Pergamon

Tetrahedron Letters 43 (2002) 3193–3196

TETRAHEDRON LETTERS

Solid support synthesis of 2,4-disubstituted thiazoles and aminothiazoles

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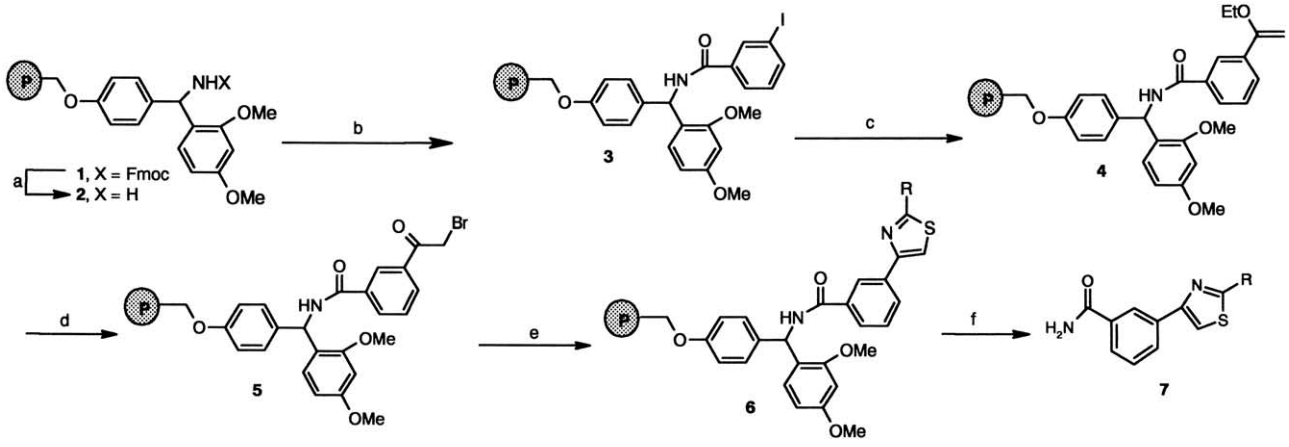
Received 24 January 2002; revised 5 March 2002; accepted 7 March 2002

Abstract—3-Iodobenzoic acid was loaded on *Rink* amide resin. Pd(0) coupling reaction with tributyl(1-ethoxyvinyl)tin followed by bromination using NBS gave an α-bromoketone bound to a solid support. Condensation of thioamide or thiourea, followed by TFA cleavage from the resin, gave 2,4-disubstituted thiazoles or 2-aminothiazoles, respectively. The primary amine of aminothiazole was treated with various acyl or sulfonyl chlorides to provide 2-substituted thiazole analogs.

The thiazole ring system is a common structural motif found in numerous biologically active molecules.[1] For example, it is known to be a ligand of estrogen receptors,[2] as well as a novel class of adenosine receptors antagonists.[3] Some thiazole derivatives found application in the development and preparation of antibiotic or anti-inflammatory drugs. Other analogs are broadly used as fungicide, inhibiting in vivo the growth of *Xanthomonas*, as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs.[4]

Up to now, solid-support syntheses have been widely used to generate small organic molecule libraries with potential pharmaceutical activities. Herein, we report the synthesis of 2,4-disubstituted thiazoles and aminothiazoles. Contrary to the already published[5] methods, in which α-bromoketones were reactive in solution, we envisioned their syntheses through a Pd(0) cross-coupling reaction under Stille conditions. Thus, an aromatic halide linked to a polystyrene resin[6] (the acid labile *Rink* linker) was reacted with tributyl-



Scheme 1. *Reagents and conditions*: (a) 20% piperidine in DMA, (b) 3-iodobenzoic acid, TBTU, HOBT, DMAP, Et_3N in 1,4-dioxane, (c) tributyl(1-ethoxyvinyl)tin, $Pd_2(dba)_3$, Ph_3As in 1,4-dioxane, 50°C, (d) NBS in THF/H_2O (4/1), (e) thioamide or thiourea in EtOH, 50°C, (f) 20/80 TFA/DCM.

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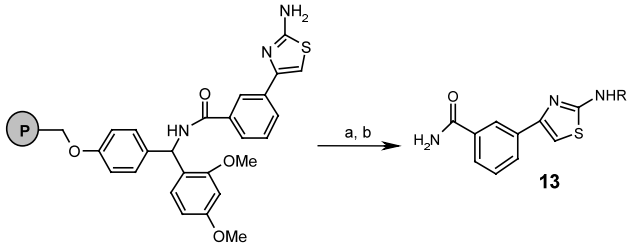
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00471-9

(1-ethoxyvinyl)tin in a Pd(0) catalysis to give after bromination the desired α-bromoketone bound to a solid support. Subsequent reaction with a thioamide or thiourea would give some thiazole derivatives (Scheme 1). This method is advantageous since it enables the synthesis of other heterocyclic ring systems from the same functionalized solid support.

It must be quoted, that all reactions reported here were performed on a scale (typically 200–250 mg beads; 0.7 or 0.87 mmol/g) allowing the isolation of at least 20 mg of crude product. Yields, therefore, refer to the weight of the crude products corrected by the purity evaluated by ^{1}H NMR (250 MHz). In some cases, yields of products purified by flash chromatography were reported in parentheses. The use of HPLC for yield and purity determination was avoided to allow a fair comparison of results obtained by traditional solution chemistry and solid phase chemistry. The structure of all compounds was established by ^{1}H, ^{13}C NMR and mass spectroscopy.

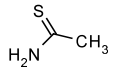
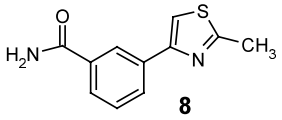
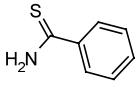
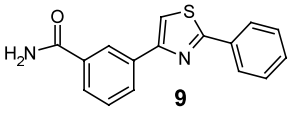
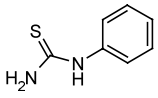
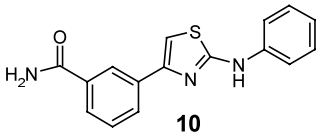
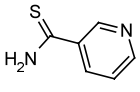
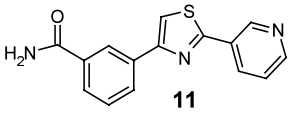
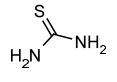
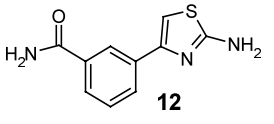
The resin **1** was deprotected with 20% piperidine in *N*,*N*-dimethylacetamide. Standard peptide coupling conditions[7] were used to introduce 3-iodobenzoic acid onto *Rink* amide resin **2**. Palladium(0) mediated coupling reaction was realized on the resin **3** in the presence of tributyl(1-ethoxyvinyl)tin, triphenylarsine[7] and tris(dibenzylidene acetone) dipalladium(0) as catalyst by heating at 50°C under argon in 1,4-dioxane allowing to obtain resin **4**. The conversion to α-bromoketone was realized by treatment of **4** with *N*-bromosuccinimide in a mixture of tetrahydrofuran and water (4/1). Thiazoles **6** were obtained by treatment of the resin **5** with an ethanol solution of a thioamide or a thiourea at 50°C. Cleavage of resin by trifluoroacetic acid gave the thiazoles **7**. All steps were monitored by cleavage of resin aliquots, followed by ^{1}H NMR and mass spectrometry.

Five examples of thiazole synthesized by this route are shown in Table 1. Yields are good (61 to 90% after six steps) and purities are excellent as judged by ^{1}H NMR. This approach allows the possibility of numerous derivatization of thiazole moiety. For instance, we have successfully synthesized (Scheme 2) and summarized (Table 2) five compounds by derivatization of primary amine in the 2-position of the aminothiazole.



Scheme 2. *Reagents and conditions*: (a) acyl chlorides or *p*-toluenesulfonyl chloride in pyridine/DCM (1/1); (b) TFA/DCM (20/80).

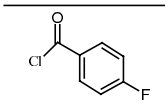
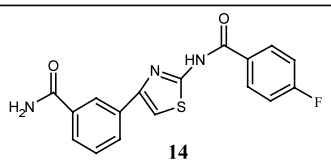
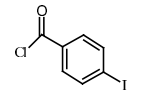
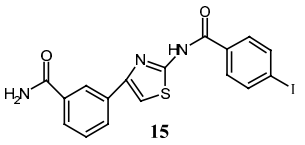
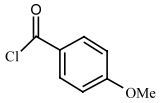
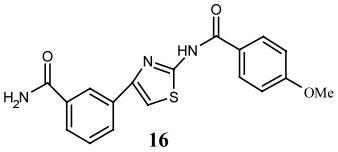
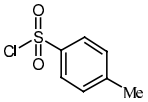
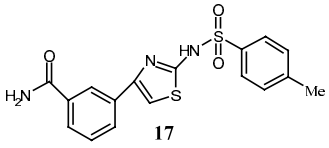
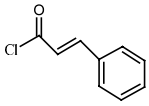
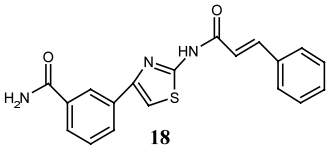
Table 1. Yields and MS of 2,4-disubstituted thiazoles

Reagents	Products[8]	Yield %[a,b]	MS (M+1)
	 **8**	98 (90)	219
	 **9**	92 (61)	281
	 **10**	79 (65)	296
	 **11**	96 (75)	282
	 **12**	91 (82)	220

[a]in parentheses are the yields of isolated product after purification.

[b] yields are calculated based on theoretical loading of the resin.

Table 2. Yields and MS of 2,4-disubstituted thiazoles

Reagents	Products[9]	Yield %[a]	MS (M+1)
	 **14**	62	342
	 **15**	45	450
	 **16**	48	354
	 **17**	33	374
	 **18**	78	350

[a]in parentheses are the yields of isolated product after purification.

2-Aminothiazole **6** ($R = NH_2$) bound to solid support was reacted with acyl chlorides or *p*-toluenesulfonyl chloride (Table 2) in a mixture of pyridine/dichloromethane (1/1), at room temperature. Yields are good (33 to 78% after seven steps) and purities found excellent (^1H NMR). It is noteworthy that these compounds were easily isolated by simple precipitation from dichloromethane/methanol (9/1) mixture.

The above-described synthesis is useful for the production of a combinatorial library, due to the large number of commercially available thioamides. In addition, derivatization of 2-aminothiazoles increases the potential diversity. Furthermore, this synthesis is compatible with several commercially-available resins and it is suitable to other aromatic halides introducing more diversity at the 4-position of the thiazole ring.

References

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8. **General procedure for preparation of compounds 8–12**: *Rink* amide resin (Nova Biochem, 0.87 mmol/gm Loding, 1 gm) was deprotected with 20% piperidine in DMA (15 ml) for 30 min at rt. The resin was washed 3 times with DMA and 3 times with CH_2Cl_2. The resin was then treated with a solution of 3-iodobenzoic acid (4 equiv. TBTU (4.4 equiv.), HOBT (2 equiv.), DMAP (1 equiv.), Et_3N (14.4 equiv.) in dioxane for 48 h. The resin was washed with 3 times of each CH_2Cl_2, water, EtOH/water, EtOH, CH_2Cl_2 and then dried over night in vacuo at rt. Dried resin was twice treated with tributyl(1-ethoxyvinyl)tin (2 equiv.), Ph_3As (0.4 equiv.), $Pd_2(dba)_3$ (0.1 equiv.) in dioxane under argon at 50°C for 24 h. The resin was washed as above described. The dried resin was treated with *N*-bromosuccinimide (2.5 equiv.) in THF/water (4/1) for 1 h at rt. The

resin was washed and dried as above. The resin bound α-bromoketone (200 mg) was treated with thioamide or thiourea (6 equiv.) in EtOH at 50°C for 12 h, then washed and cleaved with 1/4 TFA/CH_2Cl_2 for 5 min (twice). The resin was filtered off and washed with CH_2Cl_2. The filtrate was concentrated in vacuo and filtered to give compounds **8–12** (Table 1). Compound **12**, Table 1: ^{1}H NMR (250 MHz, CD_3OD) δ 8.19 (s, 1H), 7.83 (d, $J=7.7$ Hz, 1H), 7.75 (d, $J=7.9$ Hz, 2H), 7.39 (dd, $J=7.7$, $J=7.9$ Hz, 1H), 7.11 (s, 1H).

9. **General procedure for preparation of compounds 14–18**: The resin bound 2-aminothiazole (200 mg) was treated with acyl chloride or *p*-toluenesulfonyl chloride (4 equiv.) in a mixture of pyridine/CH_2Cl_2 (1/1) at rt for 12 h. The resin was washed with 3 times of each CH_2Cl_2, water, EtOH/water, EtOH, CH_2Cl_2 and cleaved with 1/4 TFA/CH_2Cl_2. The filtrate was concentrated in vacuo and precipitated from CH_2Cl_2/MeOH (9/1) to give compounds **14–18** (Table 2). Compound **16**, Table 2: ^{1}H NMR (250 MHz, $(CD_3)_2SO$) δ 8.50 (s, 1H), 8.14 (d, $J=8.7$ Hz, 2H), 8.07 (d, $J=7.8$ Hz, 1H), 7.81 (d, $J=7.8$ Hz, 1H), 7.73 (s, 1H), 7.51 (t, $J=7.8$ Hz, 1H), 7.09 (d, $J=8.7$ Hz, 2H), 3.85 (s, 3H).