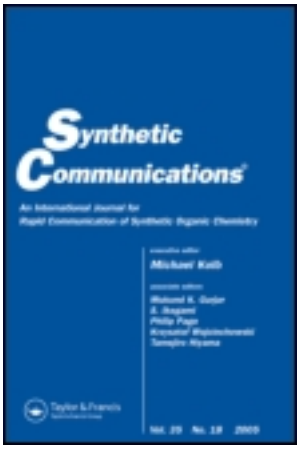

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A Facile Synthesis of 2-Mino-3H-Quinazolin-4-Ones with Tandem Aza-Wittig Reaction

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A FACILE SYNTHESIS OF 2-AMINO-3H-QUINAZOLIN-4-ONES WITH TANDEM AZA-WITTIG REACTION

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Abstract: 2-Amino-3H-quinazolin-4-ones **8** were prepared from tandem aza-Wittig reaction of iminophosphorane **5** with aromatic isocyanate and nucleaphilic reagent HY in mild condition.

Quinazolinones are heterocycles bearing good biological and pharmaceutical activities. There are many known methods for synthesis of 3H-quinazolin-4-ones[1–4], including intramolecular aza-Wittig reaction[5] and tandem aza-Wittig reaction[6].However,2-amino or other 2-nucleophile substituted 3H-quinazolin-4-ones were not easily prepared according to previous procedure. Continuing our work in the aza-Wittig reaction and carbodiimide chemistry[7–10],we studied the tandem aza-Wittig reaction of iminophosphorane **5** with aromatic isocynate and nucleaphilic reagent HY.

Iminophosphorane **5** can be easily prepared from anthranilic acid **1** according to the following procedure: **1** was esterified by ethanol in presence of HCl to give **2** in 84% yield, **2**

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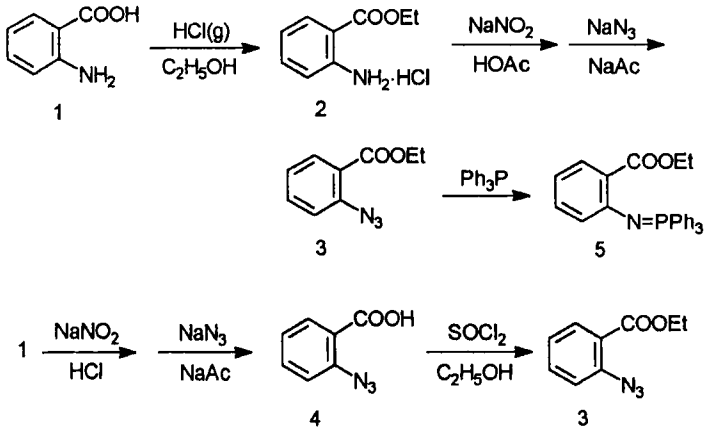
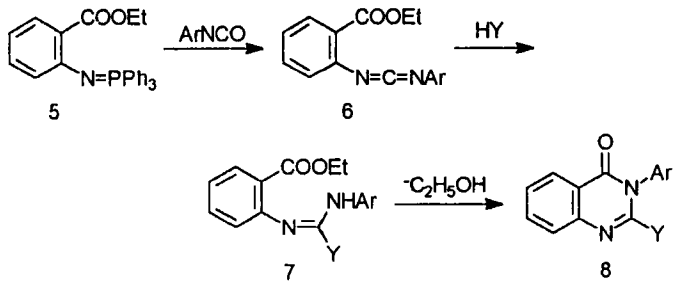
was diazotized by $NaNO_2$/HOAc and subsequent azidation to give **3** in 76% yield,**3** reacted with Ph_3P to created iminophosphorane **5** in 85% yield. **3** was also prepared from **1** by first diazotization/azidation to give **4** in 80% yield and subsequent esterification with $C_2H_5OH/SOCl_2$ in 92% yield.



The iminophosphorane **5** reacted with aromatic isocynate at room temperature to give carbodiimide **6**,which was allowed to react with nucleaphilic reagent HY subsequently to yield quinazolinone **8** via cyclization of the guanidine-type intermediate **7**. This approach supplies an easily accessible route to 3H-quinazolin-4-ones with various substituents. Since attempt to isolate the carbodiimide intermediate **6** resulted in formation of the urea due to the hydrolysis of **6** during column chromatograph, the reaction was carried out by a tandem process.



The reaction condition for this tandem process was researched. The results are listed in Table 1 and summarized as follows:

1.The reaction time for cyclization must be more than 24hr when HY is a secondary amine, different from the reaction time (2~8hr) needed for preparation of imidazolinones using similar method[8].This result shows that the cyclization to quinazolinone is more difficult.

2.When HY is bulky diisopropylamine or benzotriazole,only the guanidine intermediate **7d** or **7e** was separated at room temperature. Even after heating for 8hr in toluene,the guanidine **7d** was recovered unchanged due to the steric hindrance.

3.The cyclization is also related to the aryl substituent (Ar). When HY is piperidine or morpholine,the cyclization can be achieved with various substituted phenyl group (Ar) at room temperature (**8b**,**8c**,**8f**,**8g**,**8i**),however,when HY is diethylamine,the reaction must be carried out in refluxing toluene with chloro-substituted phenyl (**8h** and **8j**).

In summary, we demonstrate here that the tandem aza-Wittig reaction affords a new general good yield entry to a variety of 2-amino-3H-quinazolin-4-ones.

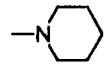
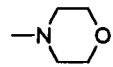
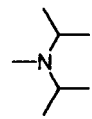
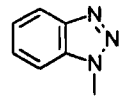
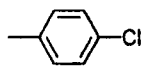
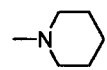
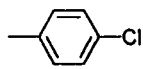
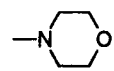
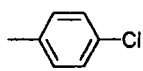
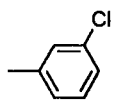
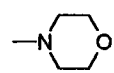
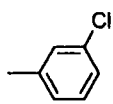
EXPERIMENTAL

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a Shimadzu IR-408 infrared spectrometer. NMR were taken on a Varian XL-200 spectrometer.

General procedure for the preparation of quinazolinone **8** or guanidine intermediate **7**:

To a solution of iminophosphorane **5** (2.12g,5mmol) in dry methylene dichloride (15ml) was added aromatic isocyanate (5mmol) under dry nitrogen at room temperature. After the reaction mixture was stand for 12 hours, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2,20ml) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **6**. To the solution of **6** in CH_2Cl_2 or toluene (15ml) was added HY (5mmol). The mixture was stirred at room temperature or

Table 1 Preparation of 2-Amino-3H-quinazolin-4-ones 8

Compounds	Ar	Y	Condition	Yield(%)*
8a	Ph	$-NEt_2$	r.t./24hr	88
8b	Ph		r.t./24hr	86
8c	Ph		r.t./24hr	85
7d	Ph		r.t./24hr	80
7c	Ph		r.t./24hr	82
8f			r.t./24hr	72
8g			r.t./24hr	76
8h		$-NEt_2$	110℃/8hr	64
8i			r.t./24hr	78
8j		$-NEt_2$	110℃/8hr	70

*isolated yield based on iminophosphorane **5**

refluxing temperature,the reaction mixture was condensed and the residual was recrystallized from methylene dichloride/petroleum ether or purified by a short silica gel column to give quinazolinone **8** or guanidine intermediate **7**.

^{1}HNMR,IR and MS data for some compounds of **8** and **7**:

8a:yield 88%,white crystals,m.p.109~110℃, ^{1}HNMR($CDCl_3$,200MHz) δ 8.16~7.20(m,9H, ArH), 3.07(q,4H,J=7.2Hz,NCH_2), 0.82(t,6H,J=7.2Hz,CH_3); IR(cm^{-1}), 1676, 1544, 1472, 1310, 1080, 774, 700; MS(m/z), 293(M^+,50.15), 264(100), 221(36.28), 188(30.55), 174(20.17), 119 (15.25), 90(28.97).

8b:yield 86%,white crystals,m.p.155~156℃, ^{1}HNMR($CDCl_3$,200MHz) δ 8.17~7.28(m,9H, ArH), 3.13(t,4H,J=5.1Hz,NCH_2), 1.44~1.24(m,6H,CH_2); IR(cm^{-1}), 1684, 1562, 1450, 1370, 1106, 770,692; MS(m/z), 305(M^+,63.02), 276(59.49), 262(16.41), 221(44.12), 160(85.12). 119(62.04), 77(100).

8c:yield 85%,white crystals,m.p.166~167℃, ^{1}HNMR($CDCl_3$,200MHz) δ 8.20~7.29(m,9H, ArH),3.46(t,4H,J=4.5Hz,OCH_2),3.17(t,4H,J=4.4Hz,NCH_2); IR(cm^{-1}), 1685, 1566, 1452, 1378, 1108, 762, 690; MS(m/z), 307(M^+,23.11), 276(10.45), 262(36.65), 250(54.03), 221(42.12), 216(32.09),174(27.95),119(47.29),77(100).

7d: yield 80%, white crystals, m.p.61~62℃, ^{1}HNMR($CDCl_3$,200MHz) δ 9.40(s,1H,NH), 7.88~6.84(m,9H,ArH),4.38(q,2H,J=7.0Hz,NCH),4.22~4.10(m,2H,OCH_2),1.44(t,3H,J=7.2Hz, $OCCH_3$), 1.41(d,12H,J=6.8Hz,$NCCH_3$); IR(cm^{-1}), 1692,1658,1586,1530,1256,1040,928,746, 698; MS(m/z), 367(M^+,5.58),324(26.62),221(55.86),146(40.58),119(91.82),58(100).

7e:yield 82%,white crystals,m.p.111~112℃, ^{1}HNMR($CDCl_3$,200MHz) δ 8.49~6.92(m, 14H,ArH and NH),4.43(q,2H,J=7.0Hz,OCH_2),1.43(t,3H,J=7.0Hz,CH_3); IR(cm^{-1}),3310,1682, 1568,1500,1250,1148,750,694; MS(m/z), 385(M^+,1.24), 310(12.12), 277(70.68), 221(55.34), 183(19.47),146(44.65),119(83.87),77(100).

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