JOC*Note*

A Mild and Efficient Synthesis of 4-Quinolones and Quinolone Heterocycles

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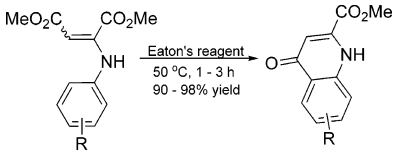
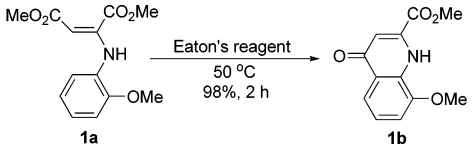


The cycloacylation of aniline derivatives to 4-quinolones in the presence of Eaton's reagent is described. This high-yielding methodology is applicable to a wide variety of functionalized anilines and requires milder conditions than those traditionally employed. This cyclization protocol is used to prepare a host of heterocycles and bis-quinolones and is characterized by relatively low reaction temperature and ease of product isolation.

Derivatives of 4-quinolone exhibit impressive antibiotic activity[1] and have been extensively investigated as antidiabetic,[2] anticancer,[3,4] and antiviral[5] agents. Given their utility, the development of synthetic methodology to access 4-quinolone derivatives is continually warranted. To date, the most frequently used strategy for their synthesis employs the Conrad−Limpach and Gould−Jacobs cyclizations.[6] These methodologies involve thermal cyclization of aniline derivatives to 4-quinolones under extremely harsh conditions. Reactions are typically carried out in mineral oil, Dowtherm, or diphenyl ether at 250 °C. The harsh reaction conditions have made synthesis and isolation of pure products difficult. Alternatively, polyphosphoric acid (PPA)[7] can be used for similar cyclizations; however, its high viscosity makes it difficult to handle for large-scale operations. The lack of a general and mild method led researchers to develop new synthetic strategies that involve an increased number of steps,[8] isolation or purification of reactive intermediates,[9] and the use of toxic reagents.[8,10] These alternative strategies typically give low yields of quinolones, making them unattractive for general large-scale synthetic applications. It is clear that an efficient protocol is needed.

Herein, we describe our discovery that Eaton's reagent,[11] an inexpensive and commercially available substance, could effectively be used to promote the cyclization of aniline derivatives to produce 4-quinolones in high yields under mild conditions (<90 °C). This observation has been found to be applicable to the synthesis of a series of quinolone and heterocyclic derivatives. In the context of a drug development program, we required a robust protocol for a multi-kilogram synthesis of 1,4-dihydro-8-methoxy-4-oxo-2-quinolone carboxylic acid, methyl ester **1b** (eq 1).



1a **1b** (1)

Our initial efforts at synthesizing **1b** employed the Conrad−Limpach protocol. We were pleased that we could obtain quinolone **1b** in 74% yield, albeit at the prohibitively high temperature of 250 °C in diphenyl ether. The harsh reaction conditions are needed presumably due to the cis stereochemical relationship of the ester groups in **1a**, which would require isomerization prior to ring closure.[12]

With PPA as a solvent the cyclization could be performed at 140 °C; however, only 20% of the product was isolated. Given the difficulties, we focused on identifying alternate conditions.[13]

† UNCF-Merck undergraduate scholarship.

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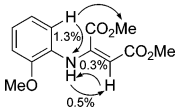
(11) For reactions employing Eaton's reagent, refer to: (a) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071−4073. (b) McGarry, L. W.; Detty, M. R. *J. Org. Chem.* ***1990***, *55*, 4349−4356. (c) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518−4526. (d) During the preparation of this manuscript, a similar transformation of an *o*-iodoaniline intermediate at 90 °C using Eaton's reagent was reported: Dorow, R. L.; Herrinton, P. M.; Hohler, R. A.; Maloney, M. T.; Mauragis, M. A.; McGhee, W. E.; Moeslein, J. A.; Strohbach, J. W.; Veley, M. F. *Org. Process Res. Dev.* **2006**, *10*, 493−499. (e) Eaton's reagent (7.7/92.3 % by weight of P_2O_5/ $MeSO_3H$) was purchased from Sigma-Aldrich

(12) Gradient 1D NOESY using Gaussian excitation pulse and 500−600 ms mixing time: (a) Kessler, H.; Oschkinat, H.; Griesinger, C.; Bermel, W. J. *J. Magn. Reson.* **1986**, *70*, 106−133. (b) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037−6038. (c) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199−4200. NOE summary:



(13) (a) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (b) Microwave-assisted synthesis of **1b** was briefly explored and found to give product, albeit in poor yields.

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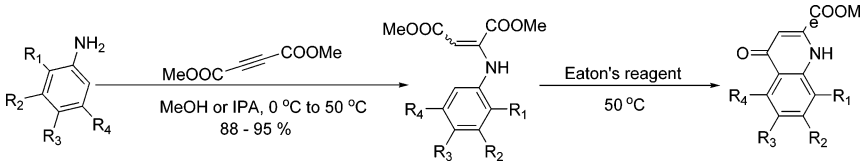
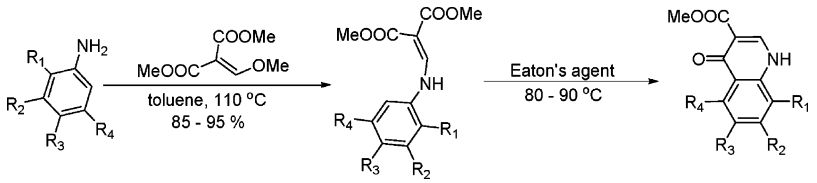
SCHEME 1. Synthesis of 4-Quinolone-2-carboxylic Acid, Methyl Esters via Cyclization Using Eaton's Reagent



SCHEME 2. Synthesis of 4-Quinolone-3-carboxylic Acid, Methyl Esters via Cyclization Using Eaton's Reagent



A variety of other acids and solvents were screened, each giving unacceptable yield of **1b**.[14] We then shifted our focus to Eaton's reagent, a mixture of P_2O_5 and $MeSO_3H$. Our preliminary investigations on the use of this reagent for cyclization of **1a** to **1b** in the presence of cosolvents[15] at temperatures ranging from 25 to 100 °C were not conclusive as it resulted in very low conversion. However, we were pleased to discover that simply dissolving **1a** in Eaton's reagent and heating to *only 50 °C resulted in quantitative conversion to **1b** within 1 h*. The ease of isolation of **1b** was notable as a simple quench into a saturated basic solution precipitates the product in acceptable purity (97% isolated yield). The importance of P_2O_5 in this reaction is illustrated by the fact that substrate **1a** does not give cyclized product after heating at 50 °C over 15 h in neat $MeSO_3H$.

Having successfully identified a facile route for large-scale preparation of quinolone **1b**, we chose to investigate the generality of this reaction for the preparation of related 4-quinolones from aryl amines with various substituents. Enamine substrates (Table 1, entries 1−9) were prepared in quantitative yield via condensation of commercially available aryl amines with dimethyl acetylenedicarboxylate (DMAD) in alcoholic solvents at temperatures ranging from 25 to 60 °C (Scheme 1).[2]

The new protocol was examined and found to be effective for the cyclization of enamines with various types of substituents, including substrates with electron-withdrawing groups which are typically poor substrates for similar cyclizations. In all cases, Eaton's reagent promoted cyclization at 50 °C and gave high yields of 2-carboxy-4-quinolones in less than 3 h.[16] The exceptional crystallinity of these products enabled facile isolation of 4-quinolones after basic quench of the reaction mixture. To further highlight the utility of this method the isopropyl-substituted quinolone (Table 1, entry 6) could be prepared in 92% yield. In Ph_2O at 230 °C this product was isolated in 44% yield.[17]

As there are several 3-carboxy-4-quinolones of medicinal interest,[1,2] we focused our attention on the application of the cyclization protocol to the synthesis of these molecules. Enamines (Table 2, entries 10−12), were prepared via condensation of aryl amines with dimethyl methoxymethylenemalonate in refluxing toluene (Scheme 2) and used without purification.

TABLE 1. Synthesis of 2-Carboxy-4-quinolones[16]

entry	R_1	R_2	R_3	R_4	% isolated yield
1	OMe	H	H	H	98
2	Cl	Cl	H	H	95
3	OMe	H	H	Cl	94
4	H	H	OMe	H	85
5	Br	H	H	H	95
6	*i*-Pr	H	H	H	92
7	H	H	CO_2Me	H	90
8	Cl	H	H	H	96
9	H	H	C_6H_{11}	H	90

TABLE 2. Synthesis of 3-Carboxy-4-quinolones

entry	R_1	R_2	R_3	R_4	% isolated yield
10	Cl	H	H	H	96
11	H	H	OMe	H	90
12	F	H	F	H	94

Cyclization was complete over 2−5 h and required higher temperatures (80−90 °C) than the compounds in Table 1, a result of relative increased steric nature of these substrates.

Encouraged by the results detailed in Tables 1 and 2, we envisioned the application of the mild cyclization conditions to the synthesis of tetracyclic bis-quinolones and quinolone heterocycles (Tables 3 and 4). Structures and derivatives similar to those shown in Table 3 have been extensively studied as medicinal agents as well as effective proton sponges[18] and may be useful as potential ligands for transition metals. The cyclization protocol was successfully implemented for the preparation of bis-quinolones (Table 3, entries 13−16). All of the products were isolated as analytically pure solids after basic quench as described above.

It is important to note that cyclization of 1,8-naphthalene diamine derivative (Table 3, entry 15) resulted in isolation of 85% of quinolinoquinolinedione. The same transformation at 230 °C in diphenyl ether gave 58% yield of product.[19] Finally,

(14) Aging a solution of **1a** in H_2SO_4, TFA, or HOAc at 50−100 °C over prolonged period of time resulted in the recovery of substrate **1a** along with significant amounts of hydrolysis product (aniline).

(15) The use of 1:1 and 2:1 mixtures of solvents including toluene, xylene, and tetramethylene sulfone along with Eaton's reagent resulted in sluggish conversion. The best conversion obtained was 3% after 20 h at 100 °C in a 1:1 mixture of toluene and Eaton's reagent.

(16) See the Experimental Section.

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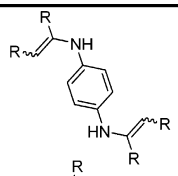
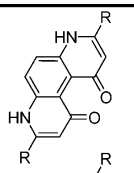
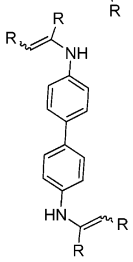
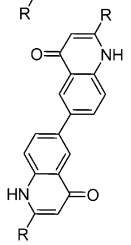
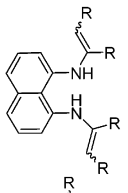
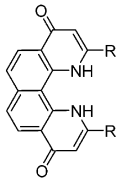
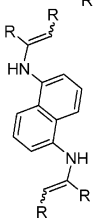
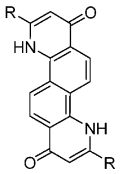
TABLE 3. Bis-Cyclization of Diamine Derivatives[a,16]

Entry	Reactant	Product	Isolated Yield (%)
13			80
14			90
15			85
16			92

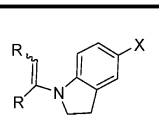
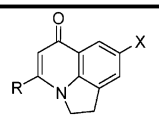
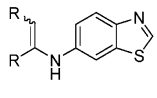
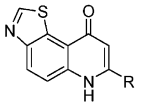
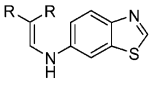
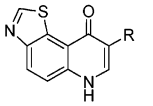
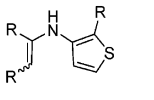
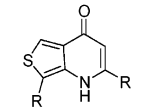
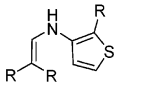
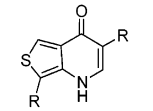
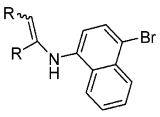
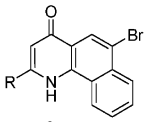
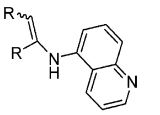
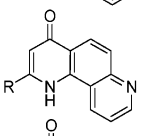
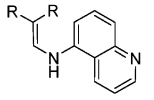
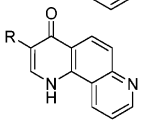
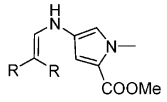
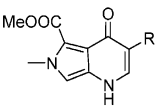
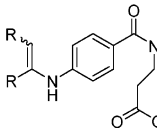
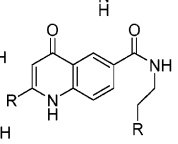
[a] Reactions were performed in 6 vol of Eaton's reagent at 50 °C. R = COOMe.

in order to further extend the utility of the cyclization protocol, several heterocyclic enamines (Table 4, entries 17−26) were prepared using identical protocols as illustrated in Schemes 1 and 2.

Gratifyingly, the cyclization protocol was applicable to the synthesis of heterocyclic quinolones. Enamine derivatives of aminoquinolines (Table 4, entries 23 and 24), aminobenzothiazoles (Table 4, entries 18 and 19), aminoindans (Table 4, entry 17), and aminothiophenes (Table 4, entries 20 and 21) were consistently prepared in good yields. Aminopyrrole derivative (Table 4, entry 25) gave a moderate yield of cyclized product. It is interesting to note that the aminobenzothiazole derivatives (Table 4, entries 18 and 19) were selectively cyclized adjacent to the sulfur atom in the molecule,[20] indicating a possible activating effect by electrons on the sulfur atom. A derivative of *N*-(4-aminobenzoyl)-*β*-alanine (Table 4, entry 26) gave 75% yield of the quinolone. The alanine portion of the molecule did not cyclize to a 7-membered ring; instead, it was converted to an ester, likely due to the presence of MeOH byproduct in the process. While the synthesis of thienopyridine (Table 4, entry 20) under thermal cyclization conditions (250 °C) has been reported,[21] yields obtained for the particular conversion were not discussed.

Despite the generality described above, this methodology does have certain limitations. In particular, the cyclization protocol

TABLE 4. Synthesis of Heterocyclic Quinolones[16]

Entry	Reactant	Product	Isolated Yield (%)
17[a]			X = H 93 X = Br 90
18[a]			88
19[b]			88
20[a]			85
21[b]			88
22[a]			90
23[a]			80
24[b]			80%
25[b]			60
26[a]			75

[a] Reactions were performed at 50 °C in 4 vol of Eaton's reagent. [b] Reactions were performed at 90 °C in 4 vol of Eaton's reagent. R = COOMe.

was not regioselective and resulted in several products when applied to a substrate derived from a meta-substituted arylamine.[22] An attempt to prepare a 7-membered ring keto benzoazepin from a substrate derived from a *p*-methoxyaniline and succinic anhydride was not effective. A known PPA cyclization[23] of 3-phenylpropanoic acid to generate a 5-membered ring compound (1-indanone) was also examined with Eaton's reagent and resulted in very little product.

(20) Sauter, F.; Jordis, U.; Tanyolac, S. *Sci. Pharm.* **1988**, *56*, 73−80.
(21) Barker, J. M.; Huddleston, P. R.; Jones, A. W.; Edwards, M. *J. Chem. Res.* **1980**, *1*, 4−5.

(22) Aryl amines with electron donating as well as withdrawing substituents at the meta position resulted in messy reaction profiles. An attempt to synthesize 1,4-dihydro-7-methoxy-4-oxo-2-quinolonecarboxylic acid, methyl ester from a substrate that was derived from *O*-methoxyaniline afforded only 30% of one major cyclized product with several unidentified side products (LC/MS studies).
(23) Guy, A.; Guette, J-P.; Gerard, L. *Synthesis* **1980**, 222−223.

Mechanistic studies for PPA-promoted cyclizations to benzoxazole derivatives have been reported.[24] While the report discusses the similarity between the active species in Eaton's reagent and PPA, no mechanistic studies have been reported for the cyclization of aniline derivatives to quinolones. As such, it is currently unclear why the mixture of P_2O_5 and $MeSO_3H$ serves to dramatically increase the rate of reaction. At the simplest level, the mechanism of the cyclization reaction is likely analogous to a Friedel−Crafts electrophilic aromatic substitution reaction. Consistent with this, preliminary kinetic studies reveal that electron rich substituents are more reactive than their electron poor counterparts.[25] Attempts to identify reaction intermediates are currently underway.

In conclusion, we have developed a very mild, efficient and scalable protocol for the synthesis of 4-quinolones, and quinolone heterocycles using an inexpensive commercially available reagent. Future work will look at extending the conditions employed in this study to the formation of thiochromenes and other heterocycles.

Experimental Section

Synthesis of 2-Butenedioic Acid, 2-[(2-Methoxyphenyl)-amino]-, Dimethyl Ester 1a. To a solution of *o*-anisidine (1 g, 8.1 mmol) in MeOH (10 mL) at 5 °C was added dimethyl acetylenedicarboxylate (DMAD) (1.4 g, 9.7 mmol, 1.2 equiv). The mixture was aged at rt over 2 h. The product precipitated during the aging process. The yellow solid was filtered and washed with MTBE (10 mL) followed by heptane (20 mL). Enamine diester **1a** was isolated as a yellow solid in 93% yield (2 g, 7.5 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.66 (s, 1H), 7.06 (m, 1H), 7.03(dd, J = 8.2, 1.8 Hz, 1H), 6.88 (m, 1H), 6.79 (d, J = 8.2, 1.8 Hz, 1H), 5.25 (s, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 169.0, 163.8, 149.9, 147.7, 128.4, 124.5, 120.6, 119.6, 111.5, 91.1, 55.5, 52.8, 51.1. *m*/*z*: 265.0950 [M^+]. ESI-HRMS: calcd for $C_{13}H_{15}NO_5$ 266.1028 [M + H]$^+$, found 266.1034.

Synthesis of 1,4-Dihydro-8-methoxy-4-oxo-2-quinolonecarboxylic Acid, Methyl Ester 1b. Enamine diester **1a** (1.8 g, 6.6 mmol) was added to a round-bottom flask that was equipped with a thermocouple and a stirrer, and Eaton's reagent (7 mL) was then added to the flask. The reaction mixture was aged at 50 °C, and the progress of the reaction was followed by HPLC. HPLC conditions: Zorbax RX-C8 column, 150 × 3 mm, gradient method, ACN: 0.1% H_3PO_4 15:85 over 20 min hold 5 min at 80:20 then to 15:85 over 1 min. Flow rate = 1 mL/min, λ = 210 nm. Retention time, **1a** = 18.0 min, **1b** = 12.2 min. When conversion reached ≥98%, the reaction mixture was cooled to 5 °C and slowly transferred to an excess saturated sodium carbonate solution that was cooled to 10 °C. The solid was filtered, washed with 20 mL of water, and dried in a vacuum oven at 50 °C. Compound **1b** was isolated as a white solid in 97% yield. This reaction has been scaled as described in this procedure to multiple kilograms and gave 98% isolated yield of **1b**. ^{1}H NMR (400 MHz, D_3CCO_2D): δ ppm 7.86 (d, J = 8.2 Hz, 1H), 7.38 (t, J = 8.2 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.19 (s, 1H), 4.07 (s, 3H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, D_3CCO_2D): δ ppm 181.3, 163.5, 149.7, 137.9, 131.6, 127.1, 126.3, 117.7, 112.9, 111.4, 57.1, 54.6. *m*/*z*: 233.0688 [M^+]. ESI-HRMS: calcd for $C_{12}H_{11}NO_4$ 256.0586 [M + Na]$^+$, found 256.0586

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Supporting Information Available: NMR spectra and ESI-HRMS data for compunds (**1**−**26**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO070181O

(24) So, Y-H.; Heeschen, J. P. *J. Org. Chem.* **1997**, *62*, 3552−3561.

(25) Conversion of substrate with *p*-OMe substituent (Table 2, entry 11), reached 40% over 40 min, while conversion of a substrate with *p*-NO_2 substituent was only 3% over the same period.