

Treatment of *o*-alkynylphenylsydnones with acids: a new route to 3-arylcinnolines

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DOI: <http://dx.doi.org/10.3998/ark.5550190.p008.474>

Abstract

Treatment of *o*-alkynylphenylsydnones with triflic acid or trifluoroacetic acid provides a novel avenue to 3-arylcinnolines. With triflic acid the best results were obtained at room temperature with alkynylsydnones containing an electron-withdrawing group (or an H) whereas with TFA an electron-donating group and reflux conditions were required.

Keywords: Cinnolines, fused-ring sydnones, acid-induced ring cleavage

Introduction

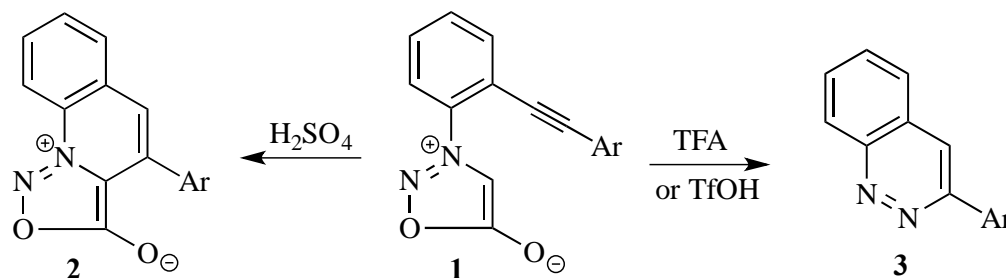
Sydnones are dipolar, nonbenzenoid aromatic compounds, which are the most studied members of the class of heterocycles known as mesoionic.¹ Since their first preparation in 1935,² on account of their intriguing structural, chemical and biological properties,¹ a large number of sydnones have been reported. The most common avenue to modification of their properties has been *via* substitution at the C-4 position and this has been achieved by electrophilic aromatic substitution,³ lithiation^{4,5} or other metallation^{6,7} followed by reaction with an electrophile.

For some years, we have been interested in the preparation of fused-ring sydnones such as **2** with a view to exploring the modification of sydnone properties thus engendered.^{8,9} In this regard, it has been speculated by Coburn and O'Donnell that, in fused-ring sydnones, the stabilization achieved by the additional conjugation from the sydnone ring "might be of practical significance, since many of the simple sydnones with potentially useful biological activities lack thermal stability and frequently darken upon exposure to light and air".¹⁰ While, previously, sydno[3,4-*a*]quinoxalines were prepared by Coburn and O'Donnell using a lithiation protocol,¹⁰ for us the most effective, general strategy to fused-ring sydnones has been to generate an electrophilic side-chain that can be trapped by the heteroaromatic sydnone ring. In this fashion, we have synthesized a sydno[4,3-*c*]benzotriazine,⁹ several 4-arylaminosydno[3,4-*a*]quinoxalines,⁸ and a limited number of 5-substituted sydno[3,4-*a*]quinazolines.^{11,12} In order to

explore further this concept, and extend the limited range of fused-ring sydnone available, we elected to examine the reactions of *o*-alkynylphenylsydnone **1** (prepared by Sonogashira coupling with *o*-iodophenylsydnone)¹³ with various acids in the expectation that sydnoquinoline derivatives **2** would result. The present manuscript reports our findings from this study.

Results and Discussion

Our first effort to effect cyclization of the sydnone alkynes **1** to the desired sydnoquinolines **2** was to examine the efficacy of concentrated sulfuric acid in this regard. While reaction of **1a** with sulfuric acid did lead to the corresponding fused-ring sydnone **2a** (Table 1, entry 1) the extremely low yield led us to consider alternative avenues. We postulated that this issue could be alleviated by the use of an organic acid and, accordingly, we explored the use of trifluoromethanesulfonic acid (TfOH) and trifluoroacetic acid (TFA) as acid replacements. Unexpectedly, treatment of alkynylsydnone **1** with TfOH or TFA resulted in the isolation of 3-arylcinnolines **3** in 60-86% yield. With TfOH, the reaction was effected in 15 minutes at room temperature and the best results were obtained with those alkynylsydnone containing electron-withdrawing moieties (or an H) attached to the alkynyl aryl group (**1a-c**, entries 2-4). In contrast, TFA, the weaker acid, required reflux conditions for 3-6 hours and a donating group attached to the alkynyl aryl group (**1d-f**, entries 5-7) to effect the transformation.



Scheme 1

Table 1. Reactions of *o*-alkynylphenylsydnone **1** with H_2SO_4 , TFA or TfOH

Entry	Reactant	Ar	Acid	Product	Yield (%)	Mp °C	Lit. Mp °C
1	1a	Ph	H_2SO_4	2a	22	244-6	-
2	1a	Ph	TfOH	3a	72	115-6	118.5-19 ¹⁴
3	1b	4-BrC ₆ H ₄	TfOH	3b	60	141-2	Ref. ¹⁵
4	1c	4-ClC ₆ H ₄	TfOH	3c	69	142-3	146.5-8 ¹⁶
5	1d	4-MeOC ₆ H ₄	TFA	3d	82	104-5	105-6 ¹⁷
6	1e	4-MeC ₆ H ₄	TFA	3e	86	121-2	101-3 ¹⁷
7	1f	4-PnC ₆ H ₄	TFA	3f	77	71-2	-

Undoubtedly, the mechanism of the reaction involves hydrolysis of the sydnone ring to a hydrazine, acid-catalyzed cyclization of the latter to the alkyne and subsequent oxidation in air. Acid-induced hydrazine formation from sydnones has been known since 1935,² however, the utility of *ortho*-substituted arylsydnones as masked hydrazines for heterocycle formation has been utilized only infrequently. Indeed, to the best of our knowledge, apart from our study of such transformations in 1992,¹⁸ there has been no systematic examination of this concept. The present findings exhibit further the utility of stable, crystalline *o*-substituted arylsydnones as valuable precursors to useful heterocycles and, given the rather efficient avenues to the alkynylsydnone precursors,¹³ may find considerable utility.

Substituted cinnolines often exhibit interesting bioactivity¹⁹ and hitherto have been prepared by a variety of methods, primary among which are intramolecular cyclizations such as the von Richter synthesis (cyclization of an arenediazonium species onto an *o*-alkyne)²⁰ and avenues involving aryl hydrazines,²¹ aryl hydrazones^{22,23} and nitriles.²⁴ More recently, valuable extensions to these routes have been developed using copper-catalyzed coupling protocols.^{15,17} In general, 3-arylcinnolines have been prepared using one or other of the aforementioned approaches^{16,17} and methods for the synthesis of cinnolines, in general, have been reviewed.²⁵

Conclusions

A convenient synthesis of 3-arylcinnolines **3** from *o*-alkynyl sydnones **1** has been developed using either treatment with trifluoroacetic acid or triflic acid, depending on the nature of the alkynyl sydnone employed. A novel fused-ring sydnone **2a** was obtained in low yield from one alkynylsydnone **1a**. It is planned to examine further both synthetic avenues (to **2** or **3**) in order to better delineate the scope and limitations of the procedures.

Experimental Section

General. The *o*-alkynylphenylsydnone **1** starting materials were prepared as reported previously.¹³ Melting points were determined on a Mel-Temp melting point device and remain uncorrected. Infrared spectra were performed on a KBr salt plate and were taken on a Nicolet 6700 FTIR. NMR spectra were obtained on a Bruker Advance 300 MHz NMR in CDCl₃ and are reported relative to tetramethylsilane as an internal standard. Column chromatography was accomplished either manually or on an Isco CombiFlash Separator System Sg100c. Thin layer chromatographic assessments were performed on silica gel. Elemental analyses were determined by Midwest Microlab LLC, Indianapolis, Indiana.

3-Hydroxy-4-phenyl[1,2,3]oxadiazolo[3,4-*a*]quinolin-10-ium inner salt (2a). Under an atmosphere of nitrogen, 3-[2-(phenylethynyl)phenyl]sydnone (**1a**) (0.10 g, 0.38 mmol), was

added to dry, conc H₂SO₄ (2 mL) frozen at -40 °C. The flask was allowed to warm slowly to room temperature whereupon the reaction was poured carefully onto crushed ice (~15 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The combined extracts were dried (MgSO₄), filtered and the solvent removed *in vacuo*. Column chromatography (silica gel, CH₂Cl₂) gave a solid, which, upon recrystallization (CH₂Cl₂/hexanes) afforded the title compound as light yellow needles (0.012 g, 12%), mp 250-251 °C; IR (KBr): 3058 (w), 1742 (vs), 1722 (s), 1560 (m), 1497 (m), 748 (s), 693 (m) cm⁻¹; ¹H NMR (DMSO-*d*₆, 100 °C): δ 8.7-8.4 (m, 9H); ¹³C NMR (DMSO-*d*₆, 100 °C): 164.1 (C=O), 134.0, 133.5, 132.0, 130.6, 129.9, 129.8, 129.5, 129.1, 128.7, 127.5, 121.9, 116.4 ppm. Elemental analysis: calculated for C₁₆H₁₀N₂O₂ (262.26) C: 73.27, H: 3.84, N: 10.68. Found C: 72.99, H: 3.83, N: 10.57 %.

General procedure for the synthesis of 3-arylcinnolines 3a-c from the corresponding *ortho*-alkynylphenylsydnones 1a-c using trifluoromethanesulfonic acid. Freshly distilled CF₃SO₃H (0.5 mL, 0.85 g, 0.006 mol) was added dropwise to a solution of the *ortho*-alkynyl sydnone **1a-c** (0.10 g) dissolved in CH₂Cl₂ (20 mL). After 15 min, the reaction was poured carefully onto crushed ice (~15 mL), basified with NaHCO₃, extracted with CH₂Cl₂ (3 × 20 mL), dried (MgSO₄) and the solvent removed *in vacuo*. Column chromatography on silica gel (CH₂Cl₂ to CH₂Cl₂/1% THF as eluent), followed by recrystallization from Et₂O or CH₂Cl₂/hexanes, afforded **3a-c** in 60-72% yield.

General procedure for the synthesis of 3-arylcinnolines 3d-f from the corresponding *ortho*-alkynylphenylsydnones 1d-f using trifluoroacetic acid. The *ortho*-alkynylsydnone **1d-f** (0.10 g) was dissolved in CF₃CO₂H (5 mL) and gently heated at reflux for 3-6 h. Subsequently, the reaction was cooled, diluted with CH₂Cl₂ (10 mL), and evaporated to dryness *in vacuo*. The residue was taken up in CH₂Cl₂ (30 mL), washed with saturated NaHCO₃ solution (3 × 10 mL), dried (MgSO₄) and the solvent removed *in vacuo*. Column chromatography (silica gel, CH₂Cl₂ to CH₂Cl₂/1% THF as eluent), followed by recrystallization from CH₂Cl₂/hexanes, Et₂O or Et₂O/hexanes afforded **3d-f** in 77-86% yield.

3-(4-Pentylphenyl)cinnoline (3f). Reaction of 3-(2-(4-pentylphenylethynyl)phenyl)sydnone (**1f**) with CF₃CO₂H in the general procedure for 6 h gave after work-up yellow-orange crystals, mp 71-72 °C; IR (KBr): 3046 (w), 2950 (m), 2921 (vs), 2849 (m), 1434 (m), 1322 (m), 1178 (m), 837 (m), 746 (m) cm⁻¹; ¹H NMR (CDCl₃): δ 8.53 (d, *J* = 9 Hz, 1H), 8.19-8.12 (m, 3H), 7.85-7.68 (m, 3H), 7.37 (d, *J* = 9 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.71-1.66 (m, 2H), 1.38-1.34 (m, 2H), 0.94-0.89 (m, 4H); ¹³C-NMR (CDCl₃): 153.8, 150.0, 144.8, 134.6, 131.4, 130.2, 130.1, 129.4, 127.4, 127.2, 126.7, 118.5, 36.0, 31.8, 31.3, 22.8, 14.3 ppm. Elemental analysis: calc. for C₁₅H₂₀N₂ (276.38) C: 82.57, H: 7.29, N: 10.14. Found C: 82.22, H: 7.21, N: 10.12%.

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