Pyrrolo- and Pyrido[1,2-*a*]indoles *via* An Intramolecular Wittig Reaction

Michael D. Crenshaw [1] and Hans Zimmer*

Department of Chemistry, University of Cincinnati,
Cincinnati, Ohio 45221

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Several pyrrolo- and pyrido[1,2-*a*]indoles were prepared *via* an intramolecular Wittig reaction in good yields. This reaction sequence represents a facile entry into the mitosene ring system.

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The biological activity of the mitomycins (*e.g.* mitomycin C, **1**) and related compounds has caused much attention to the synthesis of the pyrrolo[1,2-*a*]indole ring system [2-5]. In this communication we report a simple synthesis of this ring system and the 6,7,8,9-tetrahydropyrido[1,2-*a*]-indole homologue *via* an intramolecular Wittig reaction between an imide and a phosphorus ylid moiety.

Thus, (2-phthalimidobenzyl)triphenylphosphonium bromide, **2a** was treated with *t*-butyllithium in refluxing tetrahydrofuran to yield 6*H*-isoindolo[2,1-*a*]indol-6-one, **3a**, in 82% yield (equation 1) (Table 1). The amido group of **3a** was reduced quantitatively to the parent ring system, 6*H*-isoindolo[2,1-*a*]indole, with lithium aluminum hydride. Compounds **3b-d** were prepared similarly. An attempt to synthesize **3a** by the Horner-Emmons variant of the Wittig reaction using dimethyl 2-phthalimidobenzylphosphonate gave **3a** in only 25% yield under the same conditions.

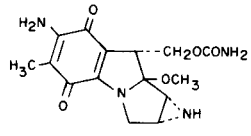
Table 1

Compound	Y	Yield, % [a,b]	Mp (°C)
3a		82	152-153 [c]
3b	-C_2H_4-	78	151-153 [d]
3c	cis 	31	88-89
3d	-C_3H_6-	88	79-81

[a] Yield of isolated product. [b] C, H analysis were acceptable (± 0.4%). [c] Lit [6] mp 153-154.5°. [d] Lit [7] mp 153-154°.

Synthesis of **2a** was achieved by way of the following sequence: 2-toluidine was condensed with phthalic anhydride to yield *N*-(2-tolyl)phthalimide. Treatment of the imide with elemental bromine or *N*-bromosuccinimide gave *N*-[2-(bromomethyl)phenyl]phthalimide. Refluxing of this compound with triphenylphosphine gave the corresponding phosphonium salt **2a** in excellent yield. Compounds **2b-d** were prepared by similar reaction sequences. (2-Maleimidobenzyl)triphenylphosphonium bromide could not be prepared because triphenylphosphine adds to the double bond of maleimides [7].

Work focusing on the appropriate substitution of **3b** tc yield compounds that more closely resemble the mitomycins is under way in this laboratory.



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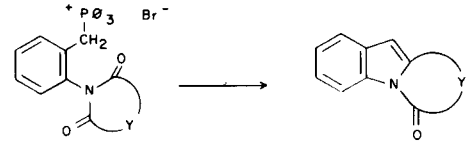

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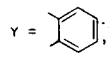
Y =  -C_2H_4-,  -C_3H_6-

EXPERIMENTAL

A General Procedure.

N-(2-Tolyl)phthalimide.

2-Toluidine and phthalic anhydride (1 eq) were heated to 160° for 3 hours without solvent. Upon cooling, the solid was washed several times with hot ethanol, yield 86%, mp 184-185° from benzene (lit [8] mp 180°).

N-[2-(Bromomethyl)phenyl]phthalimide.

N-(2-tolyl)phthalimide was dissolved in refluxing carbon tetrachloride under a nitrogen atmosphere in a pyrex flask. Bromine (1.2 eq) was added dropwise while the reaction mixture was irradiated with a Hanovia ultraviolet quartz lamp (140 watts) until the color was discharged, yield 66%, mp 179-181° (carbon tetrachloride).

(2-Phthalimidobenzyl)triphenylphosphonium Bromide (**2a**).

A chloroform solution of *N*-[2-(bromomethyl)phenylphthalimide and triphenylphosphine (1.1 eq) was refluxed overnight. The volume was reduced, ethyl ether added, and the resulting precipitate was collected, yield 86%, mp 270-274° dec (ethanol).

6*H*-Isoindolo[2,1-*a*]indol-6-one (**3a**).

t-Butyllithium (1.1 eq) was added to a THF solution of (2-phthalimidobenzyl)triphenylphosphonium bromide under a nitrogen atmosphere and the reaction mixture was heated to reflux for 12 hours. The product was separated by liquid chromatography (silica gel-chloroform), yield 82%, yellow plates, mp 152-153° (ethanol); ^{1}H-nmr (deuteriochloroform): 6.55 (S, 1H), 7.1-8.0 (m, 8H); ms: m/e 219.

Anal. Calcd. for $C_{15}H_9NO$: C, 82.17; H, 4.14. Found: C, 81.98; H, 4.17.

1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]indol-3-one (**3b**).

This compound was obtained in a yield of 78%, colorless needles, mp 151-153° (methanol); ^{1}H-nmr (deuteriochloroform): 3.02 (S, 4H), 6.10 (S, 1H), 7.1-7.65 (m, 3H), 7.90-8.1 (m, 1H); ms: m/e 171.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30. Found: C, 76.96; H, 5.31.

6a,7,8,9,10,10a-Hexahydro-6*H*-isoindolo[2,1-*a*]indol-6-one (**3c**).

This compound was obtained in a yield of 31%, yellow crystals, mp 88-89° (methanol); ^{1}H-nmr (deuteriochloroform): 1.20-2.35 (m, 8H), 2.85-3.45 (m, 2H), 6.17 (S, 1H), 7.0-7.6 (m, 3H), 7.9-8.15 (m, 1H); ms: m/e 225.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 79.85; H, 6.65. Both *cis* and *trans* isomers are assumed to exist.

6,7,8,9-Tetrahydropyrido[1,2-*a*]indol-6-one (**3d**).

This compound was obtained in a yield of 88%, colorless plates, mp 79-81° (methanol); ^{1}H-nmr (deuteriochloroform): 1.85 (m, 2H), 2.70 (m, 4H), 6.10 (S, 1H), 7.20 (m, 3H), 8.45 (m, 1H); ms: m/e 185.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.96; H, 6.00.

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