JOURNAL OF combinatorial CHEMISTRY

Report

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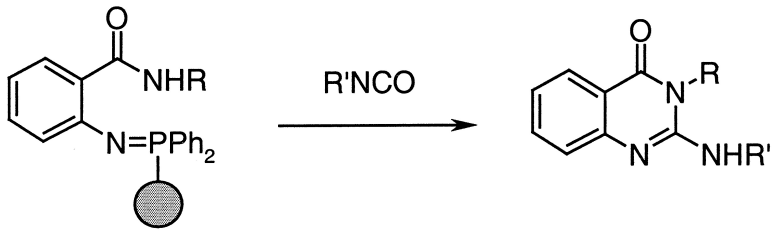
J. Comb. Chem., **2001**, 3 (3), 255-256• DOI: 10.1021/cc000113e • Publication Date (Web): 25 April 2001



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A Polymer-Bound Iminophosphorane Approach for the Synthesis of Quinazolines

Wei Zhang,[†] John P. Mayer,*[,‡] Steven E. Hall,[†] and John A. Weigel[†]

Sphinx Pharmaceuticals, 840 Memorial Drive, Cambridge, Massachusetts 02139, and Lilly Corporate Center, DC2810 Building 45, Indianapolis, Indiana 46285

Received December 29, 2000

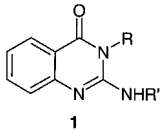
Recent years have seen combinatorial chemistry and related parallel synthesis techniques emerge as important tools for lead generation in drug discovery.[1] In particular, synthetic techniques based on solid-phase chemistry have attracted much attention because of the ease of purification and automatic manipulation.[2]

The quinazoline skeleton (see Chart 1) is an important pharmacophore that occurs frequently in medicinal chemistry literature.[3] The 2-amino-substituted quinazolinones **1** have been shown to be potential histamine H2 antagonists,[4a] thymidylate synthase inhibitors,[4b] cognition enhancement agents,[4c] and tumor necrosis factor α inhibitors.[4d] Recently several reports have described solid-phase syntheses of different quinazoline derivatives.[5] Herein, we describe a novel strategy, utilizing the aza-Wittig reaction of iminophosphoranes (phosphine imines) with heterocumulenes on solid phase, for the synthesis of 2-amino-substituted 3H-quinazoline-4-ones.

Iminophosphoranes, prepared by the Staudinger reaction[6] or Kirsanov reaction,[7] represents one of the most useful intermediates in the synthesis of nitrogen-containing heterocycles.[8] However, there are limited studies on the solid-phase application of this key intermediate.[5c,d] In particular, to the best of our knowledge, an iminophosphorane tethered to a polymer support has not been reported.

Our approach is illustrated in Scheme 1. The starting N-substituted benzamide **2**, was easily produced by treating isatoic anhydride with various primary amines.[9] Then in a modified Kirsanov reaction,[10] 3 equiv of **2** were treated with polystyryl triphenylphosphine **3**[11] in the presence of dibromotetrachloroethane[12] and triethylamine in dry dichloromethane at reflux under argon to produce the polymer-tethered iminophosphorane **4**. Subsequent heating of resin **4** with isocyanates in dry toluene or xylene under argon resulted in the formation of carbodiimide intermediate **5**, which underwent intramolecular cyclization to give the desired product **6** in good overall yield and purity (Table 1).[13] It is worth mentioning that the polymer-tethered iminophosphorane **4** was stable over several days if stored in a desiccator and therefore could be used conveniently in a parallel synthesis.

Chart 1. Quinazoline Skeleton



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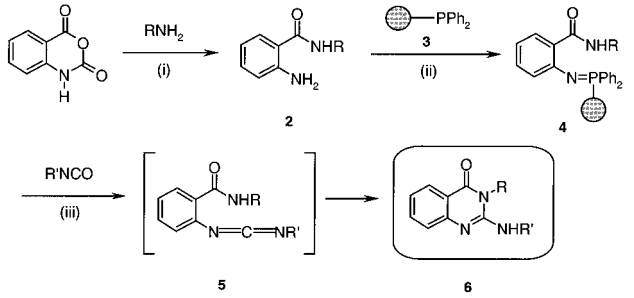
Scheme 1. Solid-Phase Synthesis of 2-Amino-Substituted 3H-Quinazoline-4-ones[a]



[a] (i) 0.1 equiv of DMAP/DMF, room temperature, 8 h; (ii) $C_2Br_2Cl_4$/TEA/CH_2Cl_2, Ar, reflux, 5 h; (iii) toluene or xylene, Ar, reflux, 8−24 h.

Table 1. Synthesis of 2-Amino-Substituted 3H-Quinazoline-4-ones

entry	R	R′	yield[a] (%)	purity[b] (%)	MS[c] (calculated/obtained)
6a	Me	Et	88	96	204.2/204.1
6b	Me	tBu	68	94	232.3/232.0
6c	Me	Ph	89	61[d]	252.3/252.2
6d	Pr	Et	83	76	232.3/232.0
6e	iPr	Et	78	77	232.3/232.1
6f	tBu	Et	74	70	246.3/246.4
6g	CH_2CH_2–N⟨O⟩	Et	78	96	303.4/303.2

[a] Crude yield based on the loading of the polystyryl triphenylphosphine. [b] Determined by HPLC analysis of the crude product at $\lambda = 254$ nm with a gradient of 50% MeOH to 100% MeOH over a period of 15 min. [c] ES-MS, MH^+ obtained. [d] The low purity was due to contamination from excess phenyl isocyanate.

The approach reported here demonstrates that iminophosphoranes can be formed on a polymer support and can be a useful solid-phase intermediate for convenient and rapid synthesis of quinazolines. This strategy also allows the construction of a large variety of other nitrogen-containing heterocycles. Further applications of this polymer-bound iminophosphorane are in progress and will be published in due course.

Acknowledgment. We are grateful to Drs. Guy Milot, Lianshan Zhang, Xianfeng Li, Yen-Shi Lai, and Raymond Patch for their help and useful discussions during this work.

Supporting Information Available. Experimental procedure for the synthesis of **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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* To whom correspondence should be addressed. E-mail: j.mayer@lilly.com.

[†] Sphinx Pharmaceuticals.

[‡] Lilly Corporate Center.

10.1021/cc000113e CCC: $20.00
Published on Web 04/25/2001

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(11) The polymer-bound triphenylphosphine (∼1.41−1.62 mmol/g; 1% DVB cross-linked) was purchased from Argonaut Technologies.

(12) Dibromotetrachloroethane, benzene, and isocyanate used in this experiment are hazardous materials. Caution should be taken when using these reagents. For the latest hazard information, please refer to MSDS.

(13) Previous solution-phase studies have shown that the conversion of iminophosphorane **4** to quinazoline **6** is through the carbodiimide intermediate **5**. (a) Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron Lett.* **1988**, *29*, 3849−3852. (b) Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron* **1989**, *45*, 4263−4286.

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