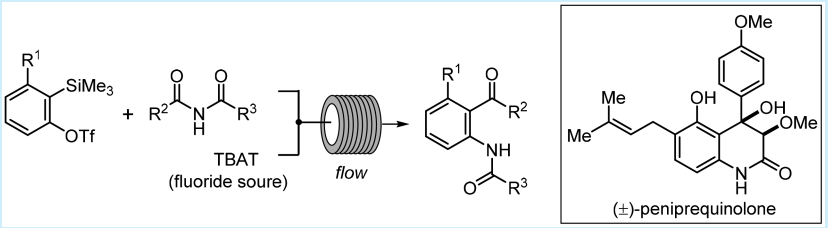
Supporting Information

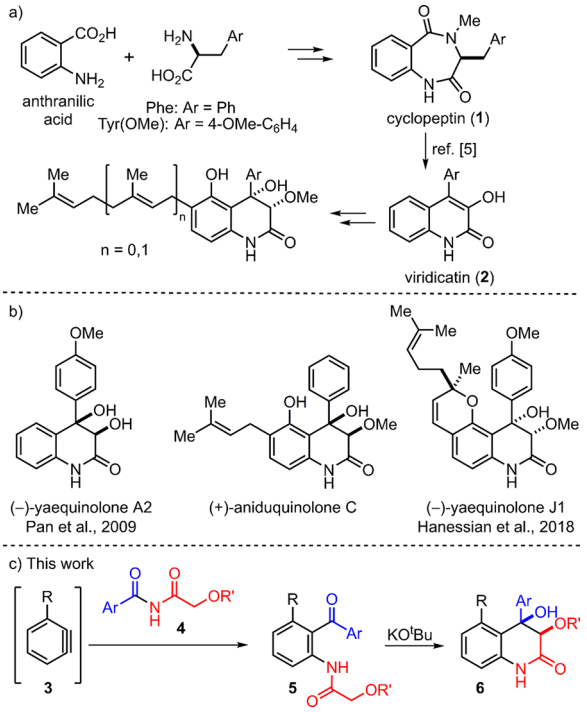


ABSTRACT: A general strategy for the synthesis of 3,4-dioxygenated quinolin-2-one natural products is reported. The key step is a regioselective insertion of arynes into unsymmetric imides. When performed in continuous flow, the reaction proceeds within minutes, while lower yields and longer reaction times are observed in batch. The resulting *N*-acylated 2-aminobenzophenones were transformed to (±)-peniprequinolone, (±)-aflaquinolones E and F, (±)-6-deoxyaflaquinolone E, (±)-quinolinones A and B, and (±)-aniduquinolone C in 1−3 steps.

The growing family of 3,4-dioxygenated quinolin-2-ones constitutes a valuable source of molecules with cytotoxic, nematicidal, and antiviral activities.[1,2] Biosynthetically, these fungal secondary metabolites are derived from the non-ribosomal peptide synthetase (NRPS) product cyclopeptin (**1**), an adduct of anthranilic acid, and either *O*-methyl-L-tyrosine[3] or phenylalanine[4] (Scheme 1a). Groll and Hintermann demonstrated that a single enzyme, AsqJ, catalyzes a multistep transformation of the benzodiazepine core of **1** into the parent quinolone **2**.[5] Downstream processing into the final natural products may involve prenylation (n = 0) and double prenylation (n = 1) as well as additional oxidation steps.[6] Following this synthetic blueprint, nature has provided a "library" of bioactive secondary metabolites[3,7] from which only yaequinolone J1, J2, and A_2 have been synthesized to date (Scheme 1b).[8] Since these natural products share a common heterocyclic core, we decided to develop a step-efficient,[9] modular approach to access the entire group of these alkaloids (Scheme 1c). Synthetically, the 3,4-dioxygenated quinolin-2-one core (**6**) can be obtained by intramolecular glycolate aldolizations.[10] We speculated that aryne chemistry[11] could provide straightforward access to *N*-glycolated 2-amino-benzophenones (**5**) and thus enable the synthesis of this natural product family. On the basis of the contributions of Greaney[11a] (acylated carbamates), Stoltz[11b] (symmetric imides), and Xu[11d] (acrylamides), we speculated that a selective σ-C−N insertion of in situ generated arynes (**3**) into unsymmetric imides **4** could deliver **5** in a one-pot operation.[12] With these substrates, the challenge lies in the differentiation of the two similar *N*-acyl groups.

As a starting point, we investigated the insertion of benzyne precursor **3a**[13] into the unsymmetric imide **4a**. Under the conditions reported by Stoltz et al.,[11b] benzophenone **5a** was formed in 16% yield with only a slight preference for **5a** over

Scheme 1. Outline of the Work



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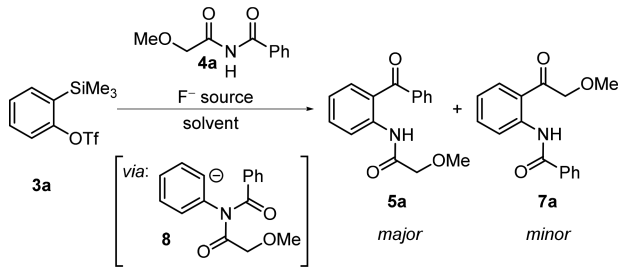
its constitutional isomer **7a** (Table 1, entry 1). A screening of solvents revealed that acetonitrile gave the best selectivity of

Table 1. Reaction Development in Batch[a]



entry	solvent	T	F⁻ source	5a:7a[b]	5a (%)[c]
1	PhMe	60	TBAT	1.3:1	16
2	THF	60	TBAT	2.0:1	18
3	MeCN	60	TBAT	5.7:1	25
4[d]	MeCN	80	TBAT	4.1:1	35
5[d]	MeCN	80	CsF	3.7:1	33
6[d,e]	MeCN	80	KF	4.0:1	20

[a]Reaction conditions: **4a** (0.26 mmol, 1 equiv), **3a** (0.39 mmol, 1.5 equiv), F⁻ source (0.52 mmol, 2 equiv), solvent (2.0 mL), 16 h. [b]Ratios were determined by ^{1}H NMR integration. [c]Isolated yield. [d]Conducted for 4 h. [e]18-crown-6 (1 equiv) and 4 Å mol sieves were used as additives.

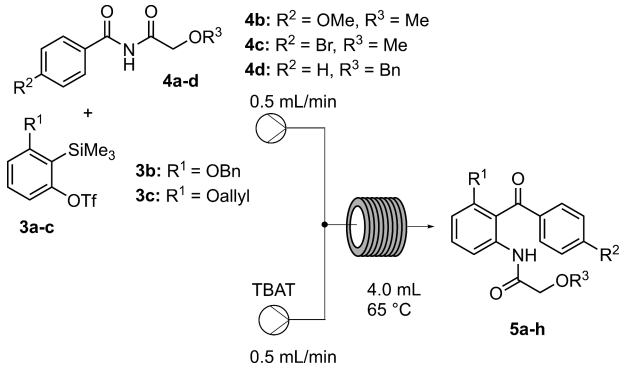
5.7:1 (entry 3). Among the different fluoride sources, tetrabutylammonium difluorotriphenylsilicate (TBAT) gave the highest yield of **5a** with 35% and an isomeric ratio of 4.1:1 (entry 4). Upon extending the reaction time, **7a** undergoes slow thermal decomposition, leading to a slightly increased isomer ratio in favor of **5a**. Furthermore, it turned out that imide **4a** also slowly decomposes to benzamide at elevated temperatures and under basic conditions.

Because of superior heat and mass transfer, reactions performed in flow can significantly be accelerated. Therefore, intermediates such as **8** often react with higher selectivity and yield, enabling reactions that are otherwise impossible.[14] Surprisingly, only a few examples are reported, where arynes are generated and used in a flow reactor.[15]

To suppress thermal imide decomposition by shortening the reaction time, a flow protocol seemed promising. Because of its high solubility, TBAT is a better fluoride source for flow reactions than cesium fluoride. An optimization of reaction time, temperature, and stoichiometry (see Supporting Information for details) increased the yield of **5a** from 25% in batch (Table 1, entry 3) to 52% when conducted at 65 °C with 1.5 equiv of **3a** at a residence time of 4 min (Table 2, entry 1). Under these conditions, a regioselectivity of 2.9:1 (**5a**:**7a**) was observed.

Using the optimized conditions, a collection of substituted arynes and imides was reacted. According to the proposed mechanism, the aryne insertion proceeds via intermediacy of **8**.[11a,b,16] Greaney et al.[11a] showed that a major byproduct results from premature protonation of **8**. Remarkably, under flow conditions, even the use of wet acetonitrile did not increase the amount of byproduct, thus rendering the flow process more sustainable. As arynes bearing a 3-alkoxy substituent have been reported to undergo regioselective nucleophilic attack in the *meta*-position,[17] we expected the resulting benzophenones to provide us access to the 5-hydroxyquinolinone cores present in aflaquinolone E (**9**)[18] and

Table 2. Aryne Insertion in Flow[a]



entry	product	R^1	R^2	R^3	5 (%)[b]
1	**5a**	H	H	Me	52
2[c]	**5b**	H	OMe	Me	60
3	**5c**	H	Br	Me	23
4	**5d**	OBn	H	Me	35
5[c]	**5e**	OBn	OMe	Me	24
6	**5f**	H	H	Bn	40
7	**5g**	OAllyl	H	Me	18
8[c]	**5h**	OAllyl	OMe	Me	30

[a]Reaction conditions: **4** (0.20 mmol, 1 equiv, 0.1 M in MeCN), **3** (0.30 mmol, 1.5 equiv, 0.15 M in MeCN), TBAT (0.36 mmol, 1.8 equiv, 0.18 M in MeCN), 4 mL reactor volume, 65 °C. [b]Isolated yield. [c]**4b** (c = 0.01 M in MeCN), **3a**–**c** (c = 0.015 M in MeCN), TBAT (c = 0.018 M in MeCN).

quinolinone B (**10**).[19c] In agreement with the literature reports,[11a,b,20] we also observed significantly lower yields with those substrates. Thus, when using 3-*O*-benzyl and 3-*O*-allyl substituted aryne precursors **3b** and **3c**, the yield dropped to 35% and to 18% (Table 2, entries 4, 5, 7, 8). The insertion was also performed with 4-bromo substituted imide **4c** to access an unnatural quinolinone derivative with a handle for cross-coupling chemistry as well as *O*-benzyl substituted imide **4d** to access aflaquinolone F (**11**).[18] For imide **4b**, the reaction had to be diluted by a factor of 10 due to limited solubility of **4b** in acetonitrile (Table 2, entries 2, 5, and 8). In all cases, benzophenones **5a**–**h** were obtained as the major product along with unreacted imides **4a**–**d**.

With the benzophenones **5a**–**h** in hand, we next investigated an intramolecular aldo reaction[10] to forge the 3,4-dioxygenated quinoline-2-one core. Using an excess of potassium *tert*-butoxide in tetrahydrofuran at 0 °C, the quinolinones **6a**–**g** were obtained as single diastereomers (Scheme 2). Following this procedure, the natural products (±)-6-deoxyaflaquinolone E (**6a**)[21] and (±)-quinolinone A (**6b**)[19c] were prepared in 91% and 84% yields, respectively.

Cyclization of **5d**, **5e**, and **5f** delivered the benzyl protected quinolinones **6d**, **6e**, and **6f**, which were subjected to hydrogenolysis to afford the natural products (±)-aflaquinolone E (**9**), F (**11**),[18] and (±)-quinolinone B (**10**)[19c] in up to 82% yield over two steps. Quinolinones **6g** and **6h** underwent Claisen rearrangement at 150 °C in 1,2-dichlorobenzene for 10 h to give **12a** and **12b** in 71% and 63% yield, respectively (Scheme 3).[21] At higher temperature and prolonged reaction time, elimination of the tertiary alcohol was observed. Grubbs' olefin cross metathesis[22] of **12a** and 2-methylbut-2-ene (excess) using Umicore M71SIMes as catalyst gave (±)-aniduquinolone C (**13a**)[23] in 81% yield, whereas (±)-penipre-

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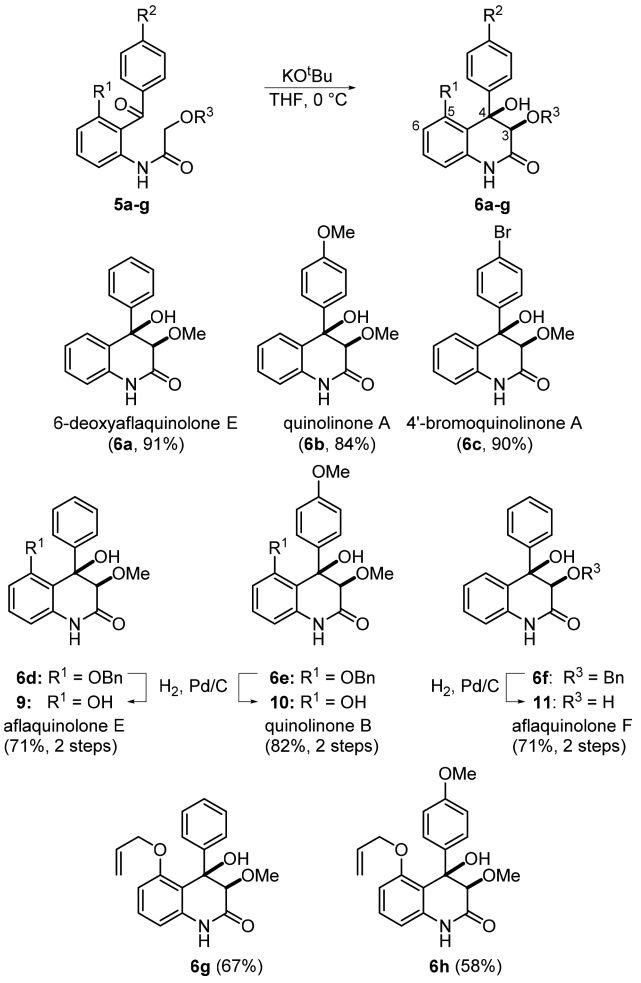
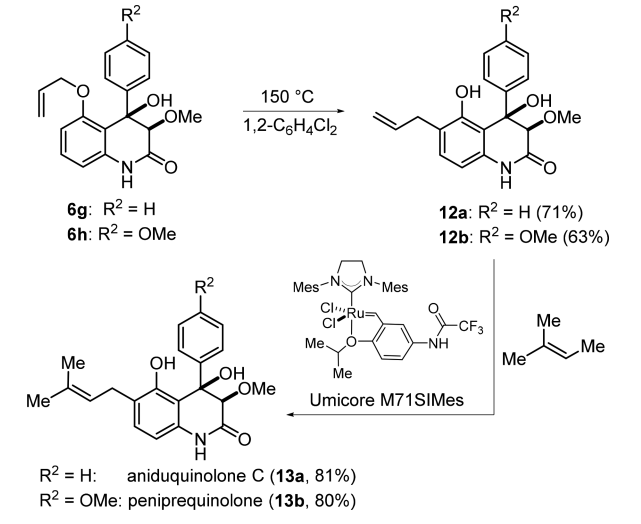
Scheme 2. Intramolecular Aldolization



Scheme 3. Synthesis of Aniduquinolone C and Peniprequinolone



quinolone (**13b**)[19a,b] was obtained in 80% yield starting from **12b**.

In conclusion, we have devised a general approach for the synthesis of 3,4-dioxygenated quinolin-2-one natural products. The sequence proceeds through an insertion of arynes into unsymmetric imides, followed by a diastereoselective intramolecular aldolization. A flow protocol for the aryne insertion was developed, which gave access to *N*-glycolated 2-aminobenzophenones within minutes. By this not immediately evident, yet powerful disconnection, the quinolinone natural products peniprequinolone, aflaquinolone E, F, quinolone A, B, and aniduquinolone C were synthesized in three to six steps.[24] Future work will focus on the synthesis of quinolinone natural products with other side chains and higher oxidation levels.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03392.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.
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