Archive of SID

Improved Synthesis of Vasicinone

Ziaee, Vahid; Jalalizadeh, Hasan; Iranshahi , Mehrdad and Shafiee, Abbas*[+]

Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center , Faculty of Pharmacy, Tehran University of Medical Sciences, P.O. Box 14155-6451, Tehran, I.R. IRAN

ABSTRACT: *A new, high yielding method for the preparation of vasicinone (7) is described. Reaction of 2-nitrobenzoic acid with N, N′-carbonyldiimidazole followed by 2-pyrrolidinone gave 1-(2-nitrobenzoyl)pyrrolidine-2-one (**3**). Reduction of the latter with 10% Pd-C afforded deoxyvasicinone (**4**). Reaction of deoxyvasicinone (**4**) with bromine yielded monobromo-deoxyvasicinone (**5**). Exchange of bromine of **5** with acetoxy followed by hydrolysis gave vasicinone in high yield.*

KEY WORDS: *Vasicinone, Synthesis, Monobromodeoxyvasicinone, Acetylvasicinone.*

INTRODUCTION

Vasicinone, the major alkaloid of *Biebersteinia multifida* DC. roots and one of the most important alkaloids of *Peganum harmala* L. seeds and *Adhatoda vasica* Nees, belongs to a group of alkaloids known as quinazolines, and has a large number of pharmacological properties such as bronchodilatory [1], antitumor [2], hypotensive [3,4], pulmonary and uterus stimulant [4], antianaphylactic, β-potentiating and phosphodiesterase inhibitory effects [5]. The mechanism of action of vasicinone is unknown but probably its pharmacological effects are involved in prostaglandine functions [6].

Vasicinone was first synthesized by Morris and his co-workers [7]. Several synthesis of this alkaloid and its precursor, Deoxyvasicinone, have been reported [8-11]. We describe here an improved facile and efficient synthesis of vasicinone.

EXPERIMENTAL

Melting points were determined on a Reichert hot plate apparatus and are uncorrected.^{1}H NMR spectra were recorded on a Brucker 80 MHz spectrometer using $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Mass spectra were obtained on a Finnigan-MAT TSQ-70 instrument. IR spectra were recorded on a Nicolet Magna IR 550 spectrophotometer.

1-(2-Nitrobenzoyl)pyrrolidine-2-one (3)

To a solution of 2-nitrobenzoic acid (2 g, 12 mmol) in dry THF (60 ml), was added N,N′- carbonyldiimidazole (2.55 g, 12 mmol) and the reaction mixture was stirred at r.t. for 1.5 hours. To the reaction mixture 2-pyrrolidinone (0.91 ml, 12 mmol) was added dropwise at r.t. and stirred for 8 hours. The reaction mixture was filtered off and

* *To whom correspondence should be addressed.*
[+] *E-mail*: *ashafiee@ams.ac.ir*
1021-9986/04/2/33 4/$/2.40

www.SID.ir

Archive of SID

evaporated to dryness. The residue was dissolved in 100 ml chloroform and washed two times with 50 ml water. The organic layer was dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified with a short silica column (petroleum ether/ethyl acetate = 19:6) to give **3** (2.46 g, 88%) m.p. 91-92˚C; lit. m.p. 98-99°C [12]; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.19 (2H, m, $NCH_2C\underline{H}_2CH_2$), 2.53 (2H, t, J = 7.2 Hz, NCH_2), 4.05 (2H, t, J = 7.2 Hz, CH_2CO), 7.61 (3H, m, ArH), 8.22 (1H, dd, J = 7.2, 1.6 Hz, ArH); IR (KBr) 1751,1700 (C=O), 1526, 1352 (NO_2) cm^{-1}; MS: m/z 234 (M^+). Spectral data were similar to the reported one [12].

Anal. Calcd. For $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.27; N, 11.97.
Found: C, 56.22, H, 4.35; N, 11.78.

Deoxyvasicinone (4)

To a solution of compound **3** (2.4 g, 10.2 mmol) in dry methanol (150 mL) was added 10% Pd-C (500 mg). The reaction mixture was stirred for 2 hours under 40 psi of hydrogen at r.t. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform (200 mL) and washed with water (50 mL). The organic phase was separated, decolorized with active charcoal, dried (Na_2SO_4) and evaporated to dryness to give **4** (1.88 g, 98.5%) as a solid: m.p. 81-83 ºC; (Deoxyvasicinone Hydrochloride, mp 196-198˚C); ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.26 (2H, m, $NCH_2C\underline{H}_2CH_2$), 3.17 (2H, t, J = 8 Hz, CH_2), 4.17 (2H, t, J = 7.2 Hz,NCH_2), 7.51 (3H, m, ArH), 8.23 (1H, d, J = 8 Hz, ArH); IR (KBr) 1680 (C=O), 1608 (C=N) cm^{-1}; MS: m/z 186 (M^+). The spectral data were similar with those reported [8].

Anal. Calcd. For $C_{11}H_{10}N_2O$: C, 70.97; H, 5.38; N, 15.05.
Found: C, 70.79, H, 5.17; N, 14.86.

Monobromodeoxyvasicinone (5)

To a stirring mixture of sodium hydride (0.26 g, 11 mmol) in dry THF (120 mL) was added **4** (2 g, 11 mmol). After 10 minutes bromine (0.55 mL) was added dropwise at 25-30˚C and refluxed for 4 hours. The reaction mixture was filtered and washed with chloroform (2 × 40 mL). The filtrate was concentrated under reduced pressure and the residue was purified on a silica column (petroleum ether/ethyl acetate = 18:7) to give **5** (2.13 g, 75%) m.p. 145-146˚C; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.71 (2H, m, $NCH_2C\underline{H}_2$), 4.30 (2H, m, NCH_2), 5.26 (1H, dd, J = 2.4, 7 Hz, CHBr), 7.62 (3H, m, ArH), 8.31 (1H, d, J = 8 Hz, ArH); IR(KBr) 1695 (C=O), 1623 (C=N) cm^{-1}. The spectral data were similar with those reported [10].

Anal. Calcd. For $C_{11}H_9BrN_2O$: C, 49.81; H, 3.40; N, 10.57.
Found: C, 49.98, H, 3.25; N, 10.38.

Acetylvasicinone (6)

To a stirring solution of compound **5** (1.6 g, 6 mmol) in dry THF (50 mL) anhydrous sodium acetate (2.46 g, 30 mmol) was added. After 5 minutes silver nitrate (1.52 g, 9 mmol) in distilled water (1 mL) was added and refluxed for 8 hours. The solvent was evaporated and the residue was dissolved in chloroform (150 ml) and filtered .The filtrate was washed with water (2 × 200 mL), decolorized with active charcoal, dried (Na_2SO_4), filtered and evaporated to give **6** (1.32 g, 90%) m.p. 175-176ºC; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.23 (3H, s, CH_3), 2.53 (2H, m, CH_2), 4.18 (2H, m, NCH_2), 6.04 (1H, t, J = 6.4 Hz, CH), 7.53 (3H, m, ArH), 8.29 (1H, d, J = 7.2 Hz, ArH); IR (KBr) 1739 (-COO-), 1686 (C=O), 1628 (C=N) cm^{-1}; MS: m/z 244 (M^+). The spectral data were similar with those reported [8].

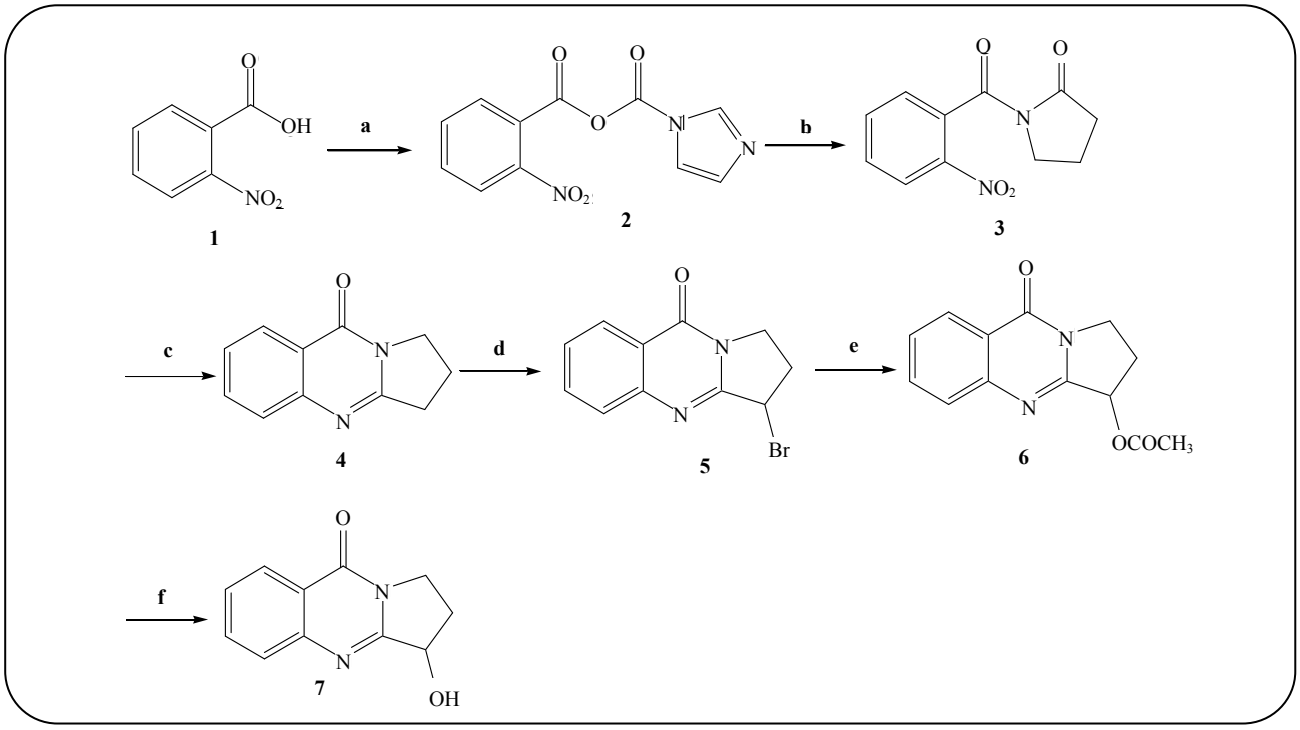
Anal. Calcd. For $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.92; N, 11.48.
Found: C, 64.08, H, 4.74; N, 11.66.

Vasicinone (7)

To a solution of compound **3** (1.32 g, 5.4 mmol) in ethanol (50 mL) was added 0.26 M aqueous KOH (10 mL), and refluxed for 2 hours. The solvent was evaporated to dryness and water (150 mL) was added. Then it was extracted with chloroform (4 × 150 ml). The combined organic extracts were decolorized with active charcoal, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on a silica column (petroleum ether/ethyl acetate = 40:60) to give **7** (1.04 g, 95%) m.p. 200-202˚C ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.48 (2H, m, CH_2), 4.24 (2H, m, NCH_2), 5.31 (1H, t, J = 7.2 Hz, CH), 7.57 (3H, m, ArH), 8.34 (1H, d, J = 7.2 Hz, ArH); IR (KBr) 3150 (OH), 1675 (C=O), 1629 (C=N) cm^{-1}; MS: m/z 202 (M^+).

www.SID.ir

Archive of SID



a: Carbonyldiimidazole; b: 2-Pyrrolidinone; c: Pd/C, H_2; d: NaH, Br_2; e:NaOAc, $AgNO_3$; f:KOH, EtOH

Scheme 1

Anal. Calcd. For $C_{11}H_{10}N_2O_2$: C, 65.35; H, 4.95; N, 13.86. The spectral data were similar with those reported [11].
Found: C, 65.54, H, 5.09; N, 13.67.

RESULTS AND DISCUSSION

The synthesis of vasicinone was accomplished as shown in Scheme 1. Reaction of 2-nitrobenzoic acid (**1**) with N,N′-carbonyldiimidazole followed by 2-pyrrolidinone afforded 1-(2-nitrobenzoyl)pyrrolidine-2-one (**3**). Hydrogenation of compound **3** in the presence of Pd/C gave deoxyvasicinone (**4**) in high yield.

For the direct conversion of **4** to vasicinone (**7**) several hydroxylation methods was examined; e.g. NBS, $CaCO_3$ in dioxane-water mixture [13], oxidation with SeO_2 in dry dichloromethane [14], and oxidation with SeO_2 and t-butyl hydroperoxide in dry dichloromethane [15]. However, none of them gave the desired compound **7**. The indirect method for the production of vasicinone is monobromination and subsequent exchange of bromine with hydroxy group. For bromination of compound **4** several methods of bromination was carried out; e.g. NBS in carbone tetrachloride [16], bromination with bromine in acetic acid [17], bromination either with phenyltrimethylammonium perbromide (PTAB) in dry THF [18], or with NBS and AIBN (2,2′-azobisisobutyronitrile) in CCl_4 [19].

However, all of them gave both mono- and di-bromodeoxyvasicinone and also product of elimination of monobrominated derivative. Finally we found out that reaction of **4** with NaH and Br_2 gave monobromo-deoxyvasicinone (**5**), in high yield [20].

Reaction of compound **5** with sodium acetate and silver nitrate gave the desired acetyl-vasicinone (**6**) in over 90% yield. Alkaline hydrolysis of **6** gave vasicinone in 95% yield.

Acknowledgment

This research was partially supported by a grant from the Tehran University of Medical Sciences Research Council.

Received: 18th October 2003 ; Accepted: 13th January 2004

www.SID.ir

Archive of SID

REFERENCES

[1] Cambridge, G.W., Jansen, A.B.A., and Jarman, D.A., *Nature* **196***,* 1217(1962).

[2] Fan, Z., Yao, X., Gu, L., Wang, J., Wang, J., He, A., Zhang, B., Wang, X., and Wang, H., Shenyang Yaoxueyuan Xuebao, **10,** 136(1993), *Chem. Abstr*., **120**, 86203Z(1994) .

[3] Jen, T., Dienel, B., Dowalo, F., Hoeven, H.V., Bender, P., and Love, B., *J. Med. Chem*., **16**, 633(1973).

[4] Gupta, O.P., Sharma, M.L., Ghatak, B. J., Ray, and Atal, C. K., *Indian J. Med. Res*., **66***,* 680(1977).

[5] Bhide, M.B., Naik, P. Y., Mahajani, S. S., Ghooi, R.B., and Joshi, R.S. Bull. Haffkine Inst. **2**, 6 (1974), *Chem.Abstr.* **82** , 38618p (1975).

[6] Chandhok, N., *Indian Drugs*, **24**, 425(1987).

[7] Morris, R. C., Hanford, W. E., and Adams, R., *J. Am. Chem. Soc.*, **57**, 951(1935).

[8] Onaka,T., *Tetrahedron Lett.*, 4387(1971).

[9] Kametani, T., Loc, C.V., Higa, T., Koizumi, M., Ihara, K., and Fukumoto, K., *J. Am. Chem. Soc.,* **99**, 2306, (1977).

[10] Mori, M., Kobayashi, H., Kimura, M., and Ban, Y., *Heterocycles*, **23**, 2803(1985).

[11] Egushi, S., Suzuki, T., Okawa, T., and Matsushita, Y. J., *Org. Chem.*, **61**, 7316(1996).

[12] Thurston, D. E. and Langley, D. r., *J. Org. Chem.*, **51**, 705(1986).

[13] Finucane, B. W., and Thomson, J. B., *Chem. Commun.*, 1220(1969).

[14] Bhalerao, U.T., and Papoport, H., *J. Am. Chem. Soc.*, **93**, 4835(1971).

[15] Umbreit, M.A., and Sharpless K.B., *J. Am. Chem. Soc.*, **99,** 5526(1977).

[16] Corey, E.J., *J. Am. Chem. Soc.*, **75**, 2301(1953).

[17] Marshall, J.A., Andersen, N.H., and Johnsen, P.C., *J. Org. Chem.*, **35**, 86(1970).

[18] Johnson, W.S., Bass, J.D., and Williamson, K.L., *Tetrahedron*, **19**, 861(1963).

[19] Zhang, P.,Liu, R., and Cook, J.M., *Tetrahedron Lett.*, **36**, 3103(1955).

[20] Boyd, R.E., and Rasmussen, R., *Press, J. B. Synth. Commun.*, **25**, 1045(1995).

www.SID.ir