ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 11, pp. 2665–2667. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © A.M. Gumerov, I.M. Sakhautdinov, M.S. Yunusov, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 11, pp. 1927–1929.

LETTERS TO THE EDITOR

Synthesis of Isoindolo[2,1-*b*]isoquinoline-5,7-dione via the Wittig Intramolecular Cyclization

A. M. Gumerov, I. M. Sakhautdinov, and M. S. Yunusov

Ufa Institute of Chemistry, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Russia
e-mail: aygumer@mail.ru

Received May 25, 2015

Keywords: isoindoloisoquinoline, isoquinoline alkaloid, phosphorus ylide, the Wittig reaction

DOI: 10.1134/S1070363215110274

Isoindoloisoquinoline contains two pharmacophore fragments and therefore serves as major structural fragment of a number of biologically active compounds used in clinical practice [1]. Isoquinoline alkaloids are widespread in nature [2, 3]. Recently, nuevamine [4], jamtine [5], and hirsutine [6] alkaloids inclusing isoindolo[1,2-*a*]isoquinoline fragment have been isolated from *Cocculus hirsutus (L.)* and *Berberis darwinii Hook* plants. Isoindolo[1,2-*a*]isoquinoline derivatives can be obtained from isoquinoline [7] and isoindole [8] derivatives. However, these methods utilize the poorly accessible starting materials.

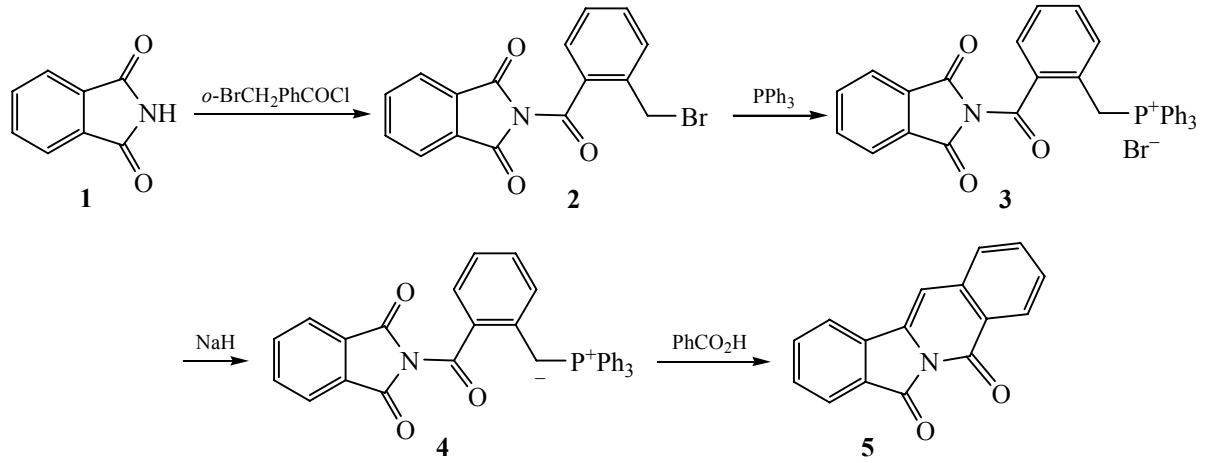
In this work, we have proposed a method to produce isoindolo[2,1-*b*]isoquinoline-5,7-dione **5**, the oxo derivative of the above-mensioned alkaloids, via the Wittig intramolecular cyclization of phosphorus ylide.

Acylation of phthalimide **1** with 1-bromomethylbenzoyl chloride afforded benzyl bromide **2** in 89% yield. The product structure was confirmed by the spectral data: the CH_2Br group of compound **2** exhibited a singlet signal at 5.01 ppm in the ^1H NMR spectrum and at 30.34 ppm in the ^{13}C NMR spectrum (Scheme 1).

The reaction of benzyl bromide **2** with PPh_3 in anhydrous benzene resulted in the formation of phosphonium salt **3** with yield of 63%. For comparison, the reaction was also performed in acetone and methylene chloride. In the case of acetone, phosphonium salt was not formed, and with methylene chloride as solvent its yield was down to 13%.

Deprotonation of the prepared salt with sodium hydride in anhydrous tetrahydrofuran afforded phos-

Scheme 1.



phorus ylide **4** in 91% yield; it underwent spontaneous intramolecular cyclization into isoindolo[2,1-*b*]isoquinoline-5,7-dione **5** at room temperature. The reaction was more efficient under conditions of refluxing the phosphorus ylide **4** in dioxane in the presence of a catalytic amount of benzoic acid, the similar effect has been noted previously [9]. The tetracyclic product **5** was obtained in a yield of 47%. The structure of the final product was confirmed by ^{1}H and ^{13}C NMR data.

In summary, synthesis of isoindolo[2,1-*b*]isoquinoline-5,7-dione via the Wittig intramolecular cyclization of phosphorus ylide prepared from commercially available phthalimide and *o*-bromomethylbenzoate was performed.

2-[2-(Bromomethyl)benzoyl]-1*H*-isoindole-1,3(2*H*)-dione (2). 3.3 mmol of thionyl chloride was added to a suspension of 0.241 g (1.1 mmol) of *o*-bromomethylbenzoic acid in 20 mL of anhydrous benzene. The mixture was refluxed until the gas evolution had ceased (≈ 6 h). After evaporation of the solvent and excess of thionyl chloride, the resulting acid chloride was used introduced in further reactions without additional purification.

A solution of the acid chloride in 5 mL of tetrahydrofuran was added dropwise upon stirring and cooling to a solution of 1 mmol of the phthalimide and 1.1 mmol of triethylamine in 20 mL of tetrahydrofuran over 10 min. The reaction mixture was then heated to ambient stirred during 2 h. The precipitate was filtered off; the filtrate was poured into 50 mL of dilute hydrochloric acid and then extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on silica gel (chloroform : acetone = 9 : 1). Yield 0.31 g (89%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.01 m (2H, CH_2), 7.42–8.29 m (4H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 30.34 (CH_2), 123.62 (CH_{Ar}), 128.85 ($2CH_{Ar}$), 129.02 (CH_{Ar}), 131.94 (CH_{Ar}), 132.17 (C_{Ar}), 133.41 (C_{Ar}), 134.34 (CH_{Ar}), 134.59 ($2CH_{Ar}$), 139.77 (C_{Ar}), 168.07 (2C=O), 170.44 (C=O). Mass spectrum: m/z = 345 $[M + H]^+$. Found, %: C 55.87; H 2.95; N 4.03; Br 23.23. $C_{16}H_{10}BrNO_3$. Calculated, %: C 55.84; H 2.93; N 4.07; Br 23.22.

{2-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]benzyl}(triphenyl)phosphonium bromide (3). A solution of 1.1 mmol of triphenylphosphine in 3 mL of benzene was added in a single portion to a stirred solution of 0.35 g (1 mmol) of benzyl bromide in 10 mL of anhydrous benzene. The reaction mixture was stirred during 3 h and then refluxed during one day. The solvent was then decanted, and the residue was washed with hot benzene and evaporated. Yield 0.38 g (63%). Found, %: C 67.37; H 4.13; N 2.37; Br 13.15. $C_{34}H_{25}BrNO_3P$. Calculated, %: C 67.34; H 4.16; N 2.31; Br 13.18. P 5.11.

2-{2-[(Triphenylphosphoranylidene)methyl]-benzoyl}-1*H*-isoindole-1,3(2*H*)-dione (4). 5 mmol of sodium hydride was added to a stirred suspension of 0.61 g (1 mmol) of phosphonium salt **3** in 20 mL of tetrahydrofuran, and the reaction mixture was stirred during 1.5 h. The precipitate was filtered off, and the solvent was removed to give red oily product. Yield 0.47 g (91%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.34 s (1H, CH), 7.30–8.35 m (23H, Ar). Found, %: C 77.68; H 4.64; N 2.71. $C_{34}H_{24}NO_3P$. Calculated, %: C 77.70; H 4.60; N 2.67; P 5.89; O 9.13.

Isoindolo[2,1-*b*]isoquinoline-5,7-dione (5). Catalytic amount of benzoic acid was added to a suspension of 0.53 g (1 mmol) of phosphorus ylide in 10 mL of anhydrous toluene. The reaction mixture was refluxed during 5 h under argon. After removal of toluene, the residue was purified by chromatography on silica gel (petroleum ether : ethyl acetate = 4 : 1). Yield 116 mg (47%). IR (nujol), ν, cm^{-1}: 1157, 1641, 1730. ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 6.61 s (1H, CH), 7.33–7.55 m (4H, C_6H_4), 7.68–8.35 m (4H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz): 105.87 (=CH), 120.33 (=C), 125.78 (CH_{Ar}), 125.96 (CH_{Ar}), 128.41 (C_{Ar}), 129.16 (C_{Ar}), 129.57 (CH_{Ar}), 131.04 (CH_{Ar}), 131.91 (CH_{Ar}), 132.75 (CH_{Ar}), 134.79 (CH_{Ar}), 136.73 (CH_{Ar}), 137.48 (C_{Ar}), 140.08(C_{Ar}), 162.52 (C=O), 167.55 (C=O). Mass spectrum: m/z = 345 $[M + H]^+$. Found, %: C 77.74; H 3.63; N 5.70. $C_{16}H_9NO_2$. Calculated, %: C 77.72; H 3.67; N 5.67.

IR spectra were recorded using a Specord M-80 instrument (thin layer or with paraffin oil). NMR spectra were obtained with a Bruker AM-500 spectrometer operating at 500.13 (^{1}H) or 125.76 (^{13}C) MHz. The reaction progress was monitored by TLC using Sorbfil PTLC-AF-A plates. Mass spectra (APCI) were taken using a LCMS-2010EV Shimadzu GC–MS instrument. Elemental analysis was performed with a EURO EA-3000 CHNS-analyzer. Column chromatography was carried out using Chemapol silica gel (40/100 and 100/160 mesh).

ACKNOWLEDGMENTS

This work was financially supported by the Russian Science Foundation (grant no. 14-13-01307) and the Russian Foundation for Basic Research (grant no. 13-00-14056) taking advantage of the equipment installed at the Center for Collective Usage "Chemistry" of Ufa Institute of Chemistry, Russian Academy of Sciences.

REFERENCES

1. Zubkov, F.I., Zaytsev, V.P., Ershova, Y.D., Mertsalov, D.F., Sorokina, E.A., Nikitina, E.V., Varlamov, A.V., Obushak, M.D., Gorak, Y.I., and Lytvyn, R.Z., *Chem. Heterocycl. Compd*., 2013, vol. 49, no. 5, p. 746. DOI: 10.1007/s10593-013-1306-1.
2. Shklyev, Yu.V., *Butlerovsk. Soobshch*., 2002, vol. 2, no. 7, p. 21.
3. *Prirodnye izokhinoliny: khimiya i biologicheskaya aktivnost'* (Natural Isoquinolines: Chemistry and Biological Activity), Kartsev, V.G., Ed., Moscow: ICSPF, 2011, vol. 8, p. 22.
4. Valencia, E., Freyer, A.J., and Shamma, M., *Tetrahedron Lett*., 1985, vol. 25, p. 599. DOI: 10.1016/S0040-4039(00)99948-9.
5. Ahmad, V.U., Rahman, A., Rasheed, T., and Rehman, H., *Heterocycles*, 1987, vol. 26, p. 1251. DOI: 10.3987/R-1987-05-1251.
6. Rasheed, T., Khan, M.N.I., Zhadi, S.S.A., and Durrani, S., *J. Nat. Prod*., 1991, vol. 54, p. 582. DOI: 10.1021/np50074a037.
7. Tang, Y., Fettinger, J.C., and Shaw, J.T., *Org. Lett*., 2009, vol. 11, p. 3802. DOI: 10.1021/ol901018k.
8. Selvakumar, J., Rao, R.S., Srinivasapriyan, V., Marutheeswaran, S., and Ramanathan, C.R., *J. Org. Chem*., 2015, vol. 10, p. 2175. DOI: 10.1002/ejoc.201403617.
9. Kolodiazhnyi, O.I., *Phosphorus Ylides. Chemistry and Applications in Organic Synthesis*, New York: John Wiley, 1999, p. 388.