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Efficient synthesis of 4(3*H*)-quinazolinones using a soluble polymeric support

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Abstract

4(3*H*)-Quinazolinones have been synthesized from poly(ethylene glycol) (PEG) supported aza-Wittig reaction. 2-Dialkylamino-4(3*H*)-quinazolinones **6** were synthesized efficiently by reaction of secondary amine with PEG-supported carbodiimides **4**, which were obtained from aza-Wittig reaction of PEG-supported iminophosphoranes **3** with isocyanates.

Keywords: 4(3*H*)-Quinazolinone; Poly(ethylene glycol) supported; Aza-Wittig reaction; Carbodiimide; Iminophosphorane

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4(3*H*)-Quinazolinones have received considerable attention over the last few years due to their interesting biological activities. Some of them have exhibited promising pharmacological activities, such as antimicrobial, antifungal, antitumor and AMPA receptor antagonistical activities [1–4]. Hence these heterocycles have become an attractive target for combinatorial chemistry groups involved in drug discovery and crop protection. There are many known methods for the synthesis of 4(3*H*)-quinazolinones in homogeneous solution or in solid phase [5–12], however, there is still no report on the use of soluble polymer support to synthesis these molecules.

In recent years, the soluble polymer-supported synthesis of small heterocyclic molecules has been a subject of intense research activity, since it represents one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry [13–15]. It profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis without following the cleavage-and-check technique) and of solid-phase methods (use of excess reagents and easy isolation and purification of products). Moreover, owing to the homogeneity of liquid phase reactions, the reaction conditions can be readily shifted from solution phase systems without large changes, and the amount of the excessive reagents is less than that in solid phase reactions.

Poly(ethylene glycol) (PEG) is used more than other polymers as soluble polymer supports. PEG is readily functionalized with different spacer and linker, is soluble in many organic solvents and is insoluble in poorly polar solvents such as hexane, diethyl ether and *t*-butylmethylether. Thus one can carry out reactions on a modified PEG immobilized compound in homogeneous conditions (e.g. in CH_2Cl_2, $CHCl_3$, THF, CH_3OH or H_2O) and can be

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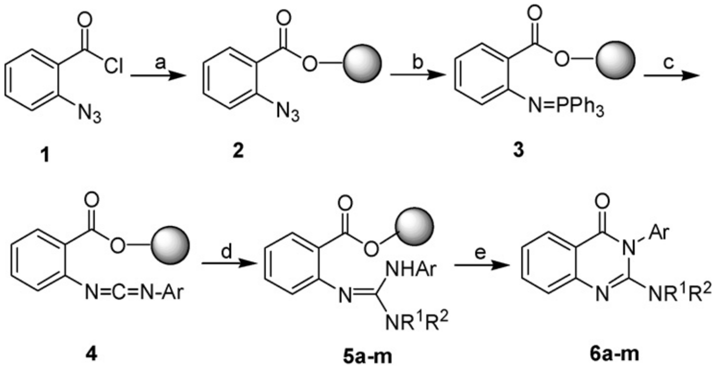

Scheme 1. (a) PEG-4000, CH_3CN, NEt_3, 24 h, 95%; (b) Ph_3P, CH_2Cl_2, r.t., 2 h, 91%; (c) ArNCO, CH_2Cl_2, r.t., 12 h; (d) R^1R^2NH, CH_2Cl_2, r.t., 2 h; (e) EtONa, CH_2Cl_2, r.t., 2–8 h, 72–90%.

precipitated from a solution by addition of a poorly polar solvent (typically Et_2O) and removing the unreacted materials and by-products by filtration. As a part of our ongoing project devoted toward the efficient synthesis of diverse heterocyclic systems via soluble polymer supported method [16], we have focused our attention on the benzopyrimidone (quinazoline) nucleu. Here we wish to report an efficient synthesis of 4(3*H*)-quinazolinones from PEG-supported iminophosphorane in parallel fashion. Commercially available cheap difunctional PEG-4000 was chosen as a soluble polymer support.

As shown in Scheme 1, 2-azidobenzoyl chloride **1** was added dropwise to the soluble support PEG-4000 in the presence of NEt_3 in dry CH_3CN at 0 °C, then the mixture was refluxed for 24 h. The resulted PEG-supported azide **2** was obtained by precipitation in diethyl ether in 95% yield. Further reaction of **2** with triphenylphosphine created the PEG-supported iminophosphorane **3**, which was also isolated by precipitation in diethyl ether. With the PEG-supported iminophosphorane **3** in hand, we switched our attention to its application in liquid-phase combinatorial synthesis. The PEG-supported iminophosphorane **3** was allowed to react with aromatic isocyanates to produce PEG-supported carbodiimides **4** via intermolecular aza-Wittig reaction. After the PEG-supported carbodiimides **4** reacted with secondary amine at room temperature in the presence of catalytic amount of sodium ethoxide, the PEG was precipitated by addition of diethyl ether and was separated by simple filtration. The 4(3*H*)-quinazolinones **6a–m** were obtained by recrystallization from a mixed solvent of dichloromethane/petroleum ether (1:1–1:3, v/v). In some cases, a trace amount of the PEG residue and the outgrowth (Ph_3PO) might contaminate the final products **6a–m**. This problem could be easily solved by passing the crude product through a pad of silica gel using EtOAc–petroleum ether (1:3–1:1, v/v) as the eluent. A variety of secondary amine and isocyanate could be used for this synthetic strategy and the products were obtained in good yields (Table 1).

Table 1
Liquid-phase synthesis of 4(3*H*)-quinazolinones **6a**–**m** by aza-Wittig reaction

	Ar	NR^1R^2	Condition	Yield (%)	Elementary analysis (%, Calcd.)		
					C	H	N
6a	Ph	Pyrrolidin-1-yl	r.t., 2 h	81	73.90 (74.20)	5.70 (5.88)	14.70 (14.42)
6b	4-Cl-C_6H_4	Piperidin-1-yl	r.t., 3 h	78	67.05 (67.16)	5.58 (5.34)	12.41 (12.37)
6c	4-Cl-C_6H_4	Morpholin-4-yl	r.t., 3 h	83	63.32 (63.25)	4.61 (4.72)	12.47 (12.29)
6d	4-Cl-C_6H_4	Pyrrolidin-1-yl	r.t., 2 h	75	66.10 (66.36)	5.04 (4.95)	12.70 (12.90)
6e	4-F-C_6H_4	NEt_2	r.t., 5 h	80	69.73 (69.44)	5.69 (5.83)	13.45 (13.50)
6f	4-F-C_6H_4	N(*n*-Pr)$_2$	r.t., 6 h	90	70.80 (70.78)	6.70 (6.53)	12.60 (12.38)
6g	4-F-C_6H_4	N(*n*-Bu)$_2$	r.t., 8 h	85	71.80 (71.91)	6.90 (7.13)	11.70 (11.43)
6h	4-F-C_6H_4	Morpholin-4-yl	r.t., 3 h	72	66.70 (66.45)	4.70 (4.96)	13.10 (12.92)
6i	4-F-C_6H_4	Pyrrolidin-1-yl	r.t., 2 h	88	70.13 (69.89)	5.17 (5.21)	13.32 (13.58)
6j	3-Cl-C_6H_4	NEt_2	r.t., 3 h	77	65.87 (65.95)	5.66 (5.53)	12.80 (12.82)