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

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Dedicated to Prof. Alberto Brandi on the occasion of his 60th birthday.

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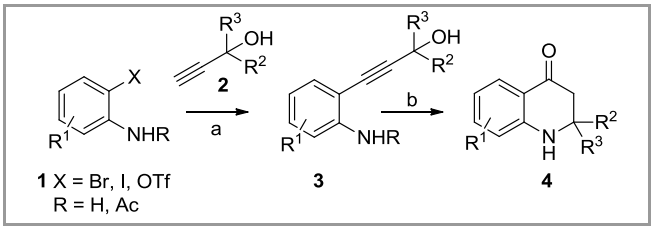
Abstract: A range of 2-substituted 2,3-dihydro-1*H*-quinolin-4-ones have been synthesized from anilines by a two-step process involving Sonogashira coupling with a propargyl alcohol then acid catalyzed cyclization of the resulting 2-(3'-hydroxypropynyl)anilines. The cyclization reaction appears to proceed *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, alkynes.

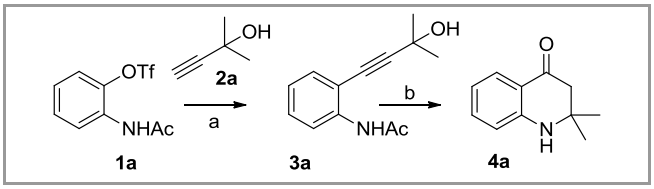
Quinolines and quinolinones constitute the core unit of numerous alkaloids and synthetic compounds with interesting pharmacological properties.[1,2] 2-Substituted 2,3-dihydro-1*H*-quinolin-4-ones have shown analgesic[3] and antimalarial[4] activity and have attracted attention recently as antimitotic 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-1*H*-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-1*H*-quinolin-4-ones **4** *via* a two-step process which starts from readily available 2-(pseudo)halogenated anilines **1**. The process involves Sonogashira coupling with a propargylic 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).



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

2-Methyl-3-butyn-2-ol (**2a**, R^2 = R^3 = 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 acetone.[19,20] It was in the context of the use of this reagent as a partner for Sonogashira coupling with 2-trifloxy-*N*-acetylaniline (**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-1*H*-quinolin-4-one (**4a**) in 98% yield after basic workup and chromatographic purification (Scheme 2).

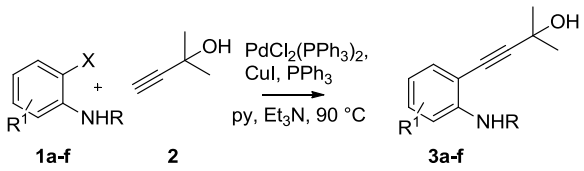


Scheme 2 Synthesis of 2,2-dimethyl-2,3-dihydro-1*H*-quinolin-4-one (**4a**). *Reagents and conditions*: a) 2-methyl-3-butyn-2-ol (**2a**), $PdCl_2(PPh_3)_2$, CuI, PPh_3, py, Et_3N, 90 °C, 3 h (76%); b) conc. HCl, H_2O, 120 °C , 1.5 h (98%).

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 (Ac_2O in AcOH) then *O*-triflation (Tf_2O, pyridine in CH_2Cl_2). Moderate to good yields were obtained for all these Sonogashira coupling reactions (Table 1).[22,28]

Table 1 Sonogashira Coupling to give 2-alkynylanilines **3**.



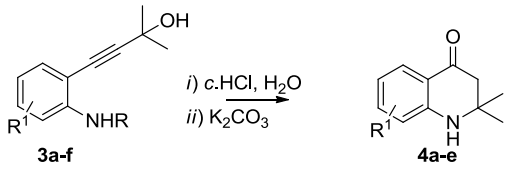
1a-f **2** **3a-f**

Entry	X	R	R_1	Time (h)	Yield (%)
1	OTf	Ac	H	3	76 (**1a** → **3a**)[a]
2	OTf	Ac	5-Cl	1.5	57 (**1b** → **3b**)
3	OTf	Ac	5-Me	2	43 (**1c** → **3c**)
4	Br	Ac	4-OCF_3	3	67 (**1d** → **3d**)
5	Br	H	4-CF_3	3	42 (**1e** → **3e**)
6	I	H	H	3	63 (**1f** → **3f**)

[a] as described in the text (Scheme 2).

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 *c*.HCl/water (1:1, v/v) followed by basic workup, as for the initial example described above (Table 2).

Table 2 Acid catalyzed ring-closure of 2-alkynylanilines **3** to give 2,3-dihydro-1*H*-quinolin-4-ones **4**.



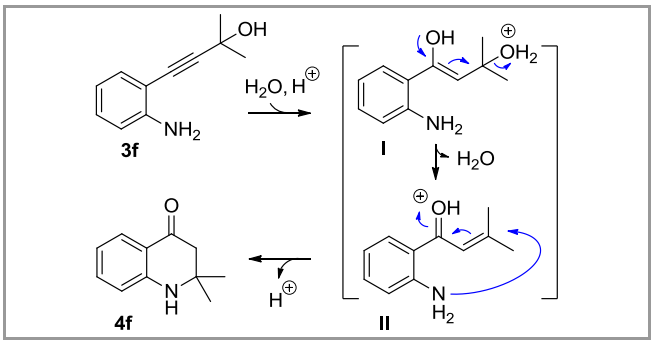
3a-f **4a-e**

Entry	R	R_1	Time (h)	Yield (%)
1	Ac	H	1	98 (**3a** → **4a**)[a]
2	Ac	5-Cl	1.5	68 (**3b** → **4b**)
3	Ac	5-Me	4	70 (**3c** → **4c**)
4	Ac	4-OCF_3	8	60 (**3d** → **4d**)
5	H	4-CF_3	4	35 (**3e** → **4e**)
6	H	H	1.5	70 (**3f** → **4a**)

[a] as described in the text (Scheme 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).[29]

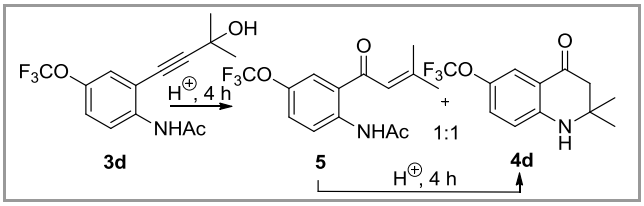
We envisage that the cyclization, in the case of the free aniline **3f**, probably proceeds *via* regioselective hydrative/dehydrative rearrangement of the alkyne moiety, possibly *via* aldol **I**, to give α,β-unsaturated ketone **II**, then 6-*endo*-trig Michael-type ring-closure to give quinolin-4-one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



Scheme 3 Proposed mechanism for the acid catalyzed cyclization.

The acid catalyzed rearrangement of propargylic alcohols to α,β-unsaturated ketones (*cf.* **3f** → **II**) is known as a Rupe rearrangement[23] and may proceed as indicated in Scheme 3 or *via* an allenyl intermediate with assistance from the 2-amino group.[24] The cyclization of 2-aminochalcones to 2-aryl-2,3-dihydro-1*H*-quinolin-4-ones (*cf.* **II** → **4f**) is also well-documented[25] and the acid catalyzed variant is sometimes referred to as a Donnelly-Farrell cyclization.[11,12] 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).

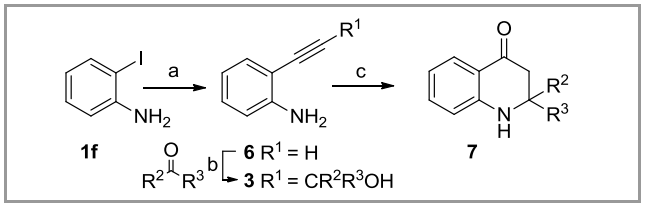


Scheme 4 Isolation of α,β-unsaturated ketone intermediate **5** during a cyclization reaction to give quinolin-4-one **4d**.

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-iodoaniline (**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^3 = Ph) in 26% unoptimized yield. Reaction with acetophenone

required transmetallation to the organocerate ($CeCl_3$)[26,27] 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, $PdCl_2(PPh_3)_2$, CuI, PPh_3, iPr_2NH, 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_2O, 120 °C , 1.5 h (**7a**, R^2 = H, R^3 = Ph, 50%; **7b**, R^2 = Me, R^3 = Ph, 26%.

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-1*H*-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-trifloxy anilines or *N*-acetylanilines *via* Sonogashira coupling, making the route attractive for accessing this class of heterocycle 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*-acetylanilines it comprises Rupe rearrangement/acetamide hydrolysis/Donnelly-Farrell cyclization.

Supporting Information for this article is available online at http://www.thieme-connect.de/ejournals/toc/synlett.

Acknowledgment

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(28) General procedure for the Sonogashira couplings with 2-methyl-3-butyn-2-ol (**2a**): The iodo-, bromo- or triflate-aniline was dissolved in Et_3N/pyridine (1:1, 0.1 M) and nitrogen was bubbled through for 10 min at room temperature. 2-Methyl-3-butyn-2-ol (**2a** 1.5 eq) was added and the solution was stirred for 10 min with nitrogen bubbling through. CuI (0.05 eq), PPh_3 (0.5 eq) and $(PPh_3)_2PdCl_2$ (0.05 eq) were then added, and the resulting suspension was heated at 90 ºC 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 $MgSO_4$, 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 $C_{13}H_{15}NO_2Na$: 240.1000, found 240.1001 (Δ 0.4 ppm); MS (ESI): *m*/*z* (%) 240 [MNa^+] (95), 200 (100); ^{1}H NMR (400 MHz, $CDCl_3$) 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; *Me*CONH), 1.61 (s, 6H; C*Me*$_2$OH); ^{13}C NMR (101 MHz, $CDCl_3$) 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; *C*Me$_2$OH), 31.5 (q, 2C; C*Me*$_2$OH), 24.8 (q; *Me*CO); IR: ν_{max} 3360, 2924, 2853, 2400, 1662, 1523, 1447 cm^{-1}.

(29) General procedure for the acid catalyzed cyclization: Sonogashira coupling product **3a-h** was dissolved in *c*HCl/H_2O (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 K_2CO_3 up to pH = 11. The mixture was extracted twice with ethyl acetate and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Final quinolinones were purified by FC.

2,2-Dimethyl-2,3-dihydro-1*H*-quinolin-4-one (**4a**): yellow oil (70% yield); HR-MS (ESI) Calcd for $C_{11}H_{14}NO$: 176.1075, found 176.1071 (Δ –2.3 ppm); MS (ESI): *m*/*z* (%) 176 [MH^+] (78), 120 (100); ^{1}H NMR (400 MHz, $CDCl_3$) 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; $NC(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 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: ν_{max} 3333, 2924, 2853, 1659, 1613, 1481 cm^{-1}.

Running title: 2-Substituted-2,3-dihydro-1*H*-quinolin-4-one Synthesis

GRAPHICAL ABSTRACT