A FACILE SYNTHESIS OF ANTITUMOR AGENT BATRACYLIN VIA INTRAMOLECULAR AZA-WITTIG REACTION

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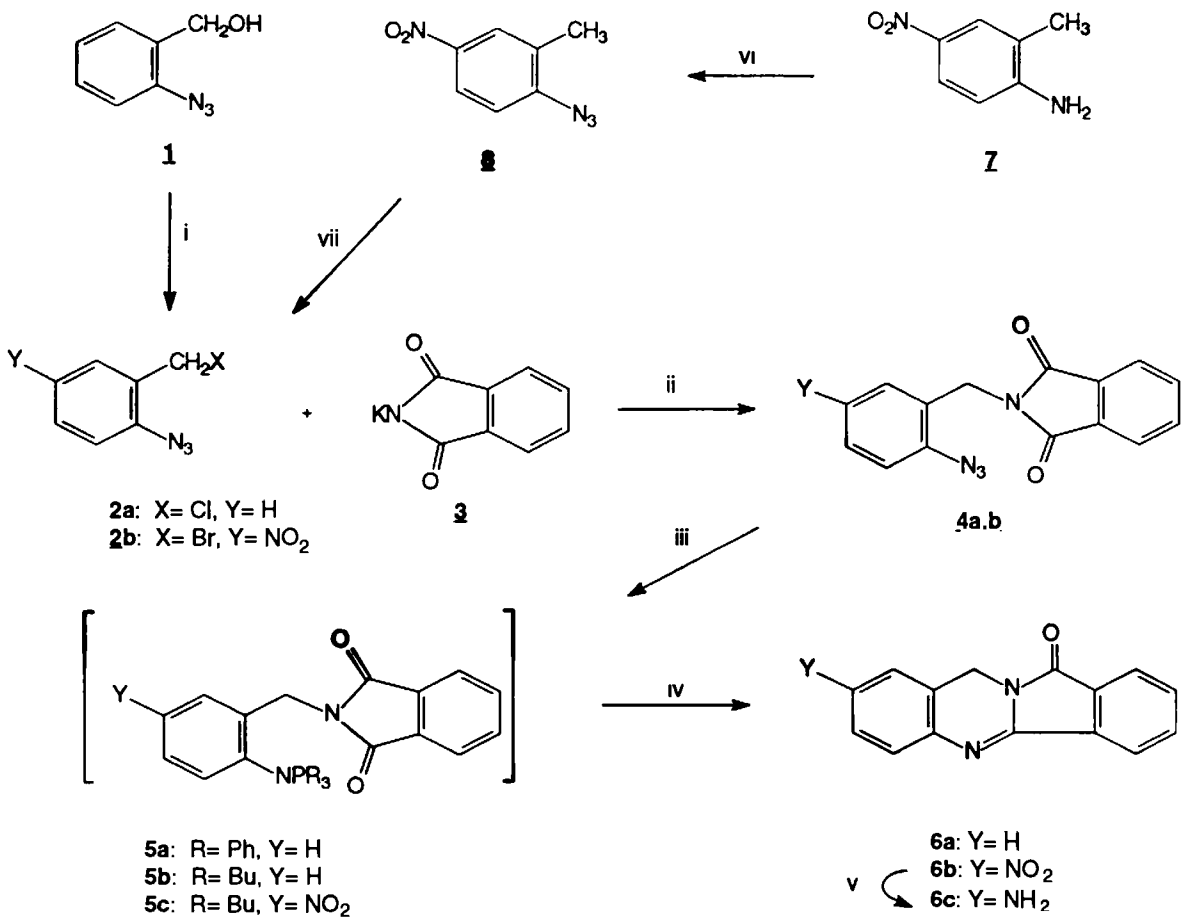
Abstract : A facile synthesis of antitumor agent Batracyclin (NSC-320846), 8-aminoisoindolo[1,2-b]-quinazolin-12(10H)-one by intramolecular aza-Wittig methodology is reported.

The aza-Wittig methodology in heterocyclic synthesis has been growing quite rapidly in recent years, however, application to synthesis of various types of ring systems seems to be yet a challenging problem, because the cyclization reactivity in the intramolecular version is goverened by many factors such as ring-size, substituents on P and N, and carbonyl groups (1). We have reported recently novel and efficient route for synthesis of oxazoles (2), imidazolinones (3a), iminolactams (4), quinazolinones (3,5), and 1,4-benzodiazepinones (6) via intramolecular aza-Wittig reactions. In this communication we wish to report a facile synthesis of dihydroquinazoline ring system by a consecutive Staudinger/aza-Wittig reaction of N-(*o*-azidobenzyl)phthalimides using triphenylphosphine or tributylphosphine, and application to a facile synthesis of antitumor agent Batracylin (NSC-320846) **6**c (7).

The reaction of *o*-azidobenzyl chloride **2**a prepared from the known azidoalcohol **1** (8) with potassium phthalimide **3** in DMF at 55 °C for 1 h gave the azido precursor **4a** in 96% yield as a faintly yellowish crystal after usual work up and flash chromatography on a silica gel column (hexane/AcOEt, 4/1) (Scheme). The reaction of **4a** with triphenylphosphine (1.1 equiv.) in dry xylene at room temperature for 5 h proceeded cleanly to generate iminophosphorane **5a** via the Staudinger reaction but the cyclization via the intramolecular aza-Wittig reaction was very sluggish as judged from TLC . By heating to 90 °C for 9 h, however, the cyclization was completed to afford 10,11-dihydroiso-indolo[1,2-b]quinazolin-12-one **6a** quantitatively after flash chromatography (silica gel, hexane/AcOEt, 2/1) as a yellowish crystal. The same reaction of **4a** with tributylphosphine (1.1 equiv.) in dry benzene proceeded more rapidly and after



Reagents and conditions: i, $SOCl_2$, CH_2Cl_2, 0 °C, 3 h, 98%; ii, DMF, 55 °C, 1 h, 96%; iii, R_3P, xylene or benzene, room temp., 2 h, 100%; iv, For **5a**, 140 °C, 9 h, 100%, or for **5b**, room temp., 10 h, 97%, for **5c**, 140 °C, 12 h, 86%; v, HCO_2NH_4, 10% Pd-C, CH_2Cl_2-MeOH, room temp., 1.5 h, 98%; vi, $NaNO_2$, 4*N* HCl, 0 °C, 1 h, NaN_3, 0-5 °C, 15 min., 87%; vii, NBS, $(PhCO_2)O_2$, C_6H_6, 80 °C, 8 h, 72%.

Scheme

12 h at room temperatutre (ca. 20-25 °C), **6a** was obtained in 97% isolated yield. Above results confirmed that the fused dihydroquinazoline ring could be synthesized efficiently in one-pot via the consecutive Staudinger/aza-Wittig reaction.

We applied this methodology to an improved synthesis of the well known synthetic antitumor agent Batracylin (NSC-320846) **6c** (7). Commercially available 2-methyl-4-nitroaniline **7** was converted to

azide **8** (87%) by the standard procedure, and benzylic bromination of **8** with NBS in dry benzene gave azidobenzyl bromide **2b** in 72% yield as a brownish solid. The reaction of **8** with potassium phthalimide in DMF at 80 °C for 6 h gave **4b** in 70% yield as a yellowish crystal after flash chromatography (silica gel, hexane/AcOEt, 2/1). Treatment of **4b** with tributylphosphine (1.1 equiv.) in dry xylene for 12 h at 140 °C afforded **6b** (86%) as a yellowish crystal after usual work up. Such heating was required for this cyclization because the electron withdrawing nitro substituent at para-position to the imno group diminished reactivity of the imino phosphorane. Reduction of the nitro group with ammonium formate and 10% Pd-C in CH_2Cl_2-MeOH afforded amino derivative, Batracyclin **6c** in 98% yield as a yellowish solid which was characterized by spectral and analytical data (Scheme).

The known synthetic routes to Batracylin use a) thermal condensation of 2,5-diaminobenzylamine with phthalic anhydride (56%) (9), and b) acid catalyzed cyclization of N-[2-ethoxycarbonylamino-5-acetylaminobenzyl]phthalimide in conc. H_2SO_4 at 100 °C (95%) (10). Compared with these two known methods, present synthesis provides a new convenient route to Batracylin and fused dihydroquinazoline derivatives from readily available precursors.

Satisfactory spectroscopic and analytical data have been obtained for all compounds:

4a: mp 184-186°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.92-7.70 (m,4H), 7.36-7.03 (m,4H), 4.86 (s,2H); MS(El) m/z(%)278(M+,19), 250(50), 249(64), 104(100).

6a: mp 186.5-188.0°C; ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.10-7.17(m, 8H), 5.01 (s,2H); MS(El) m/z(%) 234 (M+,65), 233(100).

2b: mp 55-58°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.30(dd, 1H, J=0.4, 2.6Hz), 8.24 (dd, 1H, J=2.6, 8.6Hz), 7.30 (d, 1H, J=8.6Hz), 4.48 (s,2H); MS(El) m/z(%) 256 (M+, 13), 230(21), 149(100).

4b: mp 184-188°C(dec.); ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.22 (dd, 1H, J=2.6, 8.8Hz), 8.08 (d, 1H, J=2.6Hz), 7.29 (d, 1H, J=8.8Hz), 7.94-7.76 (m, 4H), 4.89 (s,2H); MS(El) m/z(%) 323 (M+, 10), 295(40), 104(100).

6b: mp 283-287 (AcOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21 (dd, 1H, J=2.7, 8.5Hz), 8.10-8.08 (m, 2H), 7.96-7.94 (m, 1H), 7.80-7.73 (m, 2H), 7.61 (d, 1H, J=8.5Hz), 5.08 (s, 2H); MS(El) m/z(%) 279 (M+, 100).

6c: mp 244-247°C, lit, 287°C, lit. 287-288°C(16), 270°C(dec.)(17); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (d, 1H, J=7.5Hz), 7.90 (d, 1H, J=7.5Hz), 7.69 (ddd, 1H, J=7.5, 7.5, 1.0Hz), 7.63 (ddd, 1H, J=7.5, 7.5, 1.0Hz), 7.32 (d, 1H, J=8.5Hz), 6.63 (dd, 1H, J=8.5, 2.5Hz), 6.50 (d, 1H, J=2.5Hz), 4.92 (s, 2H), 3.86 (s, 2H, NH_2); MS(El) m/z(%) 249 (M+, 85), 248 (100).

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