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Solid-Phase Synthesis of 3,4-Dihydroquinazoline

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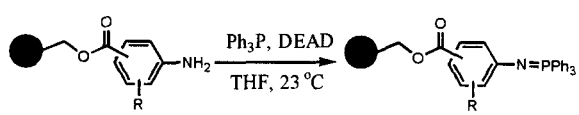
Abstract: A novel, facile and efficient method for the synthesis of aryl iminophosphorane has been developed by treating a series of Ar-NH_2 (**1**) attached to a solid support with Ph_3P and diethyl azodicarboxylate at room temperature. The resulting solid-supported cinnamyl iminophosphorane (**4**) was treated with an aryl isocyanate to generate the corresponding solid-supported carbodiimide (**5**), which upon exposure to a secondary amine underwent 1,2-addition followed by an intramolecular Michael addition to afford the desired 3,4-dihydroquinazoline (**7**). © 1997 Elsevier Science Ltd.

The promise of combinatorial approaches to drug discovery will only be realized by the application of this technique to the synthesis of small molecule, non-peptide structures.[1] Clearly, this is widely appreciated, since most of the recent publications in this field are focused on the synthesis of small, drug-like molecules.[2] Specifically, substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. As a result, a number of pharmaceutically useful heterocyclic compounds recently have been prepared by solid-phase methodology, which is a convenient method for the generation of combinatorial libraries.

The carbodiimides are well known dehydrative agents and are very useful for the selective construction of many nitrogen-containing heterocyclic systems. Access to the carbodiimide functionality is readily achieved by treating iminophosphoranes with heterocumulenes (isocyanates or thioisocyanates)[3] in an aza-Wittig reaction. Iminophosphoranes, the key intermediates in this synthetic pathway, are generally prepared by Staudinger reaction,[4] *via* the imination reaction of trivalent phosphorus derivatives with organic azides. Although there are a number of recent reports detailing the synthesis of iminophosphoranes,[3, 5] the application of this useful intermediate to the synthesis of 3,4-dihydroquinazolines in solid-phase has not been highlighted.

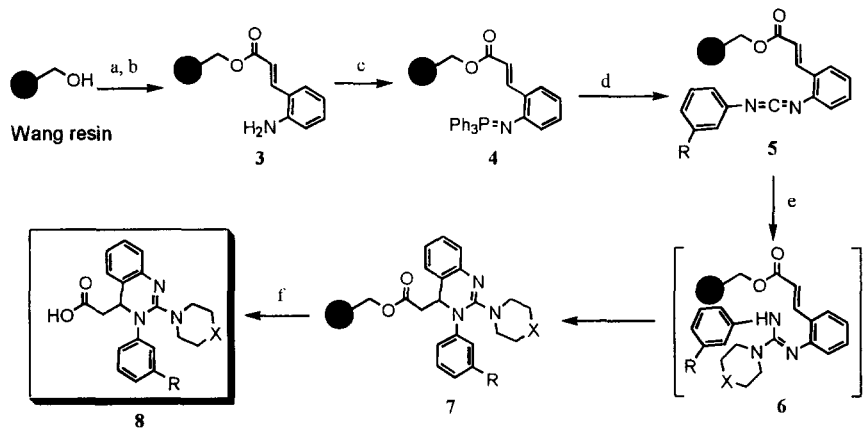
In our ongoing project directed toward the synthesis of structurally diverse heterocycles, we discovered a novel, facile and efficient method for the synthesis of aryl iminophosphorane in solid-phase (**Figure 1**) and successfully applied this protocol to the synthesis of 3,4-dihydroquinazolines. For example, substituted aminobenzoic acid attached to Wang resin was treated with Ph_3P and diethyl azodicarboxylate (DEAD) in THF at 23 °C, which are typical Mitsunobu reaction conditions[6], to form the corresponding aryl iminophosphorane in high yield (>95%) and in high purity (>97%). The reaction took place smoothly under mild, neutral conditions.



1 **2**

Figure 1. Solid-phase synthesis of aryl iminophosporane.

We next employed this intermediate in the solid-phase approach to the synthesis of 3,4-dihydroquinazoline[7] *via* aza-Wittig coupling, and subsequent addition of a secondary amine to the carbodiimide followed by a tandem intramolecular Michael addition.[8] Our synthetic approach is illustrated in **Scheme 1**.[9] Commercially available 2-nitrocinnamic acid was attached to Wang resin followed by reduction of the nitro functionality to an amino group with $SnCl_2 \cdot 2H_2O$ in DMF.[10] Treatment of the resulting **resin 3** with excess Ph_3P and DEAD in THF proceeded smoothly at room temperature to provide the iminophosphorane (**resin 4**). Very high yield and high purity were obtained as assessed by HPLC. Surprisingly, no impurities from over-reaction were observed. This was also the case when the reaction times were extended. The carbodiimide **resin 5** was prepared by the aza-Wittig reaction of the iminophosphorane with ArNCO in toluene at room temperature under nitrogen. The formation of the carbodiimide could be confirmed by the analysis of solid-phase FT-IR (KBr film), which displayed an intense absorption at 2135 cm^{-1}, which is the characteristic absorption of carbodiimides.[11] Diaromatic substituted urea was obtained by treating the **resin 5** with moist TFA/CH_2Cl_2 and assessing the purity of the structurally characterized urea by HPLC.[12]



Scheme 1. Solid-phase synthesis of 3,4-dihydroquinazoline. Reagents and conditions: (a) 2-nitrocinnamic acid, DIC, DMAP, DMF/CH_2Cl_2, 23 °C, 17 h; (b) $SnCl_2 \cdot 2H_2O$, DMF, 23 °C, 6 h; (c) Ph_3P, DEAD, THF, 23 °C, 36 h; (d) ArNCO, toluene, 23 °C, 4 h; (e) secondary amine, *m*-xylene, 23 °C, 2 h, then 80 °C, 4 h; (f) TFA/CH_2Cl_2, 23 °C, 1h.

Treatment of the carbodiimide resin with excess secondary amine in anhydrous *m*-xylene at room temperature for 2 hours generated the intermediate guanidine (**resin 6**). The reaction progress could be qualitatively monitored by the analysis of solid-phase FT-IR by following the disappearance of the carbodiimide absorption at 2135 cm^{-1}. Interestingly, the guanidine gradually underwent the intramolecular Michael addition even at this stage. For example, with piperidine ($X=CH_2$) 50-60% of the guanidine was converted to the corresponding 3,4-dihydroquinazoline, whereas only 10-25% of the desired cyclization product was observed with morpholine or thiomorpholine (X=O or S). Upon heating the mixture at 80 °C for 4 hours, the guanidine was completely cyclized to the corresponding 3,4-dihydroquinazoline (**resin 7**). The resulting resin was then treated with TFA/CH_2Cl_2, dried and lyophilized to give the desired heterocycle **8** in excellent yield and purity (**Table 1**). With more reactive aryl isocyanates (phenyl isocyanate and *m*-tolyl isocyanate), the yields and purities were more than 90%; also, the yields for the pure products were observed to be very good (>80%) even with deactivated aryl isocyanate (3-fluorophenyl isocyanate). There was no

significant difference on the course of reaction between the secondary amines and the source of the impurities was mainly from the hydrolysis of the carbodiimide. All the products were identified by ^{1}H NMR, ^{13}C NMR, HPLC, and mass spectroscopy.

In summary, an efficient route has been developed for the synthesis of 3,4-dihydroquinazoline in solid-phase. This procedure allows the construction of a 3,4-dihydroquinazoline scaffold with a set of diverse substituents at various positions in a convergent fashion.

Table 1. Solid-phase synthesis of 3,4-dihydroquinazoline **8**

3,4-Dihydroquinazoline	R	X	Yield (%)[a]	Purity (%)[b]
8a	H	CH_2	95	90
8b	H	O	100	94
8c	H	S	96	93
8d	CH_3	CH_2	94	92
8e	CH_3	O	96	93
8f	CH_3	S	91	90
8g	F	CH_2	90	83
8h	F	O	91	87
8i	F	S	87	85

a) Yields are based on mass balance of lyophilized product relative to the resin substitution level. b) Purity was determined by HPLC analysis.

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9. *A Typical Procedure for the Preparation of individual 3,4-Dihydroquinazoline* **8a.** To the Wang resin (0.10 g, 0.80 mmol/g substitution) was added 2-nitrocinnamic acid (77 mg, 0.40 mmol) in 1 mL DMF/CH_2Cl_2 (v:v = 1:1) followed by DIC (63 μL, 0.40 mmol) and DMAP (10 mg, 0.08 mmol). After shaking at 23 °C for 17 hours, the resin was washed with DMF, CH_2Cl_2, and MeOH, and added into 1 mL of 2 M $SnCl_2 \cdot 2H_2O$ in DMF then shaken at 23 °C for 6 hours. The resulting **resin 3** was washed with DMF, CH_2Cl_2, and MeOH, and dried under high vacuum. To the mixture of **resin 3** and Ph_3P (105 mg, 0.40 mmol) in 1 mL of anhydrous THF was added dropwise DEAD (63 μL, 0.40 mmol) at 23 °C. The mixture was shaken at 23 °C for 36 hours, followed by washing the resin with dry THF and CH_2Cl_2. After drying under high vacuum, **resin 4** was treated with phenyl isocyanate (43 μL, 0.40 mmol) in 1 mL of anhydrous toluene at 23 °C for 4 hours. The resulting carbodiimide **resin 5** was filtered and washed with anhydrous CH_2Cl_2 and ethyl ether under nitrogen. To the **resin 5** was added piperidine (40 μL, 0.40 mmol) in 1 mL of anhydrous *m*-xylene, and the mixture was shaken at 23 °C for 2 hours then heated at 80 °C for 4 hours. After being washed with DMF, CH_2Cl_2, and MeOH, **resin 7** was dried under high vacuum, and treated with a solution of 50% TFA in CH_2Cl_2 at 23 °C for 1 hour to release the resin-bond 3,4-dihydroquinazoline **8a**. Removal of the volatile under a stream of nitrogen followed by lyophilizing with 50% CH_3CN in water afforded the pure compound as powder. Other 3,4-dihydroquinazoline derivatives were prepared with the similar procedure.
8a: ^{1}H NMR (DMSO-d_6) δ 1.31-1.35(m, 2 H), 1.48 (bs, 4 H), 2.72 (dd, *J*=15.4 Hz, *J'*=6.4 Hz, 1 H), 2.92 (dd, *J*=15.1 Hz, *J'*=8.5 Hz, 1 H), 3.34-3.43 (m, 4 H), 5.31 (dd, *J*=8.6 Hz, *J'*=6.4 Hz, 1 H), 7.10-7.47 (m, 9 H), 12.05 (bs, 1 H). ^{13}C NMR (DMSO-d_6) δ 22.8, 24.3, 40.1, 49.1, 60.3, 118.0, 124.1, 125.8, 126.0, 126.1, 127.2, 129.1, 130.1, 132.5, 143.1, 152.0, 171.3. MS (EI) *m/z* 350.44 (MH^+).
8b: ^{1}H NMR (DMSO-d_6) δ 2.76 (dd, *J*=15.4 Hz, *J'*=6.9 Hz, 1 H), 3.01 (dd, *J*=15.4 Hz, *J'*=8.1 Hz, 1 H), 3.36-3.63 (m, 8 H), 5.35 (t, *J*=7.6 Hz, 1 H), 7.22-7.47 (m, 9 H), 12.18 (bs, 1 H). ^{13}C NMR (DMSO-d_6) δ 40.0, 48.3, 60.3, 64.8, 118.0, 124.0, 125.9, 126.0, 126.1, 127.4, 129.2, 130.2, 132.2, 142.7, 152.1, 171.3. MS (EI) *m/z* 352.31 (MH^+).
8c: ^{1}H NMR (DMSO-d_6) δ 2.43 (bs, 2 H), 2.58-2.64 (m, 2 H), 2.73 (dd, *J*=15.4 Hz, *J'*=6.7 Hz), 3.01 (dd, *J*=15.6 Hz, *J'*=8.3 Hz, 1 H), 3.57-3.76 (m, 4 H), 5.31 (dd, *J*=8.1 Hz, *J'*=6.8 Hz, 1 H), 7.25-7.50 (m, 9 H), 12.20 (bs, 1 H). ^{13}C NMR (DMSO-d_6) δ 25.3, 40.0, 50.9, 60.3, 118.2, 124.4, 125.9, 126.1, 127.5, 128.8, 129.2, 130.2, 132.3, 142.9, 152.9, 171.3. MS (EI) *m/z* 368.20 (MH^+).
8e: ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3 H), 2.74 (dd, *J*=15.4 Hz, *J'*=6.9 Hz, 1 H), 2.98 (dd, *J*=15.4 Hz, *J'*=7.8 Hz, 1 H), 3.35-3.61 (m, 8 H), 5.32 (t, *J*=7.6 Hz, 1 H), 7.10-7.45 (m, 8 H), 12.19 (bs, 1 H). ^{13}C NMR (DMSO-d_6) δ 20.8, 40.0, 48.3, 60.2, 64.7, 117.9, 121.0, 124.4, 125.9, 126.1, 128.0, 129.2, 129.6, 129.9, 132.2, 139.9, 142.6, 152.0, 171.2. MS (EI) *m/z* 366.33 (MH^+).
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