2-Substituted-2,3-dihydro-1H-quinolin-4-ones via acid catalyzed tandem Rupe rearrangement/Donnelly-Farrell ring-closure of 2-(3’-hydroxypropynyl)anilines

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Abstract: A range of 2-substituted 2,3-dihydro-1H-quinolin-4-ones have been synthesized from anilines by a two-step process involving Sonogashira coupling with a propargyl alcohol then acid catalyzed cyclization of the resulting 2-(3'-hydroxypropynyl)anilines. The cyclization reaction appears to proceed via regioselective rearrangement of the propargyl alcohol to an α,β-unsaturated ketone (Rupe rearrangement) and then 6-endo-trig ring-closure (Donnelly-Farrell cyclisation). The isolation of the α,β-unsaturated ketone intermediate in one example supports this pathway.

Key words: quinolinone, Sonogashira coupling, Rupe rearrangement, cyclization, alkaloids, alkenes.

Quinolines and quinolinones constitute the core unit of numerous alkaloids and synthetic compounds with interesting pharmacological properties. 1,2 2-Substituted 2,3-dihydro-1H-quinolin-4-ones have shown analgesic 3 and antimalarial 4 activity and have attracted attention recently as antimitotic and antitumor agents. 5-6 Interest in these compounds led to a significant number of synthetic methods being described in the literature for their preparation. 7-16 However, the direct preparation of 2,3-dihydro-1H-quinolin-4-ones from readily available anilines has received relatively little attention. 9,13,16

Here, we report a general and straightforward approach to 2,3-dihydro-1H-quinolin-4-ones via a two-step process which starts from readily available 2-(pseudo)halogenated anilines 1. The process involves Sonogashira coupling with a propargyl alcohol 2, 17,18 followed by a Brønsted acid catalyzed cyclization of the resulting 2-(3’-hydroxypropynyl)anilines 3 to give quinolin-4-ones 4 (Scheme 1).

2-Methyl-3-butyn-2-ol (2a, R2 = R3 = Me) has been used widely as a readily available, cheap, non-volatile protected form of acetylene (cf. e.g. TMS-acetylene) which is unmasked via thermolysis in the presence of base with evolution of aceton. 19,20 It was in the context of the use of this reagent as a partner for Sonogashira coupling with 2-trifloxy-N-acetylanilines (1a) that we serendipitously discovered the facile cyclization process described herein. Thus, following Pd/Cu catalyzed coupling to yield alkynyl aniline 3a in 76% yield, attempted acid catalyzed hydrolysis of the acetamide by heating in c.HCl/water (1:1, v/v), was found to furnish dimethyl-2,3-dihydro-1H-quinolin-4-one (4a) in 98% yield after basic workup and chromatographic purification (Scheme 2).

To determine the scope of this ring closure, we investigated the synthesis and acid catalyzed cyclization of a range of 2-(3’-hydroxypropynyl)anilines.

A series of Sonogashira coupling reactions were carried out between 2-methyl-3-butyn-2-ol (2a) and 2-trifloxy- and 2-bromo-N-acetylanilines 1a-d and 2-bromo- and 2-iodoanilines (1e,f) using standard conditions involving Pd(II)/Cu(I) pre-catalysts. 21 The 2-trifloxy-N-acetylanilines were synthesized from the corresponding 2-hydroxyanilines by N-acetylation (Ac2O in AcOH) then O-triflation (Tf2O, pyridine in CH2Cl2). Moderate to good yields were obtained for all these Sonogashira coupling reactions (Table 1). 22,28

Scheme 1 Synthesis of 2,3-dihydro-1H-quinolin-4-ones 3. a) Sonogashira coupling, b) acid catalyzed cyclization.

Scheme 2 Synthesis of 2,2-dimethyl-2,3-dihydro-1H-quinolin-4-one (4a). Reagents and conditions: a) 2-methyl-3-butyn-2-ol (2a), PdCl2(PPh3), CuI, PPh3, py, Et3N, 90 °C, 3 h (76%); b) conc. HCl, H2O, 120 °C, 1.5 h (98%).
The cyclization served to have low cf.

The ring closure reactions of these 2-alkynylanilines 3 to give the quinolin-4-ones 4 were performed in all cases by heating at 120 °C in cHCl/water (1:1, v/v) followed by basic workup, as for the initial example described above (Table 2).

The electron demand of substituents on the aryl ring appeared to have no significant effect on the cyclization process. The yields ranged from 60 to 98% with the exception of the 4-trifluoromethyl derivative 3e which was obtained in just 35% yield. Both the aniline 1e and the 2-alkynylaniline 3e leading to this product were observed to have low thermal stability; probably explaining the reduced yields in this sequence. The acetamide is not critical for successful cyclization as the free aniline 3f cyclized efficiently, albeit in reduced yield relative to its acetamide analogue 3a (cf. entries 1 and 6, Table 2).

We envisage that the cyclization, in the case of the free aniline 3f, probably proceeds via regioselective hydrative/dehydrative rearrangement of the alkyn moiety, possibly via aldol 1, to give α,β-unsaturated ketone II, then 6-endo-trig Michael-type ring-closure to give quinolin-4-one 4f (Scheme 3).

The acid catalyzed rearrangement of propargylic alcohols to α,β-unsaturated ketones (cf. 3f → II) is known as a Rupe rearrangement and may proceed as indicated in Scheme 3 or via an allenyl intermediate with assistance from the 2-amino group. The cyclization of 2-aminochalcones to 2-aryl-2,3-dihydro-1H-quinolin-4-ones (cf. II → 4f) is also well-documented and the acid catalyzed variant is sometimes referred to as a Donnelly-Farrell cyclization. However, our tandem Rupe rearrangement/Donnelly-Farrell cyclization to give quinolin-4-ones is new and potentially provides access to a wider variety of eventual C2 substituents than have been accessible from chalcones.

For the cyclization of the N-acetyl compounds 3a-d, acetamide hydrolysis, at least in the case of the 4-trifluoromethoxy substituted substrate 3d occurs in situ immediately prior to ring-closure as evidenced by our isolation after 4 h of a ~1:1 mixture of the expected quinolin-4-one 4d and the N-acetyl-α,β-unsaturated ketone 5 (Scheme 4).

When compound 5 was resubjected to the same conditions for additional 4 h, complete conversion to quinolin-4-one 4d was achieved. Direct conversion of anilide 3d to quinolin-4-one 4d required 8 h (Table 2, entry 5, 60% yield).

With the aim to further widen the scope of this new approach, we investigated the introduction of different groups at C2 of the quinolin-4-one ring. Thus, we synthesized 2-ethynyl aniline 6 from 2-idoaniline (1f) by Sonogashira coupling with trimethylsilylacetylene then protonolysis of the trimethylsilyl group. Deprotonation of this terminal alkyne (BuLi) and quenching with benzaldehyde gave propargyl alcohol 3g (R^2 = H, R^1 = Ph) in 26% unoptimized yield. Reaction with acetophenone...
required transmetallation to the organocerate (CeCl$_3$)$_2$, to suppress enolization but gave propargyl alcohol 3h ($R^2$ = Me, $R^3$ = Ph) in 60% yield (Scheme 5).

![Scheme 6 Reagents and conditions: a) i. TMS-acetylene, PdCl$_2$(PPh)$_3$.CuI, PPh$_3$.H$_2$P$_2$NH. toluene rt, 16 h; ii) KOH, MeOH/water, rt, 3 h (38%) b) n-BuLi. THF, −5 °C → rt (6 → 3g. $R^2$ = H, $R^3$ = Ph, 26%) or n-BuLi, CeCl$_3$, THF, −5 °C → rt (6 → 3h. $R^2$ = Me, $R^3$ = Ph, 60%) c) conc. HCl, H$_2$O, 120 °C, 1.5 h (7a, $R^2$ = H, $R^3$ = Ph, 50%; 7b, $R^2$ = Me, $R^3$ = Ph, 26%).](image)

After heating at 120 °C in c.HCl/water (1:1, v/v) as previously, we were very pleased to observe that quinolin-4-ones 7a ($R^2$ = H, $R^3$ = Ph) and 7b ($R^2$ = Me, $R^3$ = Ph) were obtained in 50 and 26% yields, respectively. No attempt was made to optimize these yields but it is apparent that the process is applicable to the synthesis of quinolin-4-ones with alternative substitution patterns at C2.

In conclusion, we have reported a straightforward method for the preparation of 2-substituted-2,3-dihydro-1H-quinolin-4-ones by acid catalyzed cyclization of 2-(3'-hydroxypropynyl)anilines. These substrates can be prepared from readily available 2-bromo-, 2-iodo- and 2-trifluoro anilines or $N$-acylanilines via Sonogashira coupling, making the route attractive for accessing this class of heterocyclic which is found in many biologically active substances. For the free aniline substrates ring-closure is postulated to comprise Rupe rearrangement/Donnelly-Farrell cyclization whereas for the $N$-acylanilines it comprises Rupe rearrangement/acetamide hydrolysis/Donnelly-Farrell cyclization.

Supporting Information for this article is available online at [http://www.thieme-connect.de/ejournals/toe/synlett](http://www.thieme-connect.de/ejournals/toe/synlett).

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(22) Although we did not explore this, it is also possible to synthesize 2-alkynylanilines directly from anilines by C-H activation at the 2-position, see: Tobisu, M.; Ano, Y.; Chatani, N. Org. Lett. 2009, 9, 3250-3252.
General procedure for the Sonogashira couplings with 2-methyl-3-butyln-2-ol (2a): The iodo-, bromo- or triflate-aniline was dissolved in Et₃N/pyridine (1:1, 0.1 M) and nitrogen was bubbled through for 10 min at room temperature. 2-Methyl-3-butyln-2-ol (2a, 1.5 eq) was added and the solution was stirred for 10 min with nitrogen bubbling through. CuI (0.05 eq), PPh₃ (0.5 eq) and (PPh₃)₂PdCl₂ (0.05 eq) were then added, and the resulting suspension was heated at 90 °C for 1.5–3 h (see Table 1). The reaction mixture was cooled to rt and quenched with a saturated solution of NaCl. The mixture was then extracted twice with ethyl acetate, and the combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The desired products were purified by FC.

N-[2-(3-Hydroxy-3-methylbut-1-ynyl)-phenyl]acetamide (3a): colorless oil (76% yield); HR-MS (ESI) Calcd for C₁₃H₁₅NO₂Na: 240.1000, found 240.1001 (Δ 0.4 ppm); MS (ESI): m/z (%) 240 [MNa⁺] (95), 200 (100); ¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, J = 8.3, 1H; 6-H), 7.81 (br s, 1H; NH), 7.31 (dd, J = 1.3, 7.7, 1H; 3-H), 7.26 (td, J = 1.5, 8.3, 1H; 5-H), 6.96 (t, J = 7.4, 4-H), 2.15 (s, 3H; MeCONH), 1.61 (s, 6H; CMe₂OH); ¹³C NMR (101 MHz, CDCl₃) δ 168.4 (s; CO), 138.9 (s; Ar), 131.5 (d; Ar), 129.7 (d; Ar), 123.4 (d; Ar), 119.4 (d; Ar), 111.4 (s; Ar), 101.5 (s, 2C; C≡), 65.7 (s; CMe₂OH), 31.5 (q, 2C; CMe₂OH), 24.8 (q; MeCO); IR: νmax 3360, 2924, 2853, 2400, 1662, 1523, 1447 cm⁻¹.

General procedure for the acid catalyzed cyclization: Sonogashira coupling product 3a-h was dissolved in cHCl/H₂O (1:1, v/v; 0.1 M) and heated at 120 °C for 1.5–8 h (see table 4). The reaction mixture was then concentrated in vacuo. Water was then added followed by K₂CO₃ up to pH = 11. The mixture was extracted twice with ethyl acetate and the combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. Final quinolinones were purified by FC.

2,2-Dimethyl-2,3-dihydro-1H-quinolin-4-one (4a): yellow oil (70% yield); HR-MS (ESI) Calcd for C₁₁H₁₄NO: 176.1075, found 176.1071 (Δ –2.3 ppm); MS (ESI): m/z (%) 176 [M⁺] (78), 120 (100); ¹H NMR (400 MHz, CDCl₃) δ 7.83 (dd, J = 1.4, 7.9, 1H; Ar), 7.35 – 7.27 (m, 1H; Ar), 6.71 (m, J = 7.5, 1H; Ar), 6.63 (d, J=8.2, 1H; Ar), 4.18 (s, 1H; NH), 2.61 (s, 2H; 3-H), 1.35 (s, 6H; NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 194.0 (s; CO), 149.8 (s; Ar), 135.4 (d; Ar), 127.2 (d; Ar), 118.1 (d; Ar), 117.5 (d; Ar), 115.8 (s; Ar), 53.6 (s; 2-C), 50.6 (t, 3-C), 27.7 (q, 2C; Me); IR: νmax 3333, 2924, 2853, 1659, 1613, 1481 cm⁻¹.
Running title: 2-Substituted-2,3-dihydro-1H-quinolin-4-one Synthesis

GRAPHICAL ABSTRACT