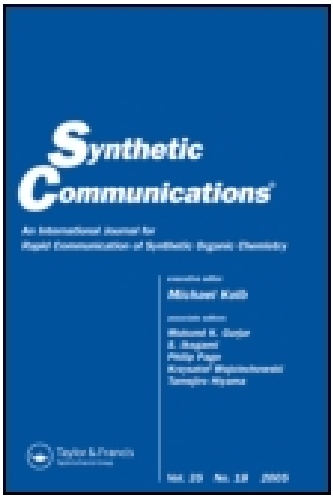

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Abstract: A simple and single-step process for coupling (2R,1S)-1-[2-(2,4-difluorophenyl)-2-oxiranyl]ethanol and various 1,2,4-triazolones utilizing the Mitsunobu protocol is described. The product so formed is a key intermediate in the synthesis of azole antifungals with potent and broad-spectrum activity against yeast and filamentous fungi.

Keywords: Azole antifungal, Mitsunobu coupling

BACKROUND

We have identified 2[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-yl)propyl]-4-[4-(4-chlorophenyl)-1-piperizinyl]phenyl]-3-(2H,4H)-1,2,4-thiotriazolone (**1**) as an azole antifungal with potent and broad-spectrum activity against yeast and filamentous fungi. The in vitro activity correlated well with in vivo protection, indicating adequate pharmacokinetic properties in mouse, the efficacy model used. Further preclinical development necessitated a robust and simple synthesis to generate this compound in multigram quantities. Synthesis of **1** involves Lawesson's[1a,b] (or modified Lawesson's,[1c]) reagent–mediated transformation of

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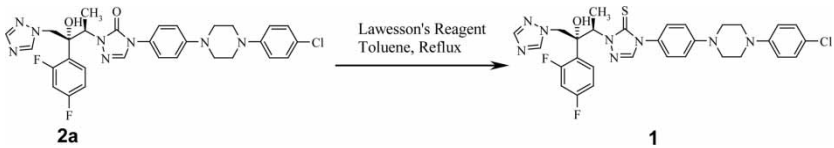
corresponding triazolone **2a** to the desired thio analogue **1**. We undertook development of a simple and efficient synthesis of the key intermediate required for the generation of penultimate triazolone **2a** (Scheme 1).

Analogous triazolones have been synthesized following a general literature procedure[2] (Scheme 2) involving conversion of (2R,1S)-1-[2-(2,4-difluorophenyl)-2-oxiranyl]ethanol[3] (**3**) to the key intermediate **4**, in ~20–60% yields (conversion of **3** to the corresponding activated triflate intermediate followed by nucleophillic displacement with the anion of triazolone **5** at low temperatures). Intermediate **4** is then converted to the desired triazolone **2** following standard protocol for epoxide ring opening with 1,2,4-triazole. This reported sequence, however, could not be applied efficiently for the synthesis of desired candidate molecule **2a**, partly because of the inherent labile nature of the triflate intermediate (as reflected in only low to moderate yields for **4**) and more importantly the highly insoluble nature of the triazolone side chain **5a** in solvents used for this transformation at low temperatures. Hence, an alternate and more efficient route to generate **2a** in multigram quantities was required.

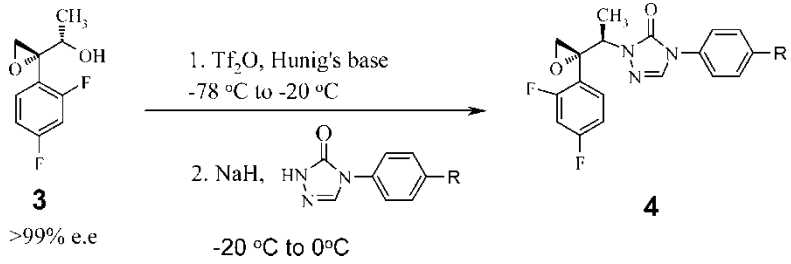
PRESENT WORK

Discrete generation of amide anion followed by addition of an alkylating group has been the most widely used methodology in literature[4] for alkylating amidic nitrogen. Several variations of bases, additives, and cosolvents have been used to effect this transformation. Interestingly, there has been very limited[5] application of the Mitsunobu protocol for the alkylation of amidic nitrogen.

Although the Mitsunobu protocol offers distinct advantages for N-alkylation because it does not require discrete generation of nucleophilic anions or an activated displaceable group (e.g., halide or sulfonate) because the anion and the necessary electrophile are generated in situ, the use of this methodology has not been explored in the synthesis of azole antifungals. We report successful utilization of the Mitsunobu protocol as an efficient alternative for the conversion of epoxy alcohol **3** to the key intermediate **4** in a simple one-pot process[6] (Scheme 3). Thus, diisopropylazodicarboxylate (DIAD) was added slowly to a suspension of epoxy alcohol **3**, triphenylphosphine, and triazolone **5a** in DMF at 0°C. The clear solution thus obtained



Scheme 1.



Scheme 2.

(after the complete addition of DIAD) was stirred overnight at ambient temperature to afford, after workup and purification, **4a** in ∼35% isolated yield with complete inversion of stereochemistry at the 2° carbon, as desired (Scheme 1).

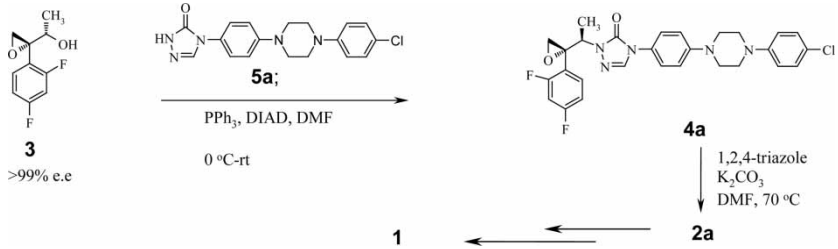
We have further successfully applied this protocol (Scheme 4) to the synthesis of other analogous triazolones (**4b–g**) and pyrimidinone analogs **4h** in moderate to good yields (Table 1).

In conclusion, we have demonstrated the utility of the Mitsunobu protocol for the synthesis of the key intermediate **4a** required for the generation of **1**. This alternate procedure is simple and offers distinct advantages as compared to earlier methods used for the synthesis of analogous triazolones.

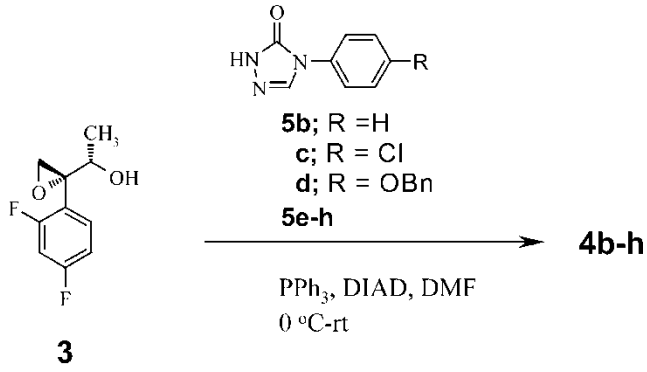
EXPERIMENTAL

General Procedure for Alkylation of Triazolones

Under nitrogen and stirring, nucleophile (1.1 mmol) and triphenylphosphine (1.2 mmol) were added to dry DMF (5 mL) in a three-neck round-bottom flask, and the mixture was cooled to 0°C. A solution of epoxy alcohol **3** (1.0 mmol) in DMF (1 mL) was added at 0°C followed by DIAD (1.2 mmol). The reaction mixture was stirred at 25–30°C and the progress



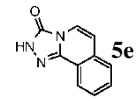
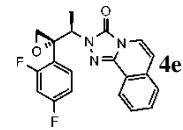
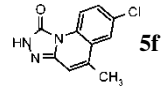
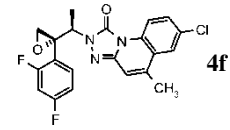
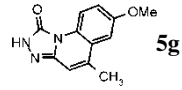
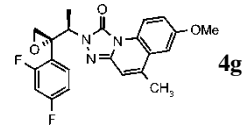
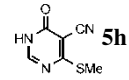
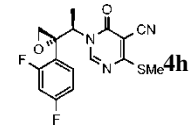
Scheme 3.



Scheme 4.

was monitored by TLC. The reaction mixture was poured into ice-cold water (100 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvent removed in vacuo. The residue was purified by column chromography (silica gel, 100–200 mesh) to afford the desired product **4**. [^{1}H NMR data for

Table 1. Mitsunobu protocol in the synthesis of azole antifungals

Entry	Nucleophile 3[a]	Product 4	Yield
1	 **5e**	 **4e**	75%
2	 **5f**	 **4f**	41%
3	 **5g**	 **4g**	53%
4	 **5h**	 **4h**	34%

[a]Products **4b–d** were obtained as inseparable mixtures with reduced DIAD. They were thus subjected to epoxide ring opening with 1,2,4-triazole, and yields were calculated over two steps.

4a: MS (+ve ion mode; m/z) 539 ($M^+ + 1$); ($CDCl_3$; 300 MHz): δ 1.46 (d, $J = 7.0$ Hz, 3H), 2.87 (d, $J = 4.6$ Hz, 1H), 3.15 (d, $J = 4.6$ Hz, 1H), 3.29–3.35 (m, 8H), 4.95 (q, $J = 7.0$ Hz, 1H), 6.80–7.68 (m, 12 H).]

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