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A Solid Phase Synthesis of Miconazole Analogs via an Iodoetherification Reaction

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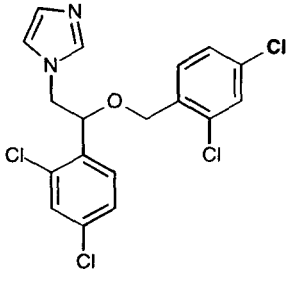
Abstract: A procedure for the preparation of various analogs of miconazole on solid support is described. A novel iodoetherification transformation is utilized as the key synthetic step. This approach has been applied to the combinatorial synthesis of 45 analogs. Copyright © 1996 Elsevier Science Ltd

The application of solid phase chemistry as a method for synthesizing large numbers of diverse molecules for drug discovery is evolving as an important tool.[1] This approach is no longer limited to the areas of peptides and oligonucleotides but has evolved to produce a diverse set of drug-like targets. Recent studies have shown that an array of different synthetic transformations can be performed on solid phase.[2] As a result, increasingly more challenging synthetic targets along with a larger variety of reaction types need to be evaluated on solid support. Herein we report the preparation of various analogs of miconazole on solid support utilizing a novel iodoetherification transformation as the key synthetic step.

Miconazole is a member of a class of imidazole agents which elicit broad spectrum antifungal activity. Since miconazole was first described, it has become an important treatment for several fungal infections.[3] Azole antifungals remain a viable lead structure in the pursuit of more potent fungicidals.



Miconazole

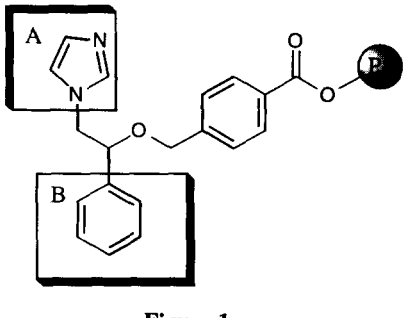
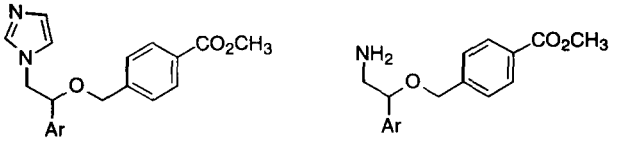


Figure 1

The benzyloxy moiety on the miconazole core structure represents a useful site for the linkage to a solid support. In our case, a *p*-carboxyl group was installed as a handle for reversible attachment to the solid support. This transformation can be performed with much ease using well defined chemical methods. Linkage at this site also allowed for variations of regions A and B (Figure 1). This flexibility in the synthetic route makes combinatorial synthesis an advantageous technique for the preparation of a large number of miconazole analogs.

The solid phase syntheses of miconazole analog **1** and primary amine **25** were first completed as an initial model study as outlined in Schemes 1 and 2. Our investigation began with tethering hydroxy acid **46** to a

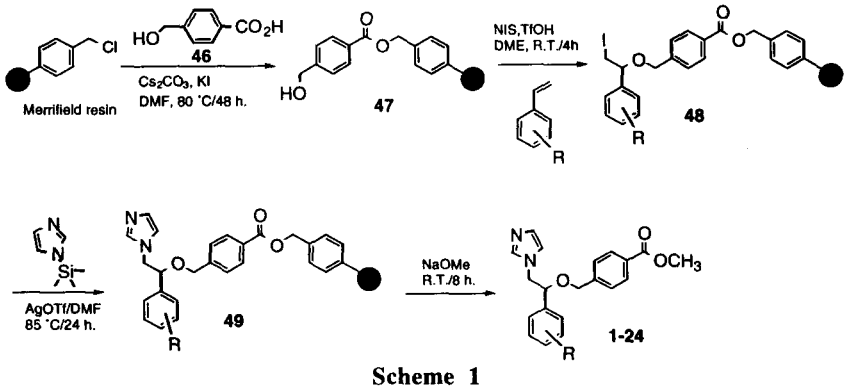
commercially available Merrifield resin[4] to provide the polymer bound benzyl alcohol **47.** Hydroxy ester **47** was then subjected to iodoetherification conditions[5] with 2,4,6-trimethylstyrene, N-iodosuccinimide and triflic acid as a catalyst to give iodo ether resin **48**. Displacement of iodide **48** was then effected with 1-(trimethylsilyl)imidazole in the presence of silver triflate to furnish the resin bound imidazole **49**. These optimized conditions[6] minimized a competing elimination pathway which produced considerable amounts of enol ether under a variety of other conditions.[7] Cleavage of the product from the resin was readily achieved by transesterification (0.2 eq NaOMe, MeOH-THF (1:4)), providing the methyl ester **1**.[8] Analysis of the crude cleavage products by ^{1}H NMR and HPLC[9] indicated 61% desired product, 10% (4-hydroxymethyl)methyl benzoate and 12% of the elimination product present. Automated preparative HPLC[10] provided azole **1**[11] in 22% overall yield.



1-24 **25-45**

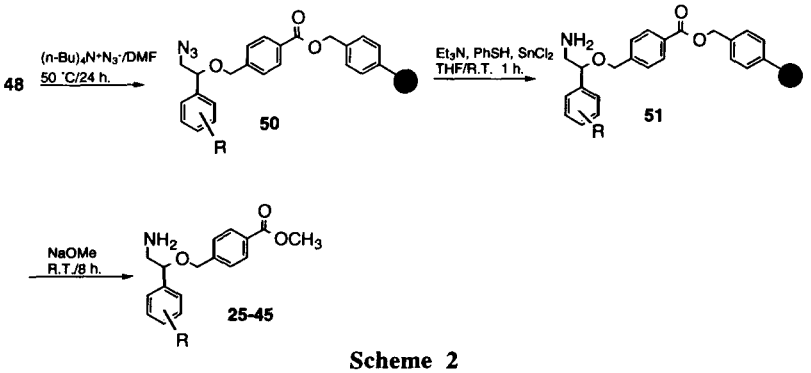
1, 25: Ar = 2,4,6-tri-Me-Ph

The synthesis of primary amines **25-45** was carried out from intermediate iodide **48** by displacement of the iodide with tetra-N-butylammonium azide, followed by reduction to amine **51** using thiophenol/Et_3N/$SnCl_2$ (4:5:1). The reduction was quite rapid (<1h at room temperature) and the reaction progress was easily monitored by IR. Cleavage of the product from the resin was accomplished by transesterification to give the methyl ester **25**.[12] HPLC[9] and ^{1}H NMR analysis of the crude cleavage product indicated 45% desired product, 7% elimination product and 18% (4-hydroxymethyl)methyl benzoate present. Automated preparative HPLC[10] was utilized to provide pure amine **25**[11] in 10% overall yield.



Scheme 1

The successful solid phase approach used for the synthesis of miconazoles **1** and **25** has been applied to the combinatorial synthesis of 45 analogs. In addition substrate **51** presents a primary amine which can serve as a site for further diversification. The reaction components, overall yields and purities are shown in Table 1. Product quality was assessed by HPLC and MS.



Scheme 2

Table 1:

Compound #	Ar	Imidazoles 1-24		Amines 25-45	
		% Purity[a]	% Yield[b]	% Purity[a]	% Yield[b]
1, 25	2,4,6-tri-Me-Ph	99	22	96	10
2, 26	4-t-Bu-Ph	88	4	96	14
3, 27	3,5-di-F-Ph	98	12	98	29
4, 28	4-CF_3-Ph	96	12	91	24
5, 29	3-CF_3-Ph	96	9	94	32
6, 30	3-F-Ph	97	14	92	9
7, 31	4-phenoxy-Ph	97	14	98	14
8	3-NO_2-Ph	89	15	c	c
9, 32	4-cyclohexyl-Ph	92	11	97	17
10, 33	4-octyl-Ph	95	7	93	17
11, 34	2-Me-Ph	87	1	92	19
12	4-NO_2-Ph	91	2	c	c
13, 35	2-I-Ph	93	2	84	19
14, 36	2,5-di-Me-Ph	88	1	98	42
15, 37	4-CH_3O-Ph	87	2	83	5
16, 38	3-Cl-Ph	98	9	96	14
17, 39	2-Br-Ph	95	3	98	42
18, 40	2-F-Ph	94	3	93	35
19, 41	3-Br-Ph	96	7	94	16
20, 42	2,6-di-Cl-Ph	74	1	90	40
21, 43	3-Me-Ph	94	4	80	4
22, 44	4-Me-Ph	93	2	70	4
23	3,5-di-CF_3-Ph	93	5	c	c
24, 45	2-CF_3-Ph	81	2	91	16

[a]Purity after automated preparative HPLC.
[b]Isolated yield after automated preparative HPLC.
[c]No product obtained.

In summary, this solid phase approach has been successfully employed in the synthesis of a diverse array of miconazole analogs. The key iodoetherification step proceeds with a large variety of styrenes, including those having electron withdrawing and donating groups. Overall isolated yields are low and variable with no apparent trends. However, even the most modest example rapidly provides a sufficient quantity of product for biological testing. These compounds are currently under biological evaluation.

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References and Notes

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4. (a.) Barrany, G.; and Merrifield, R.B. (1980) Peptides **2**, 1. (b.) Brodansky, M.; Klausner, Y.S.; Ondetti, M.A.; Peptide Synthesis, 2nd ed., Wiley, 1976. (c.) Merrifield resin purchased from Advanced ChemTech, copolymer of chloromethylpolystyrene cross-linked with 1% divinyl benzene, 100-200 mesh, 1.2 mmol of Cl/g resin.
5. A typical procedure (entry 1) for the iodoetherificaton step is as follows. To a suspension of the polymer bound alcohol **47** (500 mg; loading 1.05 mmol/g resin) in DME (4.5 mL) was added 2,4,6-trimethylstyrene (595 mg, 4.07 mmol, 7.7 eq), N-iodosuccinimide (916 mg, 4.07mmol, 7.7 eq) and trifluoromethanesulfonic acid (7 μL). The reaction mixture was shaken at room temperature for 16 h. and then washed successively with DME (5x10 mL), 1% Et_3N in DME (2x10 mL), DME:H_2O (1:1, 5x10 mL), DME (5x10 mL), MeOH (5x10 mL) and then dried under high vacuum. A second treatment was performed to ensure high conversion.
6. A typical procedure (entry 1) for the displacement step is as follows. To a suspension of the polymer bound iodo ether **48** (621 mg; loading 0.85 mmol/g resin) in DMF (5.0 mL) was added silver triflate (167 mg, 0.69 mmol, 1.3 eq) and 1-(trimethylsilyl)imidazole (1.47g, 10.5 mmol, 20 eq). The reaction mixture was shaken at 85 °C for 16 h. and then washed successively with DMF (5x10 mL), DMF:H_2O (1:1, 5x10 mL), DMF(3x1 mL), MeOH (5x10 mL) and then dried under high vacuum. A second treatment was performed to ensure high conversion.
7. Other conditions attempted: a.) displacement of iodide **48** with imidazole in DMF at 75°C, b.) displacement with imidazole in the presence of silver triflate in DMF at 75 °C and c.) displacement with 1-(trimethylsilyl)imidazole in DMF at 75 °C.
8. NMR data for **1**: ^1H NMR (270 MHz, $CDCl_3$) δ 2.10 (s, 6H), 2.27 (s, 3H), 3.14 (dd, *J*=14.0, 5.5 Hz, 1H), 3.43 (dd, *J*=14.6, 7.0 Hz, 1H), 3.93 (s, 3H), 4.52 (dd, *J*=66.2, 12.3 Hz, 2H), 5.50 (t, *J*=6.5 Hz, 1H), 6.83 (s, 2H), 7.14 (d, *J*=8.2 Hz, 2H), 7.23 (s, 1H), 7.44 (s, 1H), 7.95 (d, *J*=8.2 Hz, 2H), 8.68 (s, 1H); MS (EI) m/z: 379(MH^+).
9. UV detection at 215 nm.
10. Samples were purified by preparative HPLC using a YMC S5 ODS column, 30 x 250 mm, eluted with a gradient from 20% to 100% aqueous methanol containing 0.1% TFA over 20 minutes. Appropriate fractions were collected based on UV absorbance at 215 nm and were concentrated in vacuo. System hardware included a Shimadzu SCL-10A system controller, 2-Shimadzu LC-8A solvent pumps, a Shimadzu SPD-10A detector (equipped with preparative flow cell), a Shimadzu SIL 10-A autosampler equipped for 2-ml injection and a Shimadzu FRC-10A fraction collector.
11. Purified compound isolated as TFA salt.
12. NMR data for **25**: ^1H NMR (270 MHz, $CDCl_3$) δ 2.26 (s, 9H), 3.05 (m, 1H), 3.45 (m, 1H), 3.87 (s, 3H), 4.38 (dd, *J*=40.0, 12.0 Hz, 2H), 5.14 (m, 1H), 6.83 (s, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 7.93 (d, *J*=8.2 Hz, 2H), 8.05 (bs, 2H); MS (EI) m/z: 328(MH^+).

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