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

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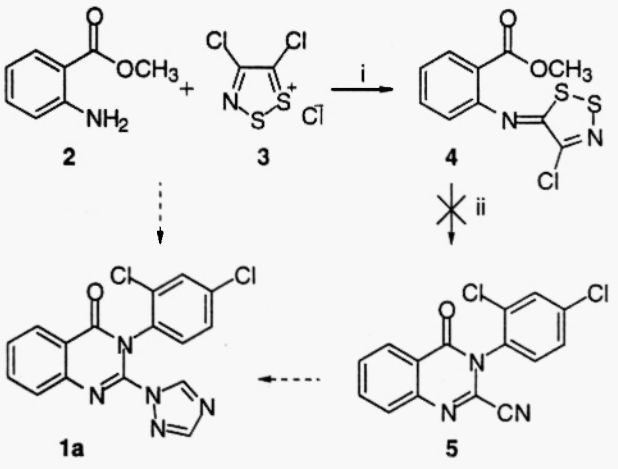
Abstract

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.

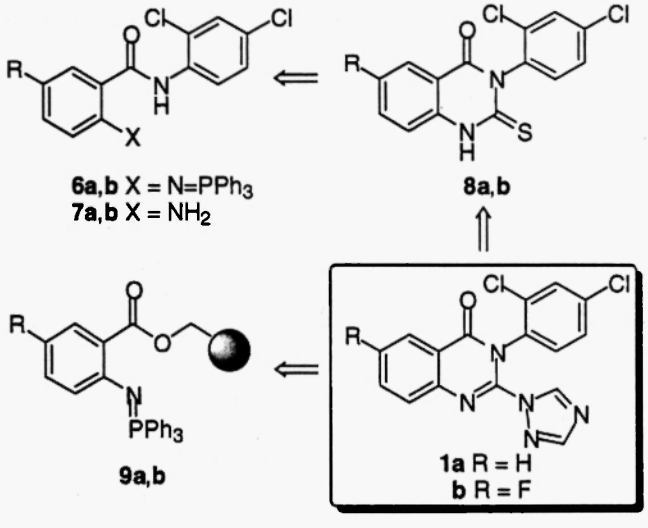
Many effective fungicides used today belong to triazole group of compounds. Triazolylquinazolinone compounds, including quinconazole (**1a**)[1] and fluquinconazole (**1b**, cf. Schemes 1 and 2)[2] which belong to ergosterol biosynthesis inhibitors group,[3] are being developed for worldwide use alone 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 planed 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 method[5] 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-Cl_2-$C_6H_3NH_2$ (3.5 equiv.), THF, room temp., 24 h.

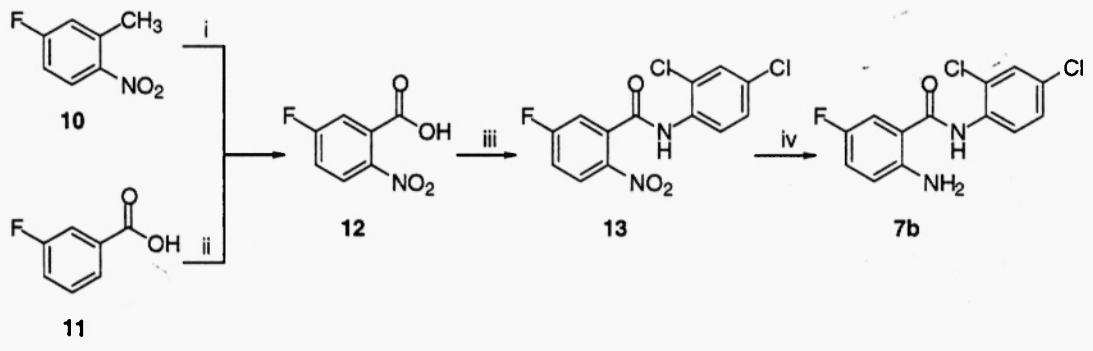
Therefore, we moved to another approach to triazolylquinazolinones of type **1**, which is based on synthesis of 3-aryl-2-thioxoquinazolin-4(3*H*)-ones **8** followed by their further elaboration to **1** (Scheme 2). Scanning the literature on the subject we found that different methods are now at hand 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 **6**a 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 Villalgordo 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 planed (Scheme 2) to utilize the above-mentioned approach for synthesis of quinconazole (1a) and

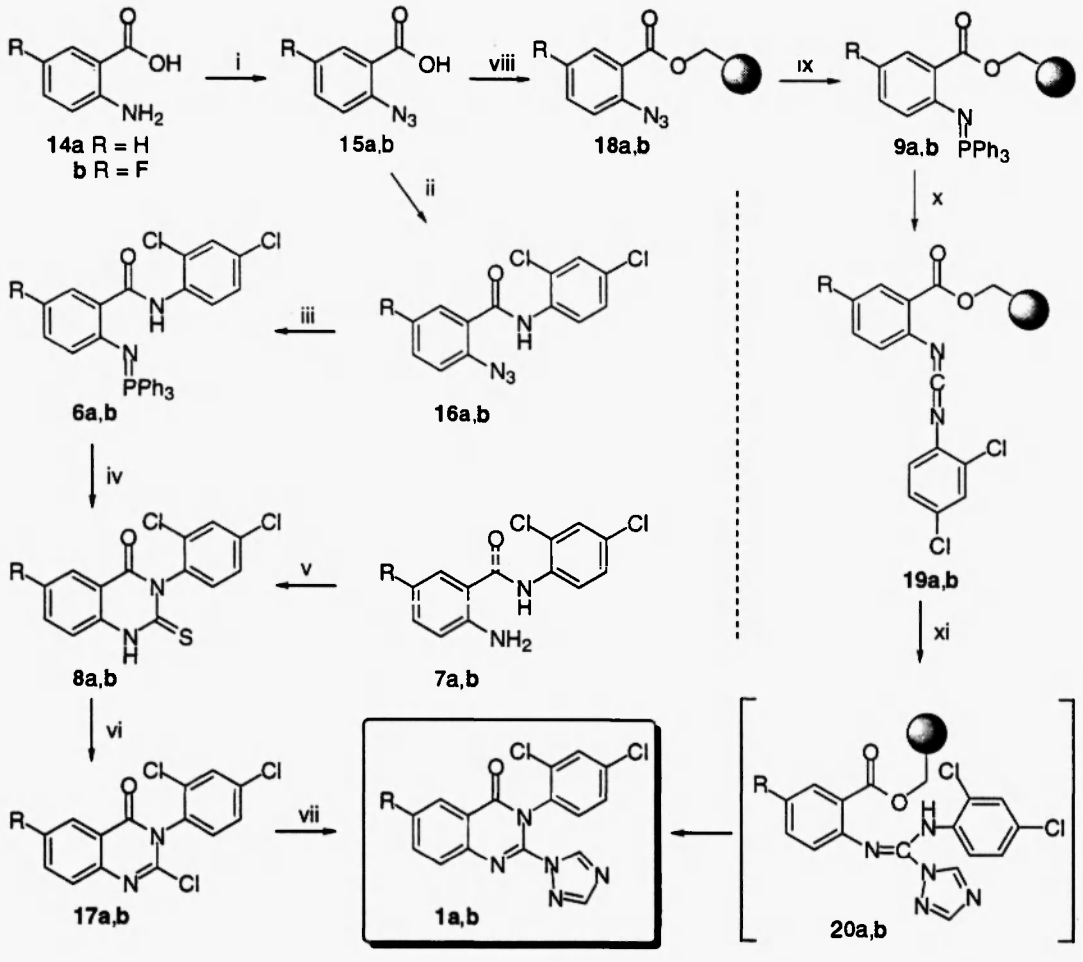
fluquinconazole (**1b**). For annulation reaction studies, *o*-aminobenzamides **7** and aryliminophosphoranes **6** were synthesized. *o*-Aminobenzamide **7a**[10] was prepared in one step by reaction of commercially available isatoic anhydride with 2,4-dichloroaniline in dry DMF by a method of Coyne 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 Ely[15] 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 nitration[16] of 3-fluorobenzoic acid (**11**). Finally, *N*-arylamide **13** was prepared through dicyclohexylcarbodiimide-mediated condensation[17] of 2,4-dichloroaniline and 5-fluoro-2-nitrobenzoic acid (**12**) followed by reduction of nitro group in **13** with PtO_2/H_2 (63%, method A)[17] or Fe/AcOH (68%, method B)[18] to give the desired N^1-(2,4-dichlorophenyl)-2-amino-5-fluorobenzamide (**7b**).



Scheme 3. *Reagents and conditions*: i, *Method A*: $KMnO_4$, H_2O, reflux, 7 h (43%); *Method B*: Air, $Co(OAc)_2 \cdot 4H_2O$ (0.05 equiv.), NaOAc (0.5 equiv.), AcOH, H_2O, 110°C, 4 h, then MeCHO, 70°C, 3 h (59%); ii, HNO_3 (fuming, d 1.49), H_2SO_4 (conc.), 0–5°C, 1 h, then precipitated with H_2O (89%); iii, DCC, DMF, 2,4-Cl_2-$C_6H_3NH_2$, room temp., 1.5 h (72%); iv, *Method A*: PtO_2–H_2, 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 reaction[21] 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 yielded[22] 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 sulfuryl chloride in chloroform afforded 2-chloroderivatives **17a,b**.[25] Their further reaction with 1,2,4-triazole sodium salt in DMF at room temperature[26] gave the desired quinconazole (**1a**) and fluquinconazole (**1b**).[27]



Scheme 4. *Reagents and conditions*: i, $NaNO_2$, HCl (conc.), H_2O, 0–5°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-Cl_2-$C_6H_3NH_2$, 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 ($C_2H_2N_3Na$), 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.), KI (0.33 equiv.), DMF, 80°C, 9 h; ix, Ph_3P (1 M in THF, 5 equiv.), room temp., 6 h; x, 2,4-Cl_2-C_6H_3N=C=O (5 equiv.); CH_2Cl_2, room temp., 6 h; xi, 1*H*-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 triazolylquinazolinones **1a** and **b** were synthesized by using a solid-phase method (Scheme 4). Recently Villalgordo 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 led[31] (Scheme 4) to targeted triazolylquinazolinones **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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