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Ionic Liquid-Catalyzed and Microwave-Assisted Syntheses of Pyrrolizine- and Indolizinedione Derivatives

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Abstract—3*H*-Pyrrolo[2,1-*a*]isoindole-2,5-diones and isoindolo[2,1-*a*]quinoline-5,11-diones were synthesized by intramolecular cyclization of *N*-[2-oxo-3-(triphenyl-λ^5-phosphanylidene)propyl]- and *N*-[2-(triphenyl-λ^5-phosphanylidene)acetyl]phthalimides, respectively, in the presence of ionic liquid ([bmim][BF_4], 10 mol %) as catalyst or under microwave irradiation.

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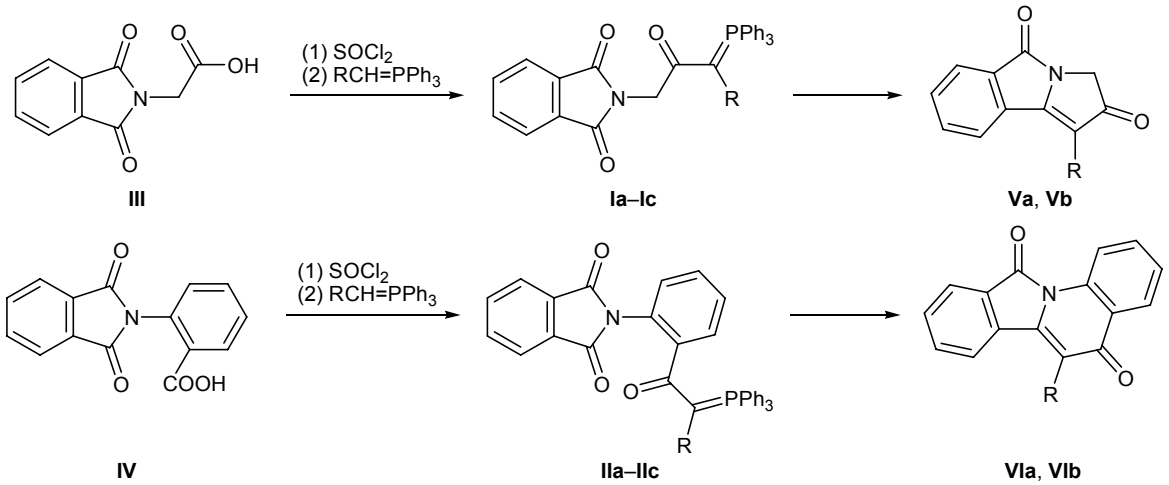
Pyrrolizidine and indolizidine alkaloids constitute a class of pharmacologically important compounds [1–3] isolated from natural sources. Pyrrolizidine- and indolizidinedione derivatives have found versatile applications in medicine, primarily as CNS stimulators and antidiabetic, antiviral, antimicrobial, and antitumor drugs [4–7]. Recent studies have shown that natural alkaloids of the pyrrolizidine and indolizidine series (mappicine and mappicine ketone) exhibit high anti-retroviral activity, so that they can be used as efficient drugs in a new line of AIDS chemotherapy [8]. Increased interest in pyrrolizidine- and indolizidinedione derivatives stimulates search for and development of new simple, inexpensive, and general methods for their preparation.

We previously showed [9–13] that keto-stabilized sulfonium and phosphonium ylides derived from N-substituted α- and β-amino acids undergo intramolecular cyclization. We synthesized compounds having pyrrolizine and indolizine fragments from phosphorus ylides **I** and **II** which were obtained by acylation of simple alkylidenephosphoranes with *N*-phthaloyl amino acids **III** and **IV** (transylidation), which allowed us to considerably reduce the number of

Scheme 1.



R = H (**a**), Me (**b**), MeOC(O) (**c**).

Intramolecular cyclization of phosphorus ylides **Ia**–**Ic** and **IIa**–**IIc** under different conditions (argon atmosphere)

Reaction conditions	Reaction time, h	Yield, %			
		Va	**Vb**	**VIa**	**VIb**
$PhCO_2H$, PhMe	56	53	55	15	27
[bmim][BF_4], PhMe	40	61	67	32	36
MW, 450 W, THF	1	72	77	39	78
MW, 750 W, PhMe	0.5	85	89	58	81

steps as compared to salt and carbene procedures used previously. In the present work we examined specific effects of a ionic liquid and microwave irradiation on the rate of intramolecular cyclization of keto-stabilized phosphorus ylides.

Keto-stabilized phosphorus ylides **Ia**, **Ib**, **IIa**, and **IIb** were synthesized from phthalimidoglycine (**III**) and *o*-phthalimidobenzoic acid (**IV**) which were prepared by fusion of phthalic anhydride with the corresponding amino acids according to Reese [14]. Acids **III** and **IV** were then treated with $SOCl_2$ to obtain the corresponding acid chlorides, and the latter (without isolation) were brought into reaction with 2 equiv of alkylidenephosphorane prepared by dehydrohalogenation of phosphonium salts with butyllithium (Scheme 1). Heating of ylides **Ia**, **Ib**, **IIa**, and **IIb** in toluene in the presence of benzoic acid as catalyst gave cyclic products **Va**, **Vb**, **VIa**, and **VIb** having pyrrolizine- and indolizinedione fragments. Doubly stabilized ylides **Ic** and **IIc** did not undergo intramolecular cyclization under the same conditions and were recovered from the reaction mixtures.

With a view to improve the yield of intramolecular cyclization products we carried out the reaction in ionic liquid and under microwave irradiation [15–18]. Ionic liquids are widely used in organic synthesis. It is known that the use of 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] considerably increases the yield of the Wittig reaction [15]. In fact, the yields of compounds **Va**, **Vb**, **VIa**, and **VIb** increased when phosphorus ylides **Ia**, **Ib**, **IIa**, and **IIb** were heated in toluene in the presence of [bmim][BF_4] as catalyst. Moreover, multimode microwave irradiation not only considerably increased the yield of the cyclization products but also appreciably shortened the reaction time (see table). However, no heterocyclic products were obtained from ylides **Ic** and **IIc** in the presence of ionic liquid or under microwave irradiation.

The structure of compounds **Va**, **Vb**, **VIa**, and **Vb** was confirmed by spectral methods; the physicochemical parameters of **Va** were consistent with published data [19]. The ^{1}H NMR spectra of **Va**, **Vb**, **VIa**, and **Vb** displayed symmetry violation for two multiplet signals from four protons in the phthaloyl fragment in the region δ 7.46–8.32 (**Vb**), 7.49–9.15 (**VIa**), and 7.07–9.18 ppm (**VIb**), a singlet from protons in the methyl group was observed at δ 1.58 (**Vb**) and 2.55 ppm (**VIb**), and the 12-H proton in **VIa** resonated as a singlet at δ 6.76 ppm. Signals from the double-bonded carbon atom were located in the ^{13}C NMR spectra at δ_C 103.57 (**Vb**, C^1), 106.58 (**VIa**, C^{12}), and 104.25 ppm (**VIb**, C^{12}), while methyl carbon atoms gave signals at δ_C 12.43 (**Vb**) and 10.58 ppm (**VIb**).

Taking into account that the synthesized compounds are promising as biologically active substances, they were subjected to computer-assisted screening for biological activity using PASS program. The results showed a probability of more than 70% for immunomodulatory and anti-inflammatory activity of the cyclic products.

To conclude, we have synthesized compounds with pyrroloisoindoledione and isoindoloquinolinedione structures from phosphorus ylides. The use of ionic liquid ([bmim][BF_4]) and microwave irradiation considerably increases the yield in intramolecular cyclization and shortens the reaction time. Electron-acceptor substituents on the ylide carbon atom hamper the cyclization process.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument from thin films or mineral oil mulls. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer at 300.13 and 75.25 MHz, respectively, using tetramethylsilane as internal reference. The progress of reactions was monitored by thin-layer chromatography on Sorbfil PTSKh-AF-A plates; spots were detected under UV light, by treatment with iodine vapor, or by spraying with a ninhydrin reagent or a solution of 4-methoxybenzaldehyde with subsequent heating to 100–120°C. The mass spectra (atmos-

pheric pressure chemical ionization) were obtained on a Shimadzu LCMS-2010EV instrument. Microwave assisted reactions were carried out in a modified SAM-OM75S-(31) multimode microwave cavity (2.45×10^9 Hz, 750 W) using a 50-ml quartz reactor equipped with a mechanical stirrer and reflux condenser; the stirrer drive and the condenser were placed out of the irradiation zone.

Acetone, methylene chloride, and ethyl acetate were distilled over P_2O_5. Toluene, tetrahydrofuran, and petroleum ether were heated under reflux over metallic sodium and then distilled. Thionyl chloride of analytical grade was used without additional purification. 1-Butyl-3-methyl-1*H*-imidazolium tetrafluoroborate [bmim][BF_4] was prepared in two steps starting from 1-methylimidazole (Acros, purity ≥ 99.2%). The reaction of 1-methylimidazole with butyl chloride gave 59% of 1-butyl-3-methylimidazolium chloride, and the latter was treated with KBF_4 according to [20] to obtain [bmim][BF_4]. Commercial 2,5 M butyllithium in hexane was used. Compounds **Va**, **Vb**, **VIa**, and **VIb** were isolated by column chromatography on silica gel (40–100, 100–160 μm). *N*-Phthaloylglycine (**III**) and 2-phthalimidobenzoic acid (**IV**) were prepared as described in [14].

Phosphorus ylides Ia–Ic and IIa–IIc (*general procedure***).** Fused acid **III** or **IV**, 10 mmol, was dispersed in 30 ml of anhydrous benzene, 50 mmol of thionyl chloride was added, and the mixture was heated under reflux until gaseous products no longer evolved (~3 h). The mixture was evaporated, and the residue (the corresponding acid chloride) was used without additional purification. In the next step it was necessary to use 2 equiv of alkylidenephosphorane to ensure deprotonation of the initially formed phosphonium salt with the second ylide molecule. Methyl (triphenyl)phosphonium iodide or ethyl(triphenyl)-phosphonium bromide, 20 mmol, was dispersed in tetrahydrofuran, 20 mmol of 2.5 M butyllithium in hexane was added dropwise using a syringe under stirring, the mixture was stirred for 1 h, a solution of the corresponding acid chloride in tetrahydrofuran was slowly added, and the mixture was stirred for 3 h. The precipitate was filtered off, and the solvent was distilled off. Ylides **IIa** and **IIb** were subjected to intramolecular cyclization without additional purification, for they rapidly decomposed even at room temperature. We failed to obtain spectra of pure ylides **IIa** and **IIb**, but their formation was confirmed by displacement of the carbonyl absorption band in the IR spectra to lower frequencies (~1550 cm^{-1}) due to the presence of neighboring carbanionic center. Compounds **Ia**–**Ic** and **IIc** were isolated by extraction with chloroform and were dried over calcined potassium carbonate.

2-[2-Oxo-3-(triphenyl-λ^5-phosphanylidene)-propyl]-1*H*-isoindole-1,3(2*H*)-dione (Ia). Yield 4.21 g (91%), red oily substance. IR spectrum ν, cm^{-1}: 1717, 1623, 1579. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.43 s (2H, CH_2), 3.36 d (1H, CH), 7.31–7.96 m (19H, H_{arom}). Found, %: C 75.04; H 4.63; N 2.96; P 6.59. $C_{29}H_{22}NO_3P$. Calculated, %: C 75.15; H 4.78; N 3.02; P 6.68.

2-[2-Oxo-3-(triphenyl-λ^5-phosphanylidene)-butyl]-1*H*-isoindole-1,3(2*H*)-dione (Ib) . Yield 4.48 g (94%), red oily substance. IR spectrum, ν, cm^{-1}: 1714, 1617, 1583. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.93 s (3H, CH_3), 4.79 s (2H, CH_2), 7.37–8.10 m (19H, H_{arom}). Found, %: C 75.61; H 5.00; N 2.88; P 6.25. $C_{30}H_{24}NO_3P$. Calculated, %: C 75.46; H 5.07; N 2.93; P 6.49.

2-{2-[1-Oxo-2-(triphenyl-λ^5-phosphanylidene)-ethyl]phenyl}-1*H*-isoindole-1,3(2*H*)-dione (IIa). IR spectrum, ν, cm^{-1}: 1721, 1613, 1569.

2-{2-[1-Oxo-2-(triphenyl-λ^5-phosphanylidene)-propyl]phenyl}-1*H*-isoindole-1,3(2*H*)-dione (IIb). IR spectrum, ν, cm^{-1}: 1725, 1629, 1567.

Methyl 4-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)butanoate (Ic). Yield 4.95 g (95%), yellow oily substance. IR spectrum, ν, cm^{-1}: 1724, 1539, 1458. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.32 s (3H, CH_3), 5.11 s (2H, CH_2), 7.41–7.81 m (19H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 46.29 (CH_2), 49.64 (CH_3), 69.55 (C_{ylide}), 122.93 (CH_{arom}), 124.86 (C_{arom}), 128.38 (CH_{arom}), 128.56 (CH_{arom}), 131.77 (CH_{arom}), 132.58 (C_{arom}), 133.32 (CH_{arom}), 168.11 (C=O), 168.37 (C=O), 187.98 (C=O). Found, %: C 71.23; H 4.76; N 2.89; P 6.21. $C_{30}H_{24}NO_3P$. Calculated, %: C 71.40; H 4.64; N 2.69; P 5.94.

Methyl 3-[2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)phenyl]-3-oxo-2-(triphenyl-λ^5-phosphanylidene)propanoate (IIc). Yield 5.72 g (98%), yellow oily substance. IR spectrum, ν, cm^{-1}: 1714, 1533, 1485. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.16 s (3H, CH_3), 7.26–7.96 m (19H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 49.96 (CH_3), 77.16 (C_{ylide}), 115.39 (CH_{arom}), 120.73 (C_{arom}), 121.59 (C_{arom}), 123.53 (CH_{arom}), 123.92 (C_{arom}), 125.21 (C_{arom}), 126.44 (CH_{arom}), 128.51 (CH_{arom}), 128.92 (CH_{arom}), 130.84

(C_{arom}), 131.95 (CH_{arom}), 132.06 (CH_{arom}), 133.27 (CH_{arom}), 133.41 (CH_{arom}), 134.35 (CH_{arom}), 134.87 (C_{arom}), 141.27 (C_{arom}), 167.03 (C=O), 167.50 (C=O), 190.11 (C=O). Found, %: C 74.13; H 4.69; N 2.52; P 5.27. $C_{36}H_{26}NO_5P$. Calculated, %: C 74.09; H 4.49; N 2.40; P 5.31.

Intramolecular Wittig reaction (*general procedures***).** *a*. Phosphorus ylide **I** or **II**, 1 mmol, was dispersed in 30 ml of anhydrous toluene, a catalytic amount (5 mol %) of benzoic acid was added, and the mixture was heated for 56 h under reflux in an argon atmosphere. The solvent was distilled off, and the product was isolated by column chromatography on silica gel.

b. Phosphorus ylide **I** or **II**, 1 mmol, was dispersed in 30 ml of anhydrous toluene, a catalytic amount (10 mol %) of [bmim][BF_4] was added, and the mixture was heated for 40 h under reflux in an argon atmosphere. The solution was separated by decanting, the solvent was distilled off, and the product was isolated by column chromatography on silica gel.

c. Phosphorus ylide **I** or **II**, 1 mmol, was dispersed in 30 ml of anhydrous tetrahydrofuran, and the mixture was subjected to microwave irradiation over a period of 1 h. The solution was separated by decanting, the solvent was distilled off, and the product was isolated by column chromatography on silica gel.

d. Phosphorus ylide **I** or **II**, 1 mmol, was dispersed in 30 ml of anhydrous toluene, and the mixture was subjected to microwave irradiation over a period of 0.5 h. The solution was separated by decanting, the solvent was distilled off, and the product was isolated by column chromatography on silica gel.

3*H*-Pyrrolo[2,1-*a*]isoindole-2,5-dione (Va). Eluent ethyl acetate–petroleum ether (1 : 3). Yield 98 mg (53%) (*a*), 113 mg (61%) (*b*), 133 mg (72%) (*c*), 157 mg (85%) (*d*). The physicochemical parameters of **Va** were consistent with published data [19].

1-Methyl-3*H*-pyrrolo[2,1-*a*]isoindole-2,5-dione (Vb). Eluent ethyl acetate–petroleum ether (1:3). Yield 109 mg (55%) (*a*), 133 mg (67%) (*b*), 153 mg (77%) (*c*), 177 mg (89%) (*d*); yellow crystals, mp 185–187°C. IR spectrum, ν, cm^{-1}: 1720, 1697, 1572. ^{1}H NMR spectrum ($CDCl_3$), δ_C, ppm: 1.58 s (3H, CH_3), 7.46–8.32 m (4H, C_6H_4), 4.43–4.55 d.d (2H, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.43 (CH_3), 40.16 (CH_2), 103.57 (C=C), 116.75 (CH_{arom}), 123.35 (CH_{arom}), 128.35 (C_{arom}), 130.22 (CH_{arom}), 131.88 (CH_{arom}), 133.98 (C_{arom}), 159.63 (C=O), 165.13 (C=C), 198.31 (C=O). Mass spectrum, *m*/*z*: 200 $[M + H]^+$, 199 $[M]^-$. Found, %: C 72.53; H 4.63; N 7.07. $C_{12}H_9NO_2$. Calculated, %: C 72.35; H 4.55; N 7.03. Calculated: *M* 199.2.

Isoindolo[2,1-*a*]quinoline-5,11-dione (VIa). Eluent ethyl acetate–petroleum ether (1 : 4). Yield 37 mg (15%) (*a*), 79 mg (32%) (*b*), 96 mg (39%) (*c*), 143 mg (58%) (*d*); yellow crystals, mp 198–200°C. IR spectrum, ν, cm^{-1}: 1768, 1704, 1665. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.76 s (1H, CH), 7.49–9.15 m (4H, C_6H_4), 7.61–7.67 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 106.85 (C=C), 117.71 (CH_{arom}), 119.90 (CH_{arom}), 121.87 (CH_{arom}), 125.27 (CH_{arom}), 129.12 (CH_{arom}), 129.29 (CH_{arom}), 132.64 (C_{arom}), 132.76 (C_{arom}), 132.91 (CH_{arom}), 134.35 (CH_{arom}), 140.08 (C_{arom}), 141.05 (C_{arom}), 145.93 (C=C), 166.01 (C=O), 179.96 (C=O). Mass spectrum, *m*/*z*: 248 $[M + H]^+$, 247 $[M]^-$. Found, %: C 77.79; H 3.54; N 5.69. $C_{16}H_9NO_2$. Calculated, %: C 77.72; H 3.67; N 5.67. *M* 247.2.

6-Methylisoindolo[2,1-*a*]quinoline-5,11-dione (VIb). Eluent ethyl acetate–petroleum ether (1 : 4). Yield 70 mg (27%) (*a*), 94 mg (36%) (*b*), 204 mg (78%) (*c*), 211 mg (81%) (*d*); yellow crystals, mp 215–217°C. IR spectrum, ν, cm^{-1}: 1715, 1634, 1603. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.55 s (3H, CH_3), 7.07–9.18 m (8H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 10.58 (CH_3), 104.25 (C=C), 117.71 (CH_{arom}), 123.89 (CH_{arom}), 125.30 (CH_{arom}), 125.46 (CH_{arom}), 127.07 (CH_{arom}), 129.53 (C_{arom}), 129.74 (C_{arom}), 131.14 (CH_{arom}), 134.12 (CH_{arom}), 134.38 (CH_{arom}), 137.81 (C_{arom}), 138.02 (C_{arom}), 152.89 (C=C), 164.37 (C=O), 180.13 (C=O). Mass spectrum, *m*/*z*: 262 $[M + H]^+$, 261 $[M]^-$. Found, %: C 78.1; H 4.3; N 5.3. $C_{17}H_{11}NO_2$. Calculated, %: C 78.15; H 4.24; N 5.36. *M* 261.3.

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