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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Received 14 December 2010

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

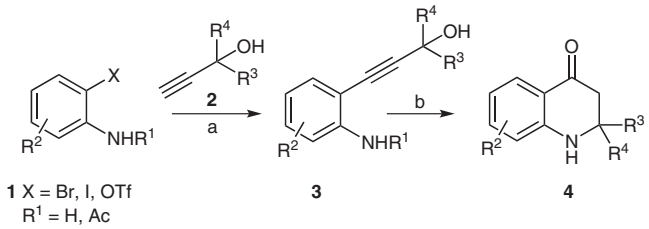
Abstract: A range of 2-substituted 2,3-dihydro-1*H*-quinolin-4-ones have been synthesized from anilines by a two-step process involving Sonogashira coupling with a propargyl alcohol then acid-catalyzed cyclization of the resulting 2-(3′-hydroxypropynyl)anilines. The cyclization reaction appears to proceed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

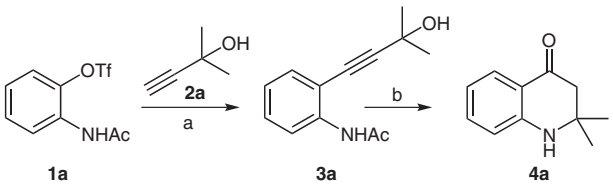
Quinolines and quinolinones constitute the core unit of numerous alkaloids and synthetic compounds with interesting pharmacological properties.[1,2] 2-Substituted 2,3-dihydro-1*H*-quinolin-4-ones have shown analgesic[3] and antimalarial[4] activity and have attracted attention recently as antimitotic 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).

2-Methylbut-3-yn-2-ol (**2a**, $R^3 = R^4 = Me$) has been used widely as a readily available, cheap, nonvolatile 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 concentrated HCl–H_2O (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 1 Synthesis of 2,3-dihydro-1*H*-quinolin-4-ones **3**: (a) Sonogashira coupling, (b) acid-catalyzed cyclization



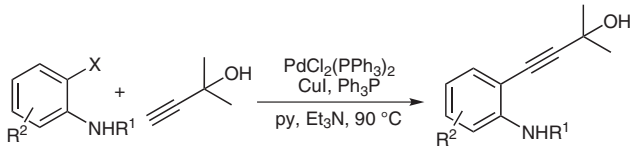
Scheme 2 Synthesis of 2,2-dimethyl-2,3-dihydro-1*H*-quinolin-4-one (**4a**). *Reagents and conditions*: (a) 2-methylbut-3-yn-2-ol (**2a**), $PdCl_2(PPh_3)_2$, CuI, Ph_3P, pyridine, Et_3N, 90 °C, 3 h (76%); (b) concd HCl, H_2O, 120 °C, 1.5 h (98%).

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-methylbut-3-yn-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

SYNLETT 2011, No. 2, pp 0241–0244
Advanced online publication: 10.01.2011
DOI: 10.1055/s-0030-1259309; Art ID: G34610ST

Table 1 Sonogashira Coupling To Give 2-Alkynylanilines **3**[28]



1a–f 2 3a–f

Entry	X	R^1	R^2	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-F_3CO	3	67 (**1d** → **3d**)
5	Br	H	4-F_3C	3	42 (**1e** → **3e**)
6	I	H	H	3	63 (**1f** → **3f**)

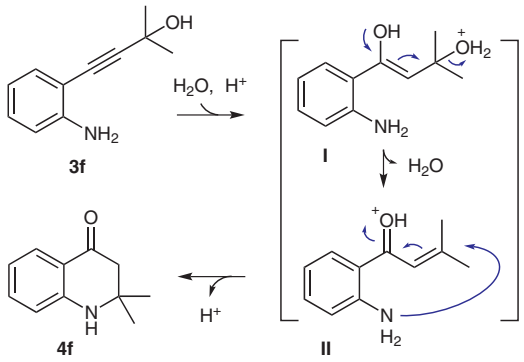
[a] As described in the text (Scheme 2).

yields were obtained for all these Sonogashira coupling reactions (Table 1).[22,28]

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 concentrated HCl–H_2O (1:1, v/v) followed by basic workup, as for the initial example described above (Table 2).[29]

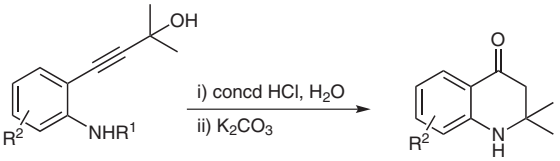
The electron demand of substituents on the aryl ring appeared to have no significant effect on the cyclization process. The yields ranged from 60–98% with the exception of the 4-trifluoromethyl derivative **3e** which was obtained in just 35% yield. Both the aniline **1e** and the 2-alkynylaniline **3e** 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 alkyne moiety, possibly via aldol **I**, to give α,β-unsaturated ketone **II**,



Scheme 3 Proposed mechanism for the acid-catalyzed cyclization

Table 2 Acid-Catalyzed Ring Closure of 2-Alkynylanilines **3** To Give 2,3-Dihydro-1*H*-quinolin-4-ones **4**[29]



3a–f 4a–e

Entry	R^1	R^2	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-F_3CO	8	60 (**3d** → **4d**)
5	H	4-F_3C	4	35 (**3e** → **4e**)
6	H	H	1.5	70 (**3f** → **4a**)

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

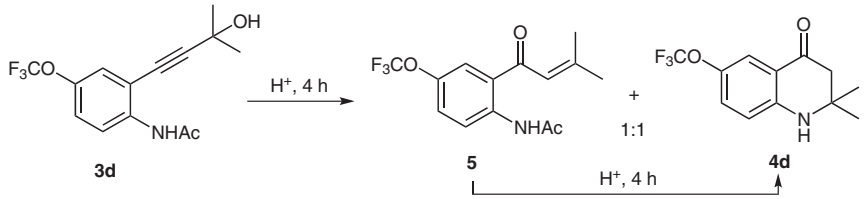
then 6-*endo*-trig Michael-type ring closure to give quinolin-4-one **4f** (Scheme 3).

The acid-catalyzed rearrangement of propargylic alcohols to α,β-unsaturated ketones (cf. **3f** → **II**) is known as a Rupe rearrangement[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 four hours of an approximately 1:1 mixture of the expected quinolin-4-one **4d** and the *N*-acetyl-α,β-unsaturated ketone **5** (Scheme 4).

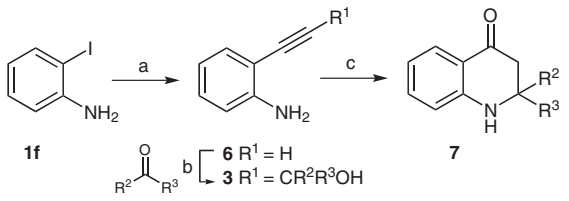
When compound **5** was resubjected to the same conditions for additional four hours, complete conversion into quinolin-4-one **4d** was achieved. Direct conversion of anilide **3d** into quinolin-4-one **4d** required eight hours (Table 2, entry 5, 60% yield).

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-ethynylaniline **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%



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

unoptimized yield. Reaction with acetophenone required transmetalation 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 5 *Reagents and conditions*: (a) *i*. TMS-acetylene, $PdCl_2(PPh_3)_2$, CuI, PPh_3, *i*-Pr_2NH, toluene, r.t., 16 h; *ii.* KOH, MeOH–H_2O, r.t., 3 h (38%); (b) *n*-BuLi, THF, –5 °C to r.t. (**6** → **3g**, R^2 = H, R^3 = Ph, 26%) or *n*-BuLi, $CeCl_3$, THF, –5 °C to r.t. (**6** → **3h**, R^2 = Me, R^3 = Ph, 60%); (c) concd 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 concd HCl–H_2O (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-trifloxyanilines 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 comprising full experimental details and spectroscopic data is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The MRC and CRUK (Grant C2536/A7602) are thanked for grant support (J.J.P.S., F.P.). We are grateful also to the Nuffield Foundation and the EU Erasmus program for provision of project support (W.H.N., C.B.).

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(28) **General Procedure for the Sonogashira Couplings with 2-Methylbut-3-yn-2-ol (2a)**
The iodo-, bromo-, or triflate-substituted aniline was dissolved in Et_3N–pyridine (1:1, 0.1 M), and nitrogen was bubbled through for 10 min at r.t. 2-Methylbut-3-yn-2-ol (**2a** 1.5 equiv) was added, and the solution was stirred for 10 min with nitrogen bubbling through. CuI (0.05 equiv), Ph_3P (0.5 equiv), and $(PPh_3)_2PdCl_2$ (0.05 equiv) 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 r.t. and quenched with a sat. solution of NaCl. The mixture was then

extracted twice with EtOAc, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The desired products were purified by flash chromatography.

***N*-[2-(3-Hydroxy-3-methylbut-1-ynyl)phenyl]acetamide (3a)**

Colorless oil (76% yield). ESI-HRMS: *m/z* calcd for $C_{13}H_{15}NO_2Na$: 240.1000; found: 240.1001 (Δ = 0.4 ppm). ESI-MS: *m/z* (%) = 240 (95) [MNa^+], 200(100). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.3 Hz, 1 H, 6-H), 7.81 (br s, 1 H, NH), 7.31 (dd, *J* = 7.7, 1.3 Hz, 1 H, 3-H), 7.26 (td, *J* = 8.3, 1.5 Hz, 1 H, 5-H), 6.96 (t, *J* = 7.4 Hz, 4-H), 2.15 (s, 3 H, CH_3CONH), 1.61 [s, 6 H, $C(CH_3)_2OH$]. ^{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, 2 C, C≡), 65.7 [s, $C(CH_3)_2OH$], 31.5 [q, 2 C, $C(CH_3)_2OH$], 24.8 (q, CH_3CO). 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 concd HCl–H_2O (1:1, v/v; 0.1 M) and heated at 120 °C for 1.5–8 h (see Table 2). 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 EtOAc, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Final quinolinones were purified by flash chromatography.

2,2-Dimethyl-2,3-dihydro-1*H*-quinolin-4-one (4a)

Yellow oil (70% yield). ESI-HRMS: *m/z* calcd for $C_{11}H_{14}NO$: 176.1075; found: 176.1071 (Δ = –2.3 ppm). ESI-MS: *m/z* (%) = 176 (78) [MH^+], 120 (100). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 7.9, 1.4 Hz, 1 H, Ar), 7.35–7.27 (m, 1 H, Ar), 6.71 (m, 1 H, Ar), 6.63 (d, *J* = 8.2 Hz, 1 H, Ar), 4.18 (s, 1 H, NH), 2.61 (s, 2 H, 3-H), 1.35 [s, 6 H, $NC(CH_3)_2$]. ^{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, 2 C, CH_3). IR: ν_{max} = 3333, 2924, 2853, 1659, 1613, 1481 cm^{-1}.