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Novel and convenient synthesis of 4(1*H*)quinolones

Jan Tois,[a] Mikko Vahermo[b] and Ari Koskinen[a,*]

[a]*Laboratory of Organic Chemistry, Helsinki University of Technology, PO Box 6100, FIN 02015, Finland*
[b]*Department of Pharmacy, Viikki Drug Discovery Technology Center, PO Box 56, FIN 00014 University of Helsinki, Finland*

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Abstract—A rapid two-step synthesis of 4(1*H*)quinolones is described. The first step involves condensation of *o*-nitroacetophenone with *N*,*N*-dimethylformamide dimethylacetal yielding highly crystalline enamines. In the second step a reductive cyclization is achieved under catalytic transfer hydrogenation (CTH) conditions. In all cases, the total time of this process was less than 3 h.

The 4(1*H*)quinolone structure[1] plays an extremely important role in the field of pharmaceutical chemistry. These compounds have been used as precursors for anticancer agents,[2] anti-malarial agents[3] and reversible (H^+/K^+) ATPase inhibitors (Fig. 1).[4] Traditionally 4-substituted quinolones have been synthesized at high temperatures.[5] Huang and Liu have even adopted this kind of thermal cyclization reaction on solid phase.[6] More recently, Nishida et al. prepared 6-methoxy-4(1*H*)quinolone using an elegant ene–enol ether metathesis.[3] Atkins et al. have summarized other interesting synthetic routes to these compounds.[7] In fact, Atkins reported in this

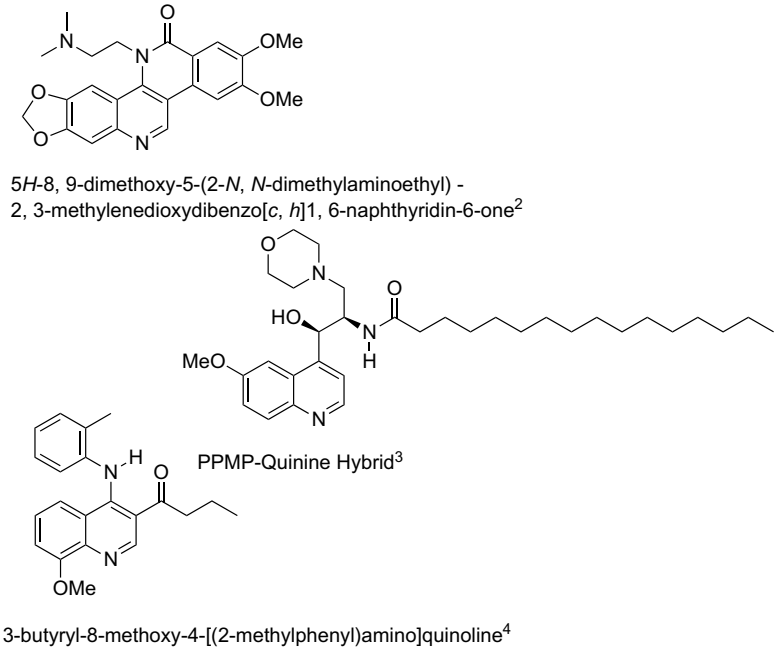

Figure 1. Pharmaceutically interesting molecules prepared from 4-substituted quinolones.

Keywords: Quinolones; Leimgruber–Batcho; Pd catalysis.
* Corresponding author. Tel.: +358 9 451 2526; fax: +358 9 451 2538; e-mail: ari.koskinen@hut.fi

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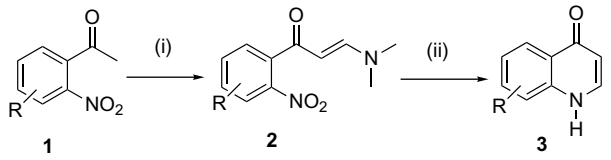


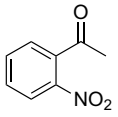
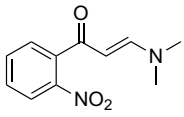
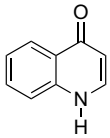
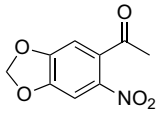
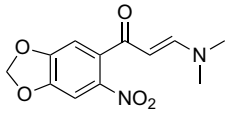
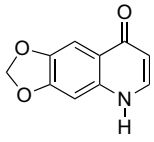
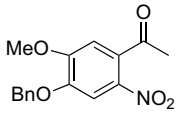
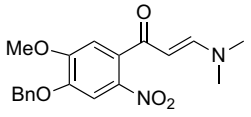
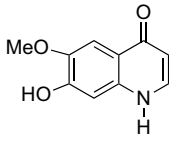
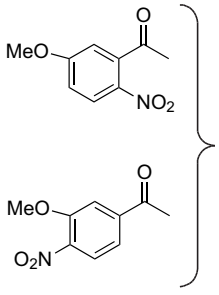
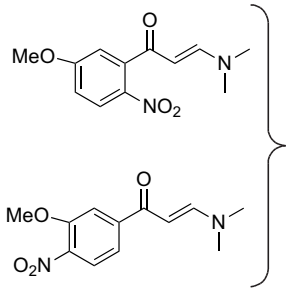
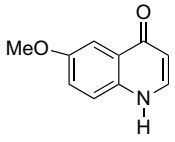
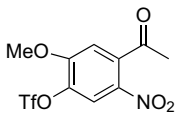
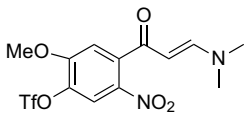
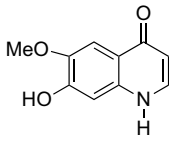
Scheme 1. Reagents and conditions: (i) DMF–DMA, DMF, 100 °C, 90 min; (ii) 10% Pd–C, cyclohexene, EtOH, reflux, 60 min.

paper a modified Leimgruber–Batcho[8] procedure to form the desired 3-substituted-4(1*H*)quinolone. However, there was only one example of this method. Herein, we present our synthetic studies towards 4-substituted quinolones without substituents on the 2- or 3-position utilizing this efficient two-step procedure.

The enamines **2** were synthesized by heating the *o*-nitroacetophenones **1** with dimethylformamide dimethylacetal in DMF at 100 °C (Scheme 1). In all cases the reactions went to completion in 90 min or less according to TLC. The solvent was evaporated in vacuo and the crude enamines were crystallized from ethanol yielding the enamines as mixtures of *E*- and *Z*-isomers. The enamines were cyclized to quinolones **3** under catalytic transfer hydrogenation conditions (CTH) using cyclohexene as hydrogen source and 10% Pd–C as catalyst.[9] The catalyst:substrate ratio was 1:5 by weight (4–7 mol% of Pd). Even lower ratios accomplished the cyclization but when a catalyst:substrate ratio of 1:1 was used, an unwanted side reaction occurred.[10] In all cases, the violent evolution of hydrogen was observed when reaction temperatures reached 80 °C and the reaction was complete in 60 min (or less) according to TLC.

The results are summarized in Table 1. With pure isomers as starting materials (**1a**, **1b**, **1c**, **1e**), the reactions

Table 1. Starting materials, products, yields and reaction times

1	Enamine **2** (yield %) [time, min]	4(1*H*)quinolone **3** (yield %) [time, min]
		
1a[a]	**2a**, (95) [50]	**3a**, (85) [20]
		
1b[a]	**2b**, (78) [60]	**3b**, (91) [15]
		
1c[b]	**2c**, (82) [60]	**3c**, (95) [60]
		
1d[c]	**2d**, (84) [40]	**3d**, (52) [60]
		
1e[b]	**2e**, (87) [60]	**3c**, (70) [30]

[a] Commercially available.
[b] Synthesized from 4-hydroxy-3-methoxyacetophenone.
[c] A mixture of 3-methoxy-2-nitroacetophenone and 3-methoxy-4-nitroacetophenone was used as starting material.[11]

proceeded smoothly affording the desired enamines and 4(1*H*)quinolones in high yields. In the case of **1c** it is noteworthy that the hydrogenation of the benzyl group and the reductive cyclization took place in one pot to give directly **3c**. To demonstrate the efficiency and advantages of this process we tested this transformation with a mixture of acetophenones **1d** as starting materials.[11] The mixture of enamines **2d** was formed in the same ratio as the starting materials. To our delight the reductive cyclization went as expected. The 6-methoxy-4(1*H*)quinolone was formed and no side reaction caused by the reduction product of the 'wrong' isomer was observed.

We also tested if it would be possible to deoxygenate **2e** under these conditions to afford **3d**. Traces of **3d** were detected on TLC but we were able to isolate only **3c**.

In summary, we have demonstrated that this Leimgruber–Batcho analog is an extremely effective method for the preparation of 4(1*H*)quinolones. Further modifications of these synthesized molecules with asymmetric compounds are now under investigation in our laboratories and the results will be presented in due course.

Acknowledgements

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References and notes

1. We will use this name throughout the text. In most published articles the tautomeric form 4-hydroxyquinoline is used. For discussion of the keto–enol tautomerism see, Cruz, A.; Elguero, J.; Goya, P.; Martínez, A. *Tetrahedron* **1992**, *48*, 6135–6150, and references cited therein.
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10. A highly non-polar by-product was observed on TLC when the catalyst:substrate ratio was 1:1. This side product was not characterized.
11. Mixture **1d** was prepared according to Robbins, R. J.; Laman, D. M.; Falvey, D. E. *J. Am. Chem. Soc.* **1996**, *118*, 8127–8135; We were not able to separate the isomers and the ratio of 3-methoxy-2-nitroacetophenone:3-methoxy-4-nitro-acetophenone (56:44) was determined by NMR spectrometry. We highly recommend the method published by Fürstner et al. for the preparation of pure 3-methoxy-2-nitroacetophenone. Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, *127*, 1125–1130.