Chemoselectivity in the Intramolecular Aza-Wittig Reaction of *N*-[2-(Trisubstituted-phosphoranylidene)aminobenzoyl]-2-pyridone-5-carboxylic Acid Derivatives

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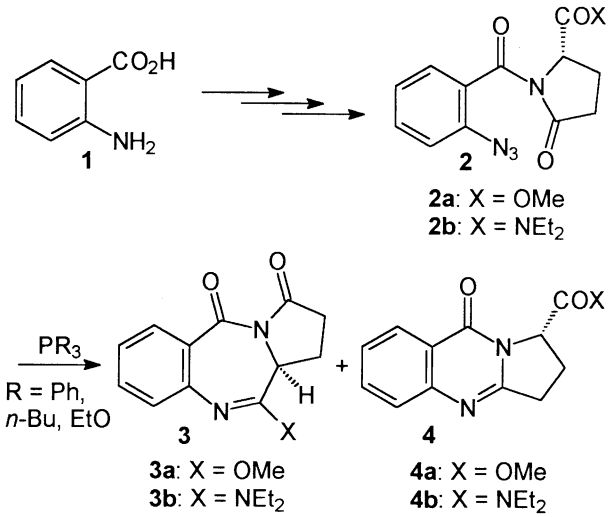
The intramolecular aza-Wittig reaction of (5*S*)-*N*-[2-(trisubstituted-phosphoranylidene)aminobenzoyl]-2-pyridone-5-carboxylic acid derivatives chemoselectively gave 5-pyrrolo[2,1-*c*][1,4]benzodiazepinone derivatives or 5(1*H*)-pyrrolo[2,1-*b*]quinazolinone derivatives depending on the substituents.

Over the past decade, not only intermolecular but also intramolecular aza-Wittig methodology has been demonstrated to be a powerful tool for the formation of carbon-nitrogen double bonds (*e.g.* imines, imidates, and amidines) and heterocumulene bonds (*e.g.* isocyanates and carbodiimides).[1] The key intermediate iminophosphoranes, aza-ylides, are conveniently generated by the Staudinger reaction or the modified Kirsanov reaction *i.e.*, Appel's method *etc.*[2] We and other workers have recently reported that the intramolecular aza-Wittig reaction is a useful methodology for synthesis of 5-7 membered nitrogen heterocyclic compounds including natural products.[3] 5-Pyrrolo[2,1-*c*][1,4]benzodiazepinone derivatives[4] are known to recognize and bind to specific sequences of DNA. Such compounds have potential as regulators of gene expression with possible application as therapeutic agents in the treatment of certain genetic disorders including some cancers. Also, quinazoline derivatives[5] are known to be one of alkaloids including natural products, *e.g.*, vasicinone[6] *etc.* We would like to report here chemoselective formation of 7-membered [1,4]benzodiazepine derivatives and 6-membered quinazoline derivatives in the intramolecular aza-Wittig reaction of (5*S*)-*N*-[2-(trisubstituted-phosphoranylidene)aminobenzoyl]-2-pyridone-5-carboxylic acid derivatives.

(5*S*)-*N*-(2-Azidobenzoyl)-2-pyridone-5-carboxylic acid derivatives **2** were readily accessible from (5*S*)-2(1*H*)-pyridone-5-carboxylic acid ester or amide and 2-azidobenzoyl chloride, which was prepared from azidation of anthranilic acid **1** followed by treatment with thionyl chloride. The intramolecular aza-Wittig reaction of (5*S*)-*N*-[2-(trisubstituted-phosphoranylidene)-aminobenzoyl]-2-pyridone-5-carboxylic acid derivatives was carried out as follows. To a solution of azide derivatives **2** in dry benzene or xylene was added phosphine reagents (Ph_3P, *n*-Bu_3P, $(EtO)_3P$). The mixture was stirred at ambient temperature for appropriate time to complete the Staudinger reaction. After disappearance of **2**, the mixture was heated at 80 °C ~ 140 °C to complete the intramolecular aza-Wittig reaction. Since iminophosphoranes are able to react with both ester carbonyl function and imide carbonyl function in the intramolecular aza-



Scheme 1. Synthetic route of **3** and **4**.

Table 1. Chemoselectivity in the Staudinger reaction/ the intramolecular aza-Wittig reaction of *N*-(2-azidobenzoyl)-2-carboxilic acid derivatives **2**

Entry	X	R[a]	reaction conditions	Yield (%)[b]	Ratio (**4** : **3**)[c]
1	OMe	*n*-Bu	r. t., 3 h	79	12 : 88
2	OMe	Ph	r. t., 4 h then 80 °C, 9 h	63	3 : 97
3	OMe	EtO	r. t., 6 h then 80 °C, 9 h	45	64 : 36
4	OMe	EtO	r. t., 6 h then 80 °C, 12 h	69	64 : 36
5	NEt_2	*n*-Bu	r. t., 3 h then 80 °C, 4 h	91	>99 : trace
6	NEt_2	Ph	r. t., 4 h then 110 °C, 2 h then 140 °C, 6.5 h	98	>99 : trace

[a] 1.1 Equivalent was used.
[b] After hydrolysis of **3a** to transform **4a**, yields were determined.
[c] Determined by 1H NMR spectra.

Wittig reaction, two kinds of cyclic compounds **3**, **4** were competitively produced. The structures of two cyclic compounds were distinguished by various spectral data, in particular, fragment ion peak of mass spectrometric analysis.[7] Furthermore, the structure of **3a** was accurately established by X-ray crystallographic analysis. Diethyl amide derivative **2b** was specifically led to **4b** because reactivity of amide carbonyl function was much lower than that of imide carbonyl function. Yields were determined after hydrolysis[8] (HCl/THF, r.t., 3 h) of **3a** to **4a** because **3a** was sensitive to moisture and correct yields were difficult to determine. Ratios of **3** to **4** were decided by ^{1}H NMR spectra directly after the intramolecular aza-Wittig reaction was finished. According to the results summarized in Table 1, the formation ratio of heterocyclic compounds (7-membered ring *versus* 6-membered ring) was considerably depended upon carbonyl function (X = OMe, NEt_2) and phosphine reagents. It is known that the oxazaphosphetane, important intermediate of the aza-Wittig reaction, of six-membered ring formation is influenced by steric effect of the substituent of phosphine reagent (Ph_3P > *n*-Bu_3P > $(EtO)_3P$).[3b] Thus, seven-membered ring compound was predominantly formed with use of Ph_3P or *n*-Bu_3P. Also, with use of $(EtO)_3P$, which was smaller reagent, six membered ring compound was predominantly formed. Both of [1,4]benzodiazepine and quinazoline derivatives are pharmacologically important including natural products such as antibiotics, alkaloids and so on. In view of this, present results may be useful for molecular design of related heterocyclic compounds by aza-Wittig methodology. Further studies on such application are under way. This work is partly supported by a Grant-in-Aid from the Ministry of Education Science and Culture of Japan.

References and Notes

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7 Some selected physical and spectral data of **2a**: *Rf* = 0.30 (AcOEt: *n*-Hexane 5:1); white solid; mp 170-172 °C; $[\alpha]_D^{23.9}$ = +919.2° (c 0.63 $CHCl_3$); IR (neat) 1769, 1653, 1601, 1458, 1437, 1333, 1314, 1292, 1244, 1177, 1150, 1047, 988, 907, 851, 829, 758, 731, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.96 (1H, ddd, *J* = 7.8, 1.6, 0.6 Hz), 7.54 (1H, ddd, *J* = 8.2, 7.4, 1.6 Hz), 7.24 (1H, ddd, *J* = 8.0, 7.4, 1.6 Hz), 7.18 (1H, ddd, *J* = 8.0, 1.4, 0.6 Hz), 4.51 (1H, dd, *J* = 8.6, 1.0 Hz), 3.97 (3H, s), 2.92-2.52 (3H, m), 2.27-2.10 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 173.69, 165.53, 162.60, 144.51, 133.57, 131.71, 127.01, 126.78, 125.14, 55.04, 54.24, 31.80, 18.45; MS (EI) *m/z* (%) $C_{13}H_{12}N_2O_3$ (244.25) 244 (M^+, 100), 216 (3), 161 (39), 146 (91).

Some selected physical and spectral data of **3a**: *Rf* = 0.21 (AcOEt: *n*-Hexane 5:1); white solid; mp 99-101 °C; $[\alpha]_D^{26.1}$ = -144.6° (c 0.63 $CHCl_3$); IR (neat) 1748, 1680, 1630, 1562, 1470, 1437, 1379, 1335, 1281, 1213, 1179, 1044, 990, 868, 774, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.27 (1H, ddd, *J* = 8.0, 1.4, 0.6 Hz), 7.76 (1H, ddd, *J* = 8.4, 6.8, 1.6 Hz), 7.67 (1H, ddd, *J* = 8.2, 1.6, 0.6 Hz), 7.46 (1H, ddd, *J* = 8.2, 6.8, 1.4 Hz), 5.18 (1H, dd, *J* = 9.4, 3.2 Hz), 3.82 (3H, s), 3.30 (1H, ddd, *J* = 17.4, 9.8, 8.8 Hz), 3.14 (1H, ddd, *J* = 17.6, 9.0, 3.8 Hz), 2.61 (1H, dddd, *J* = 13.6, 10.0, 9.4, 9.0 Hz), 2.37 (1H, dddd, *J* = 13.4, 9.0, 3.8, 3.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 170.77, 160.92, 159.22, 149.52, 134.91, 127.29, 126.93, 126.83, 120.76, 59.26, 53.09, 31.17, 24.32; MS (EI) *m/z* (%) $C_{13}H_{12}N_2O_3$ (244.25) 244 (M^+, 45), 213 (1), 185 (100).

8 The isolated **3a** was hydrolyzed to **4a** in HCl/THF at room temperature for 3 h (quantitative yield).