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Triflic anhydride-mediated tandem formylation/cyclization of cyanoacetanilides: a concise synthesis of glycocitlone alkaloids

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ABSTRACT

A method is presented for the concise synthesis of 3-formyl-4-hydroxyquinolin-2(1*H*)-ones through triflic anhydride-mediated tandem formylation/cyclization of cyanoacetanilides. This tandem process was successfully used for the rapid syntheses of glycocitlones A and C.

Substituted 4-alkoxy- and 4-hydroxyquinolin-2(*1H*)-ones **1** (Fig. 1) such as glycocitlones A–C (**2**–**4**)[1] are widely found among quinoline alkaloids of *rutaceous* plants.[2] Compound **1** also form a valuable class of biologically active molecules,[3] including human immunodeficiency virus type 1 (HIV-1) integrase inhibitors[3a] and hepatitis C virus (HCV) inhibitors.[3b,e] Therefore, a diversity-oriented strategy[4] for the preparation of this class of compounds in a practical and concise manner would be very useful for drug discovery.

In our view, the development of an efficient method for the synthesis of 3-formyl-4-hydroxyquinolin-2(1*H*)-ones **5** would be invaluable for the diversity-oriented synthesis of **1** since **5** possess hydroxy and formyl functionality that can help in the synthesis of a wide range of compounds[5] (Scheme 1). We expect that **5** can be prepared from cyanoacetanilides **6** and *N*,*N*-dimethylformamide (DMF) by simultaneous cyclization and functionalization,[6,7] which is a powerful and direct approach to prepare diverse derivatives from a simple precursor. This approach would dramatically reduce the consumption of solvents, reagents, and energy, as compared to the stepwise preparation of **5**.[3f,8]

Herein, we report a concise and practical method to obtain **5** from **6** through tandem formylation/cyclization. The salient features of our method are as follows: (1) a variety of cyanoacetanilides are readily available,[9] (2) multiple C–C bond formation allows for the rapid synthesis of functionalized quinolinones **5** from simple starting materials, and (3) facile isolation of **5** is accomplished by a simple aqueous workup.

We first examined the reaction of cyanoacetanilide **6a** in DMF (Table 1). We found that the use of trifluoromethanesulfonic anhydride (Tf_2O) in the tandem reaction yielded 3-formyl-4-hydroxyquinolin-2(1*H*)-one **5a** in 71% yield (entry 4). Other reagents such as $POCl_3$, $(COCl)_2$, and $SOCl_2$ were found to be incapable of yielding this compound (entries 1–3). Three equivalents of Tf_2O were required to obtain **5a** in good yield (entry 4 vs entry 6). It is important to note that **5a** was isolated as a precipitate by the simple aqueous workup, and a gram-scale reaction can be conducted easily (entry 5).

We next performed several experiments to gain mechanistic insights into the tandem reaction (entries 7–10). When **6a** was treated with trifluoromethanesulfonic acid (TfOH) instead of Tf_2O, no reaction occurred and unreacted **5a** was recovered (entry 7).[10] The treatment of **6a** with a combination of TfOH (2.0 equiv) and Tf_2O (1.0 equiv) resulted in almost the same result as that in entry 6 (entry 8), indicating that a Brönsted-acid-catalyzed Houben–Hoesch reaction[11,12] did not occur in the tandem reaction

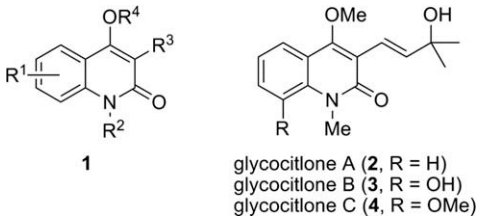
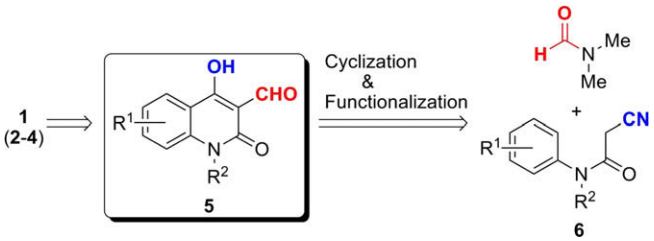


Figure 1. 4-Alkoxy- and 4-hydroxyquinolin-2(*1H*)-ones.



Scheme 1. Synthetic strategy.

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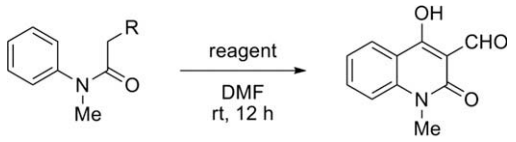
Table 1
Survey of the reaction conditions[a]

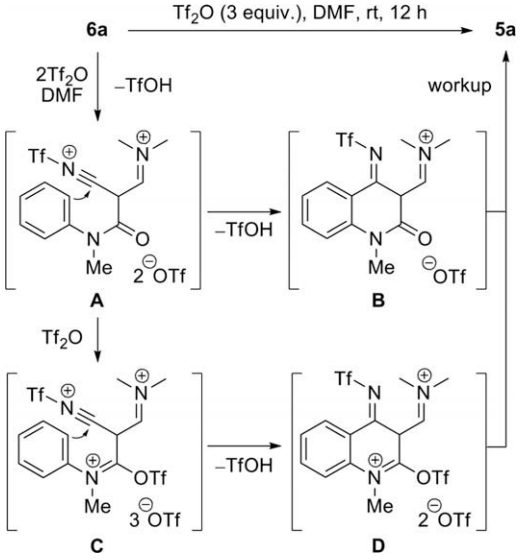


6a, **7** **5a**

Entry	Substrates (R)	Reagent[b] (equiv)	Yield of **5a**[c]
1	**6a** (CN)	$POCl_3$ (3.0)	0[d]
2	**6a**	$(COCl)_2$ (3.0)	0[d]
3	**6a**	$SOCl_2$ (3.0)	0[d]
4	**6a**	Tf_2O (3.0)	71
5[e]	**6a**	Tf_2O (3.0)	84
6	**6a**	Tf_2O (1.0)	26
7	**6a**	TfOH (3.0)	n.r.[f]
8	**6a**	Tf_2O (1.0) + TfOH (2.0)	29
9[g]	**6a**	Tf_2O (3.0)	n.r.[f]
10	**7** (CO_2Et)	Tf_2O (3.0)	0[d]

[a] Unless otherwise noted, all reactions were carried out with 3.0 mmol of substrates in *N*,*N*-dimethylformamide (3.0 mL, 13 equiv).
[b] Tf = trifluoromethanesulfonyl.
[c] Isolated yields.
[d] See the Supplementary data.
[e] 15 mmol of **6a** was employed.
[f] No reaction occurred.
[g] The reaction was carried out in *N*,*N*-dimethylacetamide (DMA).

and that Tf_2O played a crucial role in the cyclization step. Furthermore, both DMF and the CN functionality of the substrate were found to be essential for the formation of **5a** (entries 9 and 10). These results suggest that the reaction of the active methylene of

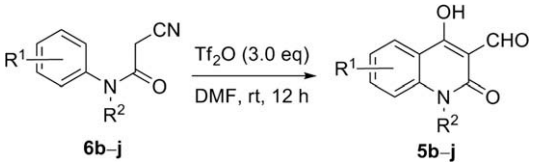


Scheme 2. Plausible mechanism.

6a with the Vilsmeier reagent[13] is likely to be an initial step in the tandem reaction[14] (Scheme 2). The introduction of an iminium substituent in a geminal position relative to the CN group may increase the electrophilicity of the CN group[15] and promote Tf_2O-mediated cyclization (**A**→**B** and/or **C**→**D**).

Once the optimum conditions were identified, we examined the substrate scope of the reaction with cyanoacetanilides **6b**–**j** (Table 2). The tandem reaction of **6b** and **6c** in which the *para* positions

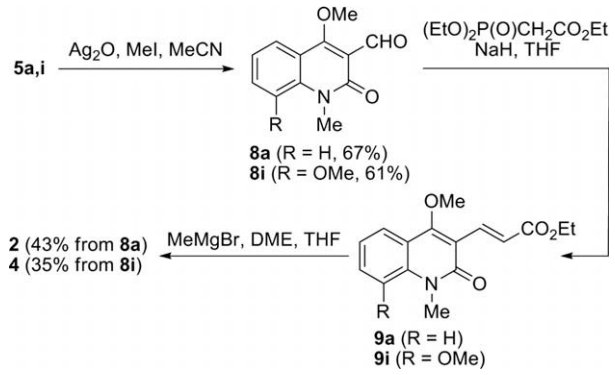
Table 2
Substrate scope of cyanoacetanilides **6**[a,b]



6b–**j** **5b**–**j**

Entry	**6** (R^1, R^2)	Products	Yield[c] (%)
1	**6b** (*p*-Me, Me)	**5b**	79
2	**6c** (*p*-OMe, Me)	**5c**	69
3	**6d** (*p*-Cl, Me)	**5d**	80
4	**6e** (*p*-Br, Me)	**5e**	68
5	**6f** (*p*-CF_3, Me)	**5f**	61
6	**6g** (*m*-Me, Me)	**5g** + **5g′**	78[d] (**5g**:**5g′** = 35:65)[e]
7	**6h** (*o*-Me, Me)	**5h**	80
8	**6i** (*o*-OMe, Me)	**5i**	69
9	**6j**	**5j**	82

[a] All reactions were carried out with 3.0 mmol of substrates in *N*,*N*-dimethylformamide (3.0 mL, 13 equiv).
[b] Tf = trifluoromethanesulfonyl.
[c] Isolated yields.
[d] The ratio between **5g** and **5g′** is given in parentheses.
[e] The ratio was determined by a ^1H NMR experiment.



Scheme 3. Synthesis of glycocitlones.

were substituted with electron-donating methyl or methoxy groups took place smoothly to afford quinolinones **5b** and **5c** in 79% and 69% yields, respectively (entries 1 and 2). Unlike the Houben–Hoesch reaction, which requires electron-rich arene substrates and dry gaseous HCl to afford decent yields of ketones, the tandem reaction can be successfully carried out with arenes bearing electron-withdrawing substituents (entries 3–5).[14e,16] The halogenated products **5d** and **5e** could in principle be further functionalized through transition-metal-catalyzed coupling reactions. Interestingly, cyanoacetanilide **6g** afforded regioisomers **5g** and **5g′** in 78% combined yield upon cyclization primarily *ortho* to the methyl group (ratio of *para* to *ortho*: 35:65) (entry 6). Further, it is noteworthy that *ortho*-substituted cyanoacetanilides **6h** and **6i** were also effective in the tandem reactions (entries 7 and 8) since the product **5i** can be used in the synthesis of quinoline alkaloids (vide infra). Moreover, when this methodology was followed using cyanoacetanilide **6j**, a tricyclic compound (**5j**) was obtained in high yield (entry 9). Furthermore, the isolation of all products **5b–j** could be easily accomplished by precipitation and filtration.

Finally, we used **5a** and **5i** for the synthesis of glycocitlone alkaloids (Scheme 3). Methylation of hydroxyl groups using MeI and Ag_2O in MeCN gave aldehydes **8a** and **8i.** Subsequently, the Horner–Wadsworth–Emmons (HWE) olefination afforded the corresponding α,β-unsaturated esters **9a** and **9i**. These esters were then treated with MeMgBr to obtain glycocitlones A (**2**) and C (**4**).

In conclusion, we have presented an efficient method for the conversion of cyanoacetanilides **6** into 3-formyl-4-hydroxyquinolin-2(1*H*)-ones **5**; the method involves a novel Meth-Cohn-type reaction.[14] The method is simple and it has the potential to be used for the synthesis of a wide variety of functionalized quinolin-2(*1H*)-ones. Further, the use of the method in synthetic applications is under investigation and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.073.

References and notes

1. Ito, C.; Kondo, Y.; Wu, T.-S.; Furukawa, H. *Chem. Pharm. Bull.* **2000**, *48*, 65–70.
2. For recent reviews, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187. and earlier annual reviews in this journal by the same author; (b) Barr, S. A.; Boyd, D. R.; Sharma, N. D.; Loke, P. L. *Heterocycles* **2009**, *79*, 831–850.
3. For recent examples, see: (a) Sechi, M.; Rizzi, G.; Bacchi, A.; Carcelli, M.; Rogolino, D.; Pala, N.; Sanchez, T. W.; Taheri, L.; Dayam, R.; Neamati, N. *Bioorg. Med. Chem.* **2009**, *17*, 2925–2935; (b) Melagraki, G.; Afantitis, A.; Sarimveis, H.; Koutentis, P. A.; Markopoulos, J.; Igglessi-Markopoulou, O. *Bioorg. Med. Chem.* **2007**, *15*, 7237–7247; (c) Detsi, A.; Bouloumbasi, D.; Prousis, K. C.; Koufaki, M.; Athanasellis, G.; Melagraki, G.; Afantitis, A.; Igglessi-Markopoulou, O.; Kontogiorgis, C.; Hadjipavlou-Litina, D. J. *J. Med. Chem.* **2007**, *50*, 2450–2458; (d) Rivkin, A.; Kim, Y. R.; Goulet, M. T.; Bays, N.; Hill, A. D.; Kariv, I.; Krauss, S.; Ginanni, N.; Strack, P. R.; Kohl, N. E.; Chung, C. C.; Varnerin, J. P.; Goudreau, P. N.; Chang, A.; Tota, M. R.; Munoz, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4620–4623; (e) Tedesco, R.; Shaw, A. N.; Bambal, R.; Chai, D.; Concha, N. O.; Darcy, M. G.; Dhanak, D.; Fitch, D. M.; Gates, A.; Gerhardt, W. G.; Halegoua, D. L.; Han, C.; Hofmann, G. A.; Johnston, V. K.; Kaura, A. C.; Liu, N.; Keenan, R. M.; Lin-Goerke, J.; Sarisky, R. T.; Wiggall, K. J.; Zimmerman, M. N.; Duffy, K. J. *J. Med. Chem.* **2006**, *49*, 971–983; (f) Abass, M.; Mostafa, B. B. *Bioorg. Med. Chem.* **2005**, *13*, 6133–6144.
4. For diversity-oriented synthesis, see: (a) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74–84; (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58; (c) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
5. (a) Narasimhan, N. S.; Bhagwat, S. P. *Synthesis* **1979**, 903–906; (b) Meth-Cohn, O. *Heterocycles* **1993**, *35*, 539–557; (c) Rajendran, S. P.; Manonmoni, M.; Vijaya-Lakshmi, S. *Org. Prep. Proced. Int.* **1994**, *26*, 383; [d] Li, J. J. *Name Reactions in Heterocyclic Chemistry*; John Wiley: Hoboken, 2005. pp 443–450; (e) Chimichi, S.; Boccalini, M.; Matteucci, A. *Tetrahedron* **2007**, *63*, 11656–11660.
6. For recent reviews, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472.
7. For selected recent examples, see: (a) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631; (b) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050–6051; (c) Mihovilovic, M. D.; Stanetty, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3612–3615; (d) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1644–1647; (e) Suzuki, Y.; Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4246–4251.
8. For the stepwise preparation of 3-formyl-4-hydroxyquinolin-2(1*H*)-ones, see: (a) Tomita, K. *J. Pharm. Soc. Jpn.* **1951**, *71*, 1100–1112; The stepwise approach suffers from harsh reaction conditions and undesired side reactions, see: (b) Ahvale, A. B.; Prokopcová, H.; Šefčovičová, J.; Steinschifter, W.; Täubl, A. E.; Uray, G.; Stadlbauer, W. *Eur. J. Org. Chem.* **2008**, 563–571. and references cited therein.
9. All cyanoacetanilides **6a–j** were easily prepared, purified, and obtained as solids; see the Supplementary data. Also see: Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603–1606.
10. We could not observe any cyclized products even by an NMR experiment using **6a** and TfOD (8.8 equiv) in DMF-d_7 (13 equiv).
11. For reviews of Friedel–Crafts and related reactions, see: (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. S. S.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3,. Chapter 1.8 (b) Olah, G. A. *Friedel–Crafts and Related Reactions*; Interscience: New York, 1964.
12. (a) Spoerri, P. E.; DuBois, A. S. *Org. React.* **1949**, *5*, 387; (b) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037–3043.
13. (a) Vilsmeier, A.; Haack, A. *Chem. Ber.* **1927**, *60*, 119; For reviews, see: (b) Jones, G.; Stanforth, S. P. The Vilsmeier Reaction of Fully Conjugated Carbocycles and Heterocycles. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley: New York, 1997; Vol. 49, pp 1–330; (c) Marson, C. M.; Giles, P. R. *Synthesis Using Vilsmeier Reagents*; CRC Press: Boca Raton, 1994. pp 1–247; (d) Jutz, C. Iminium Salts in Organic Chemistry. In *Advances in Organic Chemistry*; Taylor, E. C., Ed.; John Wiley & Sons: New York, 1976; Vol. 9, Part I, pp 225–342; (e) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659–3726.
14. For examples of the synthesis of quinolines under Vilsmeier conditions, see: (a) Wang, Y.; Xin, X.; Liang, Y.; Lin, Y.; Zhang, R.; Dong, D. *Eur. J. Org. Chem.* **2009**, 4165–4169; (b) Baruah, B.; Bhuyan, P. J. *Tetrahedron* **2009**, *65*, 7099–7104; (c) Mahata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966–3975; (d) Akila, S.; Selvi, S.; Balasubramanian, K. *Tetrahedron* **2001**, *57*, 3465–3469; (e) Ali, M. M.; Tasneem; Rajanna, K. C.; Saiprakash, P. K. *Synlett* **2001**, 251–253; (f) Paul, S.; Gupta, M.; Gupta, R. *Synlett* **2000**, 1115–1118; (g) Katritzky, A. R.; Arend, M. *J. Org. Chem.* **1998**, *63*, 9989–9991; (h) Amaresh, R. R.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 14327–14340; (i) Meth-Cohn, O.; Goon, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 85–90; (j) Meth-Cohn, O.; Taylor, D. L. *Tetrahedron* **1995**, *51*, 12869–12882; (k) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1520–1530; (l) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *Tetrahedron Lett.* **1979**, *20*, 3111–3114; (m) Meth-Cohn, O.; Narine, B. *Tetrahedron Lett.* **1978**, *19*, 2045–2048.
15. For a useful discussion, see: Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Org. Chem.* **2008**, *73*, 4219–4224.
16. For the Pd-catalyzed addition of C-H to nitrile, see: Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302–2303.