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TBHP-promoted oxidative cyclization of o-alkynylquinoline aldehydes: Metal/additive-free domino synthesis of pyrano[4,3-*b*]quinolin-1-ones

Jay Bahadur Singh, Kalpana Mishra, Tanu Gupta, Radhey M. Singh *

Department of Chemistry, Centre of Advanced Study, Institute of Science, Banaras Hindu UniversityVaranasi, India

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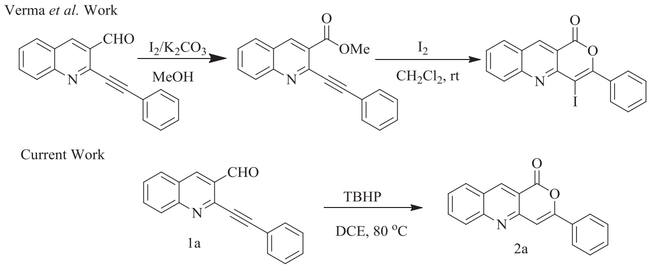
ABSTRACT

TBHP-promoted domino synthesis of pyrano[4,3-*b*]quinolin-1-ones is described from o-alkynylquinoline aldehydes. The radical reaction proceeded without metal and additive *via* oxidation of aldehydic C-H bond into C-OH bond followed by intramolecular 6-*endo-dig* cyclization. The probable mechanism is discussed.

Introduction

Development of new approaches for the synthesis of substituted quinolines and their carbo/hetero-annelated analogues has been of great interest to both synthetic and medicinal chemists because such moieties are present in various natural products along with broad spectrum of biological activities.[1] Among hetero-annelated quinolines, pyranoquinoline derivatives are important compounds because their structural units are component of many alkaloids isolated from Rutaceae family. Their derivatives possess wide range of applications as drugs, pharmaceuticals, agrochemicals and exhibit various biological activities including antifungal, anticoagulant, coronary constricting, optical brightening, antihistamine and antiallergic activity.[2] In spite of their vast biological activities, the methods reported particularly for synthesis pyranoquinolinones relative to pyranoquinoline are limited.[3] Although, the synthesis of 2-pyrone ring in isocoumarines has been reported from transition metals-catalyzed, electrophiles or Lewis acid-catalyzed cyclization reaction of o-alkynylaryl acid and ester derivatives.[4] Recently, Verma et al. have reported two steps synthesis pyrano [4,3-*b*] quinolinones from o-alkynylquinoline aldehydes involving oxidation of aldehydic group to ester followed by intramolecular cyclization using electrophile (Scheme 1).[5] However, one-pot synthesis of pyrano [4,3-*b*]quinolinones has rarely been explored.[6]



Scheme 1. Approaches for intramolecular cyclization.

In recent years, transformations of C-H bond into C-C and C-O bonds have attracted much interest because these minimize the synthetic steps in the reaction by avoiding prefunctionalized substrates.[7] Transition metal-catalyzed C-H bond functionalization and cross dehydrogenative coupling (CD C) have emerged as two efficient atom economic approaches for C-C and C-heteroatom bond formations. The CDC approach, particularly more attractive, has been extensively used for C-C bond formation from aldehyde because of higher atom economic reaction and minimize the waste.[8] In contrast, this approach has been less explored for C-O bond formation.[9] However, N-heterocyclic carbene (NHC)-catalyzed oxidations of aldehydes into acids, esters and amides have been reported in literatures.[10] Recently, metal/additive-catalyzed

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* Corresponding author.
E-mail address: rmohan@bhu.ac.in (R.M. Singh).

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TBHP oxidant has been reported for the oxidation of aldehydes into ester, perester and anhydride respectively.[11]

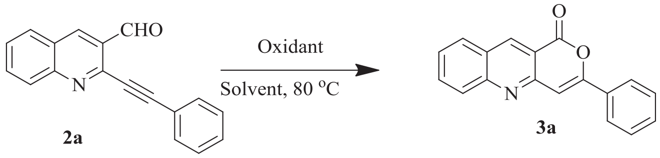
We have been involved from several years in exploring new methodology for the synthesis of nitrogen, oxygen and sulphar heterocycles-fused quinolines.[12] and recently, we have reported metal/additive-free TBHP promoted CDC reactions for the synthesis of indeno-/chromeno-annelated quinolines from o-aryl-/o-aryloxyquinoline aldehydes.[13]

However, cyclization reaction of o-alkynylquinoline aldehydes under similar conditions has not been attempted. In continuation of these studies, we now report TBHP oxidant promoted reaction of o-alkynylquinoline aldehydes in DCE affording the synthesis of pyrano[4,3-*b*]quinolin-1-ones *via* domino reaction.

Result and discussion

Initially, we began the reaction of o-alkynylquinoline-3-carboxaldehydes (**1a**)[14] with 70% aq. tert-butyl hydroperoxide (TBHP) for an aldehydic C-H bond oxidation. At first substrate **2a** was treated with 2 equiv. of TBHP in DCE solvent at 80 °C temperature in aerobic atmosphere for 24 h. The product was isolated in 40% yield along with substrate **1a** and characterized from spectral and analytical data as pyrano [4,3-*b*]quinolin-1-one **2a**. (Table 1 entry 1). Formation of **2a** suggests that reaction proceed through oxidation of aldehydic C-H bond to C-O bond followed by intramolecular cyclization *via* 6-endo-dig route of alkyne. Inspired by new result, we next examined a series of reactions to find the optimal reaction conditions. Results are summarized in Table 1. Increasing amount of aq. TBHP to 3 equiv., the reaction was incomplete after 24 h. However yield of **2a** increased to 58% (entry 2). Further, increasing TBHP to 4 equiv., the reaction was completed in 8 h and yield enhanced to 76% (entry 3). No enhancement in yield was found on further increasing mole equiv. of TBHP (entry 4). Next, various solvents such as CH_3CN, DMF, DMSO and H_2O were screened, and found lower yields in CH_3CN, DMSO and H_2O (entries 5, 7, 8), However only trace amount in DMF (entry 6). Using other oxidants like TBHP in (5.0–6.0 M) decane solvent, aq 30% H_2O_2 and Oxone, yield decreased to 49% in decane (entry 9). Reaction failed in H_2O_2 and trace amount with Oxone (entries 10, 11). Further, variation of temperatures did not improve the yield (entries 12, 13). Thus, the combination of 0.5 mmol of **1a** with 4.0 equiv. aq. TBHP in 2 mL DCE at 80 °C in aerobic atmosphere is considered optimal conditions which afforded the best yield of **2a**.

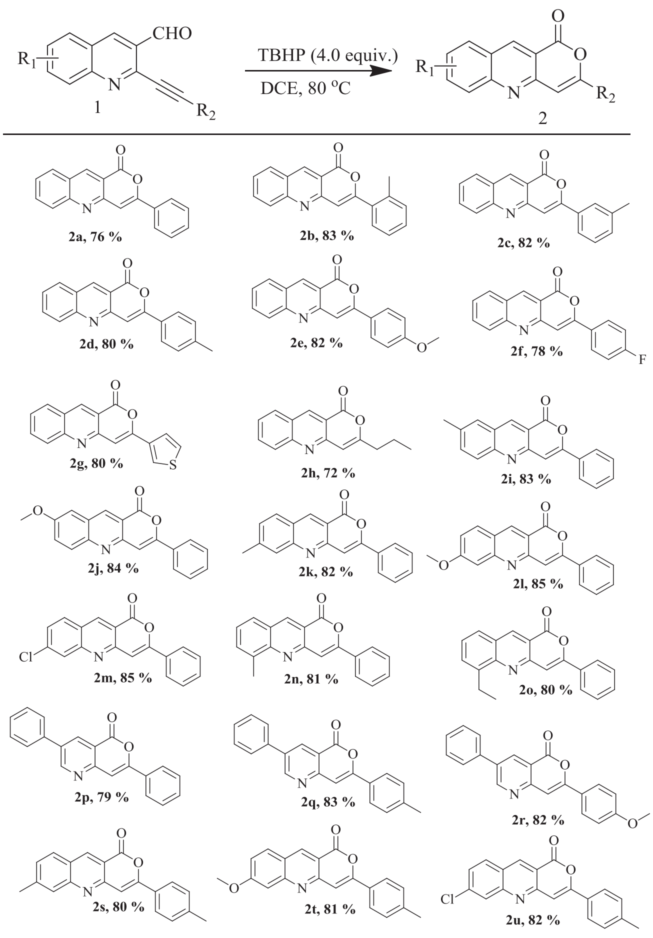
Table 1
Optimization of reaction conditions.[a]



Entry	Oxidant (equiv.)	Solvent	Time (h)	Yields[b] (%)
1	TBHP (2)	DCE	24	40 + SM
2	TBHP (3)	DCE	24	58 + SM
3	**TBHP (4)**	**DCE**	**8**	**76**
4	TBHP (5)	DCE	8	71
5	TBHP (4)	CH_3CN	10	60
6	TBHP (4)	DMF	12	Trace
7	TBHP (4)	DMSO	12	35
8	TBHP (4)	H_2O	12	40
9[c]	TBHP (4)	DCE	12	49
10	H_2O_2 (4)	DCE	12	Nr
11	Oxone (4)	DCE	12	Trace
12[d]	TBHP (4)	DCE	8	75
13[e]	TBHP (4)	DCE	12	40

[a] 1a (0.5 mmol.), Oxidant (4.0 equiv.), Solvent (2 mL), 80 °C.
[b] Isolated yield by column chromatography.
[c] TBHP solution (5.0–6.0 M in decane).
[d] Reaction was performed at 100 °C.
[e] Reaction was performed at 60 °C. SM = Starting Material.

Table 2
Substrate scope for intramolecular cyclization reactions.



Reaction condition: 1 (0.5 mmol.), aq. TBHP (4.0 equiv.), DCE (2 mL), 80 °C

With optimal condition in hand, the scope of reaction was investigated with substituent variations at alkynylaryl ring. All reactions completed in 7–8 h and afforded the synthesis of substituted pyrano[4,3-*b*]quinolin-1-ones **2b–2f** in 78–83% yields. Results are summarized in Table 2. Substituents on alkynylaryl ring did not make any significant variations in their yields. To generalize scope of the reactions, the reaction was also carried out with heteroaryl alkyne such as 2-(thiophen-3-ylethynyl) quinoline-3-carbaldehyde and afforded the corresponding cyclized products **2g** in 80% yield. Similarly, alkylalkynyl analogue afforded the cyclized product **2h** in 72% yield in 8 h. Further, scope of the reactions was investigated with substituents variation on quinoline moiety in 2-(phenylethynyl) quinoline-3-carbaldehyde. All reactions proceeded in 7–8 h and afforded corresponding pyranoquinolin-1-ones **2i–2o** in 80–85% yields.

This methodology was further extended with Pyridine analogues such as 5-phenyl-2-(phenylethynyl)-nicotinaldehyde. The oxidation cyclization proceeded smoothly under the optimal reaction conditions afforded the corresponding cyclized products **2p–2r** in 79–83% yields respectively. Substituent variations at both quinoline and alkynylaryl rings were further examined under opti-