

SOLUTION AND SOLID-PHASE APPROACHES TO QUINCONAZOLE AND FLUQUINCONAZOLE – INHIBITORS OF FUNGAL ERGOSTEROL BIOSYNTHESIS

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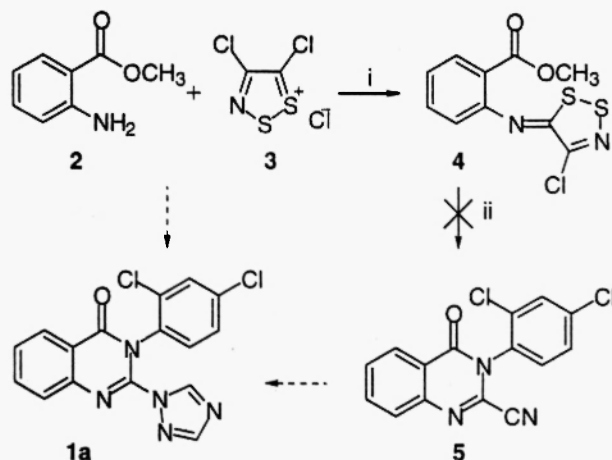
Abstract

Syntheses of quinconazole (SN 539 865) and fluquinconazole (SN 597 265), inhibitors of fungal ergosterol biosynthesis, were accomplished in two modes: (i) through solution-phase construction of 3-aryl-2-thioxoquinazolin-4(3*H*)-ones from iminophosphoranes or *o*-aminobenzamides and (ii) via solid-phase method based on aza-Wittig-mediated annulation of iminophosphoranes.

Keywords: triazoles; quinazolinones; annulation; aza-Wittig; solid-phase synthesis.

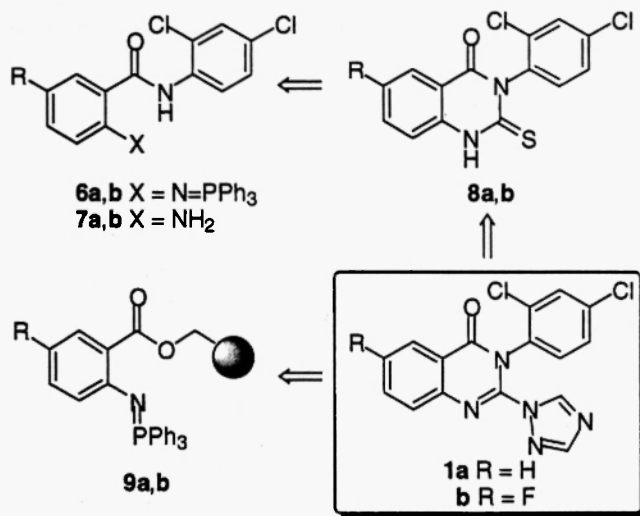
Many effective fungicides used today belong to triazole group of compounds. Triazolyquinazolinone compounds, including quinconazole (**1a**)¹ and fluquinconazole (**1b**, cf. Schemes 1 and 2)² which belong to ergosterol biosynthesis inhibitors group,³ are being developed for worldwide use alone and with various mixture partners in a range of formulations.⁴ Notably that fluquinconazole (**1b**) was discovered^{2a} as a result of a chemical design and synthesis program aimed at producing novel inhibitors of ergosterol biosynthesis to control the varied fungi pathogens. Herein we disclose the results of our studies on solution and solid-phase syntheses of quinconazole and fluquinconazole. Key synthetic strategies involved (i) convenient solution-phase construction of 3-aryl-2-thioxoquinazolin-4(3*H*)-ones **8** from iminophosphoranes **6** or *o*-aminobenzamides **7** and (ii) solid-phase approach based on aza-Wittig-mediated annulation of iminophosphoranes **9**.

Recently Kim et al.⁵ reported on a facile method for synthesis of 3-alkyl-2-cyanoquinazolin-4(3*H*)-ones and their further reactions with various nucleophiles. As depicted in Scheme 1, initially we planned to utilize the above-mentioned methodology for a simple synthesis of quinconazole (**1a**) by three step sequence involving (i) preparation of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate (**4**), (ii) synthesis of 3-aryl-2-cyanoquinazolin-4(3*H*)-one **5** from dithiazolylideneanthranilate **4**, and (iii) displacement of the cyano group in **5** by *N*-nucleophile (**5** – **1a**). The key starting compound **4** was prepared (Scheme 1) by a known method⁵ from methylanthranilate (**2**) and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) (**3**)⁶ in the presence of pyridine (2 equiv.) in dichloromethane at room temperature. However, treatment of dithiazolylideneanthranilate **4** with 2,4-dichloroaniline in tetrahydrofuran at room temperature did not afford the desired 3-aryl-2-cyanoquinazolin-4(3*H*)-one **5** due to other side reactions took place.^{5,7}



Scheme 1. Reagents and conditions: i, Pyridine (2 equiv.), CH_2Cl_2 , room temp. (47%); ii, 2,4- $\text{Cl}_2\text{-C}_6\text{H}_3\text{NH}_2$ (3.5 equiv.), THF, room temp., 24 h.

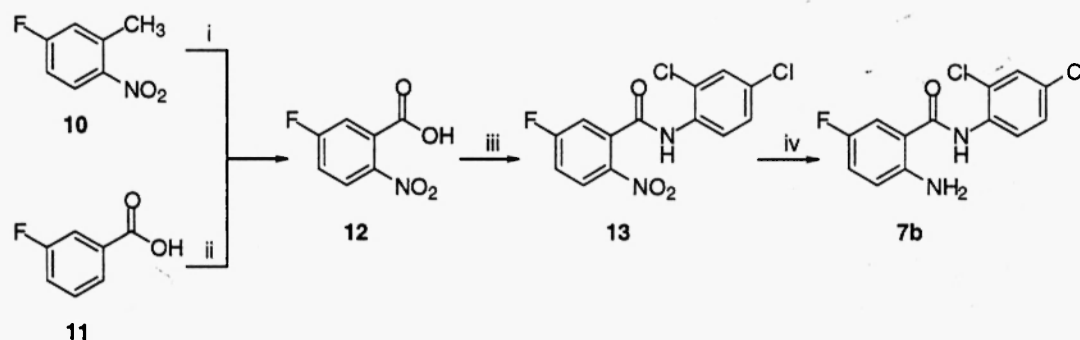
Therefore, we moved to another approach to triazolyquinazolinones of type 1, which is based on synthesis of 3-aryl-2-thioxoquinazolin-4(3*H*)-ones **8** followed by their further elaboration to **1** (Scheme 2). Scanning the literature on the subject we found that different methods are now at hand for chemists to synthesize 3-aryl-2-thioxoquinazolin-4(3*H*)-ones. General approaches include the interaction of anthranilic acids, their methyl esters, anthranilamides or isatoic anhydrides with arylisothiocyanates,^{8a-h} methyl *N*-aryldithiocarbamates^{8i,j} or triethylammonium *N*-aryldithiocarbamates.^{8k}



Scheme 2.

As shown in Scheme 2, in our approach to key intermediates **8** we envisaged that these compounds could be prepared by other methods, namely, implementing aza-Wittig reaction of iminophosphoranes 6a or b with a heterocumulene (CS_2) or even by a simpler procedure starting from *o*-aminobenzamides 7. Taking also into consideration a recent report of Villalgorido et al.⁹ on solid-phase synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones, where aza-Wittig-mediated annulation reaction was involved as a key step, we planned (Scheme 2) to utilize the above-mentioned approach for synthesis of quinconazole (1a) and

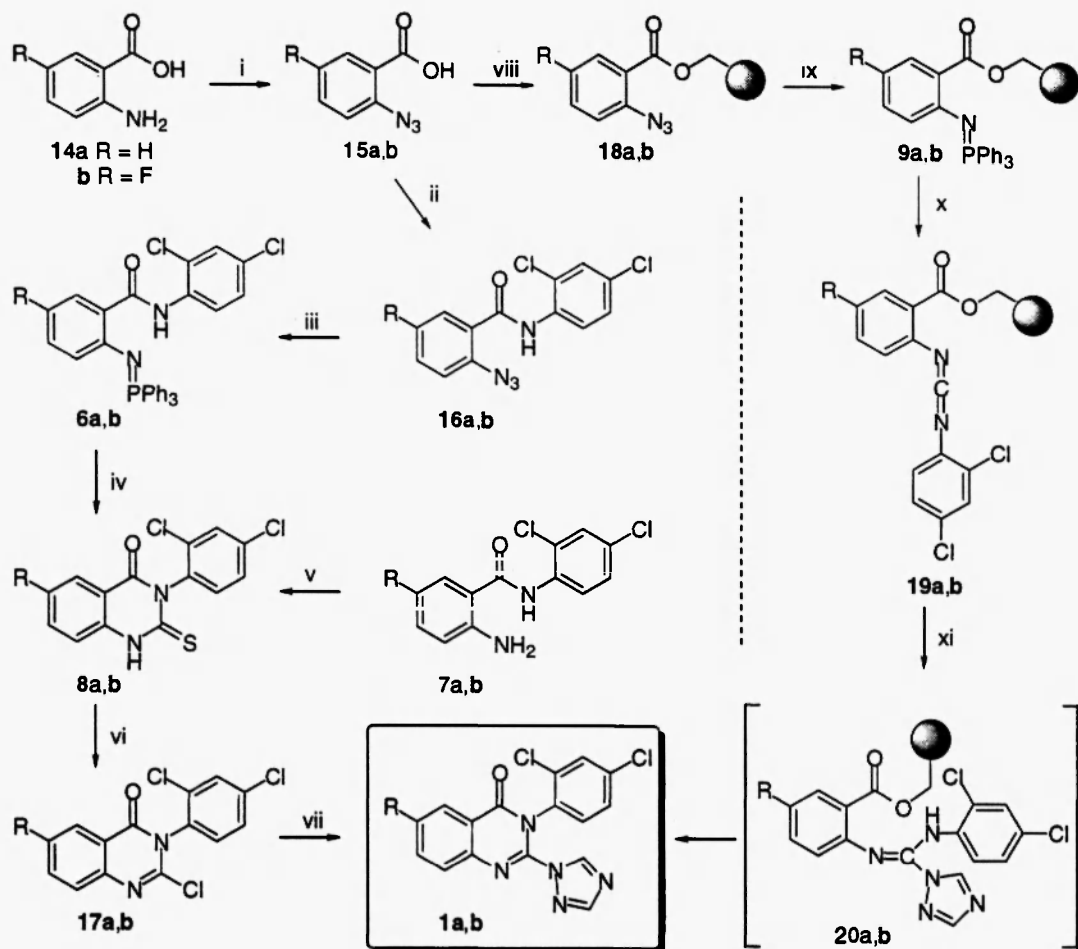
fluquinconazole (**1b**). For annulation reaction studies, *o*-aminobenzamides **7** and aryliminophosphoranes **6** were synthesized. *o*-Aminobenzamide **7a**¹⁰ was prepared in one step by reaction of commercially available isatoic anhydride with 2,4-dichloroaniline in dry DMF by a method of Coyne et al.¹² with some modifications.¹³ As shown in Scheme 3, synthesis of *o*-aminobenzamide **7b** was performed in three steps from inexpensive 5-fluoro-2-nitrotoluene (**10**) or 3-fluorobenzoic acid (**11**). In the beginning 5-fluoro-2-nitrobenzoic acid (**12**) was obtained according to Stiles et al.¹⁴ in moderate (43%) yield by oxidation of **10** with potassium permanganate (method A). Better yield of **12** (59%) was obtained by using recently reported procedure introduced by Jacobson and Ely¹⁵ for cobalt-catalyzed air oxidation of 2-nitrotoluenes to their acids (method B). But the simplest and high yielding (89%) method for synthesis of **12** was based on nitration¹⁶ of 3-fluorobenzoic acid (**11**). Finally, *N*-arylamide **13** was prepared through dicyclohexylcarbodiimide-mediated condensation¹⁷ of 2,4-dichloroaniline and 5-fluoro-2-nitrobenzoic acid (**12**) followed by reduction of nitro group in **13** with PtO₂/H₂ (63%, method A)¹⁷ or Fe/AcOH (68%, method B)¹⁸ to give the desired *N*-(2,4-dichlorophenyl)-2-amino-5-fluorobenzamide (**7b**).



Scheme 3. Reagents and conditions: i, Method A: KMnO₄, H₂O, reflux, 7 h (43%); Method B: Air, Co(OAc)₂·4H₂O (0.05 equiv.), NaOAc (0.5 equiv.), AcOH, H₂O, 110°C, 4 h, then MeCHO, 70°C, 3 h (59%); ii, HNO₃ (fuming, d 1.49), H₂SO₄ (conc.), 0–5°C, 1 h, then precipitated with H₂O (89%); iii, DCC, DMF, 2,4-Cl₂-C₆H₃NH₂, room temp., 1.5 h (72%); iv, Method A: PtO₂-H₂, EtOH, room temp., 4 h (63%); Method B: Fe (powder, 3.2 equiv.), AcOH, EtOH, reflux, 18 h (68%).

Required iminophosphoranes **6a,b** were prepared from *o*-aminobenzoic acids **14a,b**¹⁹ in a three step sequence (Scheme 4) involving (i) preparation of *o*-azidobenzoic acids **15a,b**, (ii) their further conversion to *N*-arylsubstituted *o*-azidobenzamides **16a,b**,²⁰ and (iii) classical Staudinger reaction²¹ of the azides **16a,b** with triphenylphosphine in ether at room temperature. Further aza-Wittig reaction of iminophosphoranes **6a,b** with carbon disulfide as a heterocumulene yielded²² 3-aryl-2-thioxoquinazolin-4(3*H*)-ones **8a,b**. As an alternative and simpler approach to get thioxoquinazolinones **8a,b** in good yields, a method introduced by Mizuno et al.²³ based on cycloaddition of *o*-aminobenzamides **7a,b** with carbon disulfide in the presence of DBU was adapted.²⁴ Thus, the sequence of reactions involving preparation of *o*-aminobenzamides **7a,b** and their cycloaddition with carbon disulfide in the presence of DBU constitute an effective protocol for the synthons **8**.

To complete the synthesis, arylthioxoquinazolinones **8a** and **b** were smoothly converted into quinconazole (**1a**) and fluquinconazole (**1b**) in two steps by regular procedures (Scheme 4). Refluxing of compounds **8a,b** with sulfonyl chloride in chloroform afforded 2-chloroderivatives **17a,b**.²⁵ Their further reaction with 1,2,4-triazole sodium salt in DMF at room temperature²⁶ gave the desired quinconazole (**1a**) and fluquinconazole (**1b**).²⁷



Scheme 4. *Reagents and conditions:* i, NaNO_2 , HCl (conc.), H_2O , $0-5^\circ\text{C}$, 0.5 h, then NaN_3 , NaOAc , H_2O , 15 min., room temp., then acidified with HCl (conc.) at 0°C (72% for 15a and 71% for 15b); ii, SOCl_2 , benzene, reflux, 2 h, followed by $2,4\text{-Cl}_2\text{-C}_6\text{H}_3\text{NH}_2$, pyridine, from 0°C to room temp., 1 h (82% for 16a and 67% for 16b); iii, Ph_3P , ether, room temp., 4 h (86% for 6a and 77% for 6b); iv, CS_2 (1 equiv.) CH_2Cl_2 , 40°C , 12 h (84% for 8a and 77% for 8b); v, CS_2 -DMF (2:3), DBU (1 equiv.), from room temp. to 45°C , 1.5 h (71% for 8a and 74% for 8b); vi, SO_2Cl_2 , CHCl_3 , reflux, 1 h (51% for 17a and 41% for 17b); vii, 1,2,4-Triazole sodium salt ($\text{C}_2\text{H}_2\text{N}_3\text{Na}$), DMF, room temp., 24 h (54% for 1a and 49% for 1b); viii, Merrifield's peptide resin (0.67 equiv., 3.3 mmol Cl^-/g), Cs_2CO_3 (2 equiv.), DMF, 80°C , 9 h; ix, Ph_3P (1 M in THF, 5 equiv.), room temp., 6 h; x, $2,4\text{-Cl}_2\text{-C}_6\text{H}_3\text{N}=\text{C}=\text{O}$ (5 equiv.), CH_2Cl_2 , room temp., 6 h; xi, 1H-1,2,4-Triazole, THF, 50°C , 4.5 h (71% for 1a and 46% for 1b, yields are based on initial loading of the Merrifield's resin).

In another line of research the requested triazolyquinazolinones 1a and b were synthesized by using a solid-phase method (Scheme 4). Recently Villalgorido et al.^{9,28} introduced a versatile and straightforward method to synthesize 2,3-disubstituted 4(3*H*)-quinazolinones. This approach combined aza-Wittig-mediated annulation reaction with a cleavage process.²⁹ Having *o*-azidobenzoic acids 15a and b in our hands (cf. Scheme 4) we followed the described procedures^{9,30} to get compounds 1a and b through intermediacies of polymer-bound esters 18, iminophosphoranes 9 and carbodiimides 19. Eventually, treatment of resin-bound carbodiimides 19a or b with 1*H*-1,2,4-triazole as a nucleophile led³¹ (Scheme 4) to targeted triazolyquinazolinones 1 in good (71%) yield for compound 1a and modest (46%) yield for compound 1b.

In summary, syntheses of quinconazole and fluquinconazole, inhibitors of fungal ergosterol biosynthesis, have been accomplished. Key features of these syntheses are noteworthy: a convenient solution-phase construction of 3-aryl-2-thioxoquinazolin-4(3*H*)-ones from iminophosphoranes or *o*-aminobenzamides and solid-phase approach based on aza-Wittig-mediated annulation of iminophosphoranes.

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