Compound Libraries

Combinatorial Synthesis of Functionalized 1,3-Thiazine Libraries Using a Combined Polymer-Supported Reagent/Catch-and-Release Strategy**

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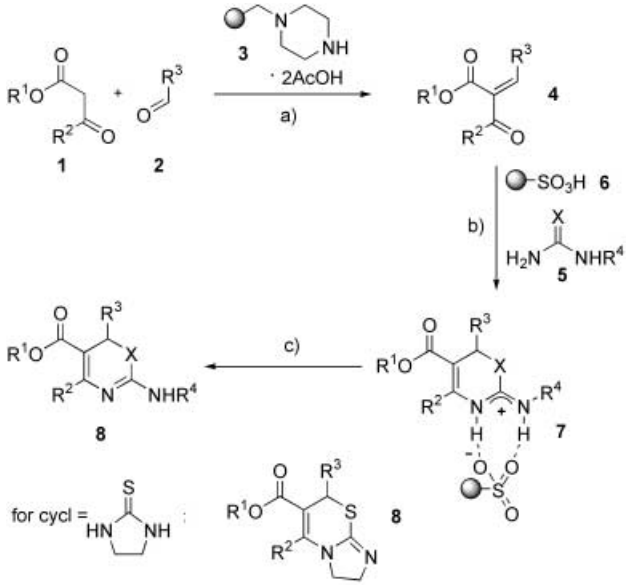
Combinatorial chemistry has emerged as a highly valuable and powerful method in medicinal chemistry, catalyst discovery, and materials science over the past few years.[1] Driven by the force to discover and develop new molecules with tailored properties more efficiently and in increasingly shorter times, scientists have developed several highly successful concepts. Combinatorial methods focusing on small organic molecules are mainly dominated by two strategies: solid-phase synthesis[2] and with increasing importance solution-phase protocols with the aid of scavenger resins and polymer-bound reagents.[3] A special concept in solution-phase synthesis is the "catch-and-release" strategy, where the formed target molecule is selectively bound (covalently or by means of an ionic bond) to a resin. After excess reagents, unreacted starting materials, catalysts, etc. are removed by simple washings, the product is released from the polymer support. One could envision that in an ideal case such catch-and-release methods could be incorporated in the synthesis step. Appropriately functionalized polymeric resins could be utilized that not only mediate a specific chemical reaction but at the same time selectively remove the desired product from the reaction mixture. However, examples for such one-pot, in situ synthesis/catch-and-release protocols are extremely rare.[4] Herein we report on the generation of libraries of densely functionalized (five diversity points) 1,3-thiazines of type **8**, employing a resin-bound sulfonic acid that acts simultaneously as reaction promoter in a cyclocondensation step and as a selective sequester of the final basic thiazine products (Scheme 1).



Scheme 1. Synthesis of thiazines **8**. a) 10 mol% **3**, chlorobenzene, 115 °C, 5 h; b) 0.6 equiv **5**, 0.5 equiv **6**, dioxane, 90 °C, 18 h; c) washing, then MeOH/TEA 3:1. TEA = triethylamine.

The 2-amino-1,3-thiazine-5-carboxylate scaffold **8** has hitherto received scant attention,[5,6] despite its close structural similarity to the dihydropyrimidinones (DHPMs), which are privileged structures with heterocyclic cores[7] and well-documented pharmacological properties.[8] The overall strategy for the generation of a library of thiazines **8** utilizing the tandem ring-closure/resin-capture approach is outlined in Scheme 1.

Our synthesis started with the Knoevenagel condensation of β-keto esters **1** with aldehydes **2** under open-vessel conditions to facilitate the removal of water formed during

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[**] We are indebted to BASF AG, Ludwigshafen (Germany), and the Austrian Science Fund (FWF, P-15582) for financial support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200352731

the reaction. A slight excess of the aldehyde was required to ensure good conversion in this step. We found the polymer-bound piperazine diacetate **3** to be a very effective catalyst for this reaction.[9] Not only is the catalyst itself easily removed, this method also removes the basic 2-amino-1,3-cyclohexadiene by-products formed by known catalyst-derived side reactions.[10,11] Importantly, these basic by-products must be removed so they do not interfere with the subsequent catch-and-release of the thiazine products (**4**→**7**→**8**). After filtration from the catalyst the crude enones were used directly in the subsequent ring-closing reaction. In the second step, the enones **4** (in excess) were treated with the appropriate thioureas and the polymer-bound sulfonic acid **6**[12,13] at 90 °C in inert dioxane, which proved superior to other solvents tested. Since the formed 1,3-thiazines are the only basic molecules in the reaction system, they are selectively captured by the supported sulfonic acid, presumably as tightly coordinated ion pairs with the strongly basic amidine-like isothiourea moiety.[14] Here, the polymer-bound sulfonic acid acts as an acidic mediator to facilitate the thiazine ring-closure and subsequently as a selective sequester for the desired basic thiazine products (see Scheme 1). Finally, by filtration and multiple washing steps, reagents, excess starting materials, solvents, and by-products (see below) are removed. The desired products are cleaved from the resin by displacement with triethylamine, which is a significantly stronger base than the 1,3-thiazines **8**.

This approach was used to prepare 28 1,3-thiazines and one 1,3-selenazine[15] in general good to excellent purities and overall yields from good to moderate over the two reaction steps (Table 1). It is evident that aldehyde building blocks **2** without or with little steric hindrance lead to generally higher yields. For aromatic aldehydes, substituents in *ortho* position, in particular if they are electron withdrawing, lower the yields significantly, although not the purities. Aliphatic substituents in position 4 of 1,3-thiazines (see R^2 in Table 1) are important for the success of the method. Despite the effects of the substituents on the efficiency of the thiazine ring-closure, it is important to note that even in cases of low yields (10–15 %) the purity of products is still high (72–98 %). This clearly demonstrates the success of the tandem ring-closure/catch-and-release strategy, since incomplete conversions—presumably as a result of the reduced reactivity of some building blocks—do not result in the propagation of impurities. The efficacy of the concept is clearly illustrated by HPLC monitoring at different stages of the synthesis.[16]

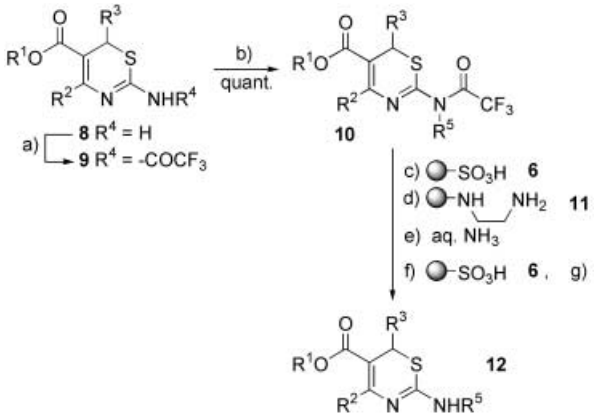
In order to synthesize more diverse derivatives of the parent scaffold, we envisioned a selective and flexible functionalization of the amino group in position 2 of the 1,3-thiazines **8**. This is of particular importance because the number of thioureas successfully applied in the ring-closure sequence **4**+**5**→**8** is limited. Therefore, we developed a protocol for the selective alkylation of the 2-amino group on the thiazine ring utilizing the Mitsunobu reaction as the diversity-generating method and again employing polymer-supported sequesteration reagents (Scheme 2).[17]

We found that activation of the amino group as a trifluoroacetamide was an effective method to provide an acidic nitrogen prone to undergo Mitsunobu alkylation.[18]

Table 1: Solution-phase synthesis of 1,3-thiazines **8**.

Entry	R^1	R^2	R^3	R^4	X	Yield [%][a]	Purity [%][b]
1	Et	Me	Ph	NH_2	S	78	93
2	Et	Me	Ph	NHMe	S	97	>98
3	Et	Me	Ph	NHPh	S	72	93
4	Et	Me	Ph	cycl[c]	S	71	96
5	Et	Me	2-CF_3-Ph	NHMe	S	18	>98
6	Me	Et	2-CF_3-Ph	NH_2	S	10	80
7	Me	Et	2-CF_3-Ph	NHBn	S	51	94
8	Et	Me	2,3-Cl-Ph	NHMe	S	89	>98
9	Et	Pr	2,3-Cl-Ph	NH_2	S	45	94
10	Et	Pr	2,3-Cl-Ph	NH_2	Se	11	90
11	Et	Pr	2-Cl-Ph	NH_2	S	35	94
12	Bn	Me	2-Cl-Ph	NHMe	S	30	98
13	Et	Pr	2-Cl-Ph	NHBn	S	70	98
14	Bn	Me	2-Cl-Ph	NH-Mes	S	42	87
15	Et	Me	2-thienyl	NH_2	S	56	96
16	Et	Me	2-thienyl	NHMe	S	15	>98
17	Et	Me	2-thienyl	cycl[c]	S	15	90
18	Et	Pr	C_5H_{11}	NH_2	S	26	85
19	Et	Me	3-OH-Ph	NH_2	S	24	84
20	Et	Me	3-OH-Ph	NHMe	S	36	90
21	*i*Pr	Me	3-Cl-Ph	NH_2	S	78	98
22	*i*Pr	Me	3-Cl-Ph	NHMe	S	75	96
23	Et	Pr	3-NO_2-Ph	NH_2	S	22	89
24	Et	Pr	3-NO_2-Ph	NHMe	S	46	78
25	Bn	Me	3-NO_2-Ph	cycl[c]	S	13	72
26	Me	Et	4-Cl-Ph	NH_2	S	32	97
27	Me	Et	4-Cl-Ph	NHPh	S	66	95
28	*i*Pr	Me	2,5-MeO-Ph	NH_2	S	43	91
29	*i*Pr	Me	2,5-MeO-Ph	NHMe	S	67	92

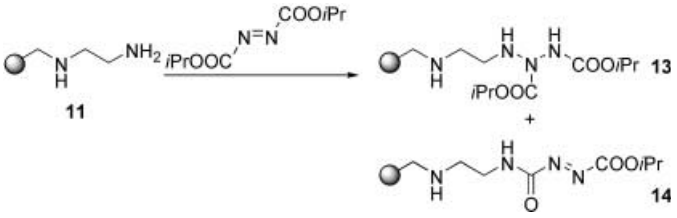
[a] Yields calculated on the basis of the experimentally determined loading of **6** (4.18 mmol g^{-1}) over two reaction steps. [b] Purity determined by LC-MS. [c] Imidazolidine-2-thione (see Scheme 1).



Scheme 2. Scaffold decoration of thiazine libraries by Mitsunobu alkylation. a) 2 equiv TFAA, dichloromethane, RT, 30 min; b) 4 equiv DIAD, 4 equiv TPP, 4 equiv R^5OH, THF, RT, 12 h; c) 5 equiv **6**, RT, 10 min; d) 2 equiv **11**, RT, 12 h; e) aq NH_3, RT, 3 h; f) 2 equiv **6**, RT, 10 min; g) MeOH/TEA 3:1. DIAD = diisopropyl azodicarboxylate, RT = room temperature, TEA = triethylamine, TFAA = trifluoroacetic anhydride, TPP = triphenylphosphane.

This intermediate (**9**) was easy to generate, and the trifluoroacetate was easy to remove at the end of the synthesis by treatment with aqueous ammonia. The alkylation sequence started with the standard acetylation of 2-aminothiazines **8**

($R^4 = H$) with trifluoroacetic anhydride and subsequent concentration to dryness to produce pure nonbasic trifluoroacetamides **9**. This change of basicity upon acylation also plays a critical role in the subsequent purification. Mitsunobu alkylation with primary alcohols was performed under classical conditions using a combination of diisopropyl azodicarboxylate (DIAD) and triphenylphosphane as well as the appropriate alcohol.[18] It should be noted that the application of a polymer-bound Mitsunobu reagent[19] did not result in useful conversions. Since the alkylated thiazine **10** remains nonbasic, it is possible to remove excess Mitsunobu reagent and the reduced *N*,*N*′-diacylhydrazide by-product by treating the reaction mixture with polymer-supported sulfonic acid **6**. In order to completely sequester all of the Mitsunobu reagent we also added a resin-bound amine base (**11**) that effectively sequestered the azodicarboxylate by forming either the polymer-bound triazene or monoamide (Scheme 3).[20,21] To the best of our knowledge this propensity



Scheme 3. Polymer-supported scavenging mechanisms for DIAD.[22]

of polymer-supported amines to react with azodicarboxylates constitutes a new strategy for the removal of Mitsunobu reagents. Procedures previously published applied tagged or polymer-supported phosphanes,[22,23] acid-labile ester groups (*tert*-butyl) for the selective degradation of Mitsunobu reagents,[23] and ROMP-based sequestration.[24] Finally the trifluoroacetate is cleaved with aqueous ammonia to yield thiazine **12** in its basic form. This recovery of basicity now allows for a catch-and-release strategy at the end using sulfonic acid resin **6** to produce pure monoalkylated thiazine products. The final purification effectively removes the excess triphenylphosphane and the formed triphenylphosphane oxide. It must be pointed out that the manipulations required for the sequence **8**→**12** consist solely of evaporation and polymer-assisted steps, and the sequence is therefore applicable to parallel synthesis.

Selective N-monoalkylation was accomplished in acceptable yield and products the were obtained with good purity over three reaction steps and subsequent catch-and-release purification (Table 2). In all cases the Mitsunobu reactions went to completion; the moderate yields were a consequence of incomplete sequestration of the product from the complex reaction mixture.

In summary, we have presented a concept for the construction of diverse libraries of 1,3-thiazines based on the dual action of a polymer-bound sulfonic acid as the mediator of a ring-closure reaction and the concomitant scavenger of the desired product. Five diversity points are addressed in the synthesis and subsequent scaffold decoration, with yields up to 97% and good to excellent purities.

Table 2: Solution-phase N-alkylation of 1,3-thiazines under Mitsunobu conditions to give products **12**.

Entry	R^1	R^2	R^3	R^5	Yield [%]	Purity [%][a]
1	Et	Me	Ph	3-Me-butyl	38	95
2	Et	Me	2,3-Cl-Ph	2-EtO-ethyl	41	80
3	Et	Me	2-thienyl	2-EtO-ethyl	52	94
4	Et	Me	C_5H_{11}	3-F-benzyl	19	75
5	Et	Me	3-Cl-Ph	hexyl	24	96
6	Me	Et	4-Cl-Ph	propyl	19	94

[a] Purity determined by LC-MS.

Experimental Section

Typical procedure for the Knoevenagel condensation (outlined for the enone leading to thiazine **8**, entry 1 in Table 1: Benzaldehyde (110 mg, 1.04 mmol), ethyl acetoacetate (118 mg, 0.91 mmol), and polymer-supported piperazine (as the diacetate) (90 mg, 10 mol%) were placed in a glass vial containing chlorobenzene (1 mL) and heated at 115 °C for 5 h under open-vessel conditions. After filtration and washing with dry dioxane (2 × 0.8 mL) the combined filtrates (approximately 2 mL) were directly subjected to the subsequent reaction.

A solution of the appropriate enone and thiourea (38 mg, 500 μmol) were added to dry DOWEX 50X2 **6** (102 mg, 426 μmol, 4.18 mmol g^{-1} as experimentally determined) in a Teflon frit (ACT Synthesizer PLS 6x4) and heated at 90 °C for 18 h. After cooling, the resin was washed (dioxane, MeOH, water, MeOH, dichloromethane), and the product was released by addition of triethylamine (500 μL) and methanol (1.5 mL). After the cocktail had been shaken for 20 min, it was filtered and the resin washed twice with 10% triethylamine in methanol (1.5 mL). The combined filtrates were evaporated to dryness, redissolved in dichloromethane, and filtered through a 1-cm plug of silica gel (eluent: ethyl acetate/petroleum ether 3:1) yielding 92.4 mg (334 μmol, 78% based on experimentally determined loading of the ion-exchange resin) of compound **8** (entry 1 in Table 1).

Received: August 28, 2003 [Z52731]

Keywords: combinatorial chemistry · heterocycles · molecular recognition · polymer-bound reagents · scavenger resins

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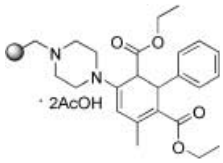

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