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Solid-Phase Library Synthesis of Triazolopyridazines via [4+2] Cycloadditions

Armen M. Boldi,* Charles R. Johnson, and Hisham O. Eissa

Axys Pharmaceuticals, Inc.,[1] 180 Kimball Way, South San Francisco, CA 94080

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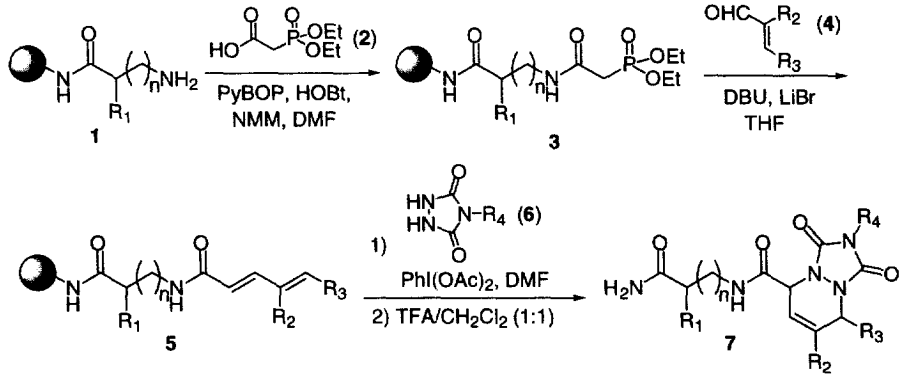
Abstract: The solid-phase library synthesis of triazolopyridazines was accomplished using a [4+2] cycloaddition strategy. The Horner-Wadsworth-Emmons (HWE) reagent diethylphosphonoacetic acid was attached to the *N*-terminus of amino acids on Rink amide solid-phase peptide synthesis support. The HWE reaction with a variety of α,β-unsaturated aldehydes gave high conversion to diene amides. Subsequent [4+2] cycloaddition with 4-substituted urazines gave triazolopyridazines upon cleavage from resin. An alternate [4+2] cycloaddition method with urazine followed by a Mitsunobu reaction also provided triazolopyridazines.

Methods for constructing heterocyclic small molecules on solid support have attracted considerable recent attention.[2] In the context of an ongoing combinatorial chemistry development program, we were attracted to triazolopyridazines due to apparent utility in angiotensin-related antihypertensive activity.[3] We have developed novel general library syntheses of this class of compounds for screening a broad range of biological targets. Here we describe the development and application of solid-phase versions of the Horner-Wadsworth-Emmons olefination, [4+2] cycloaddition, and Mitsunobu reaction to the library synthesis of triazolopyridazines.

Fmoc-amino acids were attached to the Rink amide linker of polystyrene resin. After Fmoc deprotection to amine **1**, diethylphosphonoacetic acid (**2**) was coupled to the solid-supported amino acids with PyBOP, HOBT, and NMM to give diethylphosphonate **3** (Scheme 1). Subsequent HWE reaction with α,β-unsaturated aldehydes **4** gave diene **5**. We recently reported a solid-supported Horner-Wadsworth-Emmons (HWE) reaction[4] using polyethylene glycol linked PEG-PAL resin.[5,6] We chose to use the higher loading Rink amide resin for library production. However, with the Rink amide resin, more vigorous reaction conditions were required. DBU instead of triethylamine as base, and anhydrous THF instead of acetonitrile as solvent insured complete olefination within 4 h.[7] These modifications extended the scope and utility of the HWE reaction on solid-support.

Scheme 1. Solid-phase synthesis of triazolopyridazines.



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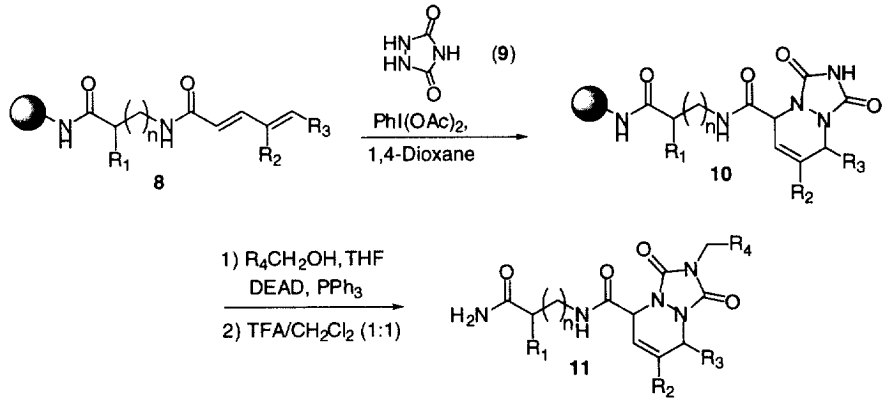
The solid-supported [4+2] cycloaddition has attracted limited attention.[8] As dienophiles in [4+2] cycloadditions, 4-substituted urazines[9] are well known.[10,11] 4-Substituted urazoles **6**, synthesized from isocyanates and ethyl carbazate,[12] are oxidized to 4-substituted urazines with iodobenzene diacetate[13] and added to the solid-supported dienes **5** to give triazolopyridazines **7** after cleavage off solid-support.[14,15] We found these urazoles to be soluble in DMF, a practical solvent for library production. All reactions proceeded smoothly to give on average 30% overall yield (7 linear steps) and 70% HPLC purity (AUC, 214 nm) with a range of amino acids, α,β-unsaturated aldehydes and urazoles. Unreacted diene **5** from the HWE olefination was occasionally observed as a minor impurity (ca. <5%).

Scheme 2. Solid-phase synthesis of triazolopyridazines via Mitsunobu reaction.

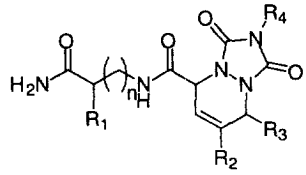


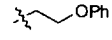
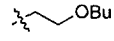
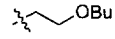
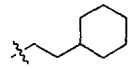
An alternate synthesis accessed the greater diversity found in commercially available alcohols than isocyanates. The cycloaddition methodology was extended to the synthesis of imide **10** (Scheme 2). Since 4-substituted urazoles performed well in cycloadditions with solid-supported dienes in DMF, we were surprised that urazine, generated by oxidation of urazole (**9**) with $PhI(OAc)_2$, decomposed in DMF, DMA and DMSO. 1,4-Dioxane proved to be the solvent of choice. In order to insure complete cycloaddition, we adapted a reported in-situ urazole oxidation procedure[16] whereby urazine was generated by portion-wise addition of oxidant to a premixed solution of urazole and diene yielding resin-bound imide **10**.[17] We found mixing to be very important for the success of this reaction. Reaction of resin-bound scaffold **10** with alcohols by the Mitsunobu reaction[18] using DEAD/PPh_3 in anhydrous THF followed by cleavage off solid-support gave triazolopyridazines **11**.[14]

We have developed library methods for solid-supported Horner-Wadsworth-Emmons olefination and [4+2] cycloaddition with 4-substituted urazoles. Extension of the [4+2] cycloaddition from 4-substituted urazoles to urazole (**9**) followed by Mitsunobu reaction of the imide nitrogen allowed expansion of the universe of triazolopyridazines that could be prepared. These methods have been successfully applied to the synthesis of two spatially separated small molecule libraries composed of 3,520 and 4,400 compounds.[19] Shown below in Table 1 are representative compounds prepared in libraries. These libraries are currently being

screened in a series of *in vitro* biological assays. Continued application of these synthetic methods in the synthesis of combinatorial libraries is under active investigation.

Table 1. Representative triazolopyridazines prepared via solid-phase library syntheses.



Entry	n	R_1	R_2	R_3	R_4	% Yield	% Purity (AUC @ 214 nm)
1	0	Me	H	Me	Me	50	92
2	0	Me	H	Ph	Me	28	62
3	0	Me	H	Ph	Ph	51	79
4	0	$PhCH_2$	H	Ph	Ph	27	89
5	1	H	H	Me	Me	64	93
6	1	H	H	Me	Ph	82	93
7	1	H	H	Ph		24	40
8	1	H	Ph	*i*-Pr		28	41
9	1	H	Pr	Bu		35	62
10	1	H	H	Ph		26	51

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14. Representative library compounds were purified and characterized by ^{1}H NMR, MS and HPLC.
15. **Urazole Cyclization. Method A.** 4-Substituted urazole (0.4 mmol, 4 equiv) and iodobenzenediacetate (0.4 mmol, 4 equiv) are placed in DMF (1.0 mL). After generation of urazine, the urazine solution is added to the resin from the Horner-Emmons olefination (0.1 mmol, 1 equiv). Shake for 12 h. The resin was washed with the following solvents [3 x (DMF then MeOH); 3 x CH_2Cl_2].
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17. **Urazole Cyclization. Method B.** To each resin lot from the HWE olefination (3.25 mmol) was added a minimum amount of 1,4-dioxane (28 mL) and urazole (15.3 mmol, 4 equiv). Add a freshly prepared solution of iodobenzenediacetate in 1,4-dioxane (0.27 M, 7.0 mL, 0.5 equiv). Stir frequently for 1 h. Repeat addition of a solution of iodobenzene diacetate in 1,4-dioxane (0.27 M, 7.0 mL, 0.5 equiv) an additional three times. Drain solution and repeat entire procedure once. The resin was washed with the following solvents [3 x (DMF then MeOH); 3 x CH_2Cl_2].
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