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Report

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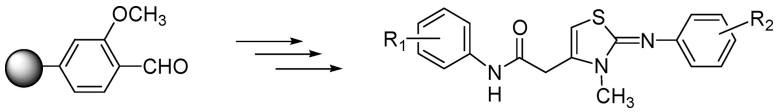

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Solid-Phase Synthesis of Fungitoxic 2-Imino-1,3-thiazolines

Suyeal Bae, Hoh-Gyu Hahn,* and Kee Dal Nam

Organic Chemistry Laboratory, Korea Institute of Science and Technology, Seoul 136-791, Korea

Heduck Mah

Department of Chemistry, Kyonggi University, Suwon 442-760, Korea

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The design and synthesis of new fungicides pose a continuing challenge in the field of agricultural chemistry, because of the persistent problem of resistance development, as well as economic and environmental pressures to find compounds with high activity and low toxicity. Although the preparation of combinatorial libraries using solid-phase synthesis is a fast growing area in the pharmaceutical research field, only a few papers have reported its use in the generation or optimization of lead for the agrochemical purposes.[1] In our study, which is aimed at the development of new agrochemical fungicides, we have previously reported the synthesis of new 2-phenylimino-1,3-thiazoline-4-acetanilides (**10**) and their antifungal activity against *Pyricularia oryzae*.[2]

As part of a continuous effort for optimization of this lead entity, we report herein a solid-phase synthesis of a focused library,[3] using a ChemSpeed ASW 2000 automated synthesizer. The information gained in the assay of a particular library for the fungitoxic activity could be incorporated into the planning of a subsequent library. The first concern was selection of suitable linker because the imine moiety is labile under acidic conditions. In addition, to synthesize compounds with diversity, an optimal linker should allow an efficient cleavage of product with high purity under mild conditions with no trace of the linkage. Our strategy for traceless synthesis of the library was based on the BAL[4] anchored on a carboxanilide group, which has received attention because of the ease of cleavage from this support with TFA under mild reaction conditions.[5] The linker has proven to be useful for the solid-phase synthesis of derivatized amines.[6] To determine the optimal reaction conditions on the fully automated synthesizer, we initially selected resin-bound aniline **3** (R_1 = 4-CH_2CH_3) as a representative starting material for a model study. The starting resin-bound aniline **3** was obtained according to the known standard reductive amination procedure of polymer-bound aldehyde **1** in the presence of 4-ethyl aniline and sodium triacetoxyborohydride. The resin-bound aniline **3** was treated with excess (3 molar equivalents) chloroacetoacetyl chloride **5** as a solution in DCM prepared independently from the reaction of ketene dimer **4** with an equimolar amount of chlorine. The obtained product was the desired anilide **6**, in addition to the hydrochloride salt **7**, which was monitored by broad stretching at 2251 cm^{-1} in the Fourier tranform infrared (FT-IR) analysis. After filtration, the resin was used in the next step, without any attempt to enhance the yield of **6** or removal the salt **7** for the following reasons. First, repeated acylation reaction after treatment of the mixture **6** and **7** with DIPEA gave only a slightly improved yield (10%). Second, the resin-bound hydrochloride salt **7** was recovered without cleavage under the reaction conditions, in which the product **10** was formed from **9** (Scheme 1).

* Corresponding author. Fax: +82-2-9585189. E-mail: hghahn@kist.re.kr.

Table 1. Dependence of the Yield and Purity of **10** (R_1 = 4-CH_2CH_3, R_2 = H) on the Reaction Time

entry	reaction time (h)	yield (%)[a]	purity (%)[b]
1	0.5	21	95
2	1	25	88
3	2	32	79
4	3	29	77
5	5	34	88
6	19	43	70

[a] Crude yields were calculated based on theoretical loading of 1.6 mmol/g of **1**. [b] As determined by high-performance liquid chromatography (HPLC).[8]

Table 2. Yield, Purity, and Molecular Weight (MW) of the Synthesized 2-Imino-1,3-thiazolines (**10**)

entry	R_1	R_2	yield (%)[a]	purity (%)[b]	MW (found)[c]
1	4-OCH_3	3-CH_3	6	95 (54)	368 (MH^+)
2	4-OCH_3	4-OCH_3	12	85	384 (MH^+)
3	4-OCH_3	H	20	71	354 (MH^+)
4	4-CH_2CH_3	3-CH_3	21	90 (71)	366 (MH^+)
5	4-CH_2CH_3	4-OCH_3	12	87 (76)	382 (MH^+)
6	H	3-CH_3	33	88 (54)	338 (MH^+)
7	H	4-CF_3	20	85 (65)	392 (MH^+)
8	H	4-OC_6H_4(4-Cl)	28	84 (69)	450 (MH^+)
9	H	3-$OCH(CH_3)_2$	32	85 (64)	382 (MH^+)
10	H	4-OCH_3	32	83 (61)	354 (MH^+)
11	H	2-OCH_3	39	93 (71)	354 (MH^+)
12	H	2-Cl, 4-CH_3	25	93	372 (MH^+)
13	H	4-CO_2Et	23	89	396 (MH^+)
14	H	H	35	87	324 (MH^+)
15	4-Cl	3-CH_3	25	91 (55)	372 (MH^+)
16	4-Cl	4-OCH_3	28	82	388 (MH^+)
17	4-Cl	H	36	92	358 (MH^+)
18	4-CF_3	3-CH_3	30	69 (68)	406 (MH^+)
19	4-CF_3	4-OCH_3	31	75 (67)	422 (MH^+)
20	4-CF_3	H	7	38	392 (MH^+)

[a] Crude yields were calculated based on theoretical loading of 1.6 mmol/g of **1**. [b] As determined by HPLC detected at 254 nm. Values given in parentheses represent data determined via HPLC conducted at 220 nm.[8] [c] Confirmed by mass spectra (ES).

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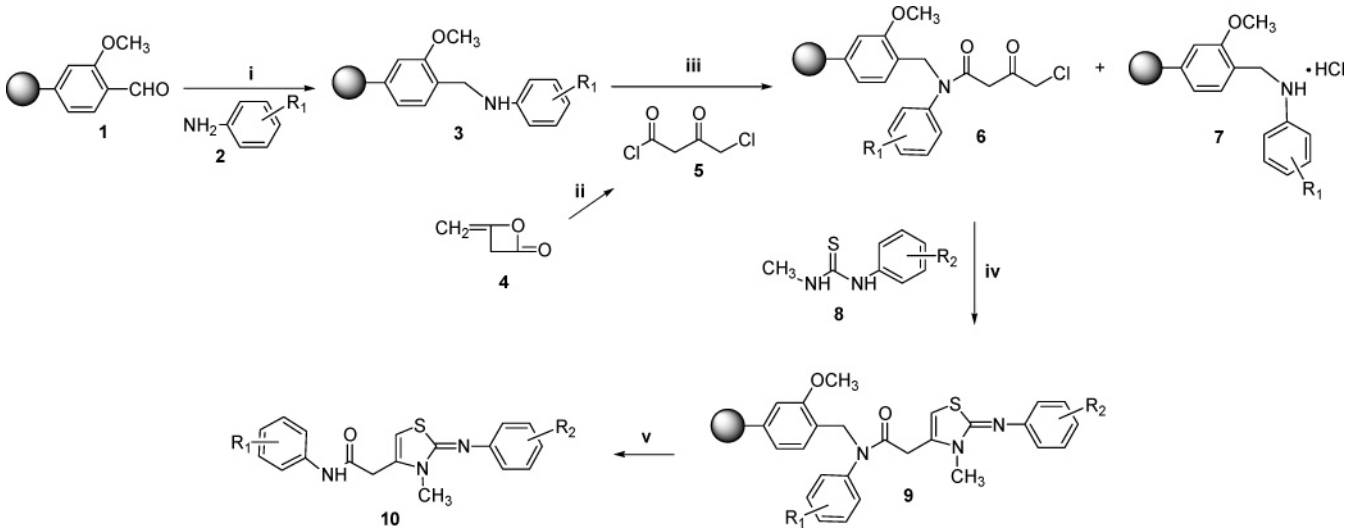
Scheme 1. Synthetic Route to 2-Imino-1,3-thiazolines (**10**)[a]



[a] Reagents and conditions: (i) aniline **2** (5 equiv), $NaB(OAc)_3H$ (3 equiv), AcOH (10 equiv), THF at room temperature for 24 h; (ii) 4% (v/v) Cl_2 solution in DCM (1 equiv) at −10 °C for 2 h; (iii) acyl chloride (3 equiv) at −10 °C for 3 h; (iv) thiourea **8** (2 equiv), DMF, at 80 °C for 12 h; (v) 50% TFA/DCM for 30 min.

Condensation of the resin-bound anilide **6** with thiourea **8** (R_2 = H) in DMF at 80 °C afforded the corresponding resin-bound 2-phenylimino-1,3-thiazoline **9** (R_1 = 4-CH_2-CH_3, R_2 = H). The optimal reaction conditions for final cleavage of traceless linker from the solid support, using TFA without hydrolysis of the imine moiety, were investigated. Several reaction conditions were examined by varying concentrations of TFA in DCM (5, 20, or 50%) and reaction time (0.5−19 h) at room temperature. The progress of the reaction was simply monitored by observing the color change on resin from light brown to deep purple.[7] From Table 1, it is obvious that a very short reaction time is a critical factor in obtaining high purity of the product with moderate yield. As shown in entry 1 of Table 1, 2-phenylimino-1,3-thiazoline **10** was obtained as a white solid with high purity via the treatment of **9** with 50% TFA/DCM for 0.5 h at room temperature.[9]

With these data from the model study in hand, a focused library was synthesized by similar methods from this scaffold, using a ChemSpeed ASW 2000 automated synthesizer.[10] Table 2 showed the list of compounds prepared in part. The purity of the materials was 38−95%, and the structures of the compounds were confirmed by ^{1}H NMR spectra after purification through flash chromatography. Primary biological assay against rice blast (*Pyricularia grisea*) was conducted (see Supporting Information for the results).

In conclusion, the efficiency of this synthetic methodology and the wide availability of substituted anilines and thioureas make this automated, traceless polymer-supported procedure ideally suited for the synthesis of a focused library. We are now using this methodology for construction of a different focused library based on the 2-imino-1,3-thiazoline template.

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Supporting Information Available. Characterization data, ^{1}H NMR, and MS spectra for all samples listed in Table 2. Result of biological assay of the compounds in part. (PDF.) This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Abbreviations used in this paper: BAL, backbone amide linker; AcOH, acetic acid; THF, tetrahydrofuran; DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; TFA, trifluoroacetic acid; and DIPEA, *N*,*N*-diisopropyllethylamine.

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(8) Analytical HPLC of crude samples of 2-imino-1,3-thiazoline **10** was performed on a Zorbax Eclipse XDB−C_8 column (5 μm, 150 mm × 4.6 mm); linear gradient over 20 min using (A) 0.1% TFA in water and (B) 0.1% TFA in CH_3CN (from 8:2 to 3:7), with a flow rate of 2.0 mL/min and UV absorbance at 220 and 254 nm.

(9) Representative analytical data of compound **10** (R_1 = 4-CH_2-CH_3, R_2 = H) is as follows. ^{1}H NMR (300 MHz, $CDCl_3$): 1.20 (t, 3H, $-CH_2CH_3$), 2.59 (q, 2H, $-CH_2CH_3$), 3.74 (s, 3H, N-CH_3), 3.83 (s, 2H, 4-CH_2), 6.58 (s, 1H, vinyl-H), 7.09−7.43 (m, 9H, Ar−H), 9.32 (s, 1H, NH). MS(ES): *m*/*z* 352 (MH^+).

(10) Fully automated synthesis was performed using a Chemspped ASW2000. BAL resin **1** (Aldrich Chemical Company, 50−100 mesh, loading 1.6 mmol/g, 100 mg) and $NaB(OAc)_3H$ (124 mg, 0.585 mmol) was placed into a 13-mL glass reaction vessel with a polyethylene filter. THF/aniline/AcOH (1 mL/0.975 mmol/112 μL) was added to the reactor, and the reactor was shaken for 24 h at room temperature. The resin was washed with MeOH (3 mL × 2), THF (3 mL × 2), 15% DIPEA/DCM (3 mL × 2), MeOH (3 mL × 2), and DCM (3 mL × 2) and then dried under vacuum for 5 h. Dry DCM (3 mL) was added to the reactor, and the reactor was cooled to −10 °C. After chloroacetoacetyl chloride **5** was prepared with ketene dimer **4**/4% Cl_2 in DCM solution, this solution (800 μmol, 0.585 mmol) was added slowly, and the reactor was shaken for 1.5 h at −10 °C. The resin was washed with DCM (3 mL × 2), MeOH (3 mL × 2), and DCM (3 mL × 2) and then dried under vacuum for 3 h. DMF/thiourea **8** (1 mL/0.32 mmol) was added to the reactor, and the reactor was shaken for 12 h at 80 °C. The resin was washed with DMF (3 mL × 2), MeOH (3 mL × 2), and DCM (3 mL × 2) and then dried under vacuum for 2 h. Finally, the resin was treated with 50% TFA/DCM for 30 min, from which the reaction mixture was filtered and concentrated within a Genevac model HT-4 evaporator.

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