Tetrahedron Letters 49 (2008) 6423–6425

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Electrophile-induced domino cyclization reaction for the synthesis of 2,2a,10,11-tetrahydrofuro[2′,4′:4,6]pyrano[2,3-*b*]quinolines

Bhawana Singh [a], Atish Chandra [a], Shraddha Upadhyay [a], Radhey M. Singh [a,*], M. C. Puerta [b], Pedro Valerga [b]

[a] Department of Chemistry, Banaras Hindu University, Varanasi 221005, India

[b] Departmento de Ciencia de los Materiales e Ingenieria Metallurgica y Quimica Inorganica, Facultad de Ciencia, Universidad de Cadiz, Apartado—40, Puerto Real 11510, Spain

ARTICLE INFO

Article history:
Received 7 June 2008
Revised 21 August 2008
Accepted 25 August 2008
Available online 28 August 2008

Keywords:
Tetracyclic pyranoquinoline
Pyranoquinoline
3-Homoallyl-2-quinolones
Diastereomers
Domino process

ABSTRACT

A new and efficient synthesis of furo[2′,4′:4,6]pyrano[2,3-*b*]quinolines, via a domino cyclization approach, has been achieved by iodine and mercuric oxide-catalyzed intramolecular cyclization of 3-homoallyl-2-quinolones in acetic acid.

The pyranoquinoline moiety is an important structural feature of many alkaloids isolated from Rutaceae family,[1] for example, flindersine, oricine and verprisine[2] which have attracted great attention from synthetic as well as medicinal chemists because of their wide applications as drugs, pharmaceuticals and agrochemicals. Derivatives of these alkaloids possess a wide range of interesting biological activities, such as anti-allergic, psychotropic, anti-inflammatory and estrogenic activities.[3] Thus, the development of an efficient method for their synthesis still attracts much interest although many methods for the synthesis of pyranoquinolines and their annulated analogues have been described in the literature.[4]

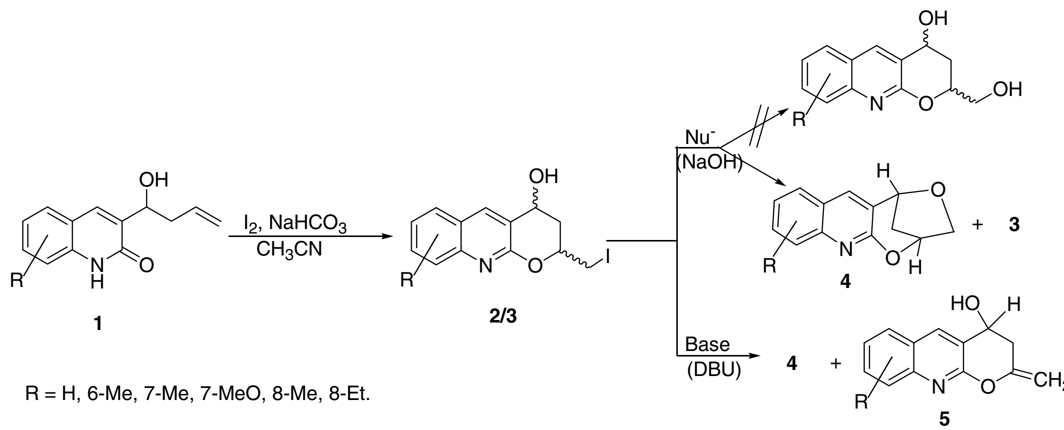
Among the various routes available, cycloaddition reactions, particularly the Lewis-acid-catalyzed aza Diels–Alder reactions, have been employed for the preparation of tri- and tetracyclic pyranoquinolines.[5] Within this class of reactions, Bhuyan et al. have developed an intramolecular 1,3-dipolar cycloaddition reaction for the synthesis of tetracyclic pyranoquinolines via construction of pyrano-fused five-membered heterocycles.[6] Besides cycloaddition reactions, acid-catalyzed cyclization reactions have also been shown to be effective path for the syntheses of pyranoquinoline derivatives.[7] Recently, in our preliminary work,[8] we reported the synthesis of diastereomeric 2,4-disubstituted pyrano[2,3-*b*]quinolines **2**/**3**, via intramolecular electrophilic cyclization of 3-homoallyl-2-quinolones **1** with iodine and sodium bicarbonate in THF, and their reactions with either base or nucleophiles afforded tetracyclic pyranoquinolines **4**, as major products (Scheme 1).

These observations encouraged us to search for effective conditions for a one-pot procedure to synthesize tetracyclic pyranoquinoline compounds from the substrates **1**. Thus, in continuation to our studies in intramolecular annulation reactions,[9] we describe here a one-pot synthesis of tetracyclic pyranoquinoline derivatives from 3-homoallyl-2-quinolones **1** via a domino electrophilic/nucleophilic cyclization reaction catalyzed by I_2/HgO in acetic acid.

As a preliminary experiment, 3-homoallyl-2-quinolone **1c** was dissolved in acetic acid, and I_2 and yellow HgO were added. The reaction mixture slowly changed colour from light yellow to orange, and reaction was completed in 2.5 h as TLC indicated the absence of starting substrate. After work-up and column chromatography, the products were characterized as an inseparable mixture of *cis*- and *trans*-pyranoquinolines **2c**/**3c** and tetracyclic pyranoquinolines **4c** from elemental analysis and spectral data, in a ratio of 36:35 in 71% yield (Table 1, entry 1). The formation of the products **2c**/**3c** is attributed to intramolecular electrophilic cyclization of the substrate **1c**, catalyzed by iodine and mercuric oxide, while formation of product **4c** could be attributed to an intramolecular domino electrophilic/nucleophilic cyclization. This suggests that the reaction initially proceeds through O–C bond formation from lactam oxygen atom to olefinic bond catalyzed by iodine to give a mixture of *cis*/*trans* **2c**/**3c**, followed ultimately by an intramolecular O–C cyclization of *cis*-diastereomer **2c** via

* Corresponding author. Tel.: +91 542 2307321.
E-mail address: rmohan@bhu.ac.in (R. M. Singh).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.08.079



Scheme 1.

Table 1
Optimization of the domino process in acetic acid

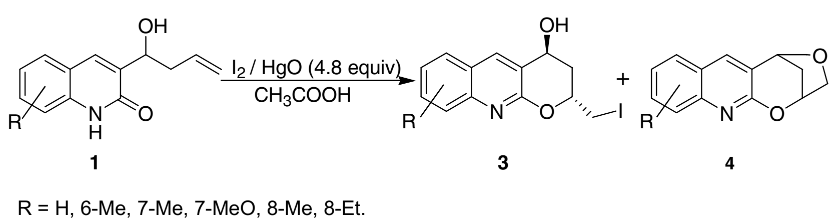
Entry	Substrate	Reagent (equiv)	Time (h)	Product yield (%)	Ratio[c] (trans/cis)
1	**1c**	I_2/HgO (2.4)	2.5	35.0 + 36.4[a]	1.0:0.6
2	**1c**	I_2/HgO (2.4)	6.0	40.0 + 29.4[a]	1.0:0.5
3	**1c**	I_2/HgO (2.4)	30.0	51.2 + 20.8[a]	1.0:0.1
4	**1c**	I_2/HgO (2.4)	36.0	53.0 + 17.0[b]	1.0:0
5	**1c**	I_2/HgO (4.8)	0.5	49.0 + 15.0[b]	1.0:0
6	**1c**	NIS/HgO (2.4)	1.0	48.0 + 17.0[b]	1.0:0

[a] Cyclized + cis and trans products isolated by column chromatography.
[b] Cyclized + trans products isolated by column chromatography.
[c] Ratio by ^{1}H NMR of C-5 proton integration.

slow attack of benzylic oxide on iodomethyl carbon to give compound **4c**. Next, the complete conversion of *cis*-diastereomer **2c** to tetracyclic pyranoquinoline **4c** was studied under different conditions by either increasing reaction time or increasing the molar concentration of reagent (Table 1). Thus, the variations in reaction times that alter the trans/cis ratios provide evidence for the intramolecular domino electrophilic/nucleophilic cyclization to product **4** (Table 1, entries 1–4, Scheme 2). The complete

Table 2
Synthesis of tetracyclic products **4** from 3-homoallyl-2-quinolones **1**

Entry	Substrate	R	Time (h)	Product	Yield (%)
1	**1a**	H	0.5	**4a**	51
2	**1b**	6-Me	0.5	**4b**	46
3	**1c**	7-Me	0.5	**4c**	49
4	**1d**	7-OMe	0.5	**4d**	41
5	**1e**	8-Me	0.5	**4e**	42
6	**1f**	8-Et	0.5	**4f**	40



Scheme 2.

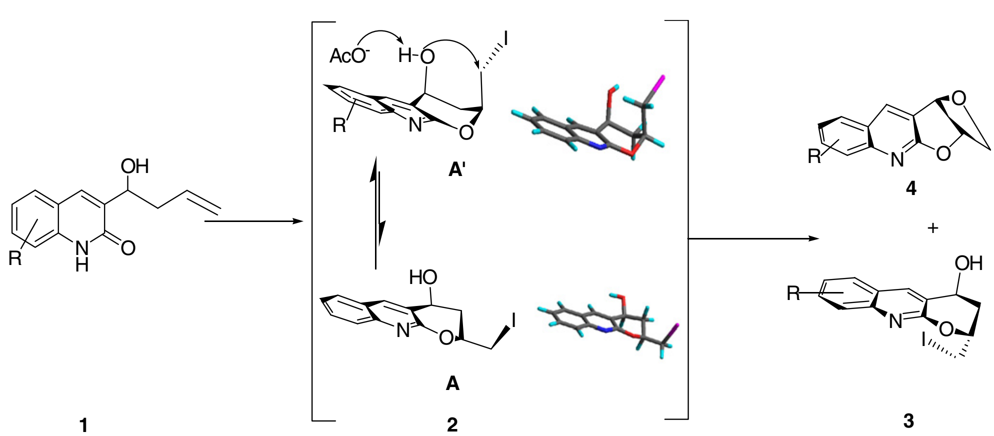


Figure 1. Chemical structure, possible mechanism and alternative conformations **A**/**A′** of *cis*-diastereomer **2**.

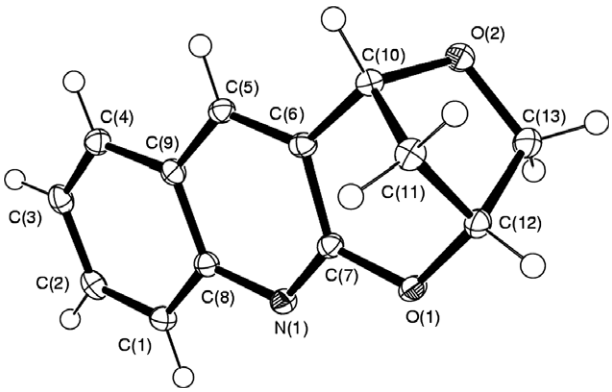


Figure 2. ORTEP drawing of the X-ray structure of **4a**.

conversion of *cis*-diastereomer **2c** to tetracyclic pyranoquinoline **4c** was achieved by stirring the reaction mixture either for 36 h (Table 1, entry 4) or for 0.5 h with 2 mol of iodine and yellow mercuric oxide, though in slightly lower yield (Table 1, entry 5).

The domino reaction with NIS/HgO gave same product **4c** in 1 h. The scope of the domino reaction was examined with other 3-homoallyl-2-quinolone derivatives **1** using double mol equivalents of reagent.[10] The results are shown in Table 2.

The plausible mechanism for the tetracyclic pyranoquinoline **4** is illustrated in Figure 1. In the presence of I_2/HgO, the less stable chair conformation **A**′ of *cis*-pyranoquinolines **2**, in which 2-iodomethyl and 4-hydroxyl groups are axial, will predominate rather than the more stable chair conformation **A** in which the 2-iodomethyl and 4-hydroxyl groups are equatorial. The 2-iodomethyl and 4-hydroxyl groups are in close proximity in the less stable conformation and undergo cyclization via nucleophilic benzylic oxide displacement of iodide to give the tetracyclic pyranoquinoline **4**. All the products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data and by comparison with authentic samples.

Although, the spectral data were sufficient to establish the structures of the tetracyclic products **4**, considering the unusual course of cyclization reaction, a single crystal X-ray crystallographic analysis[11] of **4a** was performed. An ORTEP representation of the molecule is given in Figure 2.

In conclusion, we have developed a new and efficient one-pot method for the synthesis of tetracyclic pyranoquinolines, via cyclization strategies, from readily accessible 3-homoallyl-2-quinolones. The procedure offers several advantages including mild reaction conditions, operational simplicity, inexpensive reagents and short reaction times.

Acknowledgement

The authors acknowledge CSIR, New Delhi, for financial support and fellowship to B.S. One of the authors A.C. is also thankful to CSIR for the award of Senior Research Fellowship.

References and notes

1. (a) Ramesh, M.; Mohan, P. S.; Shanmugam, P. *Tetrahedron* **1984**, *40*, 4041–4049; (b) Grundon, M. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, 1988; Vol. 32, pp 341–439; (c) Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier: Berlin, 1978; Vol. IVG, pp 171–225.
2. (a) Corrol, R. A.; Orazi, O. O. *Tetrahedron Lett.* **1967**, *8*, 583–585; (b) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Baker, R.; Forster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R. *J. Med. Chem.* **1992**, *35*, 1942–1953; (c) Puricelli, L.; Innocenti, G.; Delle Monache, G.; Caniato, R.; Filippini, R.; Cappelletti, E. M. *Nat. Prod. Lett.* **2002**, *16*, 95–100.
3. (a) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211–1213; (b) Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177–1181; (c) Johnson, J. V.; Rauckmann, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942–1949; (d) Mohmed, E. A. *Chem. Pap.* **1994**, *48*, 261. *Chem. Abstr.* **1995**, *123*, 9315x.
4. (a) Plozzi, F.; Venturella, P.; Bellino, A. *Gazz. Chim. Ital.* **1969**, *99*, 711–714; (b) Subramanian, M.; Mohan, P. S.; Shanmugam, P.; Rajendra Prasad, K. J. *Z. Naturforsch.* **1992**, *47b*, 1016–1020; (c) Duan, X. F.; Zeng, J.; Zhang, Z. B.; Zi, G. F. *J. Org. Chem.* **2007**, *72*, 10283–10286.
5. (a) Mahesh, C. J.; Makesh, S. V.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2035–2040; (b) Sabitha, G.; Reddy, M. S. K.; Arundhathi, K.; Yadav, J. S. *ARKIVOC* **2006**, *vi*, 153–160; (c) Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 7891–7896.
6. Bhuyan, P. J.; Baruah, B.; Kalita, P. K. *Tetrahedron Lett.* **2006**, *47*, 7779–7782.
7. (a) Sekar, M.; Rajendra Prasad, K. J. *J. Nat. Prod.* **1998**, *61*, 294–296; (b) Szabo, Z.; Cziaky, Z. *J. Heterocycl. Chem.* **1995**, *32*, 755–760.
8. Singh, M. K.; Chandra, A.; Singh, B.; Singh, R. M. *Tetrahedron Lett.* **2007**, *48*, 5987–5990.
9. (a) Singh, R. M.; Chandra, A.; Srivastava, A. *Indian J. Chem.* **2005**, *44B*, 2077–2084; (b) Singh, R. M.; Singh, M. K.; Srivastava, A. *Indian J. Chem.* **2006**, *45B*, 292–296; (c) Singh, R. M.; Chandra, A.; Srivastava, A. *Indian J. Chem.* **2007**, *46B*, 303–307.
10. To a stirred solution of **1** (1 mmol) in AcOH (15 ml) were added I_2 (4.8 mmol) and HgO (4.8 mmol) under a nitrogen atmosphere at room temperature, and the reaction mixture was stirred for half an hour. After the reaction had finished (monitored by TLC), the precipitate was filtered off. The filtrate was extracted with $CHCl_3$, and the combined organic extracts were washed with 0.5 N $NaHCO_3$ (10 ml), 0.5 N Na_2SO_3 (10 ml), water (3 × 10 ml) and dried over Na_2SO_4. Evaporation of the solvent under vaccum and purification of the products using silica gel column chromatography employing hexane–EtOAc (70:30, v/v) as eluent gave pure **3a** and **4a**.
trans-2-Iodomethyl-4-hydroxy-8-methyl-4H-2,3-dihydropyrano[2,3-b]quinoline **3a**: White solid; yield: 17%; mp 138–39 °C. IR (KBr): cm^{-1}. 1626, 1235, 1161. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.05 (br s, 1H, OH), 2.08 (ddd, 1H, *J* = 3.0, 11.5, 14.2 Hz, CH_2 axial), 2.40 (ddd, 1H, *J* = 3.0, 3.0, 14.2 Hz, CH_2 equatorial), 3.60 (m, 2H, CH_2I), 4.61 (m, 1H, $CHCH_2I$), 5.10 (dd, 1H, *J* = 3.0, 6.3 Hz, CHOH), 7.41 (t, 1H, *J* = 7.4, 7.8 Hz, 6-H), 7.66 (t, 1H, *J* = 7.6, 8.1 Hz, 7-H), 7.74 (d, 1H, *J* = 7.8 Hz, 5-H), 7.90 (d, 1H, *J* = 7.8 Hz, 8-H), 8.12 (s, 1H, 4-H). ^{13}C NMR (75 MHz; $CDCl_3$): δ = 8.0, 35.8, 63.5, 71.4, 119.7, 124.6, 125.2, 127.2, 127.4, 130.5, 139.7, 147.0, 158.8. Anal. Calcd for $C_{13}H_{12}NO_2I$: C, 45.77; H, 3.55; N, 4.11. Found: C, 45.65; H, 3.20; N, 4.33.
2,2a,10,11-tetrahydrofuro[2′,4′:4,6]pyrano[2,3-b]quinoline **4a**: White solid; yield: 53%; mp 96 °C. IR (KBr): cm^{-1}. 1626, 1416, 1200. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 2.27 (ddd, 1H, *J* = 3.0, 4.8, 12.3 Hz, 16-CH_2 axial), 2.43 (d, 1H, *J* = 12.3 Hz, 16-CH_2 eq), 4.12 (dd, 1H, *J* = 3.6, 10.5 Hz, 14-CH_2), 4.33 (d, 1H, *J* = 10.5 Hz, 14-CH_2), 5.16 (d, 1H, *J* = 4.8 Hz, 1-CH), 5.22 (br s, 1H, 13-CH), 7.38 (t, 1H, *J* = 7.5 Hz, 6-H), 7.63 (t, 1H, *J* = 7.5 Hz, 7-H), 7.70 (d, 1H, *J* = 7.8 Hz, 5-H), 7.82 (s, 2H, 3,8-H). ^{13}C NMR (75 MHz; $CDCl_3$): δ = 32.8, 74.3, 75.1, 77.5, 122.4, 124.5, 124.8, 127.2, 127.4, 129.9, 135.1, 147.2, 158.9. MS: *m/z* = 214 (M+1). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.89; H, 5.09; N, 6.45.
11. *Crystal data for* **4a**: Empirical formula, $C_{13}H_{11}NO_2$; formula weight, 213.23; crystal colour, habit: colourless, block; crystal system, monoclinic; lattice parameters, *a* = 5.5267(11), *b* = 16.092(3), *c* = 10.993(2) Å; *V* = 977.5(3) Å^3; space group $P2_1/n$; *Z* = 4; D_{calcd} = 1.449 g/cm^3; F_{000} = 448.00; (Mo Kα) = .099 Å; residuals: *R* = 0.0573; R_w = 0.1344. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 666668. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +441223 336033 or e-mail: deposit@ccdc.cam.ac.uk].