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LETTERS

A concise and efficient solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones

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Abstract

A concise and efficient solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones is described. Reaction of polymer-bound isothiourea with isatoic anhydride provides 2-amino-4(3*H*)-quinazolinones with good yields and excellent purity. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: quinazolinones; thioformamidines; solid-phase synthesis.

The high-throughput syntheses of small organic molecules in both solution-phase and on solid support has become a routine practice for lead discovery and lead optimization in pharmaceutical research. As a result, the development of reaction conditions suitable for automated parallel chemistry has attracted substantial attention in the past few years.[1,2]

4(3*H*)-Quinazolinone has been identified as an important class of heterocyclic compounds in medicinal chemistry, having anticonvulsant,[3] antihypertensive,[4] antidiabetic,[5] and anti-tumor[6] activity. Antimicrobial and antihistaminic activities have also been documented.[7] A number of syntheses of these types of compounds has previously been reported. Recently, Mayer and co-workers[8] disclosed a solid-phase synthesis approach to 2-alkyl substituted analogs. Villalgordo and co-workers[9] reported a solid-phase synthesis based on an aza Wittig-mediated annulation strategy; however, a mixture of two isomers was formed. More recently, a paper by Gopalsamy[10] disclosed a related solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones. Our approach differs from those previously reported in its efficiency of chemical steps and feasibility of side-chain functionality.

The general approach for the solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones is shown in Scheme 1. Thiourea **1** is efficiently loaded to a chloromethylated polystyrene resin **2** (2% DVB Merrifield resin, 2.3 mmol/g) in DMF at 80°C to form the polymer-bound isothiourea **3**. The results for the conversion of chloro resin **2** to isothiourea **3** are summarized in Table 1. All the conversions are nearly quantitative, as determined by microanalysis of sulfur and nitrogen of

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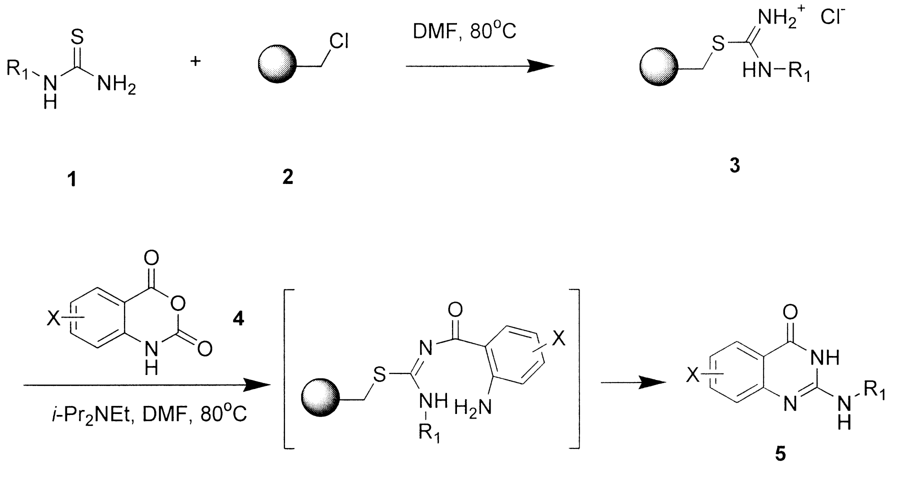


Scheme 1.

Table 1
Conversion of resin **2** to polymer-bound isothiourea **3**

Entry	Resin **3** R_1	Theo.Loading[a] mmol / g	Loading[b] mmol / g	Conversion %
1	Et	1.86	1.81	97
2	Allyl	1.82	1.80	99
3	Cyclohexyl	1.69	1.64	97
4	Ph	1.70	1.65	97

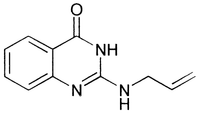
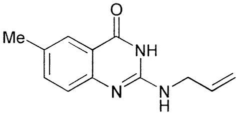
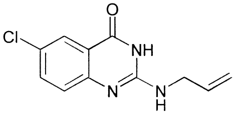
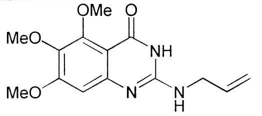
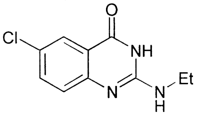
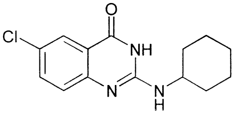
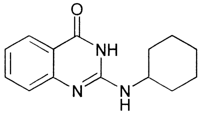
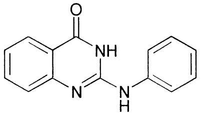
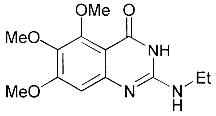
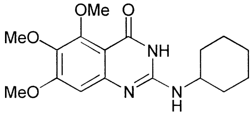
a. Theoretical loading is calculated based on 100% conversion.

b. Calculated based on the microanalysis results of S and N of polymer-bound **3**.

polymer-bound **3**. Reaction of **3** with isatoic anhydride **4** in DMF in the presence of diisopropylethylamine at 80°C afforded 2-amino-4(3*H*)-quinazolinones **5**. These products were formed via acylation of the polymer-bound isothiourea **3** by isatoic anhydride **4**, followed by cleavage of the resulting product via an intramolecular cyclization. Results are summarized in Table 2. Unlike most solid-phase chemistries that require a large excess of reagents to push the reactions to completion, this reaction proceeds well with a stoichiometric amount of isatoic anhydride **4**. Reaction conditions are general with respect to both the thiourea and the isatoic anhydride. All the desired products **5** were obtained in good to high yields with excellent purity. The results are reported as isolated yields and calculated based on the amount of compound **4** used in the reaction. Purity was determined by HPLC analysis of crude product **5** by both UV and ELSD. All of the products were also fully characterized by ^1H NMR and mass spectrometric techniques.[11]

In summary, we have disclosed a concise and efficient synthesis of 2-amino-4(3*H*)-quinazolinones on solid support. This protocol only requires a two-step procedure and provides 2-amino-4(3*H*)-

Table 2
Solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones **5**

Entry	Product **5**	Yield[a]	Purity[b]
1	 **5a**	65%	93% (100%)
2	 **5b**	67%	97% (100%)
3	 **5c**	76%	96% (100%)
4	 **5d**	64%	98% (100%)
5	 **5e**	88%	97% (100%)
6	 **5f**	88%	94% (100%)
7	 **5g**	81%	100% (100%)
8	 **5h**	53%	84% (90%)
9	 **5i**	80%	95% (100%)
10	 **5j**	60%	94% (100%)

a. Yields are calculated based on the quantity of **4** used. b. Purity was determined by HPLC using both UV (254 nm) and ELSD detectors, numbers in the brackets are from ELSD detector.

quinazolinones in good yield with excellent purity. Both building blocks mono-substituted thioureas and isatoic anhydrides used in this chemistry are readily available from commercial sources or can be easily synthesized.[12,13] Unlike the method reported by Gopalsamy,[10] which involved the release of foul smelling methylthiol, the thiol generated in this method remains attached to the solid support, thus providing a more environmentally benign and practical synthesis of 2-amino-4(3*H*)-quinazolinones.

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11. Compound **5a**: ^{1}H NMR (DMSO-d_6) δ 4.30 (s, 3H), 5.40 (d, 1H, $J = 11.0$ Hz), 5.51 (d, 1H, $J = 18.0$ Hz), 7.26 (br, 1H), 7.42 (t, 1H, $J = 8.5$ Hz), 7.58 (d, 1H, $J = 8.5$ Hz), 7.87 (t, 1H, $J = 8.5$ Hz); MS (m/z): 202 (M+H$^+$). Compound **5b**: ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H), 4.30 (s, 3H), 5.40 (d, 1H, $J = 12.0$ Hz), 5.52 (d, 1H, $J = 18.0$ Hz), 6.18 (m, 1H), 7.53 (d, 1H, $J = 8.5$ Hz), 7.72 (d, 1H, $J = 8.5$ Hz), 7.99 (s, 1H); MS (m/z): 236 (M+H$^+$). Compound **5c**: ^{1}H NMR (DMSO-d_6) δ 4.25 (s, 3H), 5.37 (d, 1H, $J = 12.0$ Hz), 5.48 (d, 1H, $J = 18.0$ Hz), 6.17 (m, 1H), 7.10 (br, 1H), 7.55 (d, 1H, $J = 8.5$ Hz), 7.82 (d, 1H, $J = 8.5$ Hz), 8.07 (s, 1H); MS (m/z): 216 (M+H$^+$). Compound **5d**: ^{1}H NMR (DMSO-d_6) δ 4.05 (s, 3H), 4.07 (s, 3H), 4.16 (s, 3H), 4.23 (m, 2H), 5.36 (d, 1H, $J = 12.0$ Hz), 5.48 (d, 1H, $J = 18.0$ Hz), 6.64 (br, 1H), 7.42 (s, 1H); MS (m/z): 292 (M+H$^+$). Compound **5e**: ^{1}H NMR (DMSO-d_6) δ 1.40 (t, 3H, $J = 6.5$ Hz), 3.62 (q, 2H, $J = 6.5$ Hz), 7.28 (br, 1H), 7.61 (d, 1H, $J = 8.5$ Hz), 7.87 (d, 1H, $J = 8.5$ Hz), 8.07 (s, 1H); MS (m/z): 224 (M+H$^+$). Compound **5f**: ^{1}H NMR (DMSO-d_6) δ 1.30–2.21 (m, 10H), 3.20 (m, 1H), 4.12 (br, 1H), 7.05 (br, 1H), 7.65 (d, 1H, $J = 8.5$ Hz), 7.90 (d, 1H, $J = 8.5$ Hz), 8.07 (s, 1H); MS (m/z): 278 (M+H$^+$). Compound **5g**: ^{1}H NMR (DMSO-d_6) δ 1.30–2.20 (m, 10H), 3.17 (m, 1H), 4.12 (br, 1H), 7.45 (t, 1H, $J = 7.8$ Hz), 7.64 (d, 1H, $J = 8.5$ Hz), 7.88 (t, 1H, $J = 7.2$ Hz), 8.18 (t, 1H, $J = 7.2$ Hz); MS (m/z): 244 (M+H$^+$). Compound **5h**: ^{1}H NMR (DMSO-d_6) δ 7.18–8.25 (m, 9H), 9.0 (s, 1H); MS (m/z): 238 (M+H$^+$). Compound **5i**: ^{1}H NMR (DMSO-d_6) δ 1.50 (t, 3H, $J = 6.5$ Hz), 3.61 (q, 2H, $J = 6.5$ Hz), 4.05 (s, 3H), 4.08 (s, 3H), 4.17 (s, 3H), 6.42 (br, 1H), 7.40 (s, 1H); MS (m/z): 280 (M+H$^+$). Compound **5j**: ^{1}H NMR (DMSO-d_6) δ 1.35–2.25 (m, 10H), 4.02 (s, 10H), 4.06 (s, 3H), 4.17 (s, 3H), 6.37 (br, 1H), 7.40 (s, 1H); MS (m/z): 334 (M+H$^+$).
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