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ARTICLE

Synthesis of 3-substituted quinolin-2(1*H*)-ones via cyclization of *o*-alkynylisocyanobenzenes

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Ailada Charoenpol, Jatuporn Meesin, Onnicha Khaikate, Vichai Reutrakul, Manat Pohmakotr, Pawaret Leowanawat, Darunee Soorukram and Chutima Kuhakarn*

A facile synthesis of various functionalized 3-substituted quinolin-2(1*H*)-ones through Ag(I) nitrate catalyzed cyclization of *o*-alkynylisocyanobenzenes is described. The reaction allows rapid and convenient access to 3-substituted quinolin-2(1*H*)-ones scaffolds in moderate to good yields.

Introduction

Quinolin-2(1*H*)-ones have proven to be an important class of attractive scaffold being found in biologically active natural products and pharmaceutically important compounds as well as valuable intermediates in organic synthesis.[1-2] In particular, quinolin-2(1*H*)-one core is present in anti-tumor agents,[3] endothelin receptor antagoists,[4] angiotensin II receptor antagonists,[5] antiplatelet agents,[6] and antibiotics.[7] Highlights on biologically active compounds bearing quinolin-2(1*H*)-one core are shown in Fig. 1. In addition, quinolin-2(1*H*)-ones were found being used as versatile synthetic intermediates in organic synthesis.[8] Consequently, the synthetic routes to access quinolin-2(1*H*)-one derivatives have drawn enormous attention and a number of approaches were addressed.[9]

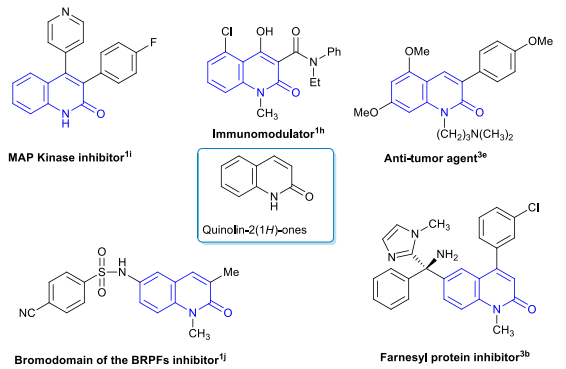


Fig. 1. Examples of biologically active compounds bearing quinolin-2(1*H*)-one core.

Isocyanobenzenes or arylisonitriles are one of the important synthetic synthons for the synthesis of nitrogen-containing heterocyclic compounds via anionic cyclization in the presence of nucleophiles, Lewis acid mediated cyclization reactions and radical mediated cyclization reactions.[10] In recent years, there have been numerous studies on cascade cyclization reaction on to *o*-arylisocyanobenzenes, leading to the rapid assembly of functionalized phenanthridines.[11-12] On the other hands, fewer reports were addressed on ring formation with *o*-alkynylisocyanobenzenes.[13]

Results and discussion

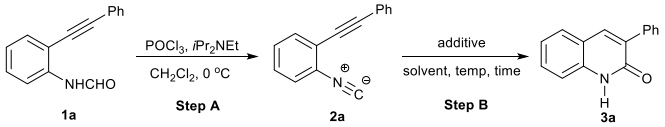
In continuation of our interest in the synthesis of functionalized nitrogen-containing heterocycles,[14] we report herein the synthesis of 3-substituted quinolin-2(1*H*)-ones through cyclization of *o*-alkynylisocyanobenzenes catalyzed by $AgNO_3$. We began our study by screening the optimized reaction conditions employing *o*-(phenylethynyl)isocyanobenzene (**2a**) as a model substrate (Table 1). The unstable *o*-(phenylethynyl)isocyanobenzene (**2a**) was readily prepared from its corresponding *N*-(2-(phenylethynyl)phenyl)formamide (**1a**) by following the previously reported procedure with slight modification in the aqueous work-up step.[13] Thus, after aqueous work-up (washed with saturated $NaHCO_3$ solution and evaporated to dryness), the crude mixture of **2a** was diluted with EtOAc and the solution was passed through a short path alumina (type E) column eluted with EtOAc. After removal of the solvent, the crude compound **2a** (^{1}H NMR analysis) was used for screening of the reaction conditions for its conversion to the corresponding 3-phenylquinolin-2(1*H*)-one (**3a**). It is worth to mention here that significant amount of 2-chloro-3-phenylquinoline was observed and lower yields of 3-substituted quinolin-2(1*H*)-ones were obtained if the crude mixture of **2a** was not filtered through an alumina column prior to the reaction. Initially, upon treatment of **2a** with $AgNO_3$ (5 mol%) using water as the solvent at 80 $^{\circ}$C for 2 h, the desired product **3a** was isolated in 15% yield after chromatographic purification (Table 1, entry 1). Next, a few solvents

Department of Chemistry and Center of Excellence for Innovation in Chemistry (PERCH-CIC), Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand. Email: chutima.kon@mahidol.ac.th

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

(THF, CH_3CN, $ClCH_2CH_2Cl$ and DMF) were screened (Table 1, entries 2–5). Delightfully, when the reaction was performed in DMF, **3a** was obtained in the moderate yield (53% yield). Efforts to use water as a co-solvent was next evaluated. While the use of DMF:H_2O (2:1 v/v) deteriorated the reaction efficiency, the yield of **3a** was increased to 80% yield when the reaction of **2a** was carried out in DMF:H_2O (2:0.1 v/v) (Table 1, entries 6–7). Attempts to optimize the yield of **3a** by extending the reaction time or performing the reaction at higher temperature did not give satisfactory results (Table 1, entries 8–9). Other Ag(I) salts, including Ag_2CO_3, AgF, AgOAc, Ag_2O and $AgClO_4$, were also evaluated; all of those gave comparable results to those obtained from $AgNO_3$ (Table 1, entries 8–14). The use of other metal salts, i.e. $CuCl_2$, $Cu(OAc)_2$, CuBr , $ZnCl_2$, $FeCl_3$ as well as Brønsted acids (*p*TolSO$_3$H) in place of Ag(I) gave inferior results (Table 1, entries 15–20). In the absence of $AgNO_3$, although the reaction readily proceeded, the results obtained were less satisfactory (Table 1, entry 21). Attempts to perform the reaction under forcing conditions either by extended the reaction time (from 2 h to 4 h) or at elevated reaction temperature (from 80 ^oC to 100 ^oC and 120 ^oC) resulted in poorer yields of **3a** (Table 1, entries 22–24). After extensive experimentation, $AgNO_3$ was chosen to be used in the present work due to reduced cost of $AgNO_3$. Thus, the optimum reactions were to use $AgNO_3$ (5 mol%) in DMF:H_2O (2:0.1 v/v) at 80 ^oC for 2 h (Table 1, entry 7).

Table 1. Optimization of reaction conditions[a]

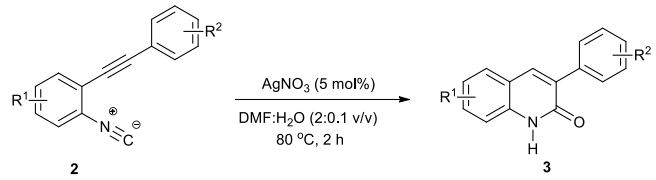


Entry	Additive (5 mol%)	Solvent (mL)	Temp (^oC)	Time (h)	Yield (%)[b]
1	$AgNO_3$	H_2O (2)	80	2	15
2	$AgNO_3$	THF (2)	80	2	-
3	$AgNO_3$	CH_3CN (2)	80	2	Trace
4	$AgNO_3$	$ClCH_2CH_2Cl$ (2)	80	2	17
5	$AgNO_3$	DMF (2)	80	2	53
6	$AgNO_3$	DMF:H_2O (2:1)	80	2	35
7	**$AgNO_3$**	**DMF:H_2O (2:0.1)**	**80**	**2**	**80**
8	$AgNO_3$	DMF:H_2O (2:0.1)	80	6	79
9	$AgNO_3$	DMF:H_2O (2:0.1)	100	2	78
10	Ag_2CO_3	DMF:H_2O (2:0.1)	80	2	78
11	AgF	DMF:H_2O (2:0.1)	80	2	79
12	AgOAc	DMF:H_2O (2:0.1)	80	2	77
13	Ag_2O	DMF:H_2O (2:0.1)	80	2	73
14	$AgClO_4$	DMF:H_2O (2:0.1)	80	2	80
15	$CuCl_2$	DMF:H_2O (2:0.1)	80	2	54
16	$Cu(OAc)_2$	DMF:H_2O (2:0.1)	80	2	67
17	CuBr	DMF:H_2O (2:0.1)	80	2	31
18	$ZnCl_2$	DMF:H_2O (2:0.1)	80	2	59
19	$FeCl_3$	DMF:H_2O (2:0.1)	80	2	28
20	*p*TsOH	DMF:H_2O (2:0.1)	80	2	38
21	-	DMF:H_2O (2:0.1)	80	2	54
22	-	DMF:H_2O (2:0.1)	80	4	62
23	-	DMF:H_2O (2:0.1)	100	2	42
24	-	DMF:H_2O (2:0.1)	120	2	33

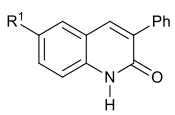
[a] Reaction conditions: **Step A**: A mixture of **1a** (0.5 mmol), ^{i}Pr$_2$NEt (8 equiv.) in CH_2Cl_2 (4 mL) was added dropwise $POCl_3$ (1.5 equiv) under Ar balloon at 0 ^oC; after conventional aqueous work-up, the crude mixture of **2a** was diluted with EtOAc and the solution was passed through a short path alumina (type E) column eluted with EtOAc; **Step B**: A crude mixture of **2a** from **Step A**, and metal salts, were stirred in solvent under indicated reaction conditions. [b] Isolated yields after chromatographic purification (SiO_2, column chromatography).

With the optimized reaction conditions in hands (Table 1, entry 7), the exploration of substrate scopes and limitations of the formation of 3-substituted quinolin-2(1*H*)-ones **3** via cyclization of *o*-alkynylisocyanobenzenes **2** were studied and the results are summarized in Scheme 1. First, substrates **2** with variation on substituents R^1 were evaluated. It was found that the reactions proceeded smoothly to yield the corresponding products **3b**–**h** in the range of 46–72% yields. Electronically different substituents (R^2) on the arylethynyl moiety (including *p*-CH_3, *p*-OCH_3, *p*-Br, *p*-Cl, *p*-F, *p*-NO_2, *m*-CH_3, *m*-Br, *m*-Cl, *m*-F) were well tolerated and gave the corresponding products **3i**–**r** in moderate to good yields (32–84% yields). Next, sterically hindrance position of the substituents was also highlighted. Although **3s** and **3t** were obtained in good yields, **3u**, and 3-(naphthalen-2-yl)quinolin-2(1*H*)-one (**3v**) were isolated in only moderate yields. The reaction can accommodate substrate bearing 2-thienyl substituent to yield **3w** in 75% yield. It is worth

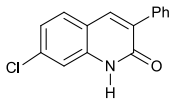
noting that aliphatic alkynyl substrates were good substrates and afforded the corresponding products **3x–z** and **3a'** in moderate yields (54–73% yields).



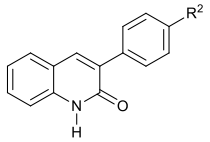
2 **3**



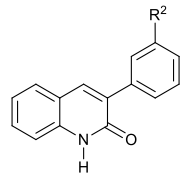
3a, R^1 = H (80%)
3b, R^1 = CH_3 (72%)
3c, R^1 = Br (72%)
3d, R^1 = Cl (61%)
3e R^1 = F (46%)
3f, R^1 = NO_2 (49%)
3g, R^1 = CF_3 (65%)



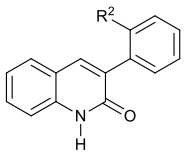
3h (55%)



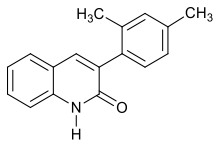
3i, R^2 = CH_3 (77%)
3j, R^2 = OCH_3 (73%)
3k, R^2 = Br (67%)
3l, R^2 = Cl (80%)
3m, R^2 = F (77%)
3n, R^2 = NO_2 (32%)



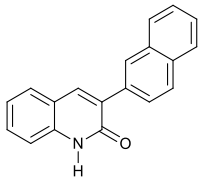
3o, R^2 = CH_3 (76%)
3p, R^2 = Br (71%)
3q, R^2 = Cl (84%)
3r, R^2 = F (73%)



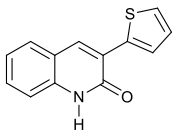
3s, R^2 = Cl (64%)
3t, R^2 = F (73%)



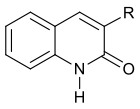
3u (34%)



3v (45%)



3w (75%)



3x, R = cyclopropyl (73%)
3y, R = $(CH_2)_3CH_3$ (68%)
3z, R^2 = $(CH_2)_2CH(CH_3)_2$ (72%)
3a', R^2 = $(CH_2)_5CH_3$ (54%)

Scheme 1 Synthesis of 3-substituted quinolin-2(1*H*)-ones **3**. Conditions: **2** [Freshly prepared from **1** (0.5 mmol)], $AgNO_3$ (5 mol%) in DMF (2 mL), H_2O (0.1 mL) at 80 °C, 2 h. In parentheses: isolated yields after chromatographic purification (SiO_2, column chromatography).

Although the exact reaction pathway is still not entirely clear, some control experiments were performed in order to shed some lights on the reaction mechanism. When D_2O was employed in place of water, a mixture of product **3b'** and **3a** (**3b'** : **3a** = 9 : 1, ^1H NMR analysis) was obtained (Scheme 2). Compound **3b'** was spectroscopically characterized (See Supplementary data for ^1H, ^{13}C, and HRMS data of **3b'**). The results obtained suggested that water served as a proton donor.

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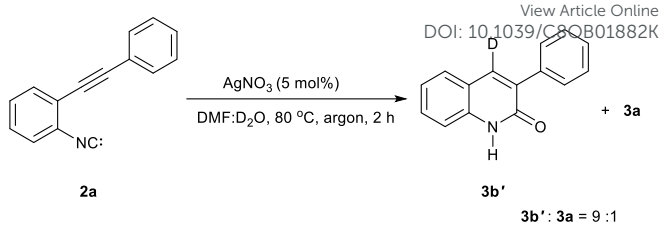
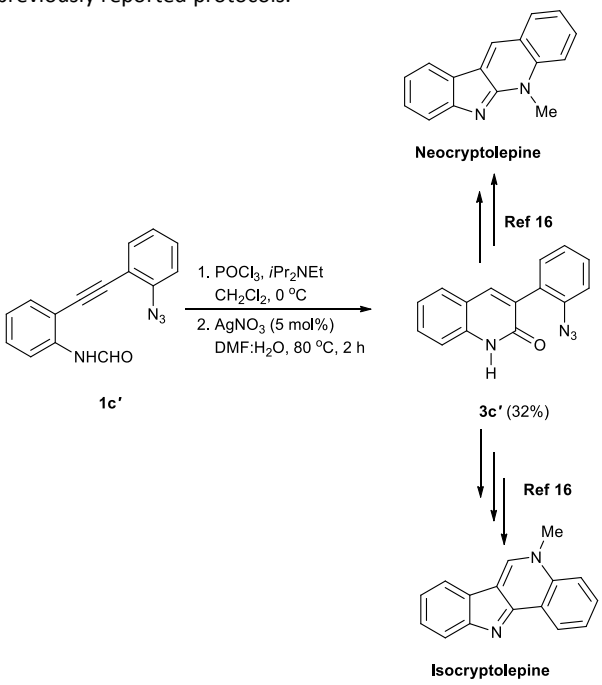


2a **3b'** **3b'** : **3a** = 9 :1

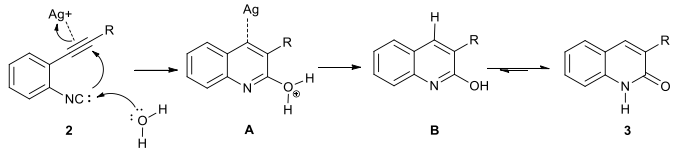
Scheme 2 The reaction of **2a** in DMF:D_2O.

To expand the synthetic utility of our developed synthetic protocol, the synthesis of **3c'**, which is a synthetic precursor of natural compounds, neocryptolepine (cryprotackieine) and isocryptolepine (cryptosanguinolentine),[15] previously isolated from *Cryptolepis sanguinolenta* (Lindl.) Schlachter (Periplocaceae) was demonstrated (Scheme 3). Under standard reaction conditions, **1c'** was employed to prepared **3c'** (32% yield). Then, **3c'** can be converted to neocryptolepine and isocryptolepine by the following previously reported protocols.[16]



Scheme 3 Synthetic application.

On the basis of the results obtained and the previously reported literature,[13] a plausible mechanism has been proposed as depicted in Scheme 4. Acting as an activator, Ag(I) initiates the reaction by chelation to the alkynyl moiety of **2**. At the same time, water acts as a nucleophile by addition to the terminal carbon of the isocyanide moiety in **2**. Cycloaddition of the resulting carbanion to the Ag(I)-chelated triple bond delivers adduct A. Subsequent protonation yields B with the release of Ag(I) ion. Finally, B undergoes tautomerization to give 3-substituted quinolin-2(1*H*)-ones **3**.



Scheme 4 Plausible mechanism.

Conclusions

In summary, a facile method for the formation of 3-substituted quinolin-2(1*H*)-ones through Ag(I)-mediated cyclization of *o*-alkynylisocyanobenzenes was accomplished. The reactions readily proceeded under open-flask conditions. Water was an oxygen and proton distributor in this transformation. The reaction can accommodate a wide variety of substrates bearing electronically and sterically different substituents to provide numerous 3-substituted quinolin-2(1*H*)-one derivatives in moderate to good yields.

Acknowledgements

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